

### In This Issue

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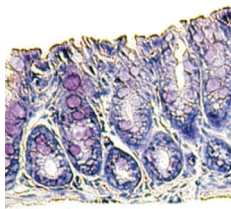
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Activation of the  $\mu$  opioid receptor — calm for the colon. Endogenous ligands of the  $\mu$  opioid receptor affect intestinal mobility and secretion as well as immunological and inflammatory reactions. Examining a potential role of this receptor in the control of intestinal inflammation, Pierre Desreumaux and colleagues found (pages 1329–1338) that subcutaneous administration of selective peripheral  $\mu$  opioid receptor agonists prevented colitis in two mouse models. Additional results suggest that the receptor exerts its anti-inflammatory effect in the colon through the regulation of cytokine production and T cell proliferation. As both of the latter are involved in inflammatory bowel disease (IBD), the results suggest that agonists of the  $\mu$  opioid receptor might have therapeutic potential in IBD patients. Transmitting tolerance. The ability to transfer diabetes with bone marrow or hematopoietic stem cells (HSCs) from affected NOD animals demonstrates not only the hematopoietic basis of the disease but the potential to prevent autoimmune diabetes by manipulating HSCs. On pages 1357–1363, Raymond Steptoe and colleagues report that they can prevent autoimmune diabetes in NOD mice that have undergone syngeneic transplantation of HSCs expressing the autoantigen proinsulin II under the control of a promoter that specifically drives expression in antigen-presenting cells. Rather than using HSCs from transgenic animals, efficient ex vivo transduction methods would have to be established for the use of a similar [...]

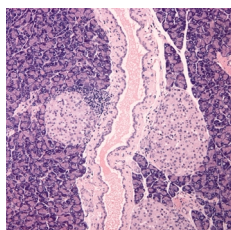
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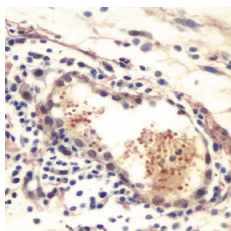




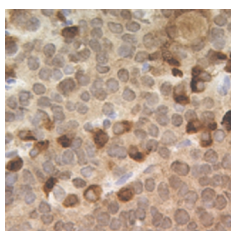
**Activation of the  $\mu$  opioid receptor — calm for the colon.** Endogenous ligands of the  $\mu$  opioid receptor affect intestinal mobility and secretion as well as immunological and inflammatory reactions. Examining a potential role of this receptor in the control of intestinal inflammation, Pierre Desreumaux and colleagues found (pages 1329–1338) that subcutaneous administration of selective peripheral  $\mu$  opioid receptor agonists prevented colitis in two mouse models. Additional results suggest that the receptor exerts its anti-inflammatory effect in the colon through the regulation of cytokine production and T cell proliferation. As both of the latter are involved in inflammatory bowel disease (IBD), the results suggest that agonists of the  $\mu$  opioid receptor might have therapeutic potential in IBD patients.



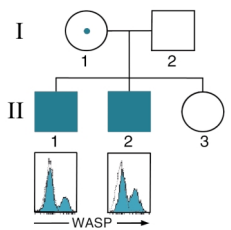
**Transmitting tolerance.** The ability to transfer diabetes with bone marrow or hematopoietic stem cells (HSCs) from affected NOD animals demonstrates not only the hematopoietic basis of the disease but the potential to prevent autoimmune diabetes by manipulating HSCs. On pages 1357–1363, Raymond Steptoe and colleagues report that they can prevent autoimmune diabetes in NOD mice that have undergone syngeneic transplantation of HSCs expressing the autoantigen proinsulin II under the control of a promoter that specifically drives expression in antigen-presenting cells. Rather than using HSCs from transgenic animals, efficient ex vivo transduction methods would have to be established for the use of a similar strategy in humans. In addition, engraftment of donor HSCs was achieved after myeloablative conditioning, which is not acceptable in asymptomatic humans. Despite these hurdles, however, the proof of principle suggests that the strategy merits further consideration.



**Estrogen promotes wound healing via MIF.** Cutaneous wound healing is associated with an initial inflammatory response followed by reformation of the epithelial barrier and matrix deposition. Excessive inflammation is thought to be a factor in age-related impaired wound healing. Interested in the role of estrogen in wound healing, Gillian Ashcroft and colleagues now present evidence (pages 1309–1318) that macrophage migration inhibitory factor (MIF) is a target of estrogen in wounded skin. In the absence of MIF, mice did not exhibit the delayed healing phenotype associated with reduced estrogen levels in wild-type controls. Taken together, the data suggest that estrogen reduces the local inflammatory response by down regulating MIF, and point to MIF as a potential specific target for therapeutic intervention in patients with impaired wound healing.



**PPAR- $\gamma$  ligands target pituitary tumors.** PPAR- $\gamma$  is expressed in breast, prostate, and colon epithelium, and administration of synthetic PPAR- $\gamma$  ligands inhibits the growth of prostate and colon cancer cells. Investigating the molecular pathology of pituitary tumors, Anthony Heaney and colleagues found (pages 1381–1388) that PPAR- $\gamma$  is abundantly expressed in several types of human pituitary tumors, including both nonfunctioning and hormone-secreting tumors. The researchers show that PPAR- $\gamma$  ligands are potent inhibitors of pituitary tumor proliferation in vitro and inhibit pituitary tumor growth and secretion of prolactin, growth hormone, and luteinizing hormone in vivo. This suggests that PPAR- $\gamma$  ligands may be suitable therapies for nonfunctioning pituitary tumors — for which no medical treatment currently exists — as well as hormone-secreting tumors that do not respond to existing treatments.



**Selection for second-site mutations.** Somatic revertant mosaicism caused by back mutations or second-site suppressor mutations has been reported in several heritable genetic diseases. Such restorative mutations are thought to be rare but should have a selective advantage. On pages 1389–1397, Taizo Wada and colleagues describe a family in which the mother and two sons carry a frameshift mutation in the gene encoding Wiskott-Aldrich syndrome protein (WASP), which abrogates protein expression. Both brothers, however, showed expression of WASP in a fraction of their T cells. This was due, in both cases, to a second mutation, which restored the reading frame and led to expression of a slightly shorter but functional protein. The revertant T lymphocytes accumulate in vivo, showing selective advantage. The nucleotide sequence surrounding the second mutation suggests that slipped mispairing was a likely mechanism, and the presence in both siblings suggests that second-site suppressor mutations might be more common than previously thought.