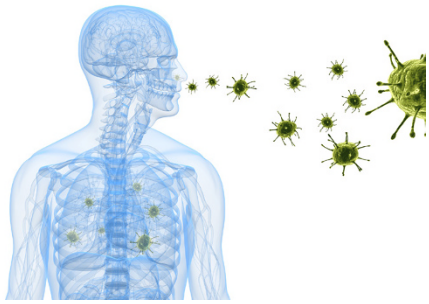
T cells on the trail

After airways become infected with influenza, the body mounts both an early and late immune response to contain the infection and kill virally infected cells. This carefully orchestrated response relies on communication between two arms of the immune system: the early response is mediated by cells of the innate immune system, including neutrophils, which are activated by conserved motifs (patterned components) of the virus; the adaptive immune response arises later and consists of T and B cells that react to the virus itself.

Animal models are essential for determining the kinetics of this response, as the first immune responders use molecular mechanisms to recruit other cells to the infection from anatomically distinct sites. Minsoo Kim and colleagues from the University of Rochester examined the interaction between neutrophils and T cells (*Science* **349**, aaa4352; 2015). In C57BL/6 mice infected with HKx31 influenza virus neutrophils are rapidly recruited to the lungs, peaking at day 4, and are followed by a wave of $CD8^+$ T cells from days 6 to 8. If neutrophils are depleted, fewer $CD8^+$ T cells accumulate in the lungs after infection and viral clearance is impaired.

Soluble factors called chemokines guide immune cells to particular anatomical sites, and during *in vivo* viral infection, neutrophils were a major source of the chemokine CXCL12. Among infected mice whose neutrophils could not produce CXCL12, T cells were recruited the lung much later. Furthermore, after neutrophils were placed on coverslips *in vitro*, allowed to migrate, then washed away, $CD8^+$ T cells that were added to the coverslips were also found to migrate. Migrating neutrophils appear to leave trails of chemokines behind them. As they migrate, the neutrophils extend processes and deposit CXCL12 with components of their membrane.

Neutrophils in infected mice exhibited similar crawling movement in the lung, extending processes as they migrated toward the site of infection and leaving behind CXCL12 in the trachea. These trails



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of chemokines persist in the airways during infection. Since chemokines are small and readily diffusible, this establishes a depot of sorts that signals T cells to migrate into the tissue and home in on the site of infection. Using mice as *in vivo* models of infection, Kim's team has now teased apart important characteristics of the tissue microenvironment to show how signals released from innate immune cells are retained in the inflammatory environment of the infected lung and recruit adaptive immune cells.

Kevin Da Silva

MODELING ABERRANT BONE GROWTH

Fibrodysplasia ossificans progressiva is a rare autosomal-dominant genetic disorder. Approximately 97% of cases are associated with the Arg206His mutation in the intracellular domain of ACVR1, the receptor for bone morphogenetic protein type I. Clinically, this mutation is characterized by conversion of soft tissue, including skeletal muscle, fascia tendons and ligaments, into bone. This process, termed heterotopic ossification, is debilitating; ultimately bones fuse together, causing immobility and asphyxiation.

Previous attempts to create a mouse model of this disease were hampered by perinatal lethality. To assess whether expression of mutant ACVR1 is sufficient to drive heterotopic ossification *in vivo*, Aris N. Economides and his colleagues at Regeneron Pharmaceuticals (Tarrytown, NY) generated a conditional-on knock-in model in which adult mice conditionally and endogenously express mutant $ACVR1^{R206H}$ after being injected with tamoxifen (*Sci. Transl. Med.* **7**, 303ra137; 2015). Following induction of the transgene, mice develop progressive heterotopic ossification in the sternum, vertebrae, hip joint and hindlimb. The researchers then administered soluble mimics of the receptor to mice to assess whether the disease process requires a ligand to activate the receptor. These mimics mop up any endogenous ligands and inhibit them from binding to receptors, and administration successfully inhibited conversion of soft tissue to bone.

One such ligand, activin A, acts as an antagonist of wild-type ACVR1 and inhibits binding of other activating ligands like bone morphogenetic protein-2. However, in the knock-in model with mutant ACVR1, activin A has the opposite effect of promoting aberrant bone formation and ossification. In a press release, Economides noted that "gaining insight into the activin A-related mechanism is a tremendous step forward for researchers, and the knowledge gained about receptor-ligand interactions and signaling in this system may prove relevant in other diseases, as well."

Surgery to remove heterotopic tissue is typically not beneficial to patients as it promotes additional episodes of heterotopic ossification. To test whether pharmacologic inhibition of activin A could prevent heterotopic ossification in these mice, the researchers developed a human antibody that targets activin A. Mice with mutant ACVR1 that were treated with this antibody did not develop heterotopic ossification up to 6 weeks after treatment. Episodes of aberrant bone formation can be triggered by tissue damage and inflammation, and activin A is released in response to injury and inflammation, so these findings suggest that activin A drives episodes of heterotopic ossification. Most generally, these findings highlight the growing potential of transgenic mice for modeling rare disorders and developing novel therapies.

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