In this issue

By John Ashkenas, Science Editor

A new role for a versatile cell

(See article on pages 1291–1302.)

Recent work has prompted a dramatic shift in thinking about cell regeneration, as researchers have come to appreciate the ability of adult stem cells to adopt the fates of many cell types, not just those in a particular tissue or a specific developmental lineage. The Verfaillie laboratory has shown that multipotent adult progenitor cells (MAPCs), a marrow-derived stem cell type with an impressive developmental repertoire, can be prepared from humans or rodents and can be used to reconstitute cells of all embryonic lineages when injected into a blastocyst. Technically more demanding — but also more useful if the hope is to develop therapeutic engraftment techniques using autologous cells — is the ability to generate uniform populations of a desired cell type ex vivo. Verfaillie's group has found that a single MAPC can be passaged for many cell divisions in an undifferentiated state or can be induced to differentiate along any of several paths, yielding angioblasts, muscle cells, or neurons, among other cell types. Whether cultured MAPCs can also generate epithelia has been uncertain, but Schwartz et al. now show that, by providing specific soluble factors and a suitable microenvironment, they can drive MAPCs to form hepatocytes. The resulting cells express albumin and other characteristic hepatocyte proteins, and they can store glycogen and adopt a normal, polarized morphology. As Schwartz et al. caution, it remains unclear whether the undisturbed marrow of healthy animals contains any single stem cell type with the developmental plasticity of MAPCs — a caveat that might be applied to much of current stem cell research.

Pattern recognition receptors on mast cells

(See article on pages 1351–1359.)

The Toll-like receptors (TLRs) fit the definition of pattern-recognition molecules, which were originally postulated to allow the innate immune system to detect the "molecular signatures" of various infectious agents. Although the innate immune system has no memory, it shows a degree of specificity, in part because the various TLRs recognize different sets of pathogen-associated molecules. Dermal mast cells are usually associated, not with the innate immune system, but with atopic dermatitis, but Supajatura et al. have found that these cells also express TLRs. They report here that TLR4, which binds the gram-negative product lipopolysaccharide (LPS), and TLR2, which binds peptidoglycan (PGN) from gram-positive organisms like *Staphylococcus aureus*, induce distinct mast cell responses. *Staphylococcus* is known to exacerbate allergic dermatitis, but it has generally been thought to act by inducing antibacterial IgE's, which trigger mast cell degranulation by stimulating the IgE receptor. Interestingly, the authors show that the interaction between PGN and TLR2 can provoke mast cell degranulation directly, sidestepping the need for IgE receptor engagement.

Cellular collaboration to form inflammatory mediators

(See article on pages 1373–1380.)

Metabolites of the fatty acid arachidonic acid (AA), short-lived, bioactive molecules like leukotrienes and prostaglandins, induce the changes in cell migration and vascular permeability that play out as local tissue inflammation. The enzymes that release AA from membrane phospholipids and that carry out the subsequent biochemical transformations to generate these products are expressed in cells of many descriptions. Complicating matters further, as researchers have long suspected, different cells can also collaborate to form these various inflammatory mediators. Here, Fabre et al. provide a rigorous demonstration that such transcellular biosynthesis can contribute to the production of the leukotriene LTB_4. Multiple mouse lines are now available with genetic defects in this biosynthetic pathway. Taking advantage of these tools, Fabre and colleagues generated chimeric mice in which host cells lack one, early-acting, biosynthetic enzyme, whereas donor leukocytes are defective in a different, later-acting, enzyme. As a result, LTB_4 can be formed in these animals only if metabolic intermediates formed by cells of one mutant genotype can be passed to cells of the other genotype. Indeed, the authors find that topically applied AA is converted to LTB_4 in chimeric mice, which respond with a vigorous local inflammation. This idea of transcellular synthesis may be important not just in prostanoid production: In his commentary on another paper in this issue (Gaut et al., page 1311), Hurst (page 1287) discusses evidence that individual macrophages cannot simultaneously generate the two free radicals needed to form peroxynitrite ($ONOO^-$). Since cultured macrophages nevertheless produce this reactive species in abundance, it may be that cells at different stages of activation, each producing different free radical reactants, collaborate to generate $ONOO^-$ in vivo.