Apratoxin chaperones EGFR to its destruction

A small toxin from a cyanobacterium pushes growth-promoting proteins such as the EGF receptor (EGFR) along an unusual path to destruction, report Shen et al. Several oncogenic proteins, including EGFR, p53, and cyclin-dependent kinases are collectively known as Hsp90 client proteins due to their reliance on the Hsp90 chaperone for maintaining their conformation and stability. Hsp90 inhibitors are undergoing cancer therapy trials, since disrupting the chaperone’s function results in its clients targeting to the proteasome for degradation.

The cyanobacterium compound Apratoxin A can also kill cancer cells—at least in vitro—but its mode of action was unknown. Shen et al. found that treating cells with Apratoxin A reduced the levels of several Hsp90 client proteins and prevented their interaction with Hsp90. But the toxin works in a different way to Hsp90 inhibitors like geldanamycin. Apratoxin A directly bound to chaperones of the Hsp70/Hsc70 family, stabilizing their association with Hsp90 client proteins such as EGFR. The client proteins could no longer bind Hsp90 and were instead delivered to the lysosomes for degradation—a process called chaperone-mediated autophagy (CMA).

Blocking the CMA pathway prevented EGFR’s degradation in response to Apratoxin A. EGFR is the first membrane protein known to undergo CMA—a process previously thought to be reserved for cytosolic proteins. But Shen et al. identified a short sequence within EGFR that allows Hsc70 to recognize it as a CMA substrate. Apratoxin A’s ability to bind Hsp70/Hsc70 chaperones and induce the degradation of EGFR and other Hsp90 client proteins makes it an interesting candidate for cancer treatments, although author Shensi Shen warns that the drug is extremely toxic and will need to be further modified.

BDNF sends mixed signals

Two different forms of the same protein have a “yin and yang” function to either promote or inhibit synaptic activity.

The nervous system modifies the strength of its connections in response to changes in synaptic activity—a process known as synaptic plasticity. One source of this plasticity is the postsynaptic cell, which sends a retrograde signal back across the synapse to either strengthen or weaken further transmissions. One such retrograde signal is brain-derived neurotrophic factor (BDNF), which promotes synaptic activity by binding to the TrkB receptor on presynaptic cells. But BDNF is also secreted in an uncleaved precursor form called pro-BDNF that binds to a different receptor called p75NTR.

Decorin has Met a new receptor

A small extracellular matrix protein called decorin blocks multiple growth factor receptors in order to inhibit tumor formation, suggest Goldoni et al.

Decorin binds to the Met receptor (green) and causes its internalization (arrows).

Mice lacking decorin are more susceptible to cancers, whereas increased levels of the protein can inhibit tumor growth and metastasis. Decorin was originally found to bind collagen fibers and regulate their assembly, but it can also inhibit EGF signaling by binding to and down-regulating the EGF receptor. Goