How to renew a stem cell

The unique cell cycle characteristics of stem cells are defined, at least in part, by a polycomb transcription factor called Bmi-1, according to Anna Molofsky, Ricardo Pardal, Sean Morrison, and colleagues (University of Michigan, Ann Arbor, MI). Bmi-1 is unique because, unlike other important cell cycle proteins such as Myc, it is needed in stem cells but not in their offspring. Thus, it is important for what it is not as for what it is.

The loss of Bmi-1, the researchers find, leaves mice deficient in stem cell capacity. The mice survive only restricted progenitor cells that are limited in both the types of cells that they can generate and the numbers of divisions in which they can do so. The resulting depletion in cells leads to growth and neurological defects, and early death.

Earlier work had established that Bmi-1, via its repression of the cell cycle inhibitor p16, is required for the proliferation of hematopoietic stem cells (HSCs). The Michigan group found a similar phenomenon with stem cells in the central nervous system, at least after birth, and found that the cause was reduced proliferation rather than increased cell death. But after differentiation factors were added, the difference disappeared. Now, both cells with and without Bmi-1 continued to proliferate.

There are two situations in which an explanation requires more than just Bmi-1 and p16. Prenatally, something other than Bmi-1 must be capable of repressing p16 expression. In the restricted progenitors, meanwhile, Bmi-1 is no longer needed because the cell cycle is now insensitive to elevated levels of p16. Future studies will be focused on understanding this difference in sensitivity, and testing downstream of Bmi-1 for pathways unrelated to p16.

Reference: Molofsky, A.V., et al. 2003. Nature. 10.1038/nature02060.

Latching onto fibrinogen

A bacterial adhesin grabs hold of its extracellular matrix target, then covers it and latches the compartment shut, according to two structures determined by Karthe Ponnuraj, Shihanam Narayan (University of Alabama, Birmingham, AL), Magnus Hook (Texas A&M, Houston, TX), and colleagues.

The first structure, of the unbound SdrG protein from Staphylococcus epidermis, shows a wide cleft between two immunoglobulin-like domains. This cleft is the binding site for a peptide from the extracellular matrix protein fibrinogen.

But this is no simple binding event. The presence of the peptide, found the researchers, induces conformational changes in a COOH-terminal region of SdrG that previously extended out from the protein’s N3 domain to wave in the wind. After peptide binding, the region now extends over the peptide, thus forming a hydrogen-bonded roof, and then inserts into a β-sheet in the adjacent N2 domain.

The latch may be far from unique. The region in N2 that receives the latching β strand makes up a motif that is present in many other gram-positive bacterial adhesins. These proteins, which are used by bacteria that replicate extracellularly, “are all like extending velcro,” says Narayan, “but there is specificity.” For SdrG, the binding also covers the thrombin-cleavage site in fibrinogen. This prevents the formation of fibrinopeptides that can act as chemoattractants for leukocytes and fibroblasts.

Reference: Ponnuraj, K., et al. 2003. Cell. 115:217–228.

Damage first; infect later

Like a picky tourist looking for a hotel room, the malaria-causing protozoan Plasmodium passes through several cells before settling on one to infect. Margarida Carrolo, Maria Mota (Instituto Gulbenkian de Ciência, Oeiras, Portugal), and colleagues now report that the initial invasions cause the damaged cells to make a factor that primes other cells for infection.

The factor turned up in culture medium from infected or wounded cells. When added to uninfected cells, this conditioned medium doubled the level of infection. The factor was identified as hepatocyte growth factor (HGF), which is made by hepatocytes in response to wounding. Those cells that were permeable to dextran (because of Plasmodium-induced wounding) were the same ones that made HGF.

Mota earlier showed that the passage through cells primes Plasmodium for infection. Once it is primed, Plasmodium induces a folding of the plasma membrane that becomes a parasitophorous vacuole. The Portuguese group noted HGF-induced changes in the actin cytoskeleton in hepatocytes, and they speculate that these changes may be necessary for early parasite development.

The HGF receptor Met is not a receptor for Plasmodium, but when the group inhibited Met’s kinase activity this did prevent Plasmodium infection, even when the inhibition occurred after invasion. Any such treatment “needs to be prophylactic, because people don’t know they are infected at this stage,” says Mota. She is contacting companies that are developing anti-cancer drugs targeting Met, and also hopes to find other targets downstream of Met activation.

Reference: Carrolo, M., et al. 2003. Nat. Med. 10.1038/nmm947.