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COMMENTARY

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Pressuromodulation at the cell membrane as the basis for small molecule hormone and peptide regulation of cellular and nuclear function

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Abstract

Building on recent knowledge that the specificity of the biological interactions of small molecule hydrophiles and lipophiles across microvascular and epithelial barriers, and with cells, can be predicted on the basis of their conserved biophysical properties, and the knowledge that biological peptides are cell membrane impermeant, it has been further discussed herein that cellular, and thus, nuclear function, are primarily regulated by small molecule hormone and peptide/factor interactions at the cell membrane (CM) receptors. The means of regulating cellular, and thus, nuclear function, are the various forms of CM Pressuromodulation that exist, which include Direct CM Receptor-Mediated Stabilizing Pressuromodulation, sub-classified as Direct CM Receptor-Mediated Stabilizing Shift Pressuromodulation (Single, Dual or Tri) or Direct CM Receptor-Mediated Stabilizing Shift Pressuromodulation (Single, Dual or Tri) cum External Cationomodulation ($\geq$3+ $\rightarrow$ 1+); which are with respect to acute CM receptor-stabilizing effects of small biomolecule hormones, growth factors or cytokines, and also include Indirect CM- or CM Receptor-Mediated Pressuromodulation, sub-classified as Indirect 1ary CM-Mediated Shift Pressuromodulation (Perturbomodulation), Indirect 2ary CM Receptor-Mediated Shift Pressuromodulation (Tri or Quad Receptor Internal Pseudo-Cationomodulation: SS 1+), Indirect 3ary CM Receptor-Mediated Shift Pressuromodulation (Single or Dual Receptor Endocytic External Cationomodulation: 2+) or Indirect (Pseudo) 3ary CM Receptor-Mediated Shift Pressuromodulation (Receptor Endocytic Hydroxylocarbonyloetheroylomodulation: 0), which are with respect to sub-acute CM receptor-stabilizing effects of small biomolecules, growth factors or cytokines. As a generalization, all forms of CM pressuromodulation decrease CM and nuclear membrane (NM) compliance (whole cell compliance), due to pressuromodulation of the intracellular microtubule network and increases the exocytosis of pre-synthesized vesicular endogolgi peptides and small molecules as well as nuclear-to-rough endoplasmic reticulum membrane proteins to the CM, with the potential to simultaneously increase the NM-associated chromatin DNA transcription of higher molecular weight protein forms, secretory and CM-destined, mitochondrial and nuclear, including the highest molecular weight nuclear proteins, Ki67 (359 kDa) and Separase (230 kDa), with the latter leading to mitogenesis and cell division; while, in the case of growth factors or cytokines with external cationomodulation capability, CM Receptor External Cationomodulation of CM receptors ($\geq$3+ $\rightarrow$ 1+) results in cationic extracellular interaction ($\geq$3+) with extracellular matrix heparan sulfates ($\geq$3+ $\rightarrow$ 1+) concomitant with lamellopodesis and cell migration. It can be surmised that the modulation of cellular, and nuclear, function is mostly a reactive process, governed, primarily, by small molecule hormone and peptide interactions at the cell membrane, with CM receptors and the CM itself. These insights taken together, provide valuable translationally applicable knowledge.

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Keywords: Direct CM receptor-mediated stabilizing shift pressuromodulation, Direct CM receptor-mediated stabilizing shift pressuromodulation cum external cationomodulation (≥3+ → 1+), Indirect 1ary CM-mediated shift pressuromodulation (Perturbomodulation), Indirect 2ary CM receptor-mediated shift pressuromodulation (SS 1+), Indirect 3ary CM receptor-mediated shift pressuromodulation (Receptor endocytic 2+), Indirect (pseudo) 3ary CM receptor-mediated shift pressuromodulation (Receptor endocytic hydroxylocarbonyloetheroylomodulation 0)

Background

The specificity of the biological interactions of small molecule hydrophiles and lipophiles can be predicted on the basis of their conserved biophysical properties, which are relative hydrophilicity or lipophilicity in context of molecular size and the distribution of charge over molecular space [1]. Based on these observations, it can be stated that small biomolecules with either cationic or anionic charge are relatively or absolutely restricted to permeation across capillary barriers with restrictive inter-cellular junctional pore complexes [1], as well as excluded from permeation across cell membrane (CM) protein channel aqueous pores in their charged forms in the absence of voltage gating required to increase the channel's physiologic upper limit of pore size [2, 3], with excess divalent cation, Ca 2+, auto-vesicularizng into the endogolgi smooth endoplasmic reticulum (SER) [4, 5]. In the case of anionic small biomolecule hydrophiles with polyvalent or divalent anionicity such as glutamate, these are impermeant to CM protein channel pores in their polyvalent or divalent anionic forms, closely associate with excess divalent cation, Ca2+, and in association with, also auto-endocytose vesiculize into cell membranes [6], as do cationic small biomolecules such as epinephrine and dopamine due to sufficient poly-univalent cationicity in molecular space (2+ cationicity equivalent: 1+ insufficient separation (IS) 1+), while small biomolecules with charge only traverse CM protein channel pores (i.e. Ca2+ channel pores) across looser channel aqueous pores during voltage gating or oxidative stress, as molecular size permits their passage in these specific instances, which is the case of excess Lactate (1−) generated during metabolic acidosis.

In the case of the endogenous steriods, these include the corticosteroids and sex steroids, the corticosteroids being small molecules of lipophilic character with van der Waals diameters (vdWDs) of ~0.87 nm (nm) and the sex steroid hormones being small molecules of lipophilic character with vdWDs of ~0.80 nm, which permeate across inter-epithelial junction pore complexes via diffusion, while both are restricted to permeation across tight junction vascular/microvascular capillary endothelium [1, 7]. At the individual cell level, the small molecule hormone steroids by being molecular size restricted at CM aqueous pores do not permeate across CM pores, and also do not associate to any significant degree with CM phospholipids, since corticosteroids (cortisol, aldosterone) are asymmetrically polyhydroxylated/carbonylated hormones and the sex steroids (estradiol, progesterone, testosterone, androstenedione) are symmetrically dihydroxylated/di-carbonylated hormones, with molecular structures favorable to association with CM alpha helix protein receptors in the context of sufficient incorporating lipophilicity for size to do so [8]. As a result of remaining at the cell membrane-to-aqueous interface, the steroids exert their molecular effects at the alpha helix-based CM receptors, whereby, the endogenous corticosteroids primarily exert their effects at the juxtaposed classical GR (97 kDa) and MR (110 kDa) (MR-classical GR complex) [9], by binding to the Mineralocorticoid Receptor (MR) portion of the classical glucocorticoid cum mineralocorticoid receptor complex for which portion they have greater binding affinities [9, 10], while the endogenous sex steroids bind to the Estrogen Receptor (ER) (65 kDa), progestorone receptor (PR) and androgen receptor (AR), in order of greatest to least potency steroid receptor respectively (MR-classical GR > ER > PR > AR) [11, 12]. Moreover, the molecular arrangement of hydrophilic groups attached directly to the immediate steroid backbone is insufficient to induce endocytosis of the respective hormone-receptor complexes, therefore, both classes of steroids are CM receptor pressuromodulators for the specific cell types expressing their receptors *vis a vis* ligand-bound receptor pressuromodulation of the specific receptor's microtubular network (MR-classical GR, ER, PR or AR)-linked to the receptor's nuclear chromatin DNA (MR-classical GR, ER, PR or AR) at the level of the nuclear membrane (NM) [13]: The intracellular microtubular network is immobile [14], as opposed to the intracellular F-Actin network, which mobilizes [14], in response to CM receptor-mediated pressuromodulation.

As the chromatin DNA is located along the NM [13], CM pressuromodulation-mediated pressure loading of the specific receptor's microtubular network-linked to the nuclear membrane (NM)-associated histone-wound DNA chromatin, temporarily unwinds the histone-wound DNA chromatin for transcription, that which upregulates the specific receptor's expression on the NM-to-RER-to-CM receptor, and importantly, also decreases whole cell cum nuclear compliance, that which results in

the immediate exocytosis of, other peptides, both pre-synthesized vesicular Golgi peptide and small molecule forms as well as CM-destined nuclear-to-RER receptor proteins, and concomitantly, simultaneously increases the likelihood of the transcription of higher molecular weight protein forms, secretory and CM receptor, mitochondrial and nuclear, including the highest molecular weight mitogenesis cell division-associated nuclear proteins, Ki67 (359 kDa) and separase (230 kDa): Thus, CM pressuromodulation of whole cell compliance is analogous to mechanical pressure-mediated decreases in whole cell compliance to the biological upper limit of increased intracellular tension [15, 16], for which there must be an upper limit of decreased whole cell compliance required to induce mitogenesis and cell division, and in corollary, that which must be equivalent for all cells, whereby, less compliant cells reach the upper limit faster, while more compliant cells reach the upper limit slower, and, in context of local microenvironment stiffness [17, 18].

As a generalization, the overall character of cell response to direct CM receptor-mediated pressuromodulation is dependent on receptor binding potential (BP), a product of the receptor density (*B*max) and 1/*K*d, and in the case of endogenous small molecule hormones, only in the case of corticosteriod, aldosterone, does the half life at the receptor ($t_{1/2}$ @ receptor) begin to be a significant determinant of pressuromodulation effect, which binds to the MR portion of the MR-classical GR with a sub-nM *K*d, in the decimolar (dM) range, whereby, aldosterone's $t_{1/2}$ @ receptor is 140 min, which makes it a significant CM pressuromodulator [4, 19–27], despite the fact that only ~170 receptors (MR-Classical GR) are expressed for it on most cell membranes [28–30]; whereas, in the case of the peptides, the half life at the receptor ($t_{1/2}$ @ receptor) stands be a significant determinant of pressuromodulation effect for the monomeric, dimeric or trimeric peptides that bind to polymeric receptors/receptor subunits (IGF-I/II for example [31–35]), those which bind with sub-nM *K*d affinities irrespective of the receptor density.

Based this recent knowledge on the conserved determinants of biological function of small biomolecules in the physiologic state, it can be stated that the biological determinants underlying peptide and factor interactions are just as conserved at the individual cell CM level, which, in turn, regulate cellular, and thus, the nuclear function of a cell. In the commentary, this unifying hypothesis is further explored for the spectrum of small molecule hormones and peptide hormones, including immunomodulatory peptide factors, supported by the findings of published studies, on the structures and functions, of the same.

Commentary

Small molecule regulation of intracellular function vis a vis interaction at the cell membrane (CM) receptor

The small biomolecules (<0.5 to 1 nm) include the: (1) small molecule hydrophiles (neutral hydrophiles, neutral cationoneutral hydrophiles, cationic-anionic hydrophiles, anionic cationoneutral hydrophiles, cationic hydrophiles); (2) small molecule hydro-lipophiles (simple cationic hydro-lipophiles, circumferentially polyhydroxylated/carbonylated hydro-lipophile [non-compact (>CM pore size)], circumferentially polyhydroxylated/carbonylated hydro-lipophile + exterior cationicity [non-compact (>CM pore size)]); and (3) small molecule lipophiles (small lipophiles, asymmetric unihydroxylated lipophiles (stable), asymmetric unihydroxylated lipophiles (unstable), asymmetric polyhydroxylated lipophiles (unstable), asymmetric unicarboxylated lipophiles (stable), asymmetric unicarboxylated lipophiles (stable), asymmetric unicarboxylated lipophiles (unstable), asymmetric polyhydroxylated sterols, symmetric dihydroxylated or trihydroxylated/dicarbonylated sterols, symmetric dihydroxylated lipophiles, polyhydroxylated/carbonylated lipophiles (compact), circumferentially polyhydroxylated/carbonylated lipophiles [non-compact (>CM pore size)], circumferentially polyhydroxylated/carbonylated/etheroylated lipophiles [non-compact (>CM pore size)] (Table 1; Additional file 1: Table S1; Additional file 2: Figure S2; Additional file 3: Figure S3; Additional file 4: Figure S4; Additional file 5: Complete Table 1 in Supplemental File Format).

The specific roles that small molecules play in the biological system is determinable on the basis of an assessment of conserved biophysical properties, relative hydrophilicity or lipophilicity in context of molecular size, as per the predicted octanol-to-water partition coefficient (OWPC)-to-van der Waals diameter (vdWD) ratio (nm^{-1}) in context of the predicted vdWD (nm) [1] (Additional file 1: Table S1).

Neurotransmitter small molecule hydrophile and hydro-lipophile regulation of intracellular function vis a vis interaction at the cell membrane (CM) receptor

The small molecule hydrophiles include the cationic neurotransmitters acetylcholine (1+) and norepinephrine (1+), which are (pure) hydrophiles due to the presence of singular cationicity (1+) cum hydroxylated hydrophilicity in the absence of cell membrane (CM) receptor protein binding lipophilicity. These, being singularly cationic (pure) hydrophiles are internal cationomodulators that cause cell membrane depolarization via the insertion of 1+ cationicity into protein receptor channel aqueous pores (Table 1; Additional file 1: Table S1; Additional file 2: Figure S2; Additional file 5: Complete Table 1 in Supplemental File Format) and potentiate the circumferential propagation of current in effector cell membranes, that which in the case

Table 1 Conservation of small biomolecule, peptide or factor and non-small molecule non-peptide function

Type	Sub-type	Example(s)	Cell membrane (CM) or CM receptor	Effect at cell membrane (CM) receptor	Intracellular result of effect
Small molecule					
Small molecule hydrophile	Neutral hydrophile	H2O, nitrogenous bases	CM receptor aqueous pore	n/a (subcellular interaction, including nuclear/mitochondrial)	CM receptor/nuclear/mitoch aqueous pore permeation → DNA/RNA
	Neutral cationoneutral hydrophile	Apolar amino acids (i.e. valine, alanine, leucine, isoleucine, etc)	CM receptor aqueous pore	n/a (subcellular interaction, including nuclear/mitochondrial)	CM receptor/nuclear/mitoch aqueous pore permeation → RNA/proteins
	Cationic–anionic hydrophile	Neurotransmitter (glycine, GABA) (IS 1+ 1−)	CM receptor aqueous pore	Receptor aqueous pore non-cationomodulation (isomodulation) and CM non-depolarization	CM receptor aqueous pore permeation
	Anionic cationoneutral hydrophile	Neurotransmitter glutamate (IS 1− 1−)	Peri-CM/peri-CM receptor aqueous pore	Ca2+ pseudo-association	Vesicular non-auto-endocytosis
	Cationic hydrophile	Neurotransmitters norepinephrine (1+), acetylcholine (1+)	CM receptor aqueous pore	Receptor aqueous pore internal cationomodulation and CM depolarization	Depolarization
	Cationic hydrophile	Neurotransmitters norepinephrine (1+), acetylcholine (1+)	CM	Direct CM cationiomodulation (Poly IS 1+)	Vesicular endocytosis
	Cationic hydrophile	Histamine @ acidic pH (IS 1+ 1+)	CM	Direct CM cationiomodulation (2+)	Vesicular auto-endocytosis
Small molecule hydro-lipophile	Simple cationic hydro-lipophile	Neurotransmitters dopamine (1+), seratonin (1+) and histamine (1+)	CM receptor protein	Receptor external cationiomodulation and CM non-depolarization	Non-depolarization
	Simple cationic hydro-lipophile	Neurotransmitters dopamine (1+), seratonin (1+) and histamine (1+)	CM	Direct CM cationiomodulation (poly IS 1+)	Vesicular endocytosis
	Circumferentially polyhydroxylated/carbonylated hydro-lipophile [non-compact (>pore size)]	i.e. Ouabain	CM receptor alpha helix isophilic aqueous pore (i.e. Na/K ATPase)	Receptor external hydroxymodulation → (Pseudo) 3ary indirect shift pressuromodulation	CM interaction receptor endocytosis [mitogenesis]
	Circumferentially polyhydroxylated/carbonylated hydro-lipophile + exterior cationicity [non-compact (>pore size)]	i.e. Doxorubicin (1+)	CM receptor alpha helix isophilic aqueous pore (i.e. Na/K ATPase)	Receptor external hydroxymodulation	CM interaction receptor endocytosis and cationicity (1+)-mediated mitochondrial toxicity
Small molecule lipophile	Small lipophile	i.e. Benzene, di.e.thyl ether	CM receptor aqueous pore	Mitochondrial membrane perturbomodulation → 1ary indirect shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Asymmetric unihydroxylated lipophile (stable)	Cholesterol (3-hydroxycholesterol), i.e. Cholecalciferol (3-hydroxyvitamin D3)	CM	CM incorporopressuromodulation	Baseline Chromatin DNA Protein Synthesis/Exocytosis
	Asymmetric unihydroxylated lipophile (unstable)	i.e. Hexan-1-ol, retinol	CM	CM perturbomodulation → 1ary indirect shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Asymmetric polyhydroxylated lipophile (unstable)	i.e. Phorbol ester 12-O-Tetradecanoylphorbol-13-acetate (TPA)	CM	CM perturbomodulation → 1ary indirect shift pressuromodulation	Chromatin DNA Protein Synthesis/exocytosis
	Asymmetric unicarboxylated lipophile (stable)	Saturated fatty acid → ester	CM	CM incorporopressuromodulation	Baseline chromatin DNA protein synthesis/exocytosis
	Asymmetric unicarboxylated lipophile (stable)	Polyunsaturated fatty acid → ester (i.e. omega-3/6)	CM	CM Incorporo-negativopressuromodulation	n/a

