Myeloproliferate no more

Four studies in April uncover a mutation that underlies myeloproliferative disorders. The mutation seems to create an activated form of the JAK2 kinase, a finding that opens the door to developing targeted treatment (*Lancet* **365**, 1054–1061; *Nature* **434**, 1144–1148; *N. Engl. J. Med.* **352**, 1985–1991; *Cancer Cell* **4**, 387–397).

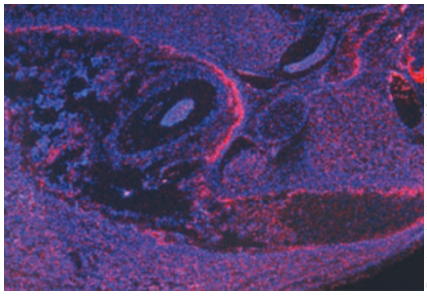
Individuals with myeloproliferative disorders—in which blood-cell development is dysregulated—suffer for years from fatigue, pain and the risk of thrombosis and bleeding.

The studies examine individuals with three myeloproliferative disorders. All researchers found the same point mutation in the gene for JAK2 in 65–97 percent of cases of polycythemia vera. The mutation was also present in individuals with the two other myeloproliferative disorders, although at a lower frequency.

Cell-based experiments suggested that the mutations resulted in a constitutively active JAK2 kinase. What's more, application of a JAK2 inhibitor could dampen this activity. This particular inhibitor is not suitable for human trials because of toxicity. But the new data should ignite efforts to develop specific, safe drugs targeting JAK2.—*CS*

Bad for the bone

Companies interested in developing drugs for bone diseases have avidly pursued activators of Wnt signaling in recent years.



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Tcf1 (red), a mediator of Wnt signaling, is expressed in regions in the mouse embryo containing differentiating osteoblasts.

Recent findings could put a damper on such efforts. The excitement about Wnt activators emerged several years ago with experiments suggesting that Wnt prompted the formation of bone. In cell culture, for instance, upregulating a putative coreceptor for Wnt nudged mesenchymal stem cells to change into osteoblasts, bone-forming cells.

New work by several groups examines mice that conditionally express β-catenin, which is downstream of many Wnt-mediated events. The results from these and other experiments clinch the notion that Wnt positively regulates the formation of osteoblasts (*Developmental Cell* 8, 727–738, 739–750, 751–764; *Development* 132, 49–60).

But the data also suggest that Wnt is active after osteoblasts are formed. Osteoblasts not only help to lay down bone—they also are known to regulate the differentiation of osteoclasts, bone-resorbing cells. One study showed how Wnt signaling in osteoblasts prompts the formation of osteoclasts. Overexpressing β-catenin in osteoblasts prompted the formation of osteoclasts in whole animals, and resulted in high bone mass—potentially dangerous from a drug-development perspective, especially considering that specific and less aggressive agents that inhibit bone resorption are already available. —*CS*

Written by Jasmine Bhatia, Juan Carlos López and Charlotte Schubert

Burrowing into bone

Like many cancers, prostate cancer metastasizes to bone, where painful lesions can develop. In the May issue of *Cancer Cell*, Conor Lynch *et al.* (7, 485–496) get a close look at cancer-induced bone degradation, proposing a role for the cysteine proteinase MMP-7.

For their experiments, the investigators transplanted prostate cancer tissue into the cranial region of rats. They found that the extent of bone destruction correlated with the upregulation of MMP-7 and RANKL, a protein that mediates the activation of osteoclasts, bone-degrading cells. What's more, MMP-7–deficient mice were much less susceptible to tumor-induced bone destruction than wild-type mice.

Researchers had long thought that MMP-7 was not expressed by osteoclasts and did not participate in bone degradation. Lynch *et al.* showed otherwise, finding that MMP-7 from osteoclasts cleaves RANKL, enabling RANKL release from tumor cells. This mechanism allows prostate cancer cells to destroy bone from a distance, which opposes the idea that prostate cancer cells and osteoclasts must be in direct contact for bone degradation to occur. —*JB*

Degrading amyloid-β

Much drug development effort for Alzheimer disease focuses on trying to eliminate amyloid-β, a protein that clumps up in the brains of individuals with Alzheimer disease. Findings by Raphaëlle Pardossi-Piquard *et al.* on amyloid-β degradation could refine such efforts.

Amyloid-β production requires cleavage from a larger, transmembrane protein, β-amyloid precursor protein (APP), by γ-secretase. Reporting in the 19 May issue of *Neuron* (46, 541–554), the researchers found that γ-secretase not only prompts production of amyloid-β—it seems to also seems to regulate amyloid-β degradation.

The secret of how this happens seems to lie with a small fragment of APP that normally gets translocated to the nucleus. This fragment is also created through cleavage by γ-secretase, but its nuclear function has not been fully described. Cell-based experiments now suggest that this fragment transcriptionally upregulates a protein that degrades amyloid-β, neprilysin. This work begins to reveal how levels of amyloid-β are normally regulated, with production balancing degradation.

Modulating proteins that control amyloid-β degradation, perhaps by targeting the nuclear fragment, offers a fresh approach to developing treatments. Targeting the nuclear fragment could result in fewer side effects than targeting γ-secretase, which also cleaves the developmental regulator Notch. —*CS*

Autoimmune folate deficiency

The molecular underpinnings of a rare and mysterious folate deficiency disorder in infants has come to light, opening the door to badly needed early diagnosis and intervention.

Infantile-onset cerebral folate deficiency is characterized by developmental retardation, motor disturbances and, in late stages, hearing and vision loss. The cerebrospinal fluid (CSF) of children with this condition has low levels of 5-methyltetrahydrofolate, whereas the serum concentration of this folate metabolite is normal.

In the 12 May *New England Journal of Medicine* (**352**, 1985–1991), Vincent Ramaekers *et al.* show that sera from individuals with the disease contains autoantibodies against high-affinity folate receptors present in the choroid plexus—the structure where CSF is formed. These autoantibodies, present in 25 out of 28 patients, blocked the receptor. —*JCL*