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Alloantigenic recognition properties of CD8$^+$ regulatory T cells

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Background

We recently reported that in a rat major histocompatibility complex (MHC) mismatched heart allograft model, treatment with CD40Ig, a chimeric molecule that blocks CD40L, leads to indefinite allograft survival mediated by CD8$^+$CD45RC^{low} Tregs [1]. Although essential, the exact role of TCR/MHC/peptide interaction in Treg activity is still unknown. We therefore characterize the allogeneic peptide(s) recognized and the TCR usage of the CD8$^+$ CD45RC^{low} Tregs.

Material and methods

Allogeneic peptide(s) were derived from polymorphic regions of donor MHC molecules [2,3]. Sixty-two overlapping peptides of sixteen amino acids (aa) were tested in a coculture of Tregs with syngeneic pDCs (ratio 4:1). Moreover, the repertoire of the TCR of the CD8$^+$ Tregs was studied by flow cytometry analysis and sequencing the CDR3 region.

Results

After six days of culture, two peptides in particular led to the activation of Tregs, as shown by the upregulation of the CD25 molecule (from 25.89% to 29.27% of CD25 expression). These activator peptides were characterized by prominent amino acids (aa) at rather central position, which could result in a large TCR repertoire diversity of the specific Tregs. We showed previously that CD8$^+$ CD45RC^{low} Tregs expressed a specific altered V 11 repertoire, with the same CDR3 length in all animals (9 aa). This upregulation was confirmed at the protein level, since 19.9±3.7% of Tregs from a CD40Ig-treated animal expressed the V 11 chain compared to 6.1±2.3% in naïve ones. Sequencing of 160 clones of V 11 TCRs from six long-surviving animals suggested a preferential use of a 9 aa long CDR3 and a particular J region (J 1.6). Interestingly, conserved sequences were frequently found but no common clonotype was shared between animals, suggesting the private nature of the repertoire.

Conclusion

This study demonstrated that CD8$^+$CD45RC^{low} Tregs recognize two potential allogeneic epitopes leading to a private TCR repertoire.

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