Table 1 continued

Type	Sub-type	Example(s)	Cell membrane (CM) or CM receptor	Effect at cell membrane (CM) receptor	Intracellular result of effect
	Asymmetric unicarboxylated lipophile (unstable)	Non-fatty acid (i.e. retinoic acid)	CM	CM perturbomodulation → 1ary indirect shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Asymmetric polyhydroxylated sterol	Aldosterone, dexamethasone, cortisol	CM receptor protein	Receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Symmetric di or trihydroxylated/dicarbonylated sterol	Testosterone, estrogen, progesterone	CM receptor protein	Receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Symmetric dihydroxylated lipophile	i.e. Calcifediol (1,25-dihydroxyvitamin D3)	CM	CM perturbomodulation → 1ary indirect shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	PolyHydroxylated/carbonylated lipophile (compact)	i.e. 3-Isobutyl-1-methylxanthine (IBMX)	CM and CM receptor aqueous pore	CM perturbomodulation → 1ary indirect shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Circumferentially polyhydroxylated/carbonylated lipophile [non-compact (>pore size)]	i.e. Forskolin	CM receptor alpha helix isophilic aqueous pore	Receptor external hydroxymodulation → (pseudo) 3ary indirect shift pressuromodulation	CM interaction receptor endocytosis [mitogenesis]
	Circumferentially polyhydroxylated/carbonylated/etheroylated lipophile [non-compact (>pore size)]	i.e. Paclitaxel (taxol), colchicine	CM receptor alpha helices	Receptor external hydroxymodulation	CM interaction receptor endocytosis and microtubular network disruption
Non-small molecule non-peptide	Polyphospholipid polysaccharide	Lipopolysaccharide (LPS)	CM	CM perturbomodulation → 1ary indirect shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
Peptide	Small (non-alpha non-beta helix) peptide	Atrial natriuretic peptide (anp) monomer (1+ IS 1+)	CM receptor protein monomer	Receptor external cationiomodulation (2+) → 3ary indirect shift pressuromodulation	Cationic (2+) CM interaction receptor endocytosis [mitogenesis]
	Small (non-alpha non-beta helix) peptide	Bradykinin monomer (1–9 AAs) (1+ IS 1+ SS 1+)	CM receptor protein monomer	Receptor external cationiomodulation (2+) → 3ary indirect shift pressuromodulation	Cationic (2+) CM interaction receptor endocytosis [mitogenesis]
	Small (non-alpha non-beta helix) peptide	Des-Arg9 Bradykinin Monomer (1-8 AAs) (1+ IS 1+)	CM Receptor Protein Monomer	Receptor External Cationiomodulation (2+) → 3ary Indirect Shift Pressuromodulation	Cationic (2+) CM Interaction Receptor Endocytosis [Mitogenesis]
	Small (non-alpha non-beta helix) peptide	Sulfate neutralized lys-bradykinin (kallidin) monomer (1–10 AAs) (IS 3+ → 1+)	CM receptor protein monomer	Receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Small (non-alpha non-beta helix) peptide	Vasopressin arginine (anti-diuretic hormone: ADH) monomer (1+)	CM receptor protein monomer	Receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Small (non-alpha non-beta helix) peptide	Neurotensin monomer (1+)	CM receptor protein monomer	Receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Small (non-alpha non-beta helix) peptide	Angiotensin II monomer	CM receptor protein monomer	Receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Small (non-alpha non-beta helix) peptide	Ps4 thyrotropin releasing hormone (TRH) monomer	CM receptor protein monomer	Receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Small (non-alpha non-beta helix) peptide	Somatostatin (growth hormone release inhibiting peptide: ghrip) monomer	CM receptor protein monomer	Receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis

Table 1 continued

Type	Sub-type	Example(s)	Cell membrane (CM) or CM receptor	Effect at cell membrane (CM) receptor	Intracellular result of effect
	Small (non-alpha non-beta helix) peptide	Oxytocin monomer	CM receptor protein monomer	Receptor stabilizing shift pressuro-modulation	Chromatin DNA protein synthesis/exocytosis
	Short monoalpha helix	Glucagon monomer	CM receptor protein monomer	Receptor stabilizing shift pressuro-modulation	Chromatin DNA protein synthesis/exocytosis
	Short monoalpha helix-loop-short 2-way beta helix	Adrenocorticotropic hormone (ACTH) monomer	CM receptor protein monomer → dimer	Receptor stabilizing shift pressuro-modulation	Chromatin DNA protein synthesis/exocytosis
	Long monoalpha helix	Parathyroid hormone (PTH)/PTH releasing peptide (PTHrP) monomer	CM receptor protein monomer	Receptor stabilizing shift pressuro-modulation	Chromatin DNA protein synthesis/exocytosis
	Long monoalpha helix-loop-short 2-way beta helix	Pro-ACTH Pro-opiomelanocortin (POMC) monomer	CM receptor protein monomer → dimer	Receptor stabilizing shift pressuro-modulation	Chromatin DNA protein synthesis/exocytosis
	Short monoalpha helix-loop-short monoalpha helix	Adrenocorticotrophin releasing hormone/factor (CRH/F) monomer	CM receptor protein dimer (2 su: 3 su)	Dual receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Short monoalpha helix-loop-short monoalpha helix	Insulin monomer	CM receptor protein dimer (2 su: 3 su)	Dual receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Short monoalpha helix-loop-short monoalpha helix-loop-short monoalpha helix	Osteocalcin monomer	CM receptor protein dimer (2 su: 3 su)	Dual receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Short monoalpha helix-loop-short monoalpha helix-loop-short monoalpha helix	Insulin-like growth factor-1 (IGF1/II; somatomedin C) monomer	CM receptor protein dimer (2 su: 3 su)	Dual receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Short monoalpha helix-loop-short monoalpha helix-loop-short monoalpha helix	Prolactin (PRL) releasing hormone/factor (PRLRH/factor) monomer	CM receptor protein dimer (2 su: 3 su)	Dual receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Short monoalpha helix-loop-short monoalpha helix-loop-short monoalpha helix	Growth hormone releasing hormone/factor (GHRH/F) monomer	CM receptor protein dimer (2 su: 3 su)	Dual receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Short monoalpha helix-loop-short monoalpha helix-loop-short monoalpha helix	Gonadotropin releasing hormone/factor (GnRH/F) monomer	CM receptor protein dimer (2 su: 3 su)	Dual receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Aligned multialpha helix	Interleukin-3 (IL-3) monomer	CM receptor protein dimer (2 su: 2 su)	Dual receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Aligned multialpha helix	Interleukin-7 (IL-7) monomer	CM Receptor Protein Dimer (2 su: 2 su)	Dual receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Aligned multialpha helix	Interleukin-12 (IL-12) monomer	CM receptor protein dimer (2 su: 2 su)	Dual receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Aligned multialpha helix	Interleukin-23 (IL-23) monomer	CM receptor protein dimer (2 su: 2 su)	Dual receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Aligned multialpha helix	Prolactin (PRL) monomer	CM receptor protein dimer (2 su: 2 su)	Dual receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Aligned multialpha helix	Growth hormone (GH) monomer	CM receptor protein dimer (2 su: 2 su)	Dual receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Aligned multialpha helix	Erythropoietin (Ep) monomer	CM receptor protein dimer (2 su: 2 su)	Dual receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis
	Aligned multialpha helix	Interferon gamma (INF-g) homodimer	CM receptor protein trimer (3 su: 3 su: <3 su>)	Dual-to-tri receptor stabilizing shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis

Table 1 continued

Type	Sub-type	Example(s)	Cell membrane (CM) or CM receptor	Effect at cell membrane (CM) receptor	Intracellular result of effect
	Semi-aligned multialpha helix cum short mono-alpha helix	Interleukin-2 (IL-2) monomer	CM receptor protein dimer (3 su: 2 su)	Dual receptor stabilizing shift presuromodulation	Chromatin DNA protein synthesis/exocytosis
	Semi-aligned multialpha helix cum short mono-alpha helix	Interleukin-6 (IL-6) monomer	CM receptor protein dimer (3 su: 2 su)	Dual receptor stabilizing shift presuromodulation	Chromatin DNA protein synthesis/exocytosis
	Semi-aligned multialpha helix cum short monobeta 2-way helix	Interleukin-4 (IL-4) monomer	CM receptor protein dimer (4 su: 2 su)	Dual receptor stabilizing shift presuromodulation	Chromatin DNA protein synthesis/exocytosis
	Semi-aligned multialpha helix cum short monobeta 2-way helix	Interleukin-13 (IL-13) monomer	CM receptor protein dimer (4 su: 2 su)	Dual receptor stabilizing shift presuromodulation	Chromatin DNA protein synthesis/exocytosis
	Semi-aligned multialpha helix cum short monobeta 2-way helix	Interleukin-5 (IL-5) monomer	CM receptor protein dimer (4 su: 2 su)	Dual receptor stabilizing shift presuromodulation	Chromatin DNA protein synthesis/exocytosis
	Semi-aligned multialpha helix cum short monobeta 2-way helix	Interleukin-15 (IL-15) monomer	CM receptor protein dimer (4 su: 2 su)	Dual receptor stabilizing shift presuromodulation	Chromatin DNA protein synthesis/exocytosis
	Semi-aligned multialpha helix cum short monobeta 2-way helix	Interleukin-20 (IL-20) monomer	CM receptor protein dimer (4 su: 2 su)	Dual receptor stabilizing shift presuromodulation	Chromatin DNA protein synthesis/exocytosis
	Semi-aligned multialpha helix cum short monobeta 2-way helix	Granulocyte monocyte-colony stimulating factor (GM-CSF) monomer	CM receptor protein dimer (4 su: 2 su)	Dual receptor stabilizing shift presuromodulation	Chromatin DNA protein synthesis/exocytosis
	Semi-aligned multialpha helix cum short mono-alpha helix cum short loop	Leukemia inhibitory factor (LIF)/oncostatin (OSM) monomer	CM receptor protein dimer (5 su: 3 su)	Dual receptor stabilizing shift presuromodulation	Chromatin DNA protein synthesis/exocytosis
	Semi-aligned multialpha helix-loop-short mono-alpha helix-loop-short monobeta 2-way helix	Granulocyte-colony stimulating factor (G-CSF)/macrophage (mouse)-colony stimulating factor (M-CSF) homodimer	CM receptor protein dimer (5 su: 3 su)	dual receptor stabilizing shift presuromodulation	Chromatin DNA protein synthesis/exocytosis
	Short monoalpha helix (neutral) cum compact loose non-aligned 3-way beta-X-2-way beta helix (cationic)	Sulfate neutralized interleukin-16 (IL-16) monomer (IS 3+ → 1+)	CM receptor protein (CD4) monomer	External cationiomodulation and receptor stabilizing shift presuromodulation	Extracellular matrix interaction and chromatin DNA protein synthesis/exocytosis
	Short monoalpha helix (neutral) cum compact loose aligned 3-way beta helix (cationic)	Sulfate neutralized macrophage inflammatory protein-1 beta (MIP-1 beta: CCL20) monomer (IS 3+ → 1+)	CM receptor protein (CCR5) monomer	External cationiomodulation and receptor stabilizing shift presuromodulation	Extracellular matrix interaction and chromatin DNA protein synthesis/exocytosis
	Short monoalpha helix (neutral) cum compact loose aligned 3-way beta helix (cationic)	Sulfate neutralized CCL3/CCL4/CCL5 (RANTES) monomer (IS 3+ → 1+)	CM receptor protein (CCR5) monomer	External cationiomodulation and receptor stabilizing shift presuromodulation	Extracellular matrix interaction and chromatin DNA protein synthesis/exocytosis
	Short angled monoalpha helix (neutral) cum compact loose aligned 3-way beta helix (cationic)	Sulfate neutralized SDF-1 (CXCL-12) monomer (IS 3+ → 1+)	CM receptor protein (CXCR4) monomer	External cationiomodulation and receptor stabilizing shift presuromodulation	Extracellular matrix interaction and chromatin DNA protein synthesis/exocytosis
	Short angled monoalpha helix (neutral) cum compact loose aligned 3.5-way beta helix (cationic)	Sulfate neutralized interleukin-8 (IL-8) monomer (IS 3+ → 1+)	CM receptor protein (CXCR1) monomer	External cationiomodulation and receptor stabilizing shift presuromodulation	Extracellular matrix interaction and chromatin DNA protein synthesis/exocytosis
	Compact loose non-aligned multibeta helix (cationic) [+/− alpha helix knob (neutral)]	Sulfate neutralized fibroblast growth factor (FGF-19/FGF-2) monomer ×2 (IS 3+ → 1+: IS 3+ → 1+)	CM receptor protein monomer (3 su) → dimer (3 su: 3 su)	External cationiomodulation and dual receptor stabilizing shift pressuromodulation	Extracellular matrix interaction and chromatin DNA protein synthesis/exocytosis

