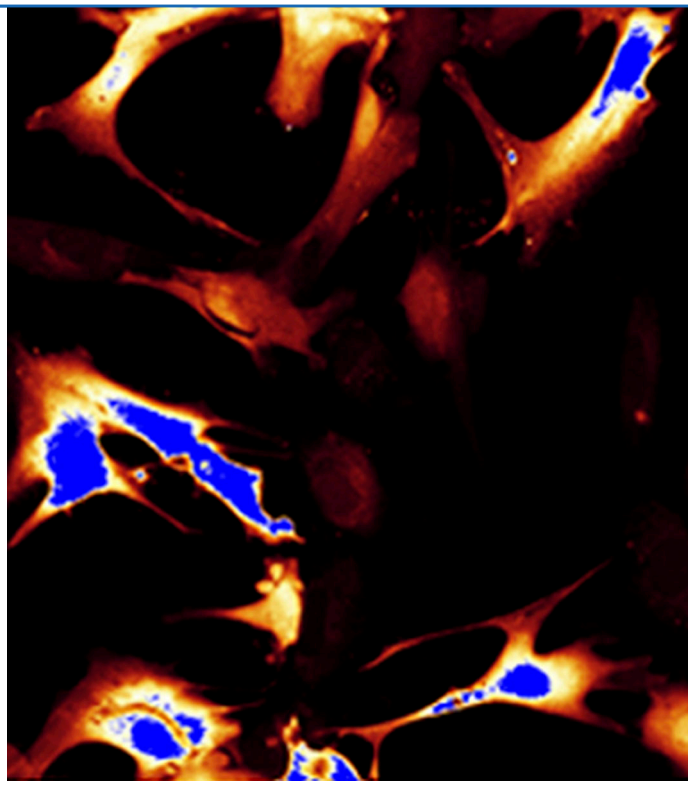
Heart-stopping antibodies

Women with lupus and rheumatoid arthritis are at increased risk for having babies with congenital heart block, and maternal autoantibodies that cross the placenta are thought to be the main cause. On page 11, Salomonsson et al. show that a subset of autoantibodies that disrupt the calcium homeostasis in heart cells is responsible.

Women with autoantibodies specific for an intracellular protein of unknown function called SSA/Ro52 (Ro52) are more likely to have babies with congenital heart block—a condition in which the electrical impulses that regulate the heart beat are disrupted. The pathogenic response has been associated with the presence of antibodies that bind to one peptide on Ro52 called p200, but the mechanism was until recently a mystery.

The authors have now pinpointed the pathogenic response even further by showing that not all p200-specific antibodies cause disease. They cloned two antibodies from rheumatic patients, which both recognized p200 but had distinct binding properties. One of these antibodies, but not the other, bound to neonatal rat heart cells and deregulated calcium homeostasis. Intracellular calcium accumulated in these cells, eventually triggering apoptosis. When sera from newborn children with congenital heart block were analyzed, there was a predominance of antibodies with binding properties similar to those of the pathogenic subset of p200-specific maternal antibodies.



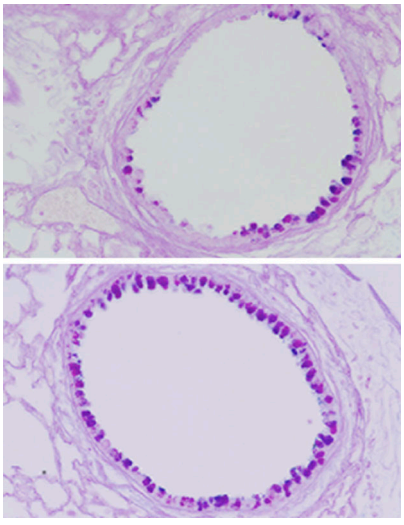
Autoantibodies cause calcium (blue) to accumulate in rat heart cells.

The mechanism by which these antibodies interfere with normal calcium flux remains unsolved. The authors believe that in vivo the p200-specific antibodies bind not to intracellular Ro52 but to a cross-reacting protein on the cell surface. They are now trying to identify that protein but meanwhile hope that this study will provide a new way to identify women who are most at risk for having children with congenital heart block. JEM

Keeping a lid on eosinophil activation

Spred-1 moderates eosinophil activation normally mediated by IL-5, according to a study by Inoue et al. on page 73. Mice lacking Spred-1 have overly exuberant eosinophils and develop exaggerated allergic responses to inhaled antigens.

Allergies and asthma are characterized by invasion of the airways by T cells and eosinophils. A subset of $CD4^+$ T cells, known as Th2 cells, produce an array of cytokines, including IL-5 and IL-13, which recruit eosinophils to the lung where they release their stores of histamine and other inflammatory proteins. The importance of Th2 cells and their associated cytokines in allergic responses is well established, but less is known about the regulation of eosinophil recruitment and activation.



Allergic responses (purple) in the lung are increased in Spred-1–deficient mice (bottom).

The Spred (Sprouty-related EVH1 domain–containing protein) family of membrane-bound proteins was identified recently by this group and shown to encode negative regulators of Ras–Erk signaling in neuronal cells. The demonstrated importance of the Erk pathway in differentiation of Th2 cells and in eosinophil survival prompted the authors to examine the role of Spred-1 in allergic asthma.

Mice lacking Spred-1 developed a more severe allergic reaction due to increased numbers of eosinophils in the lungs. T cells, by contrast, were unaffected by the lack of Spred-1—they were recruited in similar numbers and produced comparable amounts of cytokines in its absence and its presence.

The authors attributed the exaggerated eosinophil recruitment to an increased sensitivity to IL-5, since injection of IL-5, but not IL-13, into the lungs of Spred-1–deficient mice caused increased recruitment of eosinophils. IL-5 stimulation of primary eosinophils also resulted in hyperactivation of the Ras–Erk signaling pathway, but not of other signaling pathways. Why a lack of Spred-1 had no effect on Th2 responses is not completely clear, but it may simply reflect the low expression levels of Spred-1 by T cells. JEM