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In this issue

Sticks and stones may break our bones, but here's what spares them from resorption In inflammatory osteolysis, bone-resorbing osteoclasts erode periarticular bone and cause joint collapse and potential disfigurement. Numerous osteoclasts appear at sites of synovitis, suggesting that products of local inflammation recruit the cells. The cytokine TNF-α, a key player in bone loss associated with inflammation, exerts its effects by stimulating the production of the osteoclastogenic cytokine RANKL from stromal cells. Despite the apparent therapeutic potential of this pathway, blocking TNF-α in patients causes problems such as infection. Combination therapy targeting multiple molecules is expected to be more useful. Now, Kitaura et al. expose 2 new therapeutic targets for inflammatory skeletal diseases (pages 3418–3427). Both osteoclast precursor cells and bone marrow stromal cells are TNF-α targets, so the authors examined mice in which these cell types are chimeric for the presence of TNF receptors in order to determine their relative contributions to inflammatory osteoclastogenesis. They find that both cell types mediate osteoclastogenesis, but stromal cells make the greater contribution. TNF-α stimulates expression of the stromal cell product M-CSF — a cytokine responsible for maintaining the survival of osteoclast precursors. Treatment of mice with inflammatory arthritis with an antibody against M-CSF receptor eliminated the severe osteoclastogenesis and bone resorption typically seen. M-CSF and its receptor are prospective therapeutic targets for […]

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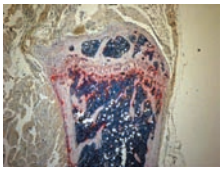

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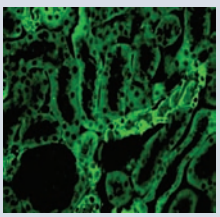
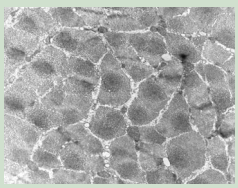
Kicking up kidney failure treatment

Ischemia/reperfusion injury is the most common cause of acute renal failure. Despite advances in supportive treatments such as dialysis, severe acute renal failure remains a major cause of death and has no specific therapies. In this issue of the *JCI*, Thakar et al. define the early pathways activated by ischemic injury (pages 3451–3459). The authors find that a protein called thrombospondin 1 (TSP-1) can cause severe kidney failure when normal blood flow is disrupted. TSP-1, known for its ability to prevent angiogenesis and promote apoptosis in cancerous cells, is also the molecule with the highest induction level at 3 hours of reperfusion injury in rodent kidneys subjected to ischemia/reperfusion. The predominant sites of expression of TSP-1 are the injured proximal tubules, where TSP-1 colocalizes with activated caspase-3. Cultured kidney cells exposed to TSP-1 also demonstrated signs of apoptotic damage. Additionally, mice lacking TSP-1 were protected against ischemic injury–induced renal failure and tubular damage. Thus, TSP-1 is a novel mediator of ischemic damage in the kidney and may be a target for drugs that will reduce the risk of kidney failure in humans.



Why children of parents with type 2 diabetes are at risk themselves

Young, lean, insulin-resistant offspring of parents with type 2 diabetes have reduced mitochondrial function. But the precise role of this decreased function in relation to the pathogenesis of insulin resistance and type 2 diabetes had not been clear. As reported in this issue, Morino et al. took muscle biopsies from these offspring and show that they have reduced mitochondrial content as assessed by electron microscopy (pages 3587–3593). The subjects also have lower insulin-stimulated muscle glucose uptake and increased lipid content in muscle cells. However, in contrast to 2 recent studies, the authors did not find any alterations in PGC-1α or PGC-1β or other downstream regulators of mitochondrial gene expression. These results provide new insights into the earliest defects that may be responsible for the pathogenesis of type 2 diabetes. Moreover, reduced mitochondrial content could result in decreased mitochondrial function; this predisposes the offspring of type 2 diabetic parents to muscle cell lipid accumulation, which then leads to defective insulin signaling and action.



Whooping whooping cough with pertussis toxin

Although the use of vaccines has decreased the incidence of childhood whooping cough, the causative agent, *Bordetella pertussis,* somehow remains endemic in vaccinated populations, in which the bacteria causes a coughing illness of variable severity. This poses a threat to children who are too young to be vaccinated and who often get whooping cough from adult, nonsymptomatic or mildly symptomatic carriers. Now, Kirimanjeswara et al. use mouse models to examine sterilizing immunity to *B. pertussis* (pages 3594–3601). The authors propose that pertussis toxin (PTx), which is expressed by *B. pertussis* and inhibits specific G protein pathways, delays antibody-mediated clearance of *B. pertussis* by inhibiting recruitment of neutrophils to the site of infection. This allows the bacteria to survive and to remain a health risk, even in immunized populations. The authors show that *B. pertussis* blocked both neutrophil migration and recruitment to the lungs during the first week of infection by a PTx-dependent mechanism. But a PTx mutant of *B. pertussis* induced neutrophil recruitment and was quickly cleared from the lungs by adoptively transferred antibodies. These results indicate that expression of PTx may be an adaptation strategy used by *B. pertussis* to permit the bacteria to delay antibody-mediated clearance, allowing repeated infection of immune hosts. These findings may explain the ability of *B. pertussis* to persist in immune human populations and suggest that effective vaccination strategies against the bacteria will require an antibody response to PTx.