in humans), a lectin that binds peptidoglycan and is also found in the intestinal epithelium. Reg3-γ has been proposed to inhibit bacterial translocation across the mucosa, and Gal-4 and Gal-8 may have a similar function.

The results of Stowell et al. point to a new role for Gal-4 and Gal-8, and perhaps other galectins, in innate immunity, posing at the same time new questions for future research. For example, what is the relative importance of the bactericidal action of Gal-4 and Gal-8 in host innate immunity? In their work, the authors tested the specificity of endogenous Gal-4 and Gal-8 activity against B antigen–positive E. coli in vivo by using thiogalactoside, an inhibitor of galectin activity. This saccharide may inhibit not only Gal-4 and Gal-8 but also other lectins, raising the possibility that other molecules contribute to the antibacterial effect that the authors described.

It will therefore be important to investigate the susceptibility of mice deficient in one or both of these galectins toward infection by B antigen–positive E. coli. However, the interpretation of such genetic knockout experiments may not be straightforward, because these lectins might substantially contribute to innate immune defense through mechanisms other than direct killing of E. coli. Perhaps mutations that selectively block bactericidal activity while sparing other galectin functions could be identified and introduced into endogenous galectins to address this question.

It is intriguing that target ligands for Gal-3, Gal-4 and Gal-8 are the human blood group antigens. Stowell et al. suggest that such specificity might complement the adaptive immune responses. Depending on the host blood type, adaptive immune responses to pathogens with A- or B-like antigens are limited, and this slack may be picked up by the galectins. This idea may become experimentally testable as Gal-4 and Gal-8 genetic knockout models emerge. At this point, perhaps the converse question is more tractable—determining how Gal-4 and Gal-8 differentiate self from non-self in terms of target specificity.

Galectins bind other glycans and many cell surface glycoproteins and glycolipids on various cell types. In fact, the most extensively documented function of galectins is their induction of apoptosis. For example, Gal-1, Gal-3 and Gal-9 can induce apoptosis in activated T cells. Moreover, Gal-8 can induce apoptosis in a carcinoma cell line but, in this case, Gal-8 may be inhibiting cells’ adhesion to the extracellular matrix, triggering anoikis. To avoid their action over self antigens, it is possible that Gal-4 and Gal-8 are selectively secreted into the intestinal lumen, where they kill susceptible bacteria and spare normal tissue. If this is the case, elucidating how intestinal cells secrete these galectins will be important for understanding their functions in innate immunity.

Another possibility is that these lectins have higher affinity for microbes or that their disruptive activity over the membrane is much more effective for killing microbes. The experiments by Stowell et al. showing resistance of erythrocytes to membrane disruption by galectins, as mentioned above, are consistent with these possibilities.

Other galectins may also be involved in innate immunity through microbicidal action. In fact, Gal-3 kills Candida albicans through lectin-carbohydrate interactions. It is possible that other galectins, after their interaction with carbohydrate moieties, are also cytotoxic to their target microbes. Such findings may transform the view of galectins to key mediators of host defense.


Rebuilding Humpty Dumpty with a serotonin inhibitor

Ego Seeman

Serotonin produced in the gut reduces the formation of bone. This biology is now harnessed with an orally available inhibitor of gut serotonin synthesis (pages 308–312). The inhibitor promotes bone formation in rodents and points the way to the development of much-needed bone-building drugs.

All structures—roads, bridges and buildings—develop fatigue damage with repetitive use. Only bone has the ability to repair itself. All structures—roads, bridges and buildings—develop fatigue damage with repetitive use. Bone contains galaxies of interconnected osteocytes, stellate cells housed within lacunae, each cell with 50–70 dendritic processes weaving their way within bony-walled interconnected tunnels. These cells and their ‘wiring’ are the surveillance system of bone. This network detects changes in mechanical stress to initiate adaptive modeling (construction)

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and remodeling (reconstruction), which, by depositing and removing bone according to its local loading or unloading circumstances, adapt the structural design of bone so that it is ‘just right’ for the loads it must endure without cracking.

Bone remodeling is essential for bone health and works well during early adulthood. Osteoclasts resorb damaged bone, and osteoblasts replace it with exactly the same volume of new bone in the same location to maintain its pristine structure. As age advances, abnormalities in this cellular machinery appear, with the earliest being a reduction in bone formation. Bone formation on the outer surface of bone slows profoundly. Each time damage is removed, 1–2% less new bone is deposited than was removed by each remodeling unit, resulting in bone loss.

Although this net deficit is small (as 98–99% of bone removed is replaced), the high intensity of remodeling after menopause is sustained during the next 30 to 50 years, so that half of the skeleton is lost, leaving a decayed structure with a thin and porous cortical shell that looks like Swiss cheese. The trabecular latticework of plates that form an open honeycomb–like mesh becomes thinned, perforated and disconnected, increasing the possibility of fracture should a fall occur—40–50% of women and 30% of men sustain a fracture as a consequence of this structural decay.
Antiresorptive therapies, such as the bisphosphonates, effectively reduce the rapidity of this structural decay, but they do not rebuild the skeleton. Although some success has been achieved in developing anabolic treatments, such as intermittently injected parathyroid hormone (PTH 1–34),{6,7} restoration of the structure is far from complete. Compelling evidence is lacking for PTH 1–34 stimulating bone formation on bones’ outer envelope. Nor is there evidence that PTH 1–34 can refill the holes in the cortex or thicken and reconnect trabeculae. Thus, development of an anabolic agent is an urgent unmet need, particularly as an increasing proportion of the population will live into their 80s and 90s.

