NFATc1 self-promotes to build bone

Self-promotion is the way to get ahead during bone development, according to Asagiri and colleagues. They show on page 1261 that the inducible transcription factor NFATc1 must turn on its own expression for bone-resorbing osteoclasts to form. NFATc1 drives osteoclast-specific gene expression and is essential for the development of these cells in vitro. But whether NFATc1 is required in vivo was unknown, as deletion of the NFATc1 gene is lethal in mice. Another open question was whether NFATc2—NFATc1’s closest relative—can drive osteoclast formation in the absence of NFATc1.

Asagiri and colleagues now show that NFATc1 is indeed essential for osteoclast formation in vivo, as only NFATc1-expressing stem cells rescued osteoclast development when transferred into osteoclast-deficient mice. NFATc1-deficient stem cells failed at this task, despite having normal expression of NFATc2.

Transcriptional regulation explained why only NFATc1 could do the job. Stimulation of bone marrow cells with the osteoclast growth factor RANKL (receptor activator of NF-κB ligand) caused the NFATc2 protein in the cell—along with RANKL-induced NF-κB proteins—to pile onto the NFATc1 promoter at the expense of the NFATc2 promoter. This binding induced the expression of NFATc1, which then bound back to its own promoter, thus amplifying NFATc1 production. The NFATc1 promoter also hoarded histone acetylases, whose DNA modifications facilitate transcription. The authors are now analyzing the chromatin structure of the two promoters, which might help explain why these proteins avoid the NFATc2 promoter. JEM

Worming away from allergies

Worms in the gut keep allergies at bay, say Wilson and colleagues on page 1199. Parasitic helminth infections, they show, activate regulatory T (T reg) cells in the gut. These T reg cells are then dispatched to the lungs, where they dampen the immune response to inhaled allergens. Parasitic worm infections, common among children in tropical and subtropical regions, are associated with decreased responsiveness to allergens. The hygiene hypothesis, which posits that decreased childhood exposure to T helper (Th) 1 and Th2 cytokines upon stimulation, NKT cells can either promote or suppress immune responses, likely depending upon which cytokines the cells predominantly produce. Subsets of NKT cells have been identified (based on the expression of CD4) that have distinct cytokine production profiles in vitro. But whether these subsets are functionally distinct in vivo had not been tested.

In their previous work, this group had shown that NKT cells from the liver were able to combat tumors in mice. They now show that it is only CD4+NKT cells from the liver than can promote tumor rejection. CD4+NKT cells from the liver and both CD4+ and CD4−NKT cells derived from the spleen or thymus were ill equipped for the job.

The authors are now trying to determine what sets the CD4+NKT cells apart from the rest, as cytokine production among the NKT cell subsets was comparable. In the meantime, the identification of a specialized anti-tumor subset of NKT cells may provide a way to improve upon current NKT cell–based tumor therapies. JEM

NKT cells get specialized

A report on page 1279 suggests that, for anti-tumor immunity, all natural killer T (NKT) cells are not created equal. Crowe and colleagues show that a subset of liver-derived NKT cells is uniquely equipped to fight off tumors.

NKT cells are innate immune cells known for their rapid production of both T helper (Th) 1 and Th2 cytokines upon stimulation. NKT cells can either promote or suppress immune responses, likely depending upon which cytokines the cells predominantly produce. Subsets of NKT cells have been identified (based on the expression of CD4) that have distinct cytokine production profiles in vitro. But whether these subsets are functionally distinct in vivo had not been tested.

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Gassy degeneration

Nitric oxide (NO) gas spurs on brain degeneration, according to a study on page 1163. Nathan and colleagues show that the NO-producing enzyme iNOS accelerates brain destruction and death in a mouse model of Alzheimer’s disease.

Alzheimer’s disease is a lethal neurodegenerative disease that causes progressive memory loss and dementia. The disease is associated with a build-up in the brain of peptide fragments derived from a protein called β-amyloid precursor protein (APP). APP is a protein that normally gets cleaved in the brain, although the functions of APP and of its primary cleavage products are poorly understood.

Mutations in APP, or in the enzymes that chop it up, result in the overproduction of the disease-causing peptide (known as Aβ). Although it is not completely clear how Aβ contributes to disease, it has been shown to trigger iNOS expression in brain cells. This NO-producing enzyme is normally triggered by immune responses and inflammation and is needed to fight off certain infections. But in the brain, iNOS may contribute to mitochondrial and protein damage that destroys neurons.

This group and others found iNOS in brain lesions of patients with Alzheimer’s disease, but no studies had investigated whether iNOS contributed to disease progression. Nathan and colleagues now show that Alzheimer’s-prone mice that lack iNOS live twice as long and develop fewer amyloid plaques than iNOS-expressing mice. Both groups of mice developed some plaques initially, but the iNOS-deficient mice were spared the rapid accumulation of plaques later in life.

The delayed effect of the iNOS deficiency was likely due to a positive feedback loop between the enzyme and the Aβ peptide, suggests Nathan. Aβ might have to accumulate before it triggers the production of iNOS. iNOS then exacerbates Aβ accumulation, perhaps in part by blocking proteasomal degradation, a pathway the cell uses to dispose of Aβ. When this loop is interrupted, disease progression is slowed. The group now plans to test iNOS inhibitors in Alzheimer’s-prone mice to see if a pharmacological approach recapitulates the genetic approach.

Based on these results, Nathan suggests that iNOS inhibitors—which have already been produced and tested in humans—might be a promising and thus far overlooked therapy for the treatment of this devastating disease.

Crk gets hijacked

The ulcer-inducing bacterium Helicobacter pylori busts through the cells that line the stomach by hijacking a host protein, suggest Suzuki and colleagues on page 1235. The co-opted protein turns on multiple signaling pathways in gastric cells that cause the normally adhesive cells to pull apart from their neighbors.

Roughly half of all people worldwide have H. pylori living in their stomachs. Most people host the infection without consequence but, in some, H. pylori infection triggers peptic ulcers and gastric cancer. H. pylori encodes a set of proteins that allows it to adhere to and thrive in the stomach and to avoid immune attack. One of these proteins—CagA (cytotoxin-associated antigen–A)—helps ward off immune cells but also disrupts the epithelial cells that line the stomach.

Many studies have investigated how CagA, which is injected into gastric epithelial cells through a specialized bacterial secretion system, helps breach the epithelial lining of the stomach. Once inside the cells, CagA binds to a variety of intracellular signaling proteins. But it was not clear which of these proteins is required for CagA-induced cell scattering.

Suzuki and colleagues now identify a new target of CagA: the Crk family of adaptor proteins. CagA–Crk binding in infected epithelial cells triggered the activation of downstream signaling pathways, including the Ras–Raf and Rac1–WAVE pathways, which are normally induced during routine cell turnover. These signals prompted the expulsion of adhesive proteins β-catenin and E-cadherin from the adherens junctions that hold the cells together.

The liberation of β-catenin from adherens junctions not only compromises cell contacts, but likely also induces aberrant proliferation of the cells, as nuclear β-catenin drives the expression of cell cycle–promoting genes such as cyclin D1. Both cell scattering and proliferation compromise the integrity of the stomach lining, thus contributing to the development of H. pylori–induced gastric disease.