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In This Issue

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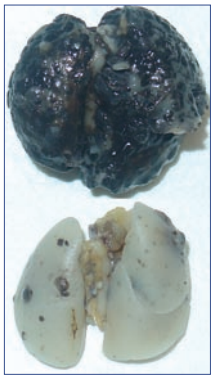
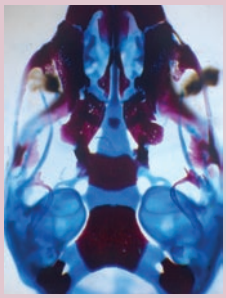


Macrophages containing large amounts of lipoprotein-derived lipids, in particular cholesterol, have a role in the formation of atherosclerotic plaques. Determining how cholesterol homeostasis is regulated in macrophages is therefore of importance for understanding the pathogenesis of atherosclerosis. In this issue (pages 2281–2290), Zhang and colleagues have characterized the protein Niemann-Pick C1 (NPC1) as a factor that protects mice from atherosclerosis through its function as a regulator of macrophage cholesterol trafficking. Mice lacking LDLR develop atherosclerosis when fed a high-fat diet, but when the authors manipulated these mice such that their macrophages lacked both LDLR and NPC1, they developed atherosclerosis more rapidly. The accelerated atherosclerosis in the absence of NPC1 was associated with increased levels of cholesterol oxidation products in macrophages as a result of impaired cholesterol efflux and increased cellular oxidative stress. Insight into the mechanisms underlying the decreased cholesterol efflux was provided by the observation that NPC1 was required for the generation of the liver X receptor (LXR) ligand 27-hydroxycholesterol and for LXR-dependent upregulation of proteins involved in cholesterol efflux. These data suggest that variation in *NPC1* expression might affect how susceptible an individual is to developing atherosclerosis.

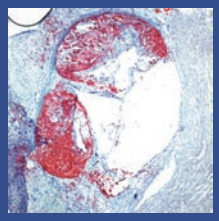
Turn off transcriptional regulators to tune in to differentiation

The cell fate determination and cellular differentiation events that occur during embryogenesis are regulated by transcription factors whose expression is tightly regulated. Indeed, once the developmental step that a transcription factor controls has been completed, it is usually silenced or inactivated. To investigate whether inactivation of transcription factors that regulate key developmental steps is important during development, Wu and colleagues engineered mice to express paired box 3 (Pax3), the transcription factor that regulates neural crest cell differentiation along several lineages, beyond the time it is normally shut off (pages 2076–2087). Defects in neural crest–derived craniofacial bone structures were observed in mice persistently expressing Pax3 in neural crest cells, and they died within two days of birth due to cleft or shortened palates. Detailed analysis revealed that Pax3 prevented neural crest cells from responding to the osteogenic factor bone morphogenetic protein 2 (BMP-2) because it directly upregulated transcription of the gene encoding sclerostin domain–containing 1 (Sostdc1), a soluble inhibitor of BMP signaling. The authors therefore conclude that one function of Pax3 is to maintain neural crest cells in an undifferentiated state by preventing them from responding to factors that induce osteogenic differentiation, and they suggest that inactivation of transcription factors is important for normal development.



A new DC target for tumor immunotherapy?

Mouse DCs expressing CD8α are efficient at capturing material from their microenvironment and presenting it on MHC class I molecules to CTLs, a process known as *cross-presentation*. Many researchers are therefore interested in developing approaches to induce antitumor CTL responses by targeting tumor proteins to CD8α$^+$ DCs. A new way to do this has been uncovered by Sancho and colleagues, who have identified a C-type lectin whose expression was found to be restricted to CD8α$^+$ DCs and plasmacytoid DCs in mice (pages 2098–2110). Functional studies indicated that the C-type lectin, which was named dendritic cell NK lectin group receptor-1 (DNGR-1), is an endocytic receptor and that if a DNGR-1–specific antibody was conjugated to a peptide, it delivered the peptide specifically to CD8α$^+$ DCs for cross-presentation. Peptide-specific CTL responses were induced in mice vaccinated with the peptide-linked DNGR-1–specific antibody and an adjuvant. Directing these CTL responses toward melanoma cells by conjugating the DNGR-1–specific antibody to known MHC class I–binding peptides from proteins overexpressed by a melanoma cell line eradicated melanoma in a therapeutic mouse model. As expression of DNGR-1 in humans was found to be restricted to a subset of DCs with characteristics similar to mouse CD8α$^+$ DCs, the authors suggest that targeting DCs via DNGR-1 might provide a new approach to tumor immunotherapy.



New gene linked to sudden irregular heartbeats

Individuals with Brugada syndrome and/or cardiac conduction disease are at increased risk of sudden death due to cardiac arrhythmias (irregular heartbeats). Although mutations in the *SCN5A* gene (which encodes $Na_V1.5$, the α subunit of the main sodium channel in the heart) can cause these syndromes, they are not detected in all patients. In this issue (pages 2260–2268), Watanabe and colleagues have identified three mutations in the *SCN1B* gene in individuals with Brugada syndrome and/or cardiac conduction disease who lacked *SCN5A* mutations. Alternative *SCN1B* splicing gives rise to two sodium channel β subunits known as β1 and β1B. The transcripts encoding these proteins were shown to be highly expressed in normal human heart tissue, in particular in the Purkinje fibers that conduct the electrical impulses that coordinate the beating of the heart. This was consistent with the hypothesis that mutant forms of these proteins might cause cardiac arrhythmias and/or defective conduction of the electrical impulses that regulate the heartbeat. Functional evidence to support this hypothesis was provided by the observation that the mutant forms of β1 and β1B reduced $Na_V1.5$ sodium currents in transfected cell lines.