Signaling together apart

After being cleaved apart, two halves of a split personality receptor protein are free to wander far away from each other, say Kirill Volynski, Yuri Ushkaryov, and colleagues (Imperial College, London, UK). But when signaling is needed the two halves reunite.

The receptor, called latrophilin, is known only as a binding site for the black widow poison latrotoxin. Although no endogenous ligand for latrophilin is known, a varied family of receptors exists with a similar organization. Each family member has two domains: an NH₂-terminal fragment (NTF) that interacts with other cell surface or possibly extracellular matrix proteins, and a COOH-terminal fragment (CTF) that resembles a G-protein-coupled receptor (GPCR). The two domains were known to be cleaved, but the persistence of the NTF on the cell surface led previous workers to assume that the transmembrane-less NTF must remain bound to CTF.

The London group now shows that this is not the case. The two fragments have distinct localizations and can be aggregated away from each other using antibodies. Addition of a latrotoxin variant, however, induces clustering of the fragments and signaling.

For the cell, the fusion of two protein functions allows for coordinated expression, but cleavage allows divergent regulation. For example, the NTF may stay attached extracellularly even as the CTF is internalized to allow for GPCR desensitization. Ushkaryov now hopes to test whether different members of the protein family mix and match their respective halves.

Dormant tumors awaken

What happens during tumor remission? After chemotherapy, tumor cell numbers may be reduced, or surviving cells may enter an altered, dormant state. Evidence for dormancy now comes from Catherine Shachaf, Dean Felsher (Stanford University, Stanford, CA), and colleagues. In their mouse model, liver tumors can be forced into dormancy and then reawakened at will.

As in previous studies, regression was induced by shutting off the over-supply of MYC, in this case using a tetracycline-controlled promoter. Transgenic mice took ~12 weeks to develop the MYC-induced tumors, but within 4 days of MYC inactivation the cells died or differentiated into normal liver cells. Tumors regressed but could later be reactivated by switching MYC back on.

The persistence of dormant tumor cells was demonstrated by transplanting tumor cells containing transgenes for both luciferase and the tetracycline-controlled MYC. Even when MYC was inactivated the luciferase signal persisted in the transplanted cells, which looked like normal liver cells. Turning MYC back on restored tumorigenesis, increasing cell number and thus luciferase activity.

Reversible dormancy has not been seen in previous MYC inactivation studies. Felsher believes that the differences are explained by the properties of the tumors’ originating tissues. Lacking MYC, tumor cells from a terminally differentiated tissue such as bone marrow to terminal differentiation; those from the apoptotic-prone hematopoietic compartment die; and those from liver (a tissue that is rich in stem cells and can regenerate) differentiate but produce many stem cells. It is those stem cells that may perpetuate the dormant state and that Felsher wants to understand.

Reference: Shachaf, C.M., et al. 2004. Nature. doi:10.1038/nature03043.

Neurons inch along

Centrosome and nucleus engage in an inchworm-like dance in certain migrating neurons, according to David Solecki, Mary Hatten, and colleagues (Rockefeller University, New York, NY).

The neurons under study migrate along glia to form the layered architecture of higher brain areas. Whereas primitive brain areas have a nuclear organization, the cortex builds its more complex circuitry by sending its neurons off on these treks.

The neurons were known to move and adhere in a periodic cycle, with a long period leading the way and the nucleus at the rear. But the Rockefeller group now shows that the centrosome moves forward first; the nucleus then closes the gap. This cycle has a similar period to the adhesion cycle. Although the relative timing of the events is not known, coordination may rely on mPar6, which the Rockefeller group identifies as a centrosome component essential for centrosome and cell movement.

The nucleus is surrounded by a perinuclear microtubule cage whose shape is distorted during the cycle. The cage and nucleus are probably moved towards the centrosome by dynein. The movement of the centrosome itself is more of a mystery, both in terms of the responsible motor and the structure against which the motor pulls.

Reference: Solecki, D.J., et al. 2004. Nat. Neurosci. doi:10.1038/nn1332.