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In This Issue

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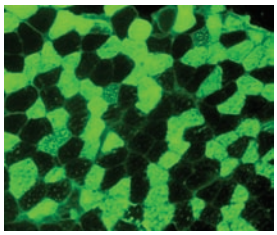
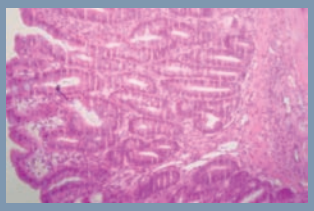


Atrophy impaired

Extended bed rest, limb immobilization, and sedentary lifestyles all lead to muscle atrophy. However, the underlying molecular processes remain largely unknown. Recent evidence has implicated NF-κB, p50, and B cell lymphoma 3 (Bcl-3) proteins in the induction of atrophy in disused muscles. Susan Kandarian and R. Bridge Hunter extend these findings using mice deficient in *p105/p50* (*Nfkb1*) and in *Bcl3* (pages 1504–1511). They found that, unlike wild-type mice, *Nfkb1*-deficient mice subject to 10 days of hindlimb unloading do not show a decreased area in soleus fiber cross-section, and this observation was accompanied by loss of luciferase expression from an NF-κB reporter in the soleus. Experiments on the *Bcl3*-knockout mice yielded similar results. Fast fibers atrophied to a greater degree than slow fibers in wild-type mice, while fast fibers were primarily atrophy resistant in the *Bcl3*- and *Nfkb1*-deficient mice. In both the $Bcl3^{-/-}$ and $Nfkb1^{-/-}$ mice, the slow-to-fast shift in myosin isoform expression was eliminated. The results indicate that *Bcl3* and *Nfkb1* are required for atrophy to occur in disused muscles and for the transition of the associated phenotype.

Having the stomach for PAR_1 activity

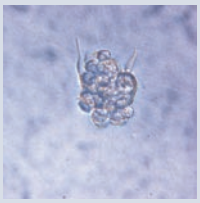


Inflammatory bowel disease (IBD) is thought to result from a variety of genetic and environmental factors; however, a great deal more work is required to obtain a complete picture of the pathogenesis of IBD. Protein-activated receptor–1 (PAR_1) is highly expressed in several types of gastrointestinal cells and is activated through cleavage by thrombin, an activity that is increased in the colon of patients with IBD. Nathalie Vergnolle and colleagues examined the impact of PAR_1 activity in IBD (pages 1444–1456). They found that PAR_1 is overexpressed in the colons of patients with IBD. In intracolonic tests in mice, PAR_1 agonists caused an inflammatory response that included edema and infiltration by granulocytes. In SCID mice, PAR_1-induced inflammation was shown to require T and B cell involvement. In different mouse models of IBD, PAR_1 activation was shown to increase the severity and duration of intestinal inflammation, while PAR_1 antagonism greatly reduced this severity and associated mortality. In both models, colitis was dramatically curtailed by PAR_1 deficiency. This work points to the importance of PAR_1 activity in the pathogenesis of IBD and indicates that inhibition of PAR_1 may be useful in treating IBD and other chronic intestinal inflammatory conditions.

Hobbling free α-hemoglobin

Hemoglobin (Hb) synthesis is carefully coordinated to avoid accumulation of free α- or β-Hb subunits, which can be cytotoxic. In the disease β-thalassemia, mutations that result in the loss of β-Hb leave α-Hb subunits unpaired. Precipitates of unpaired α-Hb produce damaging ROS that reduce the lifespan of circulating erythrocytes. In vitro studies have demonstrated that the α-Hb–stabilizing protein (AHSP) binds α-Hb and prevents its precipitation, indicating that it may function in vivo to limit damage caused by free α-Hb. Mitchell Weiss and colleagues investigated the in vivo importance of AHSP in limiting free α-Hb toxicity by developing an *AHSP*-deficient mouse (pages 1457–1466). These mice had short-lived erythrocytes that also contained Hb precipitates. Examination of hematopoietic tissues revealed higher numbers of erythrocyte precursors but also elevated levels of apoptosis. Biochemical analysis of $AHSP^{-/-}$ erythrocytes revealed evidence of oxidative damage and increased ROS as compared with wild-type erythrocytes. Additionally, purified recombinant AHSP inhibited α-Hb ROS production in vitro. Finally, mice that had β-thalassemia and were $AHSP^{-/-}$ had a more severe phenotype than did β-thalassemia mice. These data together indicate an essential role for AHSP during Hb production and erythropoiesis. This study also has suggests that developing the means to alter human AHSP expression could reduce the severity of β-thalassemia.

Converging on scatter factor



Scatter factor (SF) controls the proliferation, motility, survival, and morphology of a variety of tissues by promotion of a genetically programmed form of invasive growth in both physiological and pathological processes. SF is produced in a precursor form (pro-SF) that must be cleaved to activate its high-affinity receptor, the Met tyrosine kinase. Paolo Michieli and colleagues developed an uncleavable form of SF and used it in a gene-therapy approach to inhibit invasive tumor growth (pages 1418–1432). A single amino acid alteration in the pro-SF cleavage site produced uncleavable SF. When introduced into mice using an improved lentiviral vector system, uncleavable SF, through its ability to bind to both the protease and the receptor, inhibited the cleavage of normal pro-SF and the activation of Met via active SF. Local introduction of uncleavable SF into mice prevented tumorigenesis and metastases and inhibited angiogenesis. Systemic expression of uncleavable SF did not affect normal physiological functions, yet it did block implanted tumor growth and eliminate spontaneous metastases formation. This study demonstrates that pro-SF cleavage is a rate-limiting step in tumor progression, and developing mechanisms that inhibit this cleavage may lead to viable malignant cancer therapies.