Giving infecting bacteria a little freedom early on can be good for the host, according to a new study by Rotta et al. (page 657). Confining the bugs too quickly, they find, can tie up the immune cells that need to spread the word.

Certain bacteria, such as *Mycobacterium tuberculosis* and *Salmonella*, are quickly surrounded by macrophages, dendritic cells, and other immune cells that seal off the invaders from surrounding tissue. The convergence of these cells creates immune cages—or granulomas—that contain several extracellular matrix proteins, including SPARC, which enhances collagen assembly.

Rotta et al. now find that SPARC-induced collagen prevents *Salmonella*-laden dendritic cells from slipping out of granulomas to the nearest lymph node to alert T cells. In mice infected through the skin with an attenuated strain of *Salmonella*, bacteria were hemmed in by a SPARC-enhanced granuloma within a day. After 9 days, however, the bacteria breached the fortifications. In the resulting absence of bacterium-killing T cells, the bugs rapidly spread out into other organs, and the animals soon died.

SPARC-deficient mice, on the other hand, never formed granulomas when they were infected with this crippled strain of *Salmonella*. Immune cells found the infection site but failed to coalesce because SPARC-formed collagen was absent, thereby allowing dendritic cells to reach lymph nodes. The mice thus fought off this initial infection and survived a later challenge with a virulent strain of *Salmonella*.

The immune system’s knee-jerk reaction in trapping bacteria right away might be initially protective for widely infecting bugs that invade via the airways or the blood rather than the skin. The current findings suggest that antibacterial vaccines injected through the skin might be more effective if they are coinjected with a SPARC-blocking molecule. 

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**Less naive with age**

An aged immune system has experienced CD8⁺ T cells to combat old enemies but is missing some of the fresh CD8⁺ T cells that are also needed, according to Yager et al. (page 711).

The CD8⁺ T cell pool is finite and in flux throughout an individual’s lifetime. Each infection strengthens the numbers of T cells specific to that infecting microbe. In time, the T cell pool thus becomes skewed: the large number antigen-specific clones decreases the number and diversity of remaining naive T cells.

Yager et al. now show that this age-related shrinking of the naive T cell pool results in a loss of the ability to respond to epitopes for which there were a low number of precursors to start with. In young mice, CD8⁺ T cells specific for a particular influenza nucleoprotein (NP) epitope were at least ten times less frequent than those specific for other flu epitopes. This NP-specific naive T cell population was greatly reduced in most old mice. Age-related decay of the thymus, which maintains the naive T cell repertoire, may be at least partly to blame: young mice with a surgically removed thymus experienced similar declines in their naive T cell pool.

The resulting inability of the old mice to mount a strong immune response against the NP epitope weakened their ability to protect themselves against different flu strains. Older flu-infected mice that had the fewest NP-specific T cells were least adept at fighting off a second infection with a different flu strain, even though these mice had plenty of T cells directed against other flu epitopes. Why non-NP-specific T cells fail to protect the mice is unclear.

The findings suggest that current efforts to boost flu-fighting power in the elderly with vaccines carrying multiple T cell epitopes might misfire, as the naive T cells that would respond to these vaccines are missing. As the preferential loss of low frequency naive T cells is probably not unique to the flu, prolonging thymic function and vaccinating against as many microbes as possible before the thymus deteriorates too far might be better strategies. 

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**Disadvantages of a SPARCling defense**

Granulomas (blue) do not form when mice lack the collagen-building protein SPARC (bottom).

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Old mice that fight off a second strain of the flu (left column) have more NP epitope-specific T cells than do mice that stay infected (right column).