Karsenty and his colleagues have spent the last several years unraveling the regulatory networks responsible for determining bone modeling and remodeling and its links with intermediary metabolism.{8} Their research pointed to serotonin, derived from the gut, as a key player.{6} In this issue of *Nature Medicine*, Yadav et al. bring their work from the bench closer to the bedside. They synthesized and administered an oral inhibitor of Tph-1 to ovariectomized mice, a model of osteoporosis.{7} Treatment stimulated osteoblast proliferation, bone formation and increased bone volume without stimulating bone resorption, as occurs with PTH 1–34 (ref. 4), and without altering brain serotonin. Treatment at the time of ovariectomy maintained bone mass, whereas delaying treatment until two or six weeks after ovariectomy reversed the structural decay that occurred and increased bone mass above that in nonovariectomized controls. Repeating the experiments in rats with a PTH-treated comparator produced similar results.

As the authors point out, the new findings need to be replicated in mammalian species with bone that models and remodels more closely to that of human beings. Rodents grow throughout their lives and do not remodel their cortical bone. Cortical bone constitutes 80% of the skeleton in humans, and intracortical remodeling producing the porous skeleton accounts for most of the bone lost with aging. Thus, the experiments need to be replicated in species remodeling their cortical bone more like humans, such as nonhuman primates, before experiments move forward to human subjects.

The journey to a potential new class of therapeutics is the fruit of years of innovative research by Karsenty and his colleagues. This work demonstrates that investigation into mammalian biology must now transcend the traditional compartmentalization of the biological sciences. It is no longer possible to study systems such as bone at a molecular or cellular level independent of the context of whole-animal physiology. This new study and related work are rewriting the textbooks of bone and intermediary metabolism.{9,10}

Corrected after print 1 April 2010.

**COMPETING INTERESTS STATEMENT**
The author declares no competing financial interests.


**Ido brings down the pressure in systemic inflammation**

Franz Hofmann

*Systemic inflammation results in a life-threatening drop in blood pressure. Targeting known players of blood pressure regulation has so far failed to improve outcomes for individuals with sepsis. But a study points to a regulatory pathway involving the amino acid metabolite kynurenine that may provide new avenues for therapies (pages 279–285).*

Blood pressure is tightly regulated by various mediators released from nerve endings, endocrine glands and the endothelium. An increase in the production of factors that constrict blood vessels and a decrease in relaxing factors causes blood pressure to rise. The opposite set of conditions causes blood pressure to drop.

Systemic inflammation, as it occurs in sepsis, for example, results in a dramatic drop in blood pressure, or hypotension, often leading to organ dysfunction and death. Inflammatory factors increase the amounts of inducible nitric oxide synthase (NOS2) in the endothelial cells lining blood vessels. This enzyme converts the amino acid arginine to nitric oxide (NO), a vasorelaxing factor, which, in large amounts, can contribute to sepsis-related hypotension.{2} The inhibition of NO synthesis can temporarily improve mean arterial blood pressure in humans but does not improve survival or consistently yield long-term benefits to vascular health. Therapies aimed at other known targets for sepsis-induced hypotension also have failed to improve outcomes for patients.

These results suggest that additional pathways may be involved in the regulation of vascular tone during acute systemic inflammation. In this issue of *Nature Medicine*, Wang et al. describe one such pathway. They demonstrate that systemic inflammation induces the metabolism of the amino acid tryptophan, which results in the production of kynurenine in endothelial cells, resulting in systemic hypotension. Tryptophan metabolism emerges as a potential new target for treating sepsis-induced hypotension.

Tryptophan is an essential amino acid in the human diet. Serum concentrations of 50–100 μM tryptophan are normally maintained by liver metabolism of this amino acid. In liver cells, tryptophan is constitutively oxidized by the enzyme tryptophan-2,3-dioxygenase to N-formyl-kynurenine. N-formyl-kynurenine then decomposes spontaneously to formic acid and kynurenine. (First discovered in dog urine, the name kynurenine comes from the Greek *kýon*, meaning dog, and *ouron*, meaning urine.) Further metabolism of kynurenine yields nicotinamide adenine dinucleotide, alanine and acetyl-CoA.

In other types of cells, tryptophan can be metabolized to N-formyl-kynurenine by an alternative inducible enzyme, indoleamine-2,3-dioxygenase (Ido), that is transcribed under certain pathophysiological conditions. People have two isozymes of Ido, each with a slightly different inhibitory profile.
Corrigendum: Kynurenine is an endothelium-derived relaxing factor produced during inflammation

Yutang Wang, Hanzhong Liu, Gavin McKenzie, Paul K Witting, Johannes-Peter Stasch, Michael Hahn, Dechaboon Chansirivathanathanamrong, Ben J Wu, Helen J Ball, Shane R Thomas, Vimal Kapoor, David S Celermajer, Andrew I Mellor, John F Keaney Jr, Nicholas H Hunt & Roland Stocker

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In the version of this article initially published, the symbol key in Figure 2g,h is incorrect. The correct symbol key is open circles for Ido1−/− and filled circles for WT. The error has been corrected in the HTML and PDF versions of the article.

Corrigendum: Obesity: stressing about unfolded proteins

Ronald C Wek & Tracy G Anthony

Nat. Med. 16, 374–376 (2010); published online 7 April 2010; corrected after print 6 May 2010

In the version of this News and Views initially published, the last name of one of the authors whose work was being discussed, Jonathon N. Winnay, was incorrectly spelled as ‘Winney’. The error has been corrected in the HTML and PDF versions of the article.

Erratum: Rebuilding Humpty Dumpty with a serotonin inhibitor

Ego Seeman

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In the version of this article initially published, several articles were eliminated from the reference list during layout, and several typographical errors were introduced. These errors have been corrected in the HTML and PDF versions of the article.