In This Issue

Clash of the titin

The sarcomere is more than a complicated piece of structural machinery. According to new results by McElhinny et al. (page 125), a building block of striated muscle cells called MURF-1 may also indirectly regulate gene expression.

MURF-1 localizes to sarcomeres thanks to its interaction with titin, a major structural component of the muscle sarcomere, and the largest vertebrate protein identified to date. Titin is anchored at the sarcomere Z-lines, as are thin (actin) filaments. From there it stretches across entire half sarcomeres to overlap at the mid-line (M-line), where it helps anchor thick (myosin) filaments in a central location.

Now McElhinny et al. show that different domains of titin perform independent functions. Disturbance of the titin–MURF-1 interaction leads to a complete disruption of M-line and thick filament structure. But the remaining titin regions can still stabilize sarcomeric thin filaments and Z-lines.

Then there is the nuclear connection. The authors demonstrate nuclear localization of MURF-1, and interaction with a glucocorticoid-responsive transcriptional activator. Thus, titin may recognize structural alterations in the sarcomere and signal to the nucleus by releasing MURF-1 for translocation to the nucleus and transcriptional activation. A possible mechanism could involve titin phosphorylation of MURF-1, as titin’s kinase domain lies adjacent to its MURF-1–binding domain.

Seeing through the cilium

To understand vision in vertebrates, one might look to worms and algae, according to recent results. On page 103, Pazour et al. show that a conserved protein transport mechanism in the flagellae of algae and worms is also necessary for development and maintenance of mammalian photoreceptors.

Assembly and maintenance of motor and sensory cilia in worms and algae requires the transport of proteins via intraflagellar transport (IFT). The outer segment (OS) of a vertebrate photoreceptor, itself a modified cilium, is formed by transporting membrane and opsin through a connecting cilium that provides a link between the photoreceptor inner (metabolic) and outer (photoreceptive) segments. Photopigment molecules and phototransduction proteins must pass through this connecting cilium to replace components of the OS that have been degraded.

Now, it appears that the mechanism used to transport these photoreceptor molecules is conserved throughout eukaryotes. Pazour et al. identified mouse and human homologues of several proteins that form a complex required for IFT in algae. The vertebrate proteins form a complex of similar density to that of the algal complex and localize to the connecting cilia of photoreceptors.

Defects in one of these proteins, IFT88, leads to abnormal development of the mouse photoreceptor OS. Retinal degeneration occurs via apoptotic death of photoreceptor cells, presumably because necessary OS components are not transported. Mutations in the human IFT genes are candidates for causing degenerative vision disorders such as retinitis pigmentosa.

Peroxide perturbations

Injury triggers invasion of white blood cells into tissues. According to new results from Ji et al. (page 173), PECAM-1, an adhesion molecule on the endothelial cells (ECs) that line blood vessels, does double duty in this invasion process. Direct ligation of PECAM-1 is known to allow neutrophils to crawl between ECs. But, independent of this function in white cell invasion, PECAM-1 is now shown to activate an EC current that may prime cells by loosening their connections.

The messenger that triggers this current is the reactive oxygen species hydrogen peroxide ($H_2O_2$). Neutrophil-produced $H_2O_2$ signals increase the cation channel in response to oxidants. The cytoplasmic domain of PECAM-1 is sufficient for activation, suggesting that peroxide-induced Ca$^{2+}$ influx produced during transmigration does not require PECAM-1 binding between neutrophils and ECs. Phosphorylation of tyrosine residues in this domain is required for the $H_2O_2$-induced current, and probably allows interaction with other linker or channel proteins.

Although it is not known which channel is activated, inhibitor studies indicate that the calcium is coming from outside the cell, and not by activation of internal stores. The group plans to investigate the function of the PECAM-1–regulated channel from examining pathological responses in PECAM-1 knock-out mice.

IFT88 (green) is found in mouse photoreceptor cilium (red).