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Exclusion is spreading

Allelic exclusion simplifies the problem of immune recognition. It ensures that each B cell makes antibodies that recognize only one target because, once the DNA of a single immunoglobulin allele has rearranged to form a functional gene, the other allele is prevented from rearranging. Now Esther Roldán, Jane Skok (University College London, UK), and colleagues find that allele exclusion may rely on putting different parts of the unrearranged gene too far from each other to allow rearrangement.

Rearrangement is only possible in such huge loci because of DNA contraction and (as shown here) looping that juxtaposes distant DNA sites. Skok and colleagues now show that successful rearrangement is immediately followed by decontraction of the unrearranged allele. Proximal variable (V) regions are still within reach of the rearrangement apparatus, but the products of these rearrangements are disfavored later because they pair poorly with immunoglobulin light chains and usually fail to induce positive selection of cells.

There is a backup mechanism for allele exclusion. Coincident with decontraction, the unrearranged allele is also recruited to repressive centromeric domains. But Skok says she thinks decontraction "is the most important factor. Decontraction seems to be irreversible and immediate, whereas recruitment is reversible." JCB

Reference: Roldán, E., et al. 2004. *Nat. Immunol.* doi:10.1038/ni1150.

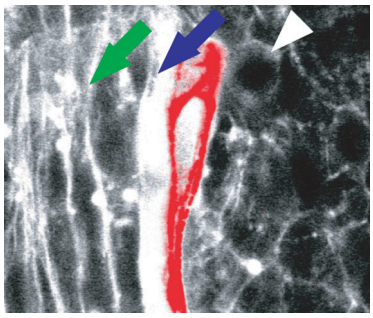
Stretch but don't follow

As slow-twitch muscle cells migrate through fast-twitch muscle precursor cells, they act as morphogenesis tutors, according to Clarissa Henry and Sharon Amacher (University of California, Berkeley, CA).

Fast-twitch muscle cells in zebrafish start off life as round blobs but must undergo anterio-posterior elongation to become functional myofibers. Henry and Amacher had noticed that this elongation process spreads in a medial-to-lateral wave, i.e., cells near the midline change shape first.

The authors first established that elongation required Hedgehog signaling. Transplantation experiments showed, however, that this effect was indirect. To restore fast-twitch elongation in a Hedgehog-signaling mutant, the critical ingredient was wild-type slow-twitch cells not wild-type fast-twitch cells.

In response to the Hedgehog signal, transplanted slow-twitch cells extended across the anterior–posterior width of a somite and migrated outwards from the notochord. Fast-twitch cells in their wake elongated. The effect could be relayed to other fast-twitch cells as long as the targets were in the same somite. In the wild type there are probably enough migrating cells to contact directly all of the fast-twitch cells.

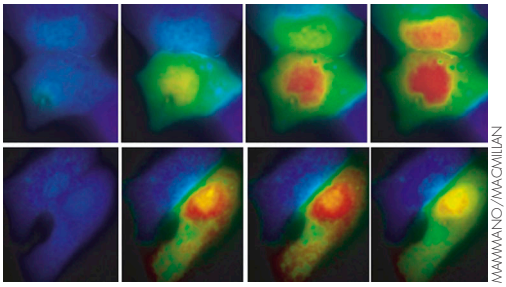


AMACHER/ELSEVIER

Ovoid fast muscle cells (white arrow) stretch out (green arrow) after a slow muscle cell (red) moves laterally (right) over them.

Future work will show if the slow-twitch cell or its discarded extracellular matrix is acting as a scaffolding for the fast-twitch cell, or if other signals are at work. In other sites of cell migration, such as the developing limb and early embryo, there may be similar drop-offs of differentiation and morphogenesis cues. JCB

Reference: Henry, C.A., and S.L. Amacher. 2004. *Dev. Cell.* 7:917–923.



MAMMANO/MACMILLAN

IP_3 spreads to elicit Ca^{2+} peaks via wild-type (top), but not mutant (bottom), connexins.

One more C means no hearing

A miniscule change in a pore protein can mean the difference between hearing and deafness, say Martina Beltramello, Valeria Piazza, Fabio Mammano (Venetian Institute of Molecular Medicine, Padua, Italy), and colleagues. They have characterized a mutant connexin from the inner ear that allows the passage of ions and a dye, but not of the intracellular messenger inositol 1,4,5-trisphosphate (IP_3). The result is a failure in hearing.

The connexin is expressed in supporting cells in the organ of Corti (http://www.vimm.it/cochlea). These cells are thought to ferry K^+ away from sensory cells, thus preventing opening of channels in these cells that would admit toxic levels of Ca^{2+}.

Most connexin mutations associated with deafness yield missorted or nonfunctional channel proteins. The Italian group focused on the V84L mutant, which is correctly sorted and, as they show, forms channels with normal unitary conductance and open channel probabilities. Ions and the higher molecular weight dye Lucifer yellow can pass through these channels.

But IP_3 introduced into cells expressing V84L mutant connexins did not, as in wild type, generate Ca^{2+} waves in adjacent cells. Failure to spread this message may be the basis for a failure in K^+ scavenging and thus sensory cell death.

Thus the addition of a single CH_2 unit can determine the difference between conductance and nonconductance of IP_3. The detailed structure of the relevant connexin is not yet known, but the minimal structural difference may be amplified if the residue in question pokes into the channel that is formed by 6 connexin subunits. JCB

Reference: Beltramello, M., et al. 2004. *Nat. Cell Biol.* doi:10.1038/ncb1205.