Muscle cells under attack

Antitumor T cells may confuse regenerating muscle cells for their intended targets and attack them, according to new data from Casciola-Rosen et al. (page 591). This unsolicited attack may be the trigger for a self-perpetuating autoimmune muscle disease.

Many proteins that are targeted in tissue-specific autoimmune diseases are expressed throughout the body. In most cases, the mechanisms that preferentially guide the autoreactive cells to the target tissue are not understood. An autoimmune muscle disease known as dermatomyositis is a good example. The helicase protein Mi-2 has been associated with dermatomyositis, but its expression in muscle and its function in the pathology of disease had never been explored.

Casciola-Rosen and colleagues now show that muscle cells from patients with dermatomyositis, but not those from healthy controls, expressed high levels of Mi-2 and other myositis autoantigens. In diseased muscle, autoantigens had a distinct pattern of expression—they were found only in immature regenerating muscle cells. The expression of the target antigen in regenerating muscle cells of patients suggested to the authors that it may be the effort of the damaged muscle to repair itself, and the resulting expression of the target antigen, that perpetuates the disease.

But how does this destructive cycle of muscle attack get activated in the first place? The authors found one possible explanation when they looked at tumors that are frequently associated with dermatomyositis. Similar to the situation in diseased muscle cells, they found that Mi-2 levels were elevated in tumor tissues but not in normal tissues. They suggest that an antitumor T cell response is generated against Mi-2 and other dermatomyositis-associated antigens. In the unlucky event that a nonspecific muscle injury occurs at the same time, these tumor-specific T cells might cross-react with newly growing muscle cells and trigger the self-perpetuating autoimmunity. JEM

Phagocytosis without inflammation

The rare brain disorder Nasu-Hakola disease is a fatal neurodegenerative syndrome that has been linked to mutations in immune signaling proteins, but the mechanism had not been explored. In a study on page 647, Takahashi et al. connect this disease to defects in phagocytic cells that are required for removal of apoptotic cells and suppression of inflammation in the brain.

The link to disease involves the TREM2 (triggering receptor expressed on myeloid cells-2) receptor and its associated adaptor protein DAP12, both known to be mutated in patients with Nasu-Hakola disease. TREMs are orphan receptors that associate with DAP12 to transmit signals in a variety of myeloid cells. The signals are primarily stimulatory; TREM1 signaling activates macrophages and neutrophils and can amplify Toll-like receptor signals, and TREM2 activates immature dendritic cells. TREM2 is also expressed on microglial cells (phagocytic cells in the brain that remove apoptotic cells and debris from the brain), but its function on these cells had not been examined until now.

Intrigued by the connection between TREM2 and Nasu-Hakola disease, Takahashi and colleagues examined the function of this molecule on primary murine microglial cells. They found that TREM2 ligation triggered phagocytosis of beads and apoptotic neurons in a process that required actin reorganization and the activation of the signaling molecule Erk. TREM2-stimulated phagocytosis did not coincide with activation of the cell or secretion of proinflammatory cytokines.

Impaired phagocytosis in the absence of TREM2 or functional DAP12 confirmed their role in phagocytosis. This experiment, however, also revealed a more striking finding. The loss of TREM2 provoked the microglial cells into producing inflammatory cytokines such as TNF and IL-1β, suggesting that TREM2 signals actively interfere with these pathways under normal circumstances. When TREM2 is missing, the lack of interference may explain the defective phagocytosis and aberrant activation of microglial cells that accompanies the buildup of cellular debris in the brain. JEM