Table 1 continued

Type	Sub-type	Example(s)	Cell membrane (CM) or CM receptor	Effect at cell membrane (CM) receptor	Intracellular result of effect
	Compact loose non-aligned multibeta helix (cationic) [+/− alpha helix knob (neutral)]	Sulfate neutralized hepatocyte growth factor alpha (hgf alpha; scatter factor) monomer ×2 (IS 3+ → 1+: IS 3+ → 1+)	CM receptor protein monomer (3 su) → dimer (3 su: 3 su)	External cationiomodulation and dual receptor stabilizing shift pressuromodulation	Extracellular matrix interaction and chromatin DNA protein synthesis/exocytosis
	Compact loose non-aligned multibeta helix (cationic) [+/− alpha helix knob (neutral)]	Sulfate neutralized epidermal growth factor (EGF) monomer ×2 (IS 3+ → 1+: IS 3+ → 1+)	CM receptor protein monomer (3 su) → dimer (3 su: 3 su)	External cationiomodulation and dual receptor stabilizing shift pressuromodulation	Extracellular matrix interaction and chromatin DNA protein synthesis/exocytosis
	Compact loose non-aligned multibeta helix (cationic) [+/− alpha helix knob (neutral)]	Sulfate neutralized interleukin-1 alpha (IL-1 alpha) monomer ×2 (IS 3+ → 1+: is 3+ → 1+)	CM receptor protein monomer (3 su) → dimer (3 su: 3 su)	External cationiomodulation and dual receptor stabilizing shift pressuromodulation	Extracellular matrix interaction and chromatin DNA protein synthesis/exocytosis
	Compact loose non-aligned multibeta helix (cationic) [+/− alpha helix knob (neutral)]	Sulfate neutralized interleukin-1 beta (il-1 beta) monomer ×2 (IS 3+ → 1+: IS 3+ → 1+)	CM receptor protein monomer (3 su) → dimer (3 su: 3 su)	External cationiomodulation and dual receptor stabilizing shift pressuromodulation	Extracellular matrix interaction and chromatin DNA protein synthesis/exocytosis
	Compact tight semi-aligned multibeta helix (cationic)	Tumor necrosis factor alpha (TNF alpha) homotrimer (SS 1+)	CM receptor protein trimer	Tri receptor internal pseudo-cationomodulation → 2ary indirect shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis [mitogenesis]
	Compact tight aligned multibeta helix (cationic)	Adiponectin homotrimer (SS 1+)	CM receptor protein trimer	Tri receptor internal pseudo-cationomodulation → 2ary indirect shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis [mitogenesis]
	Compact tight aligned multibeta helix (cationic)	RANKL homotrimer (SS 1+)	CM receptor protein trimer	Tri receptor internal pseudo-cationomodulation → 2ary indirect shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis [mitogenesis]
	Aligned long multibeta helix (cationic)	Sulfate neutralized thyroid stimulating hormone alpha and beta (TSH alpha and beta) heterodimer (IS 3+ → 1+: IS 3+ → 1+)	CM receptor protein trimer	Tri receptor stabilizing shift pressuromodulation and external cationiomodulation	Chromatin DNA protein synthesis/exocytosis and extracellular matrix interaction
	Aligned long multibeta helix (cationic)	Sulfate neutralized luteinizing hormone alpha and beta (lh alpha and beta) heterodimer (is 3+ → 1+: IS 3+ → 1+)	CM receptor protein trimer	Tri receptor stabilizing shift pressuromodulation and external cationiomodulation	Chromatin DNA protein synthesis/exocytosis and extracellular matrix interaction
	Aligned long multibeta helix (cationic)	Sulfate neutralized follicle stimulating hormone alpha and beta (fsh alpha and beta) heterodimer (IS 3+ → 1+: IS 3+ → 1+)	CM receptor protein trimer	Tri receptor stabilizing shift pressuromodulation and external cationiomodulation	Chromatin DNA protein synthesis/exocytosis and extracellular matrix interaction
	Aligned long multibeta helix (cationic)	Sulfate neutralized human chorionic gonadotropin alpha and beta (HCG alpha and beta) Heterodimer (IS 3+ → 1+: IS 3+ → 1+)	CM receptor protein trimer	Tri receptor stabilizing shift pressuromodulation and external cationiomodulation	Chromatin DNA protein synthesis/exocytosis and extracellular matrix interaction
	Aligned long multibeta helix (cationic)	Sulfate neutralized brain-derived neurotrophic factor (bdnf) homodimer (IS 3+ → 1+: IS 3+ → 1+)	CM receptor protein trimer	Tri receptor stabilizing shift pressuromodulation and external cationiomodulation	Chromatin DNA protein synthesis/exocytosis and extracellular matrix interaction

Table 1 continued

Type	Sub-type	Example(s)	Cell membrane (CM) or CM receptor	Effect at cell membrane (CM) receptor	Intracellular result of effect
	Aligned long multibeta helix (cationic)	Sulfate neutralized nerve growth factor beta (NGFb) homodimer (IS 3+ → 1+: IS 3+ → 1+)	CM receptor protein trimer	Tri receptor stabilizing shift pressuromodulation and external cationiomodulation	Chromatin DNA protein synthesis/exocytosis and extracellular matrix interaction
	Aligned long multibeta helix (cationic)	Sulfate neutralized neurotrophins (nts) homodimer (IS 3+ → 1+: IS 3+ → 1+)	CM receptor protein trimer	Tri receptor stabilizing shift pressuromodulation and external cationiomodulation	Chromatin DNA protein synthesis/exocytosis and extracellular matrix interaction
	Aligned long multibeta helix (cationic) cum short monoalpha helix (neutral)	Transforming growth factor beta (TGF beta) homodimer (SS 1+)	CM receptor protein quatramer	Quad receptor internal pseudo-cationomodulation → 2ary indirect shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis [mitogenesis]
	Aligned long multibeta helix (cationic) cum short monoalpha helix (neutral)	Bone morphogenic protein-2/7 (BMP-2/7) homodimer (SS 1+)	CM receptor protein quatramer	Quad receptor internal pseudo-cationomodulation → 2ary indirect shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis [mitogenesis]
	Aligned long multibeta helix (cationic) cum short monoalpha helix (neutral)	Platelet derived growth factor-BB (PDGF-BB) homodimer (SS 1+)	CM receptor protein quatramer	Quad receptor internal pseudo-cationomodulation → 2ary indirect shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis [mitogenesis]
	Aligned long multibeta helix (cationic) cum short angled monoalpha helix (neutral)	Placenta growth factor (PLGF) homodimer (SS 1+)	CM receptor protein quatramer	Quad receptor internal pseudo-cationomodulation → 2ary indirect shift pressuromodulation	Chromatin DNA protein synthesis/exocytosis [mitogenesis]
	Aligned long multibeta helix (cationic) cum short angled monoalpha helix (neutral)	Vascular endothelial growth factor-A (VEGF-A)/vascular permeability factor (VPF) homodimer (1+ IS 1+ SS 1+ IS 1+)	CM receptor protein quatramer	Quad receptor external cationiomodulation (2+) → 3ary indirect shift pressuromodulation	Cationic (2+) CM interaction receptor endocytosis → mitogenesis
	Compact loose non-aligned multibeta helix-intertwined-non-aligned multialpha helix	Diferric transferrin-(Fe3+ → Fe2+)2 monomers ×2 (3+ SS 3+: 3+ SS 3+ → 2+ SS 2+: 2+ SS 2+)	CM receptor protein (TfR) dimer	Fe2+ receptor external cationiomodulation (2+) → 3ary indirect shift pressuromodulation	Cationic diferric iron (Fe2+) CM interaction receptor endocytosis→ mitogenesis
	Long dualalpha helix (neutral) cum compact loose aligned beta helix cum multishort 2-way beta helix (cationic)	Hemochromatosis protein (HPE) monomers ×2 [(1+ IS 1+)n SS (1+ IS 1+)n]	CM receptor protein (TfR) dimer	Transient RSP; external beta helix CM receptor cationiomodulation (2+) → 3ary indirect shift pressuromodulation	Cationic diferric iron (Fe2+) cm interaction receptor endocytosis→ mitogenesis
	Short monoalpha helix-loop-short monoalpha helix-loop-short monoalpha helix (neutral) cum compact loose non-aligned 5-way beta-X-3-way beta helix (cationic)	Partially sulfate neutralized procollagen I peptide III C monomer (IS 4+ → 2+)	CM receptor protein dimer (3 su: 3 su)	Dual receptor external cationiomodulation (2+) → 3ary indirect shift pressuromodulation	Cationic (2+) CM interaction receptor endocytosis → mitogenesis

SS sufficient separation of 2+ cationicity in molecular space, which is important, as it precludes Heparan Sulfate neutralization of cationicity, that which requires the presence of >2+ charge insufficiently separated in molecular space

IS insufficient separation of 1+ cationicity in molecular space, which is important, as it precludes endocytosis, that which requires the presence of 2+ charge insufficiently separated in molecular space

of smooth and cardiac muscle cells results in contraction, and that which in the case of adrenal medulla cells results in depolarization-coupled exocytosis of epinephrine.

The small molecule cationic hydro-lipophile neurotransmitters dopamine (1+) and seratonin (1+), being hydro-lipophiles due to the combinatory presence of singular cationicity (1+), hydroxylated hydrophilicity and receptor protein binding lipophilicity, in contrast to the small molecule cationic hydrophile neurotransmitters (i.e. norepinephrine, acetylcholine), function as mild external cationomodulators, via lipophilic incorporation into CM receptor hydrophobic cores of commensurate lipophilicity on the basis of the incorporating lipophilicity for size of their non-cationic and non-hydroxylated portion, and thus, non-insert positive charge, that which results in non-depolarization of the CM (Table 1; Additional file 1: Table S1; Additional file 3: Figure S3; Additional file 5: Complete Table 1 in Supplemental File Format): Interaction with neuronal CM receptors in such a manner, results in decreased post-synaptic depolarization and contribute significantly towards regulating the tonicity of upper motor neuron-to-lower motor neuron meshwork of inter-neuronal connections [36, 37], and furthermore, in the case of pituitary lactotrophs results in inhibition of prolactin secretion [38], most likely due to competitive antagonism of prolactin releasing hormone (PRL), the shift pressuromodulator of lactotroph CM PRL receptors.

In the case of both the cationic hydrophile internal cationomodulators (acetylcholine and norepinephrine) and the cationic hydro-lipophile mild external cationomodulators (i.e. dopamine and seratonin), both classes with singular cationicity (1+), in the absence of protein channel aqueous pores and receptors to insert into (former) or bind to (latter), such (pure) hydrophiles and hydro-lipophiles, respectively, are reactively endocytosed by pre-synaptic neuronal cell membranes and vesicularize for subsequent re-release due to the concentration of poly 1+ charges per unit volume (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

Non-neurotransmitter hydro-lipophile regulation of intracellular function vis a vis interaction at the cell membrane (CM) receptor

The non-neurotransmitter small molecule hydro-lipophiles include circumferentially polyhydroxylated/carbonylated hydro-lipophiles [non-compact (>pore size)] such as ouabain (Na+/K+ ATPase receptor channel), and circumferentially polyhydroxylated/carbonylated hydro-lipophiles + exterior cationicity [non-compact (>pore size)] such as doxorubicin (Na+/K+ ATPase receptor channel), which are circumferentially hydroxylated and/or carbonylated hydrophiles with core lipophilicity, and therefore, pro-endocytic hydro-lipophiles [39, 40] via receptor hydroxymodulation/carbonylomodulation of receptor channel pores (Table 1; Additional file 1: Table S1; Additional file 3: Figure S3; Additional file 5: Complete Table 1 in Supplemental File Format).

The potential for the non-neurotransmitter small molecule hydro-lipophiles to be pro-endocytic at CM receptor channels is attributable to the presence of incorporating lipophilicity, in the concomitant presence of interacting polyhydroxylated/carbonylated hydrophilicity. As such, both of the circumferentially hydroxylated weak hydrophiles with core lipophilicity, ouabain and doxorubicin, interact with CM protein receptor alpha helix cum alpha helix isophilic aqueous pores, for example, such as those of the Na+/K+ ATPase, they de-stabilize the CM interaction of the multialpha helix constructs of such transmembrane proteins with internal isophilic aqueous pores, that which results in ligand-bound CM protein endocytosis.

Upon endocytosis, ouabain and doxorubicin, differentially modulate intracellular function: ouabain functions as a indirect (pseudo) 3ary CM receptor-mediated shift pressuromodulator (receptor endocytic hydroxylocarbonyloetheroylomodulation: 0) to decrease whole cell compliance significantly, that which results in the increased exocytosis of the pre-synthesized Golgi peptides as well as RER receptor proteins to the CM, and concomitantly, in the increased protein transcription of additional highest molecular weight (MW) forms (i.e. fibronectin: 240 kDa), including that of the highest molecular weight nuclear proteins, Ki67 (359 kDa) and separase (230 kDa), that which results in mitogenesis, in the concomitant presence of serum [41] [indirect (pseudo) 3ary CM receptor-mediated shift pressuromodulation (receptor endocytic hydroxylocarbonyloetheroylomodulation: 0)] (Additional file 1: Table S1; Additional file 3: Figure S3).

In contrast to ouabain, and importantly in contrast, doxorubicin, with greater interior lipophilicity sufficient to stably associate with the internal little alpha helix of the mitochondrial membrane (MM) voltage-dependent anion channel (VDAC) [42] in context of the concomitant presence of 1+ cationicity, functions more as a chemoxenobiotic hydro-lipophile, by virtue of its ability to anchor mitochondria via non-recruitment of gamma-Tubulin to the MM VDAC [43], that which results in MM disruption and liberation of MM apoptosis inducing factor (AIF), which binds X-linked inhibitor of apoptosis factor (XIAF), freeing XIAF from its association with Caspace-3, the cumulative effect of intracellularly endocytosed doxorubicin, mitochondrial dissolution-mediated cytotoxic cell death [40] (receptor endocytic cationohydroxylocarbonyloetheroylomodulation: 1+) (Additional file 1: Table S1; Additional file 3: Figure S3).

Polyhydroxylated small molecule sterol regulation of intracellular function vis a vis interaction at the cell membrane (CM) receptor

The polyhydroxylated small molecule lipophile sterols include the: (1) asymmetrically polyhydroxylated sterols, the corticosteroids, aldosterone and cortisol, which are asymmetrically hydroxylated sterols (Table 1; Additional file 1: Table S1; Additional file 4: Figure S4; Additional file 5: Complete Table 1 in Supplemental File Format) [8]; and (2) symmetrically di/trihydroxylated sterols, the sex steroids, testosterone, estrogen and progesterone, which are symmetrically dipolarly di/trihydroxylated sterols (Table 1; Additional file 1: Table S1; Additional file 4: Figure S4; Additional file 5: Complete Table 1 in Supplemental File Format) [8].

The polyhydroxylated small molecule lipophile sterols have the potential to associate with cell membrane protein receptors of commensurate lipophilcity, on the basis of the incorporating lipophilicity for size of the non-hydroxylated portion, which is of lipophilic character, and interacts with the CM receptor protein itself, while the hydroxylated hydrophilicity of the hydroxylated portion, which is of hydrophilic character, interacts with the hydrophilicity of exteriorly hydrophilic microenvironment [10], both of which [8, 40], in concert, are co-determinants of the binding affinity, and importantly, character of the polyhydroxylated small biomolecule interaction with its respective receptor. As such, the asymmetrically hydroxylated lipophiles (corticosteroids) and the symmetrically dipolarly di/trihydroxylated sterols (sex steroids), both being polyhydroxylated small biomolecules with greater incorporating lipophilicity-to-interacting hydroxylated hydrophilicity ratios (corticosteroid and sex steroid hormones) are anti-endocytic for their hormone-receptor complexes and direct CM receptor stabilizing pressuromodulators [8, 11, 20, 22, 23, 44–50] (direct CM receptor-mediated stabilizing shift pressuromodulation: 0) (Table 1; Additional file 1: Table S1; Additional file 3: Figure S3; Additional file 4: Figure S4; Additional file 5: Complete Table 1 in Supplemental File Format).

Polyhydroxylated/carbonlylated/etheroylated small molecule non-sterol lipophile regulation of intracellular function vis a vis Interaction at the cell membrane (CM) receptor

The polyhydroxylated small molecule non-sterol lipophiles include the: (1) circumferentially polyhydroxylated/carbonylated lipophiles [non-compact (>pore size)] such as forskolin, and (2) circumferentially polyhydroxylated/carbonylated/etheroylated lipophiles [non-compact (>pore size)] such as paclitaxel (taxol) and colchicine, which are circumferentially hydroxylated and/or carbonylated hydrophiles with core lipophilicity, and therefore, pro-endocytic lipophiles (Table 1; Additional file 1: Table S1; Additional file 4: Figure S4; Additional file 5: Complete Table 1 in Supplemental File Format), via CM protein receptor hydroxymodulation/carbonylomodulation/etheroylation.

