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In This Issue

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AM: a maternal gene that affects fetal growth As defects in placental development and function cause complications in pregnancy such as fetal growth restriction (FGR), identifying the factors that control implantation and placental development are areas of intensive investigation. Previous studies in the Caron laboratory showed that mouse embryos lacking both copies of the gene encoding adrenomedullin (AM) die at E14.5. However, it was also noted that fewer pups than expected (even with the loss of AM-/- embryos) were born when AM+/- mice were intercrossed. In this issue of the JCI (pages 2653–2662), Li, Caron, and colleagues now show that female AM+/- mice crossed with wild-type male mice have smaller litters than do wild-type female mice crossed with either AM+/- or wild-type male mice. Reduced litter size was associated with FGR and embryo loss at E9.5-E12.5, which is when the placenta develops. Indeed, the placentas of growth-restricted embryos were closely spaced with morphologic and histologic defects. This study indicates that a reduction in the level of AM in female mice severely decreases their fertility. In the same way, modest alterations in human AM expression might have implications for human fertility. The expanding world of imatinib mesylate Imatinib mesylate (Gleevec; Novartis) is a tyrosine kinase inhibitor used to treat individuals with chronic myelogenous leukemia caused by a Bcr/Abl chromosome translocation and […]

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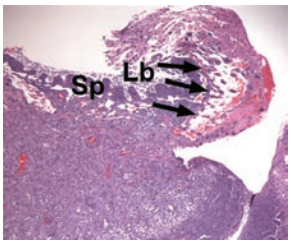
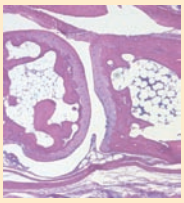


The expanding world of imatinib mesylate



Imatinib mesylate (Gleevec; Novartis) is a tyrosine kinase inhibitor used to treat individuals with chronic myelogenous leukemia caused by a *Bcr/Abl* chromosome translocation and individuals with gastrointestinal tumors that express c-Kit. In addition to Abl tyrosine kinases and the c-Kit tyrosine kinase receptor, imatinib inhibits the tyrosine kinase receptors PDGFRα, PDGFRβ, and c-Fms. Although PDGFR, c-Fms, and c-Kit are expressed by cells involved in the pathogenesis of RA, and there are 2 documented cases in which individuals taking imatinib to treat their cancer showed clinical improvement in their RA, there has been no study to date of the effects of imatinib in a mouse preclinical model of arthritis. In this issue of the *JCI* (pages 2633–2642), Paniagua and colleagues have now shown that in the collagen-induced arthritis mouse model of RA, imatinib prevents both the onset of disease and the development of established disease. Imatinib inhibited the function of many of the immune cells that contribute to the pathogenesis of RA: in mast cells, it inhibited c-Kit signaling and proinflammatory cytokine production; and in human fibroblast-like synoviocytes from patients with RA, it inhibited PDGFRβ signaling and proliferation. This study indicates that although imatinib has a narrow range of targets, these control signaling pathways important for the pathogenesis of collagen-induced arthritis, providing hope for a new treatment for RA.

Finding *EGFR* T790M — like finding a needle in a haystack

The gene encoding the tyrosine kinase receptor EGFR is mutated and amplified in a substantial proportion of individuals with non–small cell lung carcinomas (NSCLCs). In clinical trials, many of these individuals have benefited from treatment with small-molecule EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib (Iressa; AstraZeneca). However, the tumors often become drug resistant over time. In some individuals, acquired resistance to EGFR TKIs has been associated with a second *EGFR* mutation (the *EGFR* T790M mutation), but the importance of this has not previously been determined. To model acquired gefitinib resistance, Engelman and colleagues generated a human lung carcinoma cell line with such resistance (pages 2695–2706). The *EGFR* T790M mutation was undetectable in these cells by conventional sequencing techniques, but was detected in most cells using a highly sensitive HPLC technique. Ectopic expression of EGFR containing both an activating mutation and the T790M mutation in gefitinib-sensitive lung carcinoma cell lines rendered them gefitinib resistant; this was associated with activation of the PI3K/AKT signaling pathway. These cell lines were also rendered gefitinib resistant by ectopic expression of constitutively active forms of PI3K, so gefitinib resistance can be acquired in several ways. This study has clinical implications because defining the mechanism of drug resistance may help guide therapeutic decisions for the treatment of individuals with NSCLC that has acquired resistance to EGFR TKIs.

A new way to activate mast cells

The chronic inflammatory disorders atopic dermatitis (AD) and psoriasis are associated with increased numbers of cells expressing CD30, but the implications of this for disease have not yet been determined. As the number of mast cells in the inflamed skin of patients with AD and psoriasis is increased compared with the number in their healthy skin, and mast cells in the lymph nodes of individuals with Hodgkin lymphoma express CD30 ligand (CD30L), Fischer and colleagues analyzed human cord blood–derived mast cells (CBMCs) activated using a CD30-Fc fusion protein (pages 2748–2756). These activated CBMCs secreted increased amounts of several proinflammatory chemokines, including IL-8, in the absence of histamine release. Furthermore, CD30L stimulation induced mast cells in skin organ cultures of healthy donors to produce IL-8. This study provides insight into the mechanisms of mast cell activation in these chronic inflammatory diseases. Additionally, as mast cells were the predominant CD30L-expressing cell in the inflammed skin of individuals with AD and psoriasis, the authors suggest that the production of proinflammatory cytokines by mast cells activated through CD30L may support inflammatory cell recruitment and the chronic inflammatory disease state.