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Gut response

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The intestinal mucosa has to discriminate between beneficial and pathogenic organisms within the gut, a process regulated in part by specific T cells that secrete immunosuppressive cytokines. Interleukin-10 (IL-10) mediates immunoregulatory mechanisms that control inflammatory responses in the gut, and evidence is accumulating that it may have a role in the pathology of Crohn disease and ulcerative colitis, conditions collectively encompassed by the term "inflammatory bowel disease." Long-term administration of IL-10 to treat the disease is problematic because no effective delivery method has been available. In the June 16 Nature Biotechnology, Lothar Steidler and colleagues at Ghent University report a recombinant bacterium developed to produce IL-10 that also addresses the issue of containment of a live genetically modified organism following its release into the gut environment for therapeutic use (*Nature Biotechnology*, DOI:10.1038/nbt840, June 15, 2003).

Steidler et al. replaced the thymidylate synthase gene *thyA* in *Lactococcus lactis* with an expression cassette for the IL-10 gene, simultaneously enabling the microorganism to produce the cytokine and to render it dependent on thymidine or thymine for survival. They reasoned that a recombination event to restore the *thyA* gene, if it should occur at all, would simply replace the expression cassette and return the bacterial genome to its premodification state. They demonstrated survival dependence of the organism on thymidine and thymine, its viability, and the secretion of functional IL-10 both in vitro and in vivo in pig intestine, which closely resembles the human gut. One of their strains is currently undergoing clinical trials in Holland.

"The *thyA*-deficient bacteria cannot accumulate in the environment. Our approach thus provides a simple and robust system for biological containment," conclude the authors.

References

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