The potential for polyhydroxylated small molecule non-sterol lipophiles to be pro-endocytic at the CM receptor is attributable to the presence of incorporating lipophilicity in the concomitant presence of interacting polyhydroxylated/carbonylated/etheroylated hydrophilicity, as is the case for the non-neurotransmitter small molecule hydro-lipophiles (Additional file 1: Table S1; Additional file 3: Figure S3). However, the important distinction between the two categories, is that in the case of the polyhydroxylated small molecule non-sterol lipophiles, there is the presence of greater incorporating lipophilicity relative to the interacting hydroxylated hydrophilicity; while the presence of the greater incorporating lipophilicity makes these biomolecules, small molecule Lipophiles, the similar amount of circumferential hydrophilicity enables interaction with CM protein receptor alpha helixes cum alpha helix isophilic aqueous pores (Additional file 1: Table S1; Additional file 4: Figure S4), sufficient enough to de-stabilize the CM interaction of the multialpha helix constructs of such trans-membrane proteins, that which results in ligand-bound CM protein endocytosis.

Upon endocytosis, forskolin and paclitaxel/colchicine, diffferentially modulate intracellular function: Forskolin functions as a indirect (pseudo) 3ary CM receptor-mediated shift pressuromodulator to decrease whole cell compliance significantly, that which results in the increased exocytosis of the pre-synthesized Golgi peptides as well as RER receptor proteins to the CM, and concomitantly, in the increased protein transcription of additional highest molecular weight forms (i.e. fibronectin: 240 kDa) [51], including that of the highest molecular weight nuclear proteins, Ki67 (359 kDa) and Separase (230 kDa), resulting in mitogenesis and cell division, in the concomitant presence of serum [52] [indirect (pseudo) 3ary CM receptor-mediated shift pressuromodulation (receptor endocytic hydroxylocarbonyloetheroylomodulation: 0)] (Additional file 1: Table S1; Additional file 4: Figure S4).

In contrast to forskolin, and importantly in contrast to, both paclitaxel (Taxol) (0) and colchicine (0), function more as cytotoxic lipophiles, due to the presence of greater incorporating lipophilicity than that of Forskolin, in the absence of cationicity, and therefore, the further ability to associate with the intracellular microtubular network forming protein, tubulin beta [53], both paclitaxel and colchicine, are not (pseudo) 3ary CM receptor shift pressuromodulators: instead, by inhibition of tubulin polymerization re-polymerization, both paclitaxel

(taxol) and Colchicine exert significant mitochondrial membrane (MM) oxidative stress, via mitochondria anchorage during attempted movement [54, 55], that which results in MM disruption and in cytotoxic cell death via mitochondrial dissolution [40] (receptor endocytic hydroxylocarbonyloetheroylomodulation: 0) (Additional file 1: Table S1; Additional file 4: Figure S4).

Unihydroxylated and dihydroxylated small molecule lipophile regulation of intracellular function vis a vis interaction directly within the cell membrane (CM)

The asymmetric unihydroxylated small molecule lipophiles include, the cholesterols, 3beta-hydroxycholesterol, and the vitamin D form, cholecalciferol (3-hydroxyvitamin D3), which are unipolarly hydroxylated lipophiles, and directly incorporate into cell membrane (CM) phospholipid layers due to commensurate lipophilcity for size to that of the phospholipid fatty acid-ester moieties, and function as CM stabilizing incorporopressuromodulators that maintain the baseline compliance state of all cell membranes [56] (Table 1; Additional file 1: Table S1; Additional file 4: Figure S4; Additional file 5: Complete Table 1 in Supplemental File Format).

The symmetric di-hydroxylated non-sterols constitute unstable sterol forms such as calcifediol (1, 25-dihydroxyvitamin D3), which neither stably associate with CM proteins or CM bilayers; instead, such unstable small molecule lipophile forms tend to perturb cell membrane lipid layers, and function as CM perturbomodulators, first, by increasing CM compliance slightly, enough to cause the non-exocytosis and intracellular build-up of pre-synthesized Golgi reservoir non-collagenase (MMP)-higher molecular weight protein forms (i.e. fibronectin: 240 kDa; tyrosinase containing-melanosomes) that remain intracellular, secondary to which, whole cell compliance decreases significantly, then resulting in the increased exocytosis of the pre-synthesized Golgi peptides (i.e. fibronectin: 240 kDa) and nuclear-to-RER receptor proteins to the CM, as well as in the increased protein transcription of the spectrum of synthesizable proteins, including in the increased synthesis of the lowest molecular weight protein forms (i.e. osteocalcin: 6 kDa) [57] [1ary indirect shift pressuromodulation (perturbomodulation)] (Table 1; Additional file 1: Table S1; Additional file 4: Figure S4; Additional file 5: Complete Table 1 in Supplemental File Format).

Other notable 1ary indirect CM-mediated shift pressuromodulators are the other unstable phospholipid layer non-incorporating small molecule lipophile forms, the asymmetrically polyhydroxylated forms such as phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) [51] and the similar phorbol esters with fatty acid-ester tails (i.e. phorbol 12,13-dibutyrate) [58], the asymmetrically unihydroxylated forms such as Retinol and asymmetrically unicarboxylated Retinoic Acid [59, 60], the asymmetrically dihydroxylated/carbonylated forms such as blebbistatin [61], as well as the compact polyhydroxylated and/or carbonylated forms such as isobutylmethyl xanthine (IBMX) [62] [1ary indirect shift pressuromodulation (perturbomodulation)] (Table 1; Additional file 1: Table S1; Additional file 4: Figure S4; Additional file 5: Complete Table 1 in Supplemental File Format).

Along these lines, the other types of 1ary indirect shift pressuromodulation (perturbomodulation) include mild primary hypoxia [63, 64] due to primary decreases the rates of mitochondrial oxidative phosphorylation, as well as mild secondary hypoxia due to the secondary decreases the rates of mitochondrial oxidative phosphorylation viz a viz the intracellular effects of small lipophile toxins/toxicants such as benzene and diethyl ether, which due to small molecular sizes also interact non-selectively with the sub-cellular mitochondrial membrane (MM) electron transport chain (ETS) proteins resulting in secondary whole cell ATP deficiency: In both cases of mild hypoxia, primary and secondary, the overall initial effect is an increase in CM compliance due to mild ATP deficiency-mediated decreases in CM protein subunit and CM cohesiveness, that which results in intra-cellular protein build-up towards a decrease in whole cell compliance, and upon acclimatization/recovery, the overall effect being the 1ary indirect CM-mediated shift pressuromodulation effect (perturbomodulation) (Table 1; Additional file 1: Table S1; Additional file 4: Figure S4; Additional file 5: Complete Table 1 in Supplemental File Format).

Non-small molecule non-peptide regulation of intracellular function vis a vis interaction at the cell membrane (CM) receptor

The non-small molecule non-peptide biomolecules include bacterial cell wall lipopolysaccharide (LPS) comprised of lipid A (phospholipid fatty acid-ester-glycerol moiety equivalent), inner core (phosphorylated poly/monosaccharide phospholipid head phosphotidylcholine/ehtanolamine/serine equivalent) and outer core-to-'O Antigen' (short-to-long polysaccharide) in series, with the molecular weight of the rough core LPS beginning in the range of 2–5 kDa [65]: LPS is a potent 1ary indirect shift pressuromodulator of the CM, by interdigitating insertion association of its LPS Lipid A component into cell membrane phospholipid layer, which, by first increasing CM compliance slightly, enough to cause the non-exocytosis intracellular build-up of pre-synthesized

Golgi reservoir non-collagenase (MMP)-higher molecular weight protein forms (i.e. fibronectin: 240 kDa), and upon a significant decrease in whole cell compliance, secondarily, causes the increased exocytosis of the pre-synthesized Golgi peptides (i.e. fibronectin: 240 kDa) as well as RER receptor proteins to the CM [66], and concomitantly, in the chromatin DNA transcription of the lower and higher molecular weight protein forms, both mitochondrial and nuclear, including the highest molecular weight nuclear proteins, Ki67 (359 kDa) and separase (230 kDa), with the ability to induce mitogenesis and cell division [67, 68] [1ary indirect CM-mediated shift pressuromodulation effect (perturbomodulation)] (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

Small (non-alpha non-beta helix) peptide regulation of intracellular function vis a vis interaction at the cell membrane (CM) receptor

The small (non-alpha non-beta) peptides include the low molecular weight peptides [1–1.6 kDa; 9–14 amino acids (AAs)], without and with tertiary structure intramolecular disulfide bonds, that bind to so-called G protein-coupled receptors (GPRCs), which are multiple alpha helix-based CM receptor constructs that do not dimerize in response to small (non-alpha non-beta) peptide ligand binding, but may co-exist as juxtaposed dimers on the CM [69, 70] (direct CM receptor-mediated stabilizing shift pressuromodulation: 0) (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The small (non-alpha non-beta) di-cationic (1+ IS 1+) peptides include bradykinin (1+ IS 1+ SS 1+) [71] and atrial natriuretic peptide (1+ IS 1+) [72–74] and function as transient pressuromodulators cum external cationomodulators, which incorporate into CM receptor hydrophobic cores of commensurate lipophilcity on the basis of the incorporating lipophilicity for size of their non-cationic portion in the concomitant presence of tertiary structure 1+ cationicity insufficiently separated (IS) in molecular space (1+ IS 1+); thus, via external interaction with the cell membrane phospholipid heads, cause CM and CM receptor endocytosis and vesiculo-vacuolization-through-and-through diaphragmed fenestration of endothelial cells resulting in microvascular capillary hyperpermeability [75], in which case the external cationomodulation-mediated endocytic transformation process decreases endothelial cell compliance significantly, that which, not only results in an almost immediate significant increase in the exocytosis of RER endothelial NOS (eNOS) to the CM and increased nitric oxide (NO) [76], a potent competitive antagonist of smooth muscle cell O_2 at the electron transport chain (ETS) and in endothelial cell-mediated smooth muscle relaxation and vascular-microvascular vasodilation [71, 72, 75], but also in a significant increase in protein transcription of the entire spectrum of synthesizable proteins, importantly, the highest molecular weight nuclear proteins, Ki67 (359 kDa) and Separase (230 kDa), and in mitogenesis and endothelial cell division [77] [indirect 3ary CM receptor-mediated shift pressuromodulation (single or dual) receptor endocytic external cationomodulation: 2+)] (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The mono-cationic (1+) and non-cationic small (non-alpha non-beta) peptides such as vasopressin arginine (1+) (anti-diuretic hormone), neurotensin (1+) [78], angiotensin II [47, 79], Ps4 thyrotropin releasing hormone [80, 81], somatostatin (growth hormone release inhibiting peptide) and oxytocin incorporate into CM receptor hydrophobic cores of commensurate lipophilcity, thus, via insertion, stabilize receptor G protein-coupled protein receptor monomers and shift pressuromodulate cell membranes by decreasing CM compliance sufficiently enough to cause the increased synthesis and exocytosis of the higher molecular proteins, but not yet the lower molecular weight proteins, and therefore, masquerade as release inhibiting peptides (direct CM receptor-mediated stabilizing shift pressuromodulation: 1+) (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

Monoalpha helix peptide and loop-interconnected dual/poly monoalpha helix peptide regulation of intracellular function vis a vis interaction at the cell membrane (CM) receptor(s)

The monoalpha helix peptides are the singular short and long alpha helix (monoalpha helix) peptides, the singular alpha helix peptides with a short 2-way beta helix tail peptides (monoalpha helix-loop-short 2-way beta helix), and the peptides with loop-interconnected two or more singular alpha helixes (short monoalpha helix-loop-short monoalpha helix, short monoalpha helix-loop-short monoalpha helix-loop-short monoalpha helix), which are of greater molecular weights than the small (non-alpha non-beta) peptides (>1.6 to <14 kDa) without tertiary structure disulfide bonds, which, like the low molecular weight peptides (<1.5 to 2 kDa) (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The short and long monoalpha helix peptides include glucagon and parathyroid hormone (PTH)/PTH releasing peptide (PTHrP) [82–84] that bind to the multiple alpha helix-based Class A GPCRs, which do not dimerize in response to monoalpha helix peptide ligand binding, but provide greater stability to the ligand-receptor complex than the low molecular weight peptides (<1.5 to 2 kDa), and also to bind to alpha helix cum 2-way-X-2-way beta

helix-based Class B GPRCs [83], which can dimerize in response to monoalpha helix peptide ligand binding; in comparison the small (non-alpha non-beta) peptides (Neural or 1+), are more effective CM receptor and CM pressuromodulators than the low molecular weight peptides, longer monoalpha helix peptides (PTH/PTHrP) [85, 86] more effective than shorter monoalpha helix peptides (Glucagon) [87] (direct CM receptor-mediated stabilizing shift pressuromodulation) (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The short and long monoalpha helix-loop-short 2-way beta helix peptides such as adrenocorticotropic hormone (ACTH) [88–91] and pro-ACTH pro-opiomelanocortin (POMC) [92], respectively, which, in contrast to the short and long monoalpha helix peptides (without 2-way beta helix tails), bind to one G protein-coupled receptor via the singular alpha helix motif with the potential to dimerize another G protein-coupled receptor via the 2-way beta helix tail, which are known to be expressed on cell membranes in close proximity to one another [70], and thus, provide greater stability to the ligand-receptor complex than the short and long monoalpha helix peptides (without the 2-way beta helix tail) that engage only one G protein-coupled receptor, therefore, in comparison, more effective CM receptor, and CM, pressuromodulators (direct CM receptor-mediated stabilizing shift pressuromodulation) (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The short monoalpha helix-loop-short monoalpha helix peptides include adrenocorticotrophin releasing hormone/factor (CRH/F) [78] and insulin [31, 93–102], and the short monoalpha helix-loop-short monoalpha helix-loop-short monoalpha helix peptides include osteocalcin [103], insulin-like growth factor-1 (IGF1/II; somatomedin C) [31, 34, 35, 93, 104, 105], prolactin (PRL) releasing hormone/factor (PRLRH/factor) [106], growth hormone releasing hormone/factor (GHRH/F) [107] and gonadotropin releasing hormone/factor (GnRH/F), which, in contrast to the short and long monoalpha helix peptides (glucagon, PTH) and the short and long monoalpha helix-loop-short 2-way beta helix monoalpha helix peptides (ACTH, POMC), bind to mixed alpha cum beta helix-construct non-G protein-coupled tyrosine kinase type receptors that homodimerize in response to loop-interconnected dual/poly singular alpha helix peptide binding and adopting a condensed globular conformation, which therefore, function as more effective shift pressuromodulators at the cell membrane than the monoalpha helix peptides (direct CM receptor-mediated stabilizing shift pressuromodulation) (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

Aligned multialpha helix peptide and semi-aligned multialpha helix peptide regulation of intracellular function vis a vis interaction at the cell membrane (CM) receptor(s)

