

In This Issue

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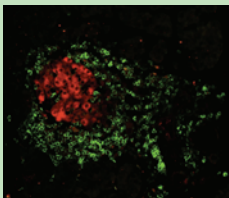




3BP2 performs a balancing act in bone

Cherubism is a genetic disorder characterized by craniofacial abnormalities that result from excessive bone resorption by activated osteoclasts. It is caused by mutations in the SH3-domain-binding protein 2 (*SH3BP2*) gene that result in gain-of-function effects on the protein encoded by the gene, the adaptor protein 3BP2. To date, little is known about the normal function of wild-type 3BP2 in regulating bone homeostasis. To investigate this, Levaot and colleagues analyzed mice lacking 3BP2 (3244–3257). They found that these mice developed osteoporosis and that this was not due to increased bone resorption by osteoclasts but rather a result of reduced bone formation by osteoblasts. Further analysis revealed cell-intrinsic defects in both osteoblasts and osteoclasts in vivo and in vitro and determined that these defects were a result of 3BP2 being a pivotal adaptor protein required for Abl activation in osteoblasts and Src activation in osteoclasts. These data indicate that 3BP2 has a key role in regulating bone homeostasis because it is essential for the normal function of both osteoblasts and osteoclasts.

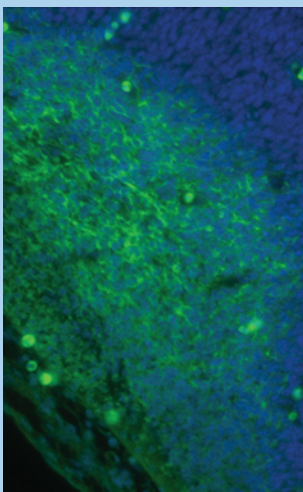
New recruits slow type 1 diabetes



Type 1 diabetes is caused by effector T cell-mediated destruction of insulin-producing β cells in the pancreatic islets of Langerhans. Some researchers are seeking to develop ways to harness the immunosuppressive potential of the patient's own immune system to treat the condition. In this context, Tregs are of particular interest given their pivotal role in suppressing effector T cell proliferation and function. Hence, Montane, Bischoff, and colleagues set out to test the hypothesis that overexpression of

a known Treg chemoattractant, CCL22, in β cells in mice could limit their autoimmune destruction (3024–3028). Consistent with this hypothesis, adeno-associated virus-mediated expression of CCL22 in the pancreatic islets of NOD mice led to the recruitment of endogenous Tregs to the islets and long-term protection from autoimmune diabetes. Further, adenoviral-mediated expression of CCL22 in syngeneic islets transplanted into diabetic NOD mice led to endogenous Treg recruitment to the islet grafts, prevention of β cell destruction by autoreactive T cells, and thereby delayed diabetes recurrence. The authors therefore suggest that manipulation of endogenous Treg migration, by delivering Treg chemoattractants using gene or peptide delivery approaches, may provide a new way to treat type 1 diabetes.

A VIP for normal cortical development



Individuals with autosomal recessive primary microcephaly (MCPH) are born with a very small head and a small brain and suffer mild developmental delay, hyperkinesia, and mild to severe cognitive impairment. Although mutations in any one of seven genes cause MCPH, a lack of good animal models has made it hard to understand the underlying mechanisms. New insight has now been provided by the work of Passemard and colleagues using a mouse model in which microcephaly is induced by blocking vasoactive intestinal peptide (VIP) during gestation using a VIP antagonist (VA) (3072–3087). Initial analysis indicated that prenatal administration of VA gives rise to cortical abnormalities that mimic those observed in patients with MCPH. At the cellular level, prenatal administration of VA reduced neuroepithelial progenitor proliferation. At the molecular level, it mediated these effects by inhibiting expression of the MCPH-associated gene *McpH1*, which in turn

led to decreased expression and activity of Chk1, a known controller of cell cycle progression. The authors therefore suggest that the VIP/*McpH1*/Chk1 pathway is key for normal cortical development and that environmental factors, including maternal ones, can influence neural progenitor proliferation and thereby the size of the brain.

IDOLizing low cholesterol

Having high levels of low-density lipoprotein cholesterol (LDL-C) is a risk factor for developing atherosclerotic cardiovascular disease (ASCVD). Although the use of statins and adoption of lifestyle changes to reduce LDL-C levels have decreased the incidence of and mortality from ASCVD, many individuals fail to reach target levels of LDL-C. Researchers are therefore seeking new targets for LDL-C-lowering therapeutics. In this context, recent genome-wide association studies in populations of mixed European descent identified noncoding variants in a locus containing the gene encoding the E3 ubiquitin ligase myosin regulatory light chain-interacting protein (MYLIP; also known as IDOL) as being associated with LDL-C levels. By studying a population demographically distinct from the discovery population, to ensure a different pattern of linkage disequilibrium, Weisglass-Volkov and colleagues have now fine-mapped an actual *MYLIP* susceptibility variant (3062–3071). Specifically, they found that the nonsynonymous SNP rs9370867, which encodes an N342S amino acid substitution, is associated with high total cholesterol in a Mexican population. Mechanistically, this was because the asparagine-containing MYLIP protein was associated with more potent LDLR degradation and decreased LDL uptake. The authors therefore suggest that MYLIP might provide a new target for therapeutics to treat dyslipidemia and ASCVD.