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Early-onset inflammatory bowel disease caused by mutant IL10 receptor

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Background

The molecular etiology of inflammatory bowel diseases (IBD) is largely unknown.

Methods

We performed genetic linkage analysis and candidate gene sequencing in two unrelated consanguineous families with children affected by early-onset IBD. We screened six additional patients for mutations in two candidate genes and carried out functional assays in patients' peripheral blood mononuclear cells. We treated one patient with an allogeneic hematopoietic stem cell transplant (HSCT).

Results

We identified three distinct homozygous mutations in the genes *IL10RA* and *IL10RB*, encoding the IL10R1 and IL10R2 proteins, respectively (which form a heteromer to make up the interleukin-10 receptor) in four of nine patients with early-onset colitis. The mutations abrogate IL10-induced signaling, as demonstrated by deficient STAT3 phosphorylation upon IL10 stimulation. Consistent with this observation is the increased secretion of TNFα and other proinflammatory cytokines from peripheral blood mononuclear cells from IL10R-deficient patients, suggesting that IL10-dependent "negative feedback" regulation is disrupted in these cells. One patient was successfully treated by an allogeneic HSCT.

Conclusions

Mutations in genes encoding the IL10R subunit proteins cause human enterocolitis, involving hyperinflammatory immune responses in the intestine. Allogeneic HSCT may offer a cure for IL10 receptor deficiency.

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