The mulialpha helix peptides are the aligned multiple alpha helix peptides (aligned multialpha helix), the semi-aligned multiple alpha helix peptides (semi-aligned multialpha helix cum short monoalpha helix), the semi-aligned multiple alpha helix with a short singular beta 2-way helix peptides (semi-aligned multialpha helix cum short monobeta 2-way helix), the semi-aligned multiple alpha helix with a short singular alpha helix and short end-loop (semi-aligned multialpha helix cum short monoalpha helix cum short loop), and the peptides with a loop-interconnected semi-aligned multiple alpha helix, short singular alpha helix and short singular beta 2-way helix (semi-aligned multialpha helix-loop-short monoalpha helix-loop-short monobeta 2-way helix) (<30 kDa in monomeric form) (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The aligned multialpha helix peptides include interleukin-3 (IL-3) [108], interleukin-7 (IL-7) [109], interleukin-12 (IL-12) [110, 111], interleukin-23 (IL-23) [112], prolactin (PRL) [113, 114], growth hormone (GH) [115–121] and erythropoietin (Ep) monomers, which function as dual CM receptor stabilizing shift pressuromodulators by stabilizing heteromeric amorphous loop cum beta helix-rich receptor subunits (2 su: 2 su), as well as Interferon gamma (INF-g) homodimer (25 kDa × 2) [122–131], which function as dual-to-tri CM receptor stabilizing shift pressuromodulators by stabilizing heteromeric amorphous loop cum beta helix-rich receptor subunits (3 su: 3 su: <3 su>), and of the aligned multialpha helix peptides, interferon gamma (INF-g) being a homodimer with the potential for receptor trimerization, functions as a more effective pressuromodulator, that which stimulates increased protein transcription of the higher molecular weight proteins including the highest molecular weight, secreted, Fibronectin (240 kDa) [128, 129], as well as nuclear, separase (230 kDa) and Ki67 (359 kDa), thus, with the potential to be mitogenic for certain cell types (with greater baseline compliance) [130, 131] (direct CM receptor-mediated stabilizing shift pressuromodulation) (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The semi-aligned multialpha helix cum short monoalpha helix peptides include interleukin-2 (IL-2) [111, 132, 133] and interleukin-6 (IL-6) [134] monomers, which function as effective dual CM receptor stabilizing shift pressuromodulators by stabilizing heteromeric amorphous loop cum beta helix-rich receptor subunits (3 su: 2 su) (direct CM receptor-mediated stabilizing shift

pressuromodulation) (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The semi-aligned multialpha helix cum short monoBeta 2-way helix peptides include interleukin-4 (IL-4) [135, 136], interleukin-13 (IL-13), interleukin-15 (IL-15) [111, 137], interleukin-20 (IL-20) and granulocyte monocyte-colony stimulating factor (GM-CSF) [138–142] monomers, which function as effective dual CM receptor stabilizing shift pressuromodulators by stabilizing heteromeric beta helix-rich receptor subunits (4 su: 2 su) (direct CM receptor-mediated stabilizing shift pressuromodulation) (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The semi-aligned multialpha helix cum short monoalpha helix cum short loop peptides include the leukemia inhibitory factor (LIF)/oncostatin (OSM) [143] monomer, which function as effective dual CM receptor stabilizing shift pressuromodulators by stabilizing heteromeric amorphous loop cum beta helix-rich receptor subunits (5 su: 3 su) (direct CM receptor-mediated stabilizing shift pressuromodulation) (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The semi-aligned multialpha helix-loop-short monoalpha helix-loop-short monobeta 2-way helix peptides include the granulocyte-colony stimulating factor (G-CSF)/macrophage (mouse)-colony stimulating factor (M-CSF) homodimer (60 kDa) [144–147], which functions as effective dual CM receptor stabilizing shift pressuromodulators by stabilizing heteromeric beta helix-rich receptor subunits (3 su: 3 su) (direct CM receptor-mediated stabilizing shift pressuromodulation) (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

Compact loose non-aligned multibeta helix, compact disperse non-aligned multibeta helix peptide and compact tight aligned/non-aligned multibeta helix peptide regulation of intracellular function vis a vis Interaction at the cell membrane (CM) receptor(s)

The compact mulibeta helix peptides are the compact loose non-aligned/aligned multiple beta helix peptides with a short singular non-angled/angled alpha helix (short monoalpha helix cum compact loose non-aligned 3-way beta-X-2-way beta helix, short monoalpha helix cum compact loose aligned 3-way beta helix, short angled monoalpha helix cum compact loose aligned 3-way beta helix, short angled monoalpha helix cum compact loose aligned 3.5-way beta helix), the compact loose non-aligned multiple beta helix peptides ± an ancillary alpha knob (compact loose non-aligned multibeta helix ± alpha helix knob), and the compact tight semi-aligned/aligned multiple beta helix peptides (compact tight semi-aligned multibeta helix, compact tight aligned multibeta helix) (<35 kDa in monomeric form) (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The compact loose non-aligned multibeta helix cum short monoalpha helix peptides include sulfate neutralized CD4 receptor ligand interleukin-16 (IL-16) (IS 3+ → 1+) [148–151], sulfate neutralized CCR5 receptor ligands macrophage inflammatory protein-1 beta (MIP-1 beta: CCL20) (IS 3+ → 1+), CCL3, CCL4 and CCL5 (RANTES) (IS 3+ → 1+) [152, 153], sulfate neutralized CXCR4 receptor ligand SDF-1 (CXCL-12) (IS 3+ → 1+) [152] and sulfate neutralized CXCR1 ligand interleukin-8 (IL-8) (IS 3+ → 1+) [154, 155], all monomeric, which, function as CM receptor stabilizing shift pressuromodulators by binding to alpha helix-rich chemokine receptor cores via neutral short alpha helix or short angled alpha helix association for the pressuromodulating effect, and exceptionally effective external cationomodulators by draping over receptor exteriors via cationic compact loose non-aligned multibeta helix motifs (3-way beta-X-2-way beta helix, 3-way beta helix or 3.5-way beta helix) for the external cationomodulation effect (3+ → 1+) [direct CM receptor-mediated stabilizing shift pressuromodulation (single, dual or tri) cum external cationomodulation (≥3+ → 1+)], that which results in exocytosis and transcription of higher molecular weight protein forms, and CM-to-extracellular matrix interactions associated with lamellopodesis and cell migration, respectively (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The compact loose non-aligned Multibeta helix ± alpha helix knob peptides include sulfate neutralized fibroblast growth factor (FGF-19/FGF-2) (IS 3+ → 1+) [102, 156–162], sulfate neutralized hepatocyte growth factor alpha (HGF alpha; Scatter Factor) (IS 3+ → 1+) [163, 164], sulfate neutralized epidermal growth factor (EGF) (IS 3+ → 1+) [165, 166], sulfate neutralized Interleukin-1 alpha (IL-1 alpha) (IS 3+ → 1+) [167] and sulfate neutralized interleukin-1 beta (IL-1 beta) (IS 3+ → 1+) [156, 168], each monomers, however, capable of binding as separate monomers (IS 3+ → 1+: IS 3+ → 1+) to opposite sides of beta-rich receptors close in molecular space, which dimerize (3 su: 3 su), and thus, which function as effective CM receptor stabilizing shift pressuromodulators [direct CM receptor-Mediated stabilizing shift pressuromodulation (single, dual or tri) cum external cationomodulation (≥3+ → 1+)], that which results in exocytosis and transcription of higher molecular weight protein forms, and exceptionally effective external cationomodulators via cationic extracellular interaction (≥3+) with extracellular matrix heparan sulfate neutralizaiton of excess cationicity (≥3+ → 1+), that which results in lamellopodesis

and in cell migration (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The compact tight semi-aligned/aligned Multibeta helix peptides include tumor necrosis factor alpha (TNF alpha) (SS 1+) [164, 169–173], adiponectin (SS 1+) [174] and RANKL (SS 1+) [175–180] with the ability to self-trimerize without superimposition, and concomitantly, trimerize beta helix-based receptors, which, therefore, function as exceptionally effective pressuromodulators, indirect shift pressuromodulators, as a result of prolonged pseudo-cationic (1+) association with the CM secondary to self-trimerization and receptor trimerization, that which increases CM compliance sufficiently enough to cause the non-exocytosis of pre-synthesized Golgi reservoir collagenase (MMP)-insensitive higher molecular weight protein forms (i.e. Fibronectin: 240 kDa), which remain intracellular, the process of which results in a secondary significant decrease in whole cell compliance [indirect 2ary CM receptor-mediated shift pressuromodulation (tri or quad receptor internal pseudo-cationomodulation: SS 1+)], that which results in significantly increased protein transcription of the entire spectrum of synthesizable proteins, importantly, the highest molecular weight nuclear proteins, Ki67 (359 kDa) and separase (230 kDa), and in mitogenesis and cell division (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

Aligned long multibeta helix peptide regulation of intracellular function vis a vis interaction at the cell membrane (CM) receptor(s)

The aligned long mulibeta helix peptides are the aligned long multiple beta helix peptides (aligned long multibeta helix), the aligned long multiple beta helix peptides with a short singular alpha helix (aligned long multibeta helix cum short monoalpha helix), and the aligned long multiple beta helix with a short angled singular alpha helix (aligned long nultibeta helix cum short angled monoalpha helix) (<25 kDa in monomeric form) (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The aligned long multibeta helix peptides include the heterodimeric sulfate neutralized glycosylated hormones, thyroid stimulating hormone alpha and beta (TSH alpha and beta) (IS 3+ → 1+: IS 3+ → 1+), luteinizing hormone alpha and beta (LH alpha and beta) (IS 3+ → 1+: IS 3+ → 1+), follicle stimulating hormone alpha and beta (FSH alpha and beta) (IS 3+ → 1+) [181–183], human chorionic gonadotropin alpha and beta (HCG alpha and beta) (IS 3+ → 1+: IS 3+ → 1+) [184–187], brain-derived neurotrophic factor (BDNF) (IS 3+ → 1+: IS 3+ → 1+) [188] and nerve growth factor beta (NGFb) (IS 3+ → 1+: IS 3+ → 1+) at the p75 NGF receptor (higher *B*max) [189–192], which, by binding to amorphous loop cum beta-rich receptor subunits and receptor trimerization, function as effective CM receptor stabilizing shift pressuromodulators to induce the Golgi vesicular exocytosis of various small molecule hormones (i.e. thyroxine, testosterone, estrogen and progesterone, etc.) that require significant pressuromodulation to exocytose [8], and concomitantly, function as external cationomodulators due to the presence of solvent accessible cationic amino acid R groups that interact with extracellular matrix heparan sulfates (IS 3+ → 1+: IS 3+ → 1+) that which results in lamellopodesis and in cell migration [193, 194] [direct CM receptor-mediated stabilizing shift pressuromodulation (single, dual or tri) cum external cationomodulation (≥3+ → 1+)] (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The aligned long multibeta helix cum short/short angled monoalpha helix peptides include the non-superimposed interlocking homodimeric peptides, transforming growth factor beta (TGF beta) (SS 1+) [195–209], bone morphogenic protein-2/7 (BMP-2/7) (SS 1+) [199, 210], platelet derived growth factor-BB (PDGF-BB) (SS 1+) [131, 211–213] and placenta growth factor (PLGF) (SS 1+) [214], with solvent accessible cationic amino acid R groups sufficiently separated (SS) in molecular space (1+/R group), which, by interlocking to each other via the neutral short monoalpha helix motif, and by concomitantly interacting with beta helix-based receptor via the cationic aligned long multibeta helix motif (SS 1+), function as exceptionally effective pressuromodulators, indirect shift pressuromodulators, as a result of prolonged pseudo-cationic (1+) association with the CM secondary to beta helix-based receptor quatramerization, that which increases CM compliance sufficiently enough to cause the non-exocytosis of pre-synthesized Golgi reservoir collagenase (MMP)-insensitive higher molecular weight protein forms (i.e. Fibronectin: 240 kDa), which remain intracellular, the process of which results in a secondary significant decrease in whole cell compliance [indirect 2ary CM receptor-mediated shift pressuromodulation (tri or quad receptor internal pseudo-cationomodulation: SS 1+)], that which results in significantly increased protein transcription of the entire spectrum of synthesizable proteins, importantly, the highest molecular weight nuclear proteins, Ki67 (359 kDa) and Separase (230 kDa), and in mitogenesis and cell division (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The aligned long MultiBeta helix cum short angled monoalpha helix peptides also include the non-superimposed interlocking homodimeric peptide, vascular endothelial growth factor-A (VEGF-A)/vascular permeability factor (VPF) (1+ IS 1+ SS 1+ IS 1+) [162,

215–219], which, in contrast to TGF beta, BMP-2/7 and PDGF-BB, possesses solvent accessible cationic amino acid R groups with mono-cationicity insufficiently separated (IS) in molecular space (1+/R group IS 1+/R group), thus, similarly to the small (non-alpha non-beta) di-cationic peptides such as the bradykinin monomer (1 + IS 1 +) [indirect 3ary CM receptor-mediated shift pressuromodulation (single or dual receptor endocytic external cationomodulation: 2+)], functions as a transient pressuromodulator cum external cationomodulator, but in contrast to bradykinin, is significantly more effective as an external cationomodulator (2+), as a result of prolonged cationic association with the CM by binding to its beta helix-based receptor, the KDR receptor, as an interlocked homodimer in context of KDR receptor quatramerization, that which results in external cationomodulation (2+)-mediated endocytic endothelial cell transformation with a concomitant significant decrease in endothelial cell compliance [indirect 3ary CM receptor-mediated shift pressuromodulation (single or dual receptor endocytic external cationomodulation: 2+)] and increase in protein transcription of the entire spectrum of synthesizable proteins, importantly, the highest molecular weight nuclear proteins, Ki67 (359 kDa) and Separase (230 kDa), and in mitogenesis and endothelial cell division (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

Mixed helix and combinatory helix peptide regulation of intracellular function vis a vis interaction at the cell membrane (CM) receptor(s)

The mixed helix peptides include the transferrin receptor (TfR) [220] peptides, transferrin-(Fe3+ → Fe2+)$_2$ [221], a compact loose non-aligned multibeta helix (neutral)-intertwined-non-aligned multialpha helix peptide (Fe3+ SS Fe3+ → Fe2+ SS Fe2+), and hemochromatosis protein (HPE) [221], a long dualalpha helix (neutral) cum compact loose aligned beta helix cum multishort 2-way beta helix peptide [(1+ IS 1+)n SS (1+ IS 1+)n], and the combinatory helix peptides include the liver sinusoidal endothelial cell (LSEC) mannose receptor peptide, partially sulfate neutralized procollagen I peptide III C monomer (IS 4+ → 2+) [13, 222–225], a short monoalpha helix-loop-short monoalpha helix-loop-short monoalpha helix (neutral) cum compact loose non-aligned 5-way beta-X-3-way beta helix (cationic) (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The mixed helix transferrin receptor peptides, transferrin-(Fe3+ → Fe2+)$_2$ and Hemochromatosis Protein, as monomers, are capable of binding as separate monomers to opposite sides of juxtaposed mixed alpha-rich cum beta-rich receptors via neutral alpha helix ligand-to-alpha helix receptor association, which, due to the presence of di-cationicity, the acquired Fe2+ in the former (transferrin), and the inherent 2+ in the later (HPE) (MultiShort 2-way beta helix), function as effective external cationomodulators (2+) via external cationomodulation (2+)-mediated endocytosis, the process of which results in significant endocytosis-vesiculovacuolization-endothelial cell fenestration, particularly, at the liver sinusoidal endothelial cell (LSEC) where the concentration of hepatocyte-produced Transferrin and HPE is the greatest, and thus, maintains the highly endocytic-endothelial glycocalyx layer-devoid reticuloendothelial LSEC phenotype [7, 221], the concomitant presence of VEGF only required to maintain the openly fenestrated LSEC phenotype (versus diaphragm fenestrated) [7, 226]; furthermore, the secondary significant decrease in endothelial cell compliance from transferrin and HPE external cationomodulation (2+)-mediated endocytosis [indirect 3ary CM receptor-mediated shift pressuromodulation (single or dual receptor endocytic external cationomodulation: 2+)], results in the increased protein transcription, importantly, that of the highest molecular weight nuclear proteins, Ki67 (359 kDa) and separase (230 kDa), that which results in mitogenesis and cell division [4], and in LSEC turnover, in the physiologic state (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

The combinatory helix peptides, partially sulfate neutralized procollagen I peptide III C monomer (IS 4+ → 2+), consists of: (1) a compact loose non-aligned 5-way beta-X-3-way beta helix (cationic) motif, and in comparison to interleukin-16 (IL-16), due to the presence of 5-way beta (versus an IL-16 3-way beta helix) criss-crossed by 3-way beta helix (versus an IL-16 2-way beta helix), has 4+ cationicity insufficiently separated in molecular space (IS) (versus an IL-16 3+), in which case 3+ cationicity of the 4+ is effectively neutralized by heparan sulfate (or hyaluronate/glucoronate) in systemic circulation (IS 4+ → 1+), but at the reticuloendothelial liver sinusoidal endothelial cell (LSEC), which do not have a thick endothelial glycocalyx layer (- heparan sulfate/hyaluronate/glucoronate), the excess cationicity is not effectively neutralized (IS 4+ → 2+), that which, specifically, results in endocytosis, and uptake, of partially sulfate neutralized procollagen I peptide III C monomer (IS 4+ → 2+) at the LSEC 'cation-dependent' and cation-independent 'Mannose' receptors [224, 225] (Table 1); and (2) a short monoalpha helix-loop-short monoalpha helix-loop-short monoalpha helix (Neutral) motif, and in comparison to insulin-like growth factor (IGF) for example [31, 32], very similar, whereby, the procollagen I peptide III C peptide, binds with 'Mannose' receptors with decimolar (dM) affinity (*K*d) [33] viz a viz tight association with the neutral alpha helix amorphous

loop cum beta helix complex of the receptor construct [227], also very similar to the insulin-like growth factor receptor (IGFR) for example [33, 34]; furthermore, the secondary significant decrease in LSEC compliance from partially sulfate neutralized procollagen I peptide III C monomer (IS 4+ → 2+) external cationomodulation (2+)-mediated endocytosis [indirect 3ary CM receptor-mediated shift pressuromodulation (single or dual receptor endocytic external cationomodulation: 2+)], results in the increased protein transcription of the highest molecular weight nuclear proteins, Ki67 (359 kDa) and Separase (230 kDa), and at the LSEC, importantly, that which results in LSEC mitogenesis and cell division, and in turnover, in the physiologic state, while, when present in the fully neutralized (IS 4+ → 1+) form in vitro (heparin-containing media) functions, instead, as a direct CM receptor-mediated stabilizing shift pressuromodulator cum external cationomodulator (≥3+ → 1+) [227, 228] (Table 1; Additional file 5: Complete Table 1 in Supplemental File Format).

