which could account for the phenotype in mutant mice.

Although osteopetrosis is an uncommon disorder, it has many potential causes, most of which have been identified in mice. These include deficiencies in differentiation factors (PU.1, c-Fos, M-CSF, RANKL and NF-κB), activation factors (TRAF6, c-Src and Mitf), enzymes (cathepsin-K and carbonic anhydrase) and proton or chloride pump activity[2]. With a few exceptions (cathepsin-K and carbonic anhydrase deficiencies), most causes in humans remain to be identified.

In mice, mutations of the gene encoding microphthalmia-associated transcription factor (Mitf) provide a second example of a gene involved in both osteoclasts and pigmentation. These osteopetrotic, pigment-poor mice have small osteoclasts that do not form ruffled borders. Both the bone and pigment defects appear to be due to single point mutations that prevent MAPK- and ERK-mediated phosphorylation of Mitf and subsequent target gene transcription[7]. Mitf is essential for transcriptional regulation of genes that control pigment synthesis and melanocyte survival[8], and controls genes essential for osteoclast activation.

Many of the recent advances in osteoclast biology have come from studies of knockout mice such as *Src*$^{-/-}$ and *Fos*$^{-/-}$. Osteoclasts in these mice are particularly affected compared with other cell types, indicating that osteoclasts have restricted redundancy for some proteins. Melanocytes appear to be similarly sensitive. Why osteoclasts and melanocytes are especially sensitive to mutations of *gl* and *Mitf* remains to be determined, but the anti-apoptotic gene *Bcl2* has been implicated in both[8]. Further study aimed at understanding the similarities between these two cell types is warranted.

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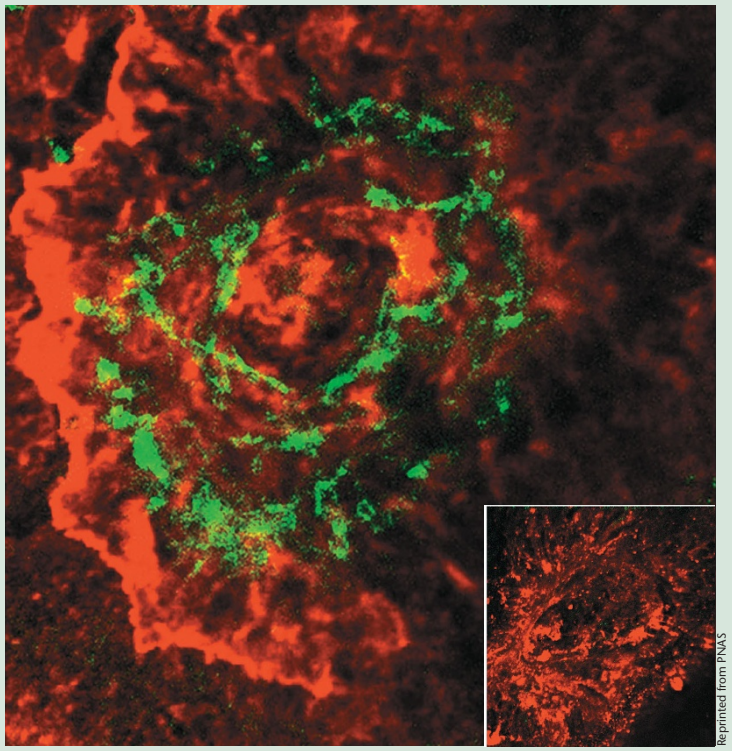
Meddling in macular degeneration



No procedure, transplant or drug can consistently thwart macular degeneration, the leading cause of blindness after age 55 in the industrialized world. A severe form of the disease, exudative or 'wet' macular degeneration, occurs when leaky blood vessels develop in a region beneath the retina and damage it. In the 4 March *Proceedings of the National Academy of Sciences*, Bora *et al.* deal a blow to exudative macular degeneration, demolishing the network of damaging blood vessels in pigs and mice.

The investigators modeled the disease by inducing vessel growth by injuring the retina with a laser. Shown is a confocal image of a whole-mount mouse retina focused on an area of damage; vessels are shown in green and elastin, a component of connective tissue, in red.

The investigators destroyed the new vessels with a molecule called an 'Icon', targeted at tissue factor, a protein expressed on the new vessels. The Icon is composed of the natural ligand for tissue factor conjugated to the Fc domain of an IgG1 molecule. The tissue factor–Icon complex activates a potent immune attack that destroys the blood vessels after they have formed (inset, retina of treated mouse). The investigators examined over 60 damaged retinal areas and found that the incidence of new blood vessel formation decreased from 97% to 5% after injection with a vector encoding the Icon. Results were similar when the Icon was injected intravenously or directly into the eye.

Tissue factor is not expressed on normal vasculature, and the animals seemed to suffer no side effects. The method, which has shown success in cancer treatments, has the potential to outshine another experimental approach aimed at preventing vessel growth with anti-angiogenic steroids and other treatments. That's because the Icon acts on vessels that have already formed, which is when most cases of exudative macular degeneration are diagnosed.

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