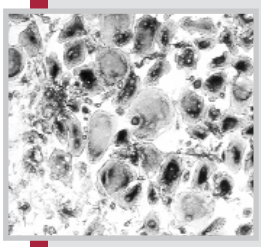
In this issue

By John Ashkenas, Science Editor

The effects of IL-6 in Paget's disease continue to RANKL

(See article on pages 1833–1838.)

In their Perspective article in this issue (pages 1663–1668), Bianco and Robey suggest that disorders of tissues derived from bone marrow stroma arise from defects in individual stromal precursor cells, whose progenitors contribute to disease in isolated regions of the resulting tissue. In their view, the consequences of such defects may be seen not only in adult stromal cells, but also in interacting hematopoietic cells. This model may be applied directly to Paget's disease, in which localized hyperactivity of osteoclasts — bone-resorbing cells of hematopoietic origin — causes focal disruptions of bone structure. The receptor for activated NF-κB (RANK) and its soluble ligand, RANKL, are known to be required for the activation of osteoclasts. Menaa and coworkers have used a cell culture system to follow the development of osteoclast precursors into multinucleated osteoclast-like cells. Here, they attempt to account for the greater number of osteoclasts in pagetic regions of the bone. Menaa et al. show that osteoclast precursors in pagetic tissue are exposed to elevated levels of RANKL and are also intrinsically more responsive to the effects of this cytokine. Interestingly, marrow from unaffected bones in individuals with Paget's disease appears normal, at least with respect to RANKL biosynthesis. The increase in sensitivity to RANKL appears to be the direct result of IL-6 stimulation, since blocking IL-6 signaling suppresses the formation of osteoclast-like cells in culture, and added IL-6 promotes the formation of such cells in cultures of normal hematopoietic precursor cells cultured with low levels of RANKL. IL-6 is expressed at increased levels in pagetic osteoclasts and may also be produced by cells of the stromal cell network. The upregulation of RANKL expression in affected skeletal tissue may likewise reflect the local action of marrow stromal cells on osteoclast precursors.



Bacterial flagella and intestinal inflammation

(See article on pages 1761–1767.)

Pathogenic isolates of *Escherichia coli* can often be distinguished from laboratory and other strains by their ability to adhere to host cells and to form a tightly packed layer, or "biofilm," on monolayers of cultured intestinal epithelial cells. Steiner et al. reported 2 years ago that such enteroaggregative *E. coli* (EAEC) strains provoke colonic cells to express the inflammatory cytokine IL-8, which is believed to contribute to the gastric inflammation and childhood diarrhea that are endemic in many Third-World settings and sporadic in developed countries. By following IL-8 release from cultured Caco-2 cells, which produce this cytokine at a low constitutive level, Steiner et al. now identify a key trigger of inflammation in this system. Having purified an IL-8–inducing factor from broth in which EAEC had grown, the authors show that this factor is identical to the flagellar protein FliC. Disruption of the *fliC* gene yields an aflaggellar strain that, except for a predictable loss of motility, is phenotypically normal. This strain still aggregates on intestinal cell cultures, but it fails to induce IL-8. However, isolated flagella, or even purified FliC protein, induce IL-8, demonstrating that this protein is sufficient to explain the inflammatory response to EAEC. The authors suggest that related proteins in other enteropathogens have similar effects, but pathogenic effects of other flagellar proteins whose expression is lost in the aflagellar *fliC* mutants may also be worth exploring.

Molecular mechanisms of sunburn

(See article on pages 1751–1759.)

Decoy oligonucleotides, short double-stranded molecules that match the consensus binding sequence for a DNA-binding protein, have been widely used to block NF-κB activity. In a novel application of this approach, Abeyama and collaborators show that many of the symptoms associated with sunburned skin — swelling, inflammation, and leukocyte infiltration, as well as accumulation of keratinocytes to produce a thickened epidermis — result from the activation of NF-κB by ultraviolet (UV) light. Both in cultured keratinocytes and in live mice, direct application of the decoy sequence blocked NF-κB–dependent gene expression, including expression of inflammatory cytokines. However, the decoy had no effect on the accumulation of DNA damage products in UV-irradiated tissue. Remarkably, other treatments that irritate the skin and provoke similar changes in skin morphology and gene expression did not respond to this treatment, suggesting that NF-κB activation is a specific and perhaps an early event in the skin's response to sunburn.