Conclusion

Building on recent knowledge that the specificity of the biological interactions of small molecule hydrophiles and lipophiles across microvascular and epithelial barriers, and with cells, can be predicted on the basis of their conserved biophysical properties, and the knowledge that biological peptides are cell membrane impermeant, it has been further discussed herein that cellular, and thus, nuclear function, are primarily regulated by small molecule hormone and peptide/factor interactions at the cell membrane (CM) receptors.

The means of regulating cellular, and thus, nuclear function, are the various forms of CM Pressuromodulation that exist, which include direct CM receptor-mediated stabilizing pressuromodulation, sub-classified as direct CM receptor-mediated stabilizing shift pressuromodulation (single, dual or tri) or direct CM receptor-mediated stabilizing shift pressuromodulation (single, dual or tri) cum external cationomodulation (≥3+ → 1+); which are with respect to acute CM receptor-stabilizing effects of small biomolecule hormones, growth factors or cytokines, and also include indirect CM- or CM receptor-mediated pressuromodulation, sub-classified as indirect 1ary CM-mediated shift pressuromodulation (perturbomodulation), indirect 2ary CM receptor-mediated shift pressuromodulation (tri or quad receptor internal pseudo-cationomodulation: SS 1+), indirect 3ary CM receptor-mediated shift pressuromodulation (single or dual receptor endocytic external cationomodulation: 2+) or indirect (Pseudo) 3ary CM receptor-mediated shift pressuromodulation (receptor endocytic hydroxylocarbonyloetheroylomodulation: 0), which are with respect to sub-acute CM receptor-stabilizing effects of small biomolecules, growth factors or cytokines.

As a generalization, all forms of CM pressuromodulation decrease CM and nuclear membrane (NM) compliance (whole cell compliance), due to pressuromodulation of the intracellular microtubule network and increases the exocytosis of pre-synthesized vesicular endogolgi peptides and small molecules as well as nuclear-to-rough endoplasmic reticulum membrane proteins to the CM, with the potential to simultaneously increase the NM-associated chromatin DNA transcription of higher molecular weight protein forms, secretory and CM-destined, mitochondrial and nuclear, including the highest molecular weight nuclear proteins, Ki67 (359 kDa) and separase (230 kDa), with the latter leading to mitogenesis and cell division; while, in the case of growth factors or cytokines with external cationomodulation capability, CM receptor external cationomodulation of CM receptors (≥3+ → 1+) results in cationic extracellular interaction (≥3+) with extracellular matrix heparan sulfates (≥3+ → 1+) concomitant with lamellopodesis and cell migration.

It can be surmised that the modulation of cellular, and nuclear, function is mostly a reactive process, governed, primarily, by small molecule hormone and peptide interactions at the cell membrane, with CM receptors and the CM itself. These insights taken together, provide valuable translationally applicable knowledge.

Additional files

Additional file 1: Table S1. Conserved biophysical properties of small molecule hydrophiles, hydro-lipophiles and lipophiles.

Additional file 2: Figure S1. Small molecule hydrophiles.

Additional file 3: Figure S2. Small molecule hydro-lipophiles.

Additional file 4: Figure S3. Small molecule lipophiles.

Additional file 5: Complete Table 1 in Supplemental File Format.

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References

1. Sarin H. Permeation thresholds for hydrophilic small biomolecules across microvascular and epithelial barriers are predictable on the basis of conserved biophysical properties. In Silico Pharmacol. 2015;3:5.
2. McCleskey E, Almers W. The Ca channel in skeletal muscle is a large pore. Proc Natl Acad Sci. 1985;82(20):7149–53.
3. Zuscik MJ, et al. Characterization of voltage-sensitive calcium channels in growth plate chondrocytes. Biochem Biophys Res Commun. 1997;234(2):432–8.

4. Christ M, Wehling M. Rapid actions of aldosterone: lymphocytes, vascular smooth muscle and endothelial cells. Steroids. 1999;64(1–2):35–41.
5. Zuscik MJ, et al. Activation of phosphoinositide metabolism by parathyroid hormone in growth plate chondrocytes. Cell Calcium. 1994;16(2):112–22.
6. Kukley M, Capetillo-Zarate E, Dietrich D. Vesicular glutamate release from axons in white matter. Nat Neurosci. 2007;10(3):311–20.
7. Sarin H. Physiologic upper limits of pore size of different blood capillary types and another perspective on the dual pore theory of microvascular permeability. J Angiogenesis Res. 2010;2:14.
8. Sarin H. Conserved mechanisms underlying the physiologic and pathophysiologic effects of corticosteroid axis small molecule hormones and peptides. TBD. 2015 (under preparation). TBD.
9. Beavan S, et al. Colocalization of glucocorticoid and mineralocorticoid receptors in human bone. J Bone Miner Res. 2001;16(8):1496–504.
10. Hellal-Levy C, et al. Specific hydroxylations determine selective corticosteroid recognition by human glucocorticoid and mineralocorticoid receptors. FEBS Lett. 1999;464(1):9–13.
11. Newton C, et al. Dexamethasone blocks antioestrogen-and oxidant-induced death of pituitary tumour cells. J Endocrinol. 2001;169(2):249–61.
12. Weihua Z, et al. Estrogen receptor (ER) β, a modulator of ERα in the uterus. Proc Natl Acad Sci. 2000;97(11):5936–41.
13. Clay WF, Katterman FR, Bartels PG. Chromatin and DNA synthesis associated with nuclear membrane in germinating cotton. Proc Natl Acad Sci USA. 1975;72(8):3134–8.
14. Logie JJ, et al. Glucocorticoid-mediated inhibition of angiogenic changes in human endothelial cells is not caused by reductions in cell proliferation or migration. PLoS One. 2010;5(12):e14476.
15. Webster KD, Ng WP, Fletcher DA. Tensional homeostasis in single fibroblasts. Biophys J. 2014;107(1):146–55.
16. Venugopalan G, et al. Multicellular architecture of malignant breast epithelia influences mechanics. PLoS One. 2014;9(8):e101955.
17. Yeung T, et al. Effects of substrate stiffness on cell morphology, cytoskeletal structure, and adhesion. Cell Motil Cytoskeleton. 2005;60(1):24–34.
18. Loring JF, et al. A global assessment of stem cell engineering. Tissue Eng Part A. 2014;20(19–20):2575–89.
19. Wehling M, et al. Effect of aldosterone on sodium and potassium concentrations in human mononuclear leukocytes. Am J Physiol. 1987;252(4 Pt 1):E505–8.
20. Chen D, et al. Aldosterone stimulates fibronectin synthesis in renal fibroblasts through mineralocorticoid receptor-dependent and independent mechanisms. Gene. 2013;531(1):23–30.
21. Yu M, et al. Effect of aldosterone on epithelial-to-mesenchymal transition of human peritoneal mesothelial cells. Kidney Res Clin Prac. 2015;34(2):83–92.
22. Isobe A, et al. Aldosterone stimulates the proliferation of uterine leiomyoma cells. Gynecol Endocrinol. 2010;26(5):372–7.
23. King S, et al. Evidence for aldosterone-dependent growth of renal cell carcinoma. Int J Exp Pathol. 2014;95(4):244–50.
24. Rombouts K, et al. Effect of aldosterone on collagen steady state levels in primary and subcultured rat hepatic stellate cells. J Hepatol. 2001;34(2):230–8.
25. Oberleithner H. Aldosterone makes human endothelium stiff and vulnerable. Kidney Int. 2005;67(5):1680–2.
26. Gravez B, et al. Aldosterone promotes cardiac endothelial cell proliferation in vivo. J Am Heart Assoc. 2015;4(1):e001266.
27. Bagley J, B.S., Iacomini J. Aldosterone acts directly on t cells, and promotes production of inflammatory cytokines [abstract], in 2015 American transplant congress. Am J Transplant. 2015. Philadelphia, Pennsylvania. pp. 15.
28. Armanini D, et al. Parallel determination of mineralocorticoid and glucocorticoid receptors in T- and B-lymphocytes of human spleen. Acta Endocrinol (Copenh). 1988;118(4):479–82.
29. Funder, J.W., et al. Vascular type I aldosterone binding sites are physiological mineralocorticoid receptors. Endocrinology. 1989;125(4):2224–6.
30. Armanini D, Strasser T, Weber PC. Characterization of aldosterone binding sites in circulating human mononuclear leukocytes. Am J Physiol. 1985;248(3 Pt 1):E388–90.
31. De Meyts P, Whittaker J. Structural biology of insulin and IGF1 receptors: implications for drug design. Nat Rev Drug Discov. 2002;1(10):769–83.
32. Garrett TPJ, et al. Crystal structure of the first three domains of the type-1 insulin-like growth factor receptor. Nature. 1998;394(6691):395–9.
33. Tong PY, Kornfeld S. Ligand interactions of the cation-dependent mannose 6-phosphate receptor. Comparison with the cation-independent mannose 6-phosphate receptor. J Biol Chem. 1989;264(14):7970–5.
34. Martinez DA, et al. Identification of functional insulin-like growth factor-II/mannose-6-phosphate receptors in isolated bone cells. J Cell Biochem. 1995;59(2):246–57.
35. McDevitt TC, Laflamme MA, Murry CE. Proliferation of cardiomyocytes derived from human embryonic stem cells is mediated via the IGF/PI 3-kinase/Akt signaling pathway. J Mol Cell Cardiol. 2005;39(6):865–73.
36. Hurley MJ, Mash DC, Jenner P. Dopamine D1 receptor expression in human basal ganglia and changes in Parkinson's disease. Mol Brain Res. 2001;87(2):271–9.
37. Miguelez C, et al. Interaction between the 5-HT system and the basal ganglia: functional implication and therapeutic perspective in Parkinson's disease. Front Neural Circuits. 2014;8:21.
38. Gibbs DM, Neill JD. Dopamine levels in hypophysial stalk blood in the rat are sufficient to inhibit prolactin secretion in vivo. Endocrinology. 1978;102(6):1895–900.
39. Liu J, et al. Ouabain induces endocytosis of plasmalemmal Na//K-ATPase in LLC-PK1 cells by a clathrin-dependent mechanism. Kidney Int. 2004;66(1):227–41.
40. Sarin H. Conserved molecular mechanisms underlying the effects of small molecule xenobiotic chemotherapeutics on cells. TBD. 2015 (under submission). TBD.
41. Golomb E, et al. Ouabain enhances the mitogenic effect of serum in vascular smooth muscle cells: role of progesterone and digoxin-like substances. Am J Hypertens. 1994;7(1):69–74.
42. Ujwal R, et al. The crystal structure of mouse VDAC1 at 2.3 Å resolution reveals mechanistic insights into metabolite gating. Proc Natl Acad Sci. 2008;105(46):17742–7.
43. Carré M, et al. Tubulin is an inherent component of mitochondrial membranes that interacts with the voltage-dependent anion channel. J Biol Chem. 2002;277(37):33664–9.
44. Shi B, et al. Dexamethasone induces hypertrophy of developing medial septum cholinergic neurons: potential role of nerve growth factor. J Neurosci. 1998;18(22):9326–34.
45. Salhanick AI, Krupp MN, Amatruda JM. Dexamethasone stimulates insulin receptor synthesis in cultured rat hepatocytes. J Biol Chem. 1983;258(23):14130–5.
46. Caulfield J, et al. CXCR4 expression on monocytes is up-regulated by dexamethasone and is modulated by autologous CD3+ T cells. Immunology. 2002;105(2):155–62.
47. Brilla CG, et al. Collagen metabolism in cultured adult rat cardiac fibroblasts: response to angiotensin II and aldosterone. J Mol Cell Cardiol. 1994;26(7):809–20.
48. Gilet A, et al. Aldosterone up-regulates MMP-9 and MMP-9/NGAL expression in human neutrophils through p38, ERK1/2 and PI3K pathways. Exp Cell Res. 2015;331(1):152–63.
49. Hamdi MM, Mutungi G. Dihydrotestosterone activates the MAPK pathway and modulates maximum isometric force through the EGF receptor in isolated intact mouse skeletal muscle fibres. J Physiol. 2010;588(Pt 3):511–25.
50. Yoshioka M, et al. Effects of dihydrotestosterone on skeletal muscle transcriptome in mice measured by serial analysis of gene expression. J Mol Endocrinol. 2006;36(2):247–59.
51. Yang R-S, et al. Regulation of fibronectin fibrillogenesis by protein kinases in cultured rat osteoblasts. Mol Pharmacol. 2002;61(5):1163–73.
52. Withers DJ, Bloom SR, Rozengurt E. Dissociation of cAMP-stimulated mitogenesis from activation of the mitogen-activated protein kinase Cascade in Swiss 3T3 cells. J Biol Chem. 1995;270(36):21411–9.
53. Löwe J, et al. Refined structure of αβ-tubulin at 3.5 Å resolution. J Mol Biol. 2001;313(5):1045–57.
54. Shprung T, Gozes I. A novel method for analyzing mitochondrial movement: inhibition by paclitaxel in a pheochromocytoma cell model. J Mol Neurosci. 2009;37(3):254–62.

