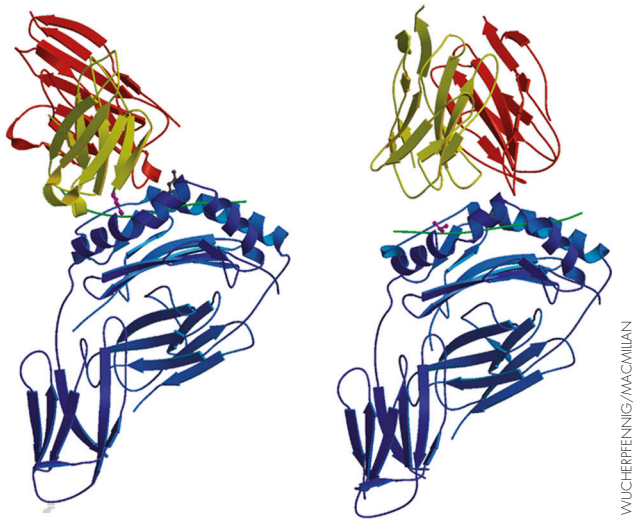
Research Roundup

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 NH_2-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.



WUCHERPFENNIG/MACMILLAN

An autoimmune TCR (left; red and yellow) sits off-center on its MHC (blue) and peptide (green) compared with a more conventional arrangement (right).

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. JCB

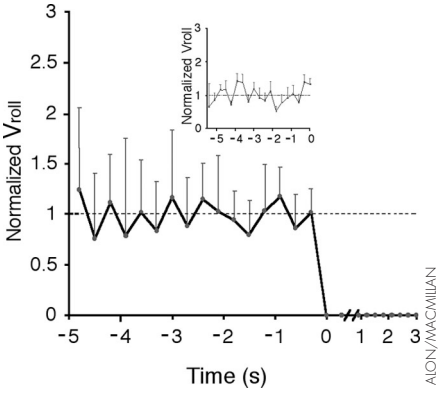
Reference: Hahn, M., et al. 2005. *Nat. Immunol.* 6:490–496.

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.



ALON/MACMILLAN

Rolling lymphocytes do not gradually decelerate before stopping.

"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 acquistion 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." JCB

Reference: Shamri, R., et al. 2005. *Nat. Immunol.* 6:497–506.

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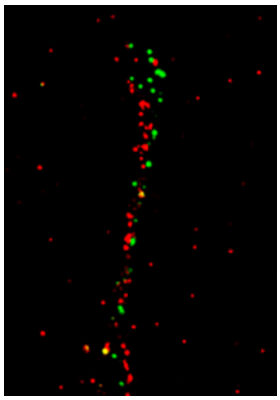
Separating receptor and ligand



PFAFF/AAAS

EphA (green) and ephrinA (red) membrane localization does not overlap.

Axonal pathfinding in motor neurons depends on surrounding guidance cues, including the membrane-bound ephrinA ligands, which repel growth cones that express EphA receptors. But many of those same growth cones also contain their own ephrinA. Now, Till Marquardt, Ryuichi Shirasaki, Samuel Pfaff, and colleagues (Salk Institute, La Jolla, CA) show how EphA ignores self-ephrinA during growth cone guidance.

The authors find that ephrinA ligands that are on the same cell as a EphA receptor do not interfere with that receptor's ability to sense ligands on other cells. The interference is avoided by segregating receptor and ligand to different submembrane domains. EphrinA ligands, which are GPI-linked, colocalized with a lipid raft marker. EphA receptors, on the other hand, were found in nearby but distinct (presumably nonraft) domains. Forced mixing of the two, by expressing a transmembrane version of the ligand, made neurons blind to ephrinA ligands outside the cell.

When external EphA receptors bind to ephrinAs, the latter are also known to signal back into their own cell, but they elicit growth cone expansion rather than collapse. As with EphA receptors, this effect depended on the separation of EphA and ephrinA. Both EphrinA and EphA can thus act as guidance receptors on the same growth cone, with opposite results.

Decreased sensitivity to external ligand or receptors might be achieved naturally by regulated colocalization. The resulting desensitization might allow, for example, several axons that express both EphA and ephrinA to grow out as a bundle without repelling each other. JCB

Reference: Marquardt, T., et al. 2005. *Cell.* 121:127–139.

Spines reach out

Bored dendritic spines look for new challenges, say David Richards, R. Anne McKinney (in work done at the University of Zurich, Switzerland), and colleagues.

Spines are small dendritic protrusions on which excitatory synapses connect to axons. Recent evidence suggested that spines are mobile even in adults. Richards et al. now suggest that this mobility allows for post-developmental synaptic rewiring.

The group found that mobile spines formed filopodium-like protrusions extending toward neighboring axons. The protrusions are a response to glutamate in situations when the spine is receiving little from its own axonal partner. Small amounts of glutamate caused the protrusions to extend toward the glutamate source. A large dose, however, repressed protrusion formation for up to 20 min. This may be due to the strong influx of calcium in excited synapses, which is known to inhibit cytoskeletal changes.

The prevalence of protrusions in inactive spines 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 [that terminal's] glutamate can diffuse and weakly activate the spine. Now it's found 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.

Motors take turns

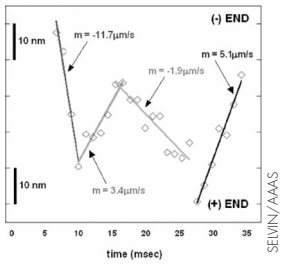
Two opposing microtubule motors are wary of competition, say Comert Kural, Paul Selvin (University of Illinois, Urbana, IL), Vladimir Gelfand (Northwestern University, Chicago, IL), and colleagues. Rather than play tug-of-war, dynein and kinesin take turns carting around their cargo—in this case, peroxisomes.

Kinesin takes peroxisomes out to the cell periphery, whereas dynein brings them back to the interior. No matter which direction ultimately prevails, the peroxisome switches direction many times along the way. These switches might stem from the alternation of active motors or from a tug-of-war with alternating short-term winners. To distinguish between these possibilities, the authors visualized peroxisome movement at high resolution in vivo. The results suggest that either dynein or kinesin, but not both, pulls at any given time.

The high resolution images revealed individual step sizes of 8 nm for each motor, which matches findings from in vitro studies. If opposing motors were pulling simultaneously, "we'd expect to see a bunch of smaller step sizes," says Selvin. Since that was not seen, Selvin concludes that "when kinesin takes a step, it's probably not dragging dynein." He guesses that dynein disconnects from the microtubule but stays attached to the peroxisome. And when dynein is working, kinesin returns the favor.

Selvin is currently puzzled by how the coordination is regulated. A small molecule might alternate between the motors, turning on one as it turns off the other. But the speed with which the directional change occurs makes Selvin skeptical of this possibility.

The group also measured peroxisome speed, which indicated that several kinesins or several dyneins often work together to move the cargo more quickly than one motor could by itself. This cooperativity has never been seen by motors pulling beads in vitro. Perhaps something in the peroxisome lipid bilayer is needed for several motors to team up. The authors hope that they might find the needed factor(s) by reconstituting peroxisome movement in vitro. JCB



SELVIN/AAAS

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

Reference: Kural, C., et al. 2005. *Science.* doi:10.1126/science.1108408.