Autoimmune TCR structure

A crooked T cell receptor (TCR)–MHC interaction may result in immune responses that are similarly skewed, based on findings from Michael Hahn, Kai Wucherpfennig, and colleagues (Dana-Farber Cancer Institute, Boston, MA). The TCR in question is associated with multiple sclerosis, suggesting that protective and autoimmune T cells recognize antigens differently.

A head-on approach has been seen in protective cases, in which the TCR sits directly atop the foreign peptide/MHC complex on an antigen-presenting cell. Now, the authors present the first crystal structure of an autoimmunity-generating complex—a TCR that binds to MHC presenting the myelin basic protein (MBP) peptide. This structure, derived from a TCR that was isolated from a multiple sclerosis patient, reveals a tilted complex in which the TCR contacted mostly the NH₂-terminal portion of the MBP peptide. The hypervariable (rearranged) TCR loops created a much larger fraction of the contact surface with the MHC and peptide than in conventional arrangements. “It’s the sequence diversity of TCRs that allows these unusual topologies,” says Wucherpfennig.

The CD4 coreceptor, which is required for T cell function, was thus unusually positioned. If this odd geometry limits T cell activation in the thymus, the cell might evade negative selection (the removal of autoreactive T cells) and escape to the periphery. Escapees remain harmless unless they are activated, possibly by microbial peptides with some structural similarity to MBP. This kind of activation might be more likely since the TCR recognizes a smaller-than-normal section of the peptide.

Reference: Hahn, M., et al. 2005. Nat. Immunol. 6:490–496.

Quick stop for lymphocytes

Lymphocytes reach out a retractable hook to stop on a dime when necessary, based on findings from Revital Shamri, Ronen Alon (Weizmann Institute of Science, Rehovot Israel), and colleagues.

Lymphocytes and other white blood cells roll along vessel walls scanning for immobilized chemokine signals that tell them where to stop on the endothelium. They only stop once their integrins, which are otherwise kept bent and inactive, are properly activated. As arrest requires dramatic adhesion changes, most scientists assumed that rolling allowed signals to accumulate and globally activate integrins, thus decelerating and eventually stopping the rolling cell. In some settings, such as neutrophils rolling on E-selectin, deceleration lasts several minutes. But the new findings show a much more abrupt stop of lymphocytes on the endothelium.

Rolling was not even necessary for neutrophils to stop. Endothelium-bound chemokines needed less than 0.3 s in contact with the neutrophil integrin LFA-1 to trigger its extension. Extended LFA-1 can more easily reach its endothelial ligand (such as ICAM-1) but does not bind it tightly. To latch on, the group shows, the integrin must encounter its ligand less than 0.5 s after seeing the initial chemokine signal.

“The integrin ligand should be very close to the chemokine,” says Alon. “If cells see sporadic chemokine spatially misorganized [with respect to the integrin’s ligand], it results in an abortive activation signal.” The hook is quickly retracted, and the cell rolls on. Integration of chemokine signaling is not necessary, so cells stop precisely where a signal lies, rather than rolling and collecting signals over a long path.

Recent structural data fit well with the findings. Integrin structures reveal an intermediate state when integrin is extended, primed, but not fully committed,” says Alon. Intracellular signals, as might be generated by rapidly activated chemokine receptors on the lymphocytes, get integrins to that state by what is known as inside-out signaling. “For proper acquisition of high affinity,” says Alon, “the ligand must do the next half.” Since the ligand must act quickly, Alon suggests that “the integrin and chemokine machineries are preformed on the lymphocyte surface.”

Reference: Shamri, R., et al. 2005. Nat. Immunol. 6:497–506.
it’s probably not dragging dynein.” He guesses that dynein sees a bunch of smaller step sizes,” says Selvin. Since that was observed in vitro, where opposing motors were pulled simultaneously, “we’d expect to see a bunch of smaller step sizes,” he says. There is an unknown around this point, which could be explained by the presence of a small molecule that alternates between the motors, turning one off and the other on. But the speed with which the directional change occurs makes Selvin skeptical of this possibility.

The prevalence of protrusions in inactive synapses might allow them to seek out more active presynaptic partners. “If activity is very low, a spine gets restless,” says Richards. “But if it is close enough to another presynaptic terminal, some of the terminal’s glutamate can diffuse and weakly activate the spine. Now it’s a [new] potential source of glutamate, so it heads in that direction.” This rewiring might explain how stroke sufferers are able to recover certain neurological functions. JCB

Reference: Richards, D.A., et al. 2005. Proc. Natl. Acad. Sci. USA. doi:10.1073/pnas.0501881102.

A peroxisome’s speed and step size suggest it is carried by several kinesins or dyneins, but not both.