55. Foland TB, et al. Paclitaxel-induced microtubule stabilization causes mitotic block and apoptotic-like cell death in a paclitaxel-sensitive strain of Saccharomyces cerevisiae. Yeast. 2005;22(12):971–8.
56. Amigo L, et al. Enrichment of canalicular membrane with cholesterol and sphingomyelin prevents bile salt-induced hepatic damage. J Lipid Res. 1999;40(3):533–42.
57. Cantatore FP, et al. Osteocalcin synthesis by human osteoblasts from normal and osteoarthritic bone after vitamin D3 stimulation. Clin Rheumatol. 2004;23(6):490–5.
58. Kim NY, et al. Biophysical induction of vascular smooth muscle cell podosomes. PLoS One. 2015;10(3):e0119008.
59. Shorts-Cary L, et al. Bone morphogenetic protein and retinoic acid-inducible neural specific protein-3 is expressed in gonadotrope cell pituitary adenomas and induces proliferation, migration, and invasion. Endocrinology. 2007;148(3):967–75.
60. Grimsrud CD, et al. Bone morphogenetic protein-7 in growth-plate chondrocytes: regulation by retinoic acid is dependent on the stage of chondrocyte maturation. J Orthop Res. 1998;16(2):247–55.
61. Gauthier NC, et al. Temporary increase in plasma membrane tension coordinates the activation of exocytosis and contraction during cell spreading. Proc Natl Acad Sci. 2011;108(35):14467–72.
62. Halaban R, et al. Regulation of tyrosinase in human melanocytes grown in culture. J Cell Biol. 1983;97(2):480–8.
63. Hwang GS, et al. Effects of hypoxia on testosterone release in rat Leydig cells. Am J Physiol Endocrinol Metab. 2009;297(5):E1039–45.
64. Machein MR, et al. Differential downregulation of vascular endothelial growth factor by dexamethasone in normoxic and hypoxic rat glioma cells. Neuropathol Appl Neurobiol. 1999;25(2):104–12.
65. Maskell JP. Electrophoretic analysis of the lipopolysaccharides of Bacteroides spp. Antonie Van Leeuwenhoek. 1994;65(2):155–61.
66. Ammon C, et al. Comparative analysis of integrin expression on monocyte-derived macrophages and monocyte-derived dendritic cells. Immunology. 2000;100(3):364–9.
67. Erwin A, Mandrell R, Munford R. Enzymatically deacylated Neisseria lipopolysaccharide (LPS) inhibits murine splenocyte mitogenesis induced by LPS. Infect Immun. 1991;59(6):1881–7.
68. Alexander C, Rietschel ET. Invited review: bacterial lipopolysaccharides and innate immunity. J Endotoxin Res. 2001;7(3):167–202.
69. Milligan G. G protein-coupled receptor dimerization: function and ligand pharmacology. Mol Pharmacol. 2004;66(1):1–7.
70. Terrillon S, Bouvier M. Roles of G-protein-coupled receptor dimerization: from ontogeny to signalling regulation. EMBO Rep. 2004;5(1):30–4.
71. Regoli D, Barabé J. Pharmacology of bradykinin and related kinins. Pharmacol Rev. 1980;32(1):1–46.
72. Sabrane K, et al. Vascular endothelium is critically involved in the hypotensive and hypovolemic actions of atrial natriuretic peptide. J Clin Investig. 2005;115(6):1666–74.
73. Lewis GD, Asnani A, Gerszten RE. Application of metabolomics to cardiovascular biomarker and pathway discovery. J Am Coll Cardiol. 2008;52(2):117–23.
74. Januzzi JL Jr, et al. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. J Am Coll Cardiol. 2011;58(18):1881–9.
75. Sarin H, et al. Metabolically stable bradykinin B2 receptor agonists enhance transvascular drug delivery into malignant brain tumors by increasing drug half-life. J Transl Med. 2009;7:33.
76. Vaziri ND, et al. Bradykinin down-regulates, whereas arginine analogs up-regulates, endothelial nitric-oxide synthase expression in coronary endothelial cells. J Pharmacol Exp Ther. 2005;313(1):121–6.
77. Morbidelli L, et al. B1 receptor involvement in the effect of bradykinin on venular endothelial cell proliferation and potentiation of FGF-2 effects. Br J Pharmacol. 1998;124(6):1286–92.
78. Alysandratos KD, et al. Neurotensin and CRH interactions augment human mast cell activation. PLoS One. 2012;7(11):e48934.
79. Zhang H, et al. Structure of the angiotensin receptor revealed by serial femtosecond crystallography. Cell. 2015;161(4):833–44.
80. Bulant M, et al. Processing of thyrotropin-releasing hormone prohormone (pro-TRH) generates a biologically active peptide, prepro-TRH-(160-169), which regulates TRH-induced thyrotropin secretion. Proc Natl Acad Sci. 1990;87(12):4439–43.
81. Fomina AF, Levitan ES. Three phases of TRH-induced facilitation of exocytosis by single lactotrophs. J Neurosci. 1995;15(7 Pt 1):4982–91.
82. Jin L, et al. Crystal structure of human parathyroid hormone 1–34 at 0.9 Å resolution. J Biol Chem. 2000;275(35):27238–44.
83. Pioszak AA, et al. Structural basis for parathyroid hormone-related protein binding to the parathyroid hormone receptor and design of conformation-selective peptides. J Biol Chem. 2009;284(41):28382–91.
84. Pateder DB, et al. PTHrP expression in chick sternal chondrocytes is regulated by TGF-beta through Smad-mediated signaling. J Cell Physiol. 2001;188(3):343–51.
85. Zhao W, et al. Bone resorption induced by parathyroid hormone is strikingly diminished in collagenase-resistant mutant mice. J Clin Investig. 1999;103(4):517–24.
86. Ishida K, Sawada N, Yamaguchi M. Expression of albumin in bone tissues and osteoblastic cells: involvement of hormonal regulation. Int J Mol Med. 2004;14(5):891–5.
87. Gradilone SA, et al. Glucagon induces the plasma membrane insertion of functional aquaporin-8 water channels in isolated rat hepatocytes. Hepatology. 2003;37(6):1435–41.
88. Bost KL, Blalock JE. Molecular characterization of a corticotropin (ACTH) receptor. Mol Cell Endocrinol. 1986;44(1):1–9.
89. Feuilloley M, et al. Structure-activity relationships of monomeric and dimeric synthetic ACTH fragments in perifused frog adrenal slices. J Steroid Biochem. 1990;35(5):583–92.
90. Mohn CE, et al. The rapid release of corticosterone from the adrenal induced by ACTH is mediated by nitric oxide acting by prostaglandin E2. Proc Natl Acad Sci USA. 2005;102(17):6213–8.
91. Alov IA. Relationship between division and functional activity of the cells of the adrenal cortex. Bull Exp Biol Med. 1963;54(3):1023–6.
92. Oliver RL, Davis JR, White A. Characterisation of ACTH related peptides in ectopic Cushing's syndrome. Pituitary. 2003;6(3):119–26.
93. McKern NM, et al. Structure of the insulin receptor ectodomain reveals a folded-over conformation. Nature. 2006;443(7108):218–21.
94. Yngen M, et al. Insulin enhances platelet activation in vitro. Thromb Res. 2001;104(2):85–91.
95. Romberger DJ, et al. Insulin modulation of bronchial epithelial cell fibronectin in vitro. Am J Physiol Lung Cell Mol Physiol. 1995;268(2):L230–8.
96. Montagnani M, et al. Insulin-stimulated activation of eNOS is independent of Ca2+ but requires phosphorylation by Akt at Ser(1179). J Biol Chem. 2001;276(suppl 32):30392–8.
97. Monaco S, et al. Insulin stimulates fibroblast proliferation through calcium-calmodulin-dependent kinase II. Cell Cycle. 2009;8(13):2024–30.
98. Kasuga M, Karlsson F, Kahn C. Insulin stimulates the phosphorylation of the 95,000-dalton subunit of its own receptor. Science. 1982;215(4529):185–7.
99. Iqbal M, et al. Insulin enhances metabolic capacities of cancer cells by dual regulation of glycolytic enzyme pyruvate kinase M2. Mol Cancer. 2013;12(1):72.
100. Hubbard SR. The insulin receptor: both a prototypical and atypical receptor tyrosine kinase. Cold Spring Harb Perspect Biol. 2013;5(3):a008946.
101. Harrison LC, Martin FI, Melick RA. Correlation between insulin receptor binding in isolated fat cells and insulin sensitivity in obese human subjects. J Clin Investig. 1976;58(6):1435–41.
102. Gospodarowicz D, Moran JS. Stimulation of division of sparse and confluent 3T3 cell populations by a fibroblast growth factor, dexamethasone, and insulin. Proc Natl Acad Sci. 1974;71(11):4584–8.
103. Malashkevich VN, Almo SC, Dowd TL. X-ray crystal structure of bovine 3 glu-osteocalcin. Biochemistry. 2013;52(47):8387–92.
104. Engert JC, Berglund EB, Rosenthal N. Proliferation precedes differentiation in IGF-I-stimulated myogenesis. J Cell Biol. 1996;135(2):431–40.
105. Butler AA, et al. Stimulation of tumor growth by recombinant human insulin-like growth factor-I (IGF-I) is dependent on the dose and the level of IGF-I receptor expression. Cancer Res. 1998;58(14):3021–7.
106. Langmead CJ, et al. Characterization of the binding of [(125)I]-human prolactin releasing peptide (PrRP) to GPR10, a novel G protein coupled receptor. Br J Pharmacol. 2000;131(4):683–8.
107. Ozawa H, Han F, Kawata M. Exocytosis sensitivity to growth hormone-releasing hormone in subsets of GH cells in rats under different corticosterone conditions. Ultrastructural study using microwave

irradiation for fixation and immunocytochemistry. J Endocrinol. 2004;183(3):507–15.
108. Stomski FC, et al. Human interleukin-3 (IL-3) induces disulfide-linked IL-3 receptor alpha- and beta-chain heterodimerization, which is required for receptor activation but not high-affinity binding. Mol Cell Biol. 1996;16(6):3035–46.
109. Park L, et al. Murine interleukin 7 (IL-7) receptor. Characterization on an IL-7-dependent cell line. J Exp Med. 1990;171(4):1073–89.
110. Ling P, et al. Human IL-12 p40 homodimer binds to the IL-12 receptor but does not mediate biologic activity. J Immunol. 1995;154(1):116–27.
111. Vitale M, et al. NK-active cytokines IL-2, IL-12, and IL-15 selectively modulate specific protein kinase C (PKC) isoforms in primary human NK cells. The Anatomical Record. 2002;266(2):87–92.
112. Lupardus PJ, Garcia KC. The structure of interleukin-23 reveals the molecular basis of p40 subunit sharing with interleukin-12. J Mol Biol. 2008;382(4):931–41.
113. Somers W, et al. The X-ray structure of a growth hormone-prolactin receptor complex. Nature. 1994;372(6505):478–81.
114. Nakajima K-I, et al. Synergistic effect of dexamethasone and prolactin on VEGF expression in bovine mammary epithelial cells via p44/p42 map kinase. Asian Aust J Anim Sci. 2009;22(6):788–95.
115. Kolle S, et al. Growth hormone (GH)/GH receptor expression and GH-mediated effects during early bovine embryogenesis. Biol Reprod. 2001;64(6):1826–34.
116. Wells JA. Binding in the growth hormone receptor complex. Proc Natl Acad Sci. 1996;93(1):1–6.
117. Clackson T, et al. Structural and functional analysis of the 1:1 growth hormone:receptor complex reveals the molecular basis for receptor affinity. J Mol Biol. 1998;277(5):1111–28.
118. Papageorgiou I, Grepper S, Unadkat JD. Induction of hepatic CYP3A enzymes by pregnancy-related hormones: studies in human hepatocytes and hepatic cell lines. Drug Metab Dispos. 2013;41(2):281–90.
119. Kassem M, et al. Growth hormone stimulates proliferation and differentiation of normal human osteoblast-like cells in vitro. Calcif Tissue Int. 1993;52(3):222–6.
120. Cater DB, Holmes BE, Mee LK. The effect of growth hormone upon cell division and nucleic acid synthesis in the regenerating liver of the rat. Biochem J. 1957;66(3):482–6.
121. Barnard R, et al. Growth hormone (GH) receptors in clonal osteoblast-like cells mediate a mitogenic response to GH. Endocrinology. 1991;128(3):1459–64.
122. Thiel D, et al. Observation of an unexpected third receptor molecule in the crystal structure of human interferon-γ receptor complex. Structure. 2000;8(9):927–36.
123. Ealick S, et al. Three-dimensional structure of recombinant human interferon-gamma. Science. 1991;252(5006):698–702.
124. Walter MR, et al. Crystal structure of a complex between interferon-[gamma] and its soluble high-affinity receptor. Nature. 1995;376(6537):230–5.
125. Cosper PF, Harvey PA, Leinwand LA. Interferon-γ causes cardiac myocyte atrophy via selective degradation of myosin heavy chain in a model of chronic myocarditis. Am J Pathol. 2012;181(6):2038–46.
126. Rouet-Benzineb P, et al. Altered balance between matrix gelatinases (MMP-2 and MMP-9) and their tissue inhibitors in human dilated cardiomyopathy: potential role of MMP-9 in myosin-heavy chain degradation. Eur J Heart Fail. 1999;1(4):337–52.
127. Huang W-C, et al. Classical macrophage activation up-regulates several matrix metalloproteinases through mitogen activated protein kinases and nuclear factor-κB. PLoS One. 2012;7(8):e42507.
128. Varani J, et al. Modulation of fibronectin production in normal human melanocytes and malignant melanoma cells by interferon-gamma and tumor necrosis factor-alpha. Am J Pathol. 1989;134(4):827–36.
129. Diaz A, Jiménez SA. Interferon-gamma regulates collagen and fibronectin gene expression by transcriptional and post-transcriptional mechanisms. Int J Biochem Cell Biol. 1997;29(1):251–60.
130. Alfinito F, et al. T cell growth-promoting activity of interferon-gamma. Mitogenic effect of the recombinant cytokine on cells from a human T-chronic lymphocytic leukemia. Leukemia. 1994;8(8):1294–300.
131. Yokota T, et al. Mitogenic activity of interferon gamma on growth-arrested human vascular smooth muscle cells. Arterioscler Thromb Vasc Biol. 1992;12(12):1393–401.
132. Fukushima K, et al. Carbohydrate recognition site of interleukin-2 in relation to cell proliferation. J Biol Chem. 2001;276(33):31202–8.
133. Liao W, et al. Modulation of cytokine receptors by IL-2 broadly regulates differentiation into helper T cell lineages. Nat Immunol. 2011;12(6):551–9.
134. Somers W, Stahl M, Seehra JS. 1.9 A crystal structure of interleukin 6: implications for a novel mode of receptor dimerization and signaling. EMBO J. 1997;16(5):989–97.
135. Seldin DC, Leder P. Mutational analysis of a critical signaling domain of the human interleukin 4 receptor. Proc Natl Acad Sci. 1994;91(6):2140–4.
136. Junttila IS, et al. Redirecting cell-type specific cytokine responses with engineered interleukin-4 superkines. Nat Chem Biol. 2012;8(12):990–8.
137. Chirifu M, et al. Crystal structure of the IL-15-IL-15R[alpha] complex, a cytokine-receptor unit presented in trans. Nat Immunol. 2007;8(9):1001–7.
138. Broughton SE, et al. The GM–CSF/IL-3/IL-5 cytokine receptor family: from ligand recognition to initiation of signaling. Immunol Rev. 2012;250(1):277–302.
139. Hansen G, et al. The structure of the GM-CSF receptor complex reveals a distinct mode of cytokine receptor activation. Cell. 2008;134(3):496–507.
140. Hercus TR, et al. The granulocyte-macrophage colony-stimulating factor receptor: linking its structure to cell signaling and its role in disease. Blood. 2009;114(7):1289–98.
141. Lyne PD, et al. Molecular modeling of the GM-CSF and IL-3 receptor complexes. Protein Sci Publ Protein Soc. 1995;4(10):2223–33.
142. Hebert JC, O'Reilly M. Granulocyte-macrophage colony-stimulating factor (GM-CSF) enhances pulmonary defenses against pneumococcal infections after splenectomy. J Trauma. 1996;41(4):663–6.
143. Huyton T, et al. An unusual cytokine:Ig-domain interaction revealed in the crystal structure of leukemia inhibitory factor (LIF) in complex with the LIF receptor. Proc Natl Acad Sci. 2007;104(31):12737–42.
144. Pandit J, et al. Three-dimensional structure of dimeric human recombinant macrophage colony-stimulating factor. Science. 1992;258(5086):1358–62.
145. Wilkins JA, et al. A study of intermediates involved in the folding pathway for recombinant human macrophage colony-stimulating factor (M-CSF): evidence for two distinct folding pathways. Protein Sci. 1993;2(2):244–54.
146. Chen X, et al. Structure of macrophage colony stimulating factor bound to FMS: diverse signaling assemblies of class III receptor tyrosine kinases. Proc Natl Acad Sci. 2008;105(47):18267–72.
147. Hebert JC, et al. Effects of exogenous cytokines on intravascular clearance of bacteria in normal and splenectomized mice. J Trauma. 1997;43(6):875–9.
148. Lynch EA, et al. Cutting edge: IL-16/CD4 preferentially induces Th1 cell migration: requirement of CCR5. J Immunol. 2003;171(10):4965–8.
149. Muhlhahn P, et al. Structure of interleukin 16 resembles a PDZ domain with an occluded peptide binding site. Nat Struct Mol Biol. 1998;5(8):682–6.
150. Mashikian MV, et al. Reciprocal desensitization of CCR5 and CD4 is mediated by IL-16 and macrophage-inflammatory protein-1β, respectively. J Immunol. 1999;163(6):3123–30.
151. Liu Y, et al. Identification of a CD4 domain required for interleukin-16 binding and lymphocyte activation. J Biol Chem. 1999;274(33):23387–95.
152. Kalinina OV, Pfeifer N, Lengauer T. Modelling binding between CCR5 and CXCR4 receptors and their ligands suggests the surface electrostatic potential of the co-receptor to be a key player in the HIV-1 tropism. Retrovirology. 2013;10(1):1–11.
153. Hoover DM, et al. The structure of human macrophage inflammatory protein-3α/CCL20: linking antimicrobial and cc chemokine receptor-6-binding activities with human β-defensins. J Biol Chem. 2002;277(40):37647–54.
154. Skelton NJ, et al. Structure of a CXC chemokine-receptor fragment in complex with interleukin-8. Structure. 1999;7(2):157–68.
155. Richardson RM, et al. Interleukin-8-mediated heterologous receptor internalization provides resistance to HIV-1 infectivity: role of signal strength and receptor desensitization. J Biol Chem. 2003;278(18):15867–73.

