**Research Roundup**

**Is Botryllus a natural killer?**

Natural killer (NK) cells in mammals attack virus-infected and tumor cells that stop making major histocompatibility complex (MHC) proteins. But the discovery by Konstantin Khalturin, Thomas Bosch (University Kiel, Kiel, Germany), and colleagues of a protein in 1050 squirts related to a key NK cell receptor suggests that the evolutionary predecessors of NK cells may have targeted genetic interlopers of their own species.

The sea squirt in question, Botryllus schlosseri, exists as a flower-shaped accumulation of petals, or zooids. When two clusters of zooids meet one another they either fuse or reject one another. For fusion to occur, the two must share at least one allele of the Fu/HC locus.

The molecular identity of Fu/HC remains unknown, and the search for direct relatives of MHC proteins, which determine transplant rejection in humans, has not produced any candidates. The recent genome sequencing of the sea squirt Ciona intestinalis also failed to turn up any MHC proteins, although Ciona is solitary and thus lacks the rejection reaction of Botryllus.

Khalturin and Bosch searched for genes whose expression changed during the rejection process. One of the down-regulated genes encodes BsCD94–1, a protein on the surface of Botryllus blood cells that is very similar to the vertebrate NK cell receptor CD94. The group does not yet have functional evidence tying the protein to rejection, but Bosch says “the structural similarity is absolutely convincing.”

The pattern of recognition in the two systems is also a match. In Botryllus, an A/B genotype rejects C/D but fuses with B/C. Likewise, NK cells kill only if CD94 fails to recognize self (in the form of class I MHC), whereas the B and T cells of the vertebrate adaptive immune system attack as long as they see any trace of nonself.

Adaptive immunity has been traced back only as far as jawed vertebrates. The new work suggests that a type of NK cell existed much earlier, but it may have been specialized not for immunity but for adjudicating land grabs.

And even those land grabs have a twist. Others have found that, although one of the colonies often dies off after fusion, its germ cells can parasitize the survivor. Hence, the sea squirt chooses to fuse only with genetic relatives, so that after fusion its energy is devoted to propagating infiltrating germ cells that are at least related. Natural killing, it seems, began with family loyalty.

Reference: Khalturin, K., et al. 2003. Proc. Natl. Acad. Sci. USA. 10.1073/pnas.0234104100.

**Bacterial aging**

The discovery of a novel substrate for CobB, a bacterial Sir2 protein, has provided a link between a cell’s energy status and carbon usage. The finding, described by Vincent Starai, Jorge Escalante-Semerena (University of Wisconsin, Madison, WI), and colleagues, may also help explain how Sir2 slows aging in yeast, worms, and, perhaps, mammals.

The team started out with a mutant, cobB-, that could not grow on low levels of acetate. They found that the acetyl coenzyme A (CoA) synthetase (Acs) that initially derivatizes acetate to form acetyl CoA was inactive because of acetylation of a specific lysine residue of Acs. CobB, the bacterial Sir2, removed this acetylation and thus activated Acs.

The link to energy status and redox comes about through NAD+. A bacterial cell that is low in energy will use up most of its NADH to generate ATP. The resulting high levels of NAD+ provide the necessary cosubstrate for Sir2 proteins like CobB. Active CobB activates Acs, which generates more acetyl CoA, thus shunting more carbon into the energy- and NADH-generating TCA cycle.

Active Sir2 is now known both to generate more acetyl CoA and to extend lifespan. How are these two phenomena linked? More acetyl CoA for the TCA cycle means more respiration, which has been associated with yeast lifespan extension when caloric intake is restricted. And perhaps Sir2 activation allows for better scavenging of acetate—a molecule that is generated by lipid breakdown and can be easily lost to excretion. How an increase in carbon utilization efficiency leads to reduced aging is anyone’s guess.

A standard aging argument is that aging involves a hunkering down—when animals are short of food they alter their metabolism so that both aging and reproduction are postponed until better times. The new findings are consistent with this metabolism-centric view. “People have taken for granted that we know everything about metabolism,” says Escalante-Semerena, but aging research may be proving them wrong.

Reference: Starai, V.J., et al. 2002. Science. 298:2390–2392.