156. Zhang JD, et al. Three-dimensional structure of human basic fibroblast growth factor, a structural homolog of interleukin 1 beta. Proc Natl Acad Sci USA. 1991;88(8):3446–50.
157. Ye S, et al. Structural basis for interaction of FGF-1, FGF-2, and FGF-7 with different heparan sulfate motifs. Biochemistry. 2001;40(48):14429–39.
158. Goetz R, Mohammadi M. Exploring mechanisms of FGF signalling through the lens of structural biology. Nat Rev Mol Cell Biol. 2013;14(3):166–80.
159. Plotnikov AN, et al. Crystal structures of two FGF-FGFR complexes reveal the determinants of ligand-receptor specificity. Cell. 2000;101(4):413–24.
160. Schlessinger J, et al. Crystal structure of a ternary FGF-FGFR-heparin complex reveals a dual role for heparin in FGFR binding and dimerization. Mol Cell. 2000;6(3):743–50.
161. Seghezzi G, et al. Fibroblast growth factor-2 (FGF-2) induces vascular endothelial growth factor (VEGF) expression in the endothelial cells of forming capillaries: an autocrine mechanism contributing to angiogenesis. J Cell Biol. 1998;141(7):1659–73.
162. Melder RJ, et al. During angiogenesis, vascular endothelial growth factor and basic fibroblast growth factor regulate natural killer cell adhesion to tumor endothelium. Nat Med. 1996;2(9):992–7.
163. Basilico C, et al. A high affinity hepatocyte growth factor-binding site in the immunoglobulin-like region of met. J Biol Chem. 2008;283(30):21267–77.
164. Haruyama T, et al. Regulation and significance of hepatocyte-derived matrix metalloproteinases in liver remodeling. Biochem Biophys Res Commun. 2000;272(3):681–6.
165. Ogiso H, et al. Crystal structure of the complex of human epidermal growth factor and receptor extracellular domains. Cell. 2002;110(6):775–87.
166. Louderbough JM, Lopez JI, Schroeder JA. Matrix hyaluronan alters epidermal growth factor receptor-dependent cell morphology. Cell Adhes Migr. 2010;4(1):26–31.
167. Chen X, et al. Interleukin-1α, 6 regulate the secretion of vascular endothelial growth factor A, C in pancreatic cancer. Hepatobiliary Pancreat Dis Int. 2005;4(3):460–3.
168. Priestle JP, Schar HP, Grutter MG. Crystal structure of the cytokine interleukin-1 beta. EMBO J. 1988;7(2):339–43.
169. Eck MJ, Sprang SR. The structure of tumor necrosis factor-alpha at 2.6 A resolution. Implications for receptor binding. J Biol Chem. 1989;264(29):17595–605.
170. Wu H, Hymowitz SG. Structure and function of tumor necrosis factor (TNF) at the cell surface. In: Bradshaw RA, Denis EA, editors. Handbook of cell signaling. Oxford: Elsevier Inc., Academic Press; 2009. p. 265–75.
171. Smith RA, Baglioni C. The active form of tumor necrosis factor is a trimer. J Biol Chem. 1987;262(15):6951–4.
172. Cha S-S, et al. High resolution crystal structure of a human tumor necrosis Factor-α Mutant with low systemic toxicity. J Biol Chem. 1998;273(4):2153–60.
173. Caux C, et al. GM-CSF and TNF-alpha cooperate in the generation of dendritic Langerhans cells. Nature. 1992;360(6401):258–61.
174. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. Endocr Rev. 2005;26(3):439–51.
175. Liu C, et al. Structural and functional insights of RANKL–RANK interaction and signaling. J Immunol. 2010;184(12):6910–9.
176. Luan X, et al. Crystal structure of human RANKL complexed with its decoy receptor osteoprotegerin. J Immunol. 2012;189(1):245–52.
177. Udagawa N, et al. Osteoblasts/stromal cells stimulate osteoclast activation through expression of osteoclast differentiation factor/RANKL but not macrophage colony-stimulating factor. Bone. 1999;25(5):517–23.
178. Yu M, et al. NF-κB signaling participates in both RANKL- and IL-4-induced macrophage fusion: receptor cross-talk leads to alterations in NF-κB pathways. J Immunol. 2011;187(4):1797–806.
179. Boeyens JCA, et al. Effects of ω3- and ω6-polyunsaturated fatty acids on RANKL-induced osteoclast differentiation of RAW264.7 cells: a comparative in vitro study. Nutrients. 2014;6(7):2584–601.
180. Childs LM, et al. In vivo RANK signaling blockade using the receptor activator of NF-kappaB: Fc effectively prevents and ameliorates wear debris-induced osteolysis via osteoclast depletion without inhibiting osteogenesis. J Bone Miner Res. 2002;17(2):192–9.
181. Cerpa-Poljak A, et al. Isoelectric charge of recombinant human follicle-stimulating hormone isoforms determines receptor affinity and in vitro bioactivity. Endocrinology. 1993;132(1):351–6.
182. Jiang X, et al. Evidence for follicle-stimulating hormone receptor as a functional trimer. J Biol Chem. 2014;289(20):14273–82.
183. Fan QR, Hendrickson WA. Structure of human follicle-stimulating hormone in complex with its receptor. Nature. 2005;433(7023):269–77.
184. Grewal N, et al. Ligand-induced receptor dimerization may be critical for signal transduction by choriogonadotropin. Biophys J. 1997;73(3):1190–7.
185. Sugahara T, et al. Biosynthesis of a biologically active single peptide chain containing the human common alpha and chorionic gonadotropin beta subunits in tandem. Proc Natl Acad Sci USA. 1995;92(6):2041–5.
186. Duncan WC, Gay E, Maybin JA. The effect of human chorionic gonadotrophin on the expression of progesterone receptors in human luteal cells in vivo and in vitro. Reproduction. 2005;130(1):83–93.
187. Komorowski J, Gradowski G, Stepień H. Effects of human chorionic gonadotropin (hCG) and beta-hCG on oncostatin M release from human peripheral blood mononuclear cells in vitro. Cytobios. 1996;92(370–371):159–63.
188. O'Leary PD, Hughes RA. Design of potent peptide mimetics of brain-derived neurotrophic factor. J Biol Chem. 2003;278(28):25738–44.
189. Bradshaw RA, et al. Nerve growth factor: structure/function relationships. Protein Sci. 1994;3(11):1901–13.
190. Chada SR, Hollenbeck PJ. Nerve growth factor signaling regulates motility and docking of axonal mitochondria. Curr Biol. 2004;14(14):1272–6.
191. Wehrman T, et al. Structural and mechanistic insights into nerve growth factor interactions with the TrkA and p75 receptors. Neuron. 2007;53(1):25–38.
192. Descamps S, et al. Nerve growth factor is mitogenic for cancerous but not normal human breast epithelial cells. J Biol Chem. 1998;273(27):16659–62.
193. Cole LA. Biological functions of hCG and hCG-related molecules. Reprod Biol Endocrinol RB&E. 2010;8:102.
194. Anderson W, et al. Interactions of gonadotropins with corpus luteum membranes. III. Electron Microscopic localization of [1 2 5I]-hCG binding to sensitive and desensitized ovaries 7 days after PMSG-hCG. Biol Reprod. 1979;20(2):362–76.
195. Hinck AP, et al. Transforming growth factor β1: three-dimensional structure in solution and comparison with the X-ray structure of transforming growth factor β2. Biochemistry. 1996;35(26):8517–34.
196. Lin SJ, et al. The structural basis of TGF-β, bone morphogenetic protein, and activin ligand binding. Reproduction. 2006;132(2):179–90.
197. Hart PJ, et al. Crystal structure of the human TβR2 ectodomain—TGF-β3 complex. Nat Struct Mol Biol. 2002;9(3):203–8.
198. Yamashita H, et al. Formation of hetero-oligomeric complexes of type I and type II receptors for transforming growth factor-beta. J Biol Chem. 1994;269(31):20172–8.
199. Rahman MS, et al. TGF-β/BMP signaling and other molecular events: regulation of osteoblastogenesis and bone formation. Bone Research. 2015;3:15005.
200. Ying S-Y, et al. Type beta transforming growth factor (TGF-β) is a potent stimulator of the basal secretion of follicle stimulating hormone (FSH) in a pituitary monolayer system. Biochem Biophys Res Commun. 1986;135(3):950–6.
201. Suzuki T, et al. TGF-β signaling regulates pancreatic β-Cell proliferation through control of cell cycle regulator p27 expression. Acta Histochem Cytochem. 2013;46(2):51–8.
202. Strutz F, et al. TGF-beta1 induces proliferation in human renal fibroblasts via induction of basic fibroblast growth factor (FGF-2). Kidney Int. 2001;59(2):579–92.
203. Shi D, et al. Stimulation of fibronectin production by TGF-beta 1 is independent of effects on cell proliferation: the example of bovine adrenocortical cells. J Cell Physiol. 1990;145(1):60–8.
204. Kondo S, et al. Transforming growth factor-beta 1 enhances the generation of allospecific cytotoxic T lymphocytes. Immunology. 1993;79(3):459–64.
205. Ignotz RA, Massagué J. Transforming growth factor-beta stimulates the expression of fibronectin and collagen and their incorporation into the extracellular matrix. J Biol Chem. 1986;261(9):4337–45.

206. Dean DC, Newby RF, Bourgeois S. Regulation of fibronectin biosynthesis by dexamethasone, transforming growth factor beta, and cAMP in human cell lines. J Cell Biol. 1988;106(6):2159–70.
207. Clark RAF, et al. TGF-β1 stimulates cultured human fibroblasts to proliferate and produce tissue-like fibroplasia: a fibronectin matrix-dependent event. J Cell Physiol. 1997;170(1):69–80.
208. Perrin A, et al. Transforming growth factor β1 is a negative regulator of steroid 17α-hydroxylase expression in bovine adrenocortical cells. Endocrinology. 1991;128(1):357–62.
209. Gupta P, et al. Transforming growth factor-beta 1 inhibits aldosterone and stimulates adrenal renin in cultured bovine zona glomerulosa cells. Endocrinology. 1992;131(2):631–6.
210. Scheufler C, Sebald W, Hulsmeyer M. Crystal structure of human bone morphogenetic protein-2 at 2.7 A resolution. J Mol Biol. 1999;287(1):103–15.
211. Hye-Ryong Shim A, et al. Structures of a platelet-derived growth factor/propeptide complex and a platelet-derived growth factor/receptor complex. Proc Natl Acad Sci. 2010;107(25):11307–12.
212. Huynh J, et al. Substrate stiffness regulates PDGF-induced circular dorsal ruffle formation through MLCK. Cell Mol Bioeng. 2013;6(2):138–47.
213. Au P, et al. Paradoxical effects of PDGF-BB overexpression in endothelial cells on engineered blood vessels in vivo. Am J Pathol. 2009;175(1):294–302.
214. Iyer S, et al. The crystal structure of human placenta growth factor-1 (PlGF-1), an angiogenic protein, at 2.0 Å resolution. J Biol Chem. 2001;276(15):12153–61.
215. Muller YA, et al. The crystal structure of vascular endothelial growth factor (VEGF) refined to 1.93 Å resolution: multiple copy flexibility and receptor binding. Structure. 1997;5(10):1325–38.
216. Muller YA, et al. Vascular endothelial growth factor: crystal structure and functional mapping of the kinase domain receptor binding site. Proc Natl Acad Sci. 1997;94(14):7192–7.
217. Grünewald FS, et al. Structure–function analysis of VEGF receptor activation and the role of coreceptors in angiogenic signaling. Biochim Biophys Acta (BBA) Proteins Proteom. 2010;1804(3):567–80.
218. Kupprion C, Motamed K, Sage EH. SPARC (BM-40, osteonectin) inhibits the mitogenic effect of vascular endothelial growth factor on microvascular endothelial cells. J Biol Chem. 1998;273(45):29635–40.
219. Yang S, et al. Vascular endothelial cell growth factor-driven endothelial tube formation is mediated by vascular endothelial cell growth factor receptor-2, a kinase insert domain-containing receptor. Arterioscler Thromb Vasc Biol. 2001;21(12):1934–40.
220. Demogines A, et al. Dual host-virus arms races shape an essential housekeeping protein. PLoS Biol. 2013;11(5):e1001571.
221. Qian ZM, et al. Targeted drug delivery via the transferrin receptor-mediated endocytosis pathway. Pharmacol Rev. 2002;54(4):561–87.
222. Melkko J, et al. Radioimmunoassay of the carboxyterminal propeptide of human type I procollagen. Clin Chem. 1990;36(7):1328–32.
223. Dion AS, Myers JC. COOH-terminal propeptides of the major human procollagens. Structural, functional and genetic comparisons. J Mol Biol. 1987;193(1):127–43.
224. Smedsrød B. Aminoterminal propeptide of type III procollagen is cleared from the circulation by receptor-mediated endocytosis in liver endothelial cells. Collagen and related research. 1988;8(4):375–88.
225. Smedsrød B, et al. Circulating C-terminal propeptide of type I procollagen is cleared mainly via the mannose receptor in liver endothelial cells. Biochem J. 1990;271(2):345–50.
226. Hwa AJ, et al. Rat liver sinusoidal endothelial cells survive without exogenous VEGF in 3D perfused co-cultures with hepatocytes. FASEB J. 2007;21(10):2564–79.
227. de Castro Bras LE, et al. MMP-9 generated collagen I C-terminus peptides enhance cardiac fibroblast wound healing response. Circulation. 2012;126:A16016.
228. Wiestner M, et al. Inhibiting effect of procollagen peptides on collagen biosynthesis in fibroblast cultures. J Biol Chem. 1979;254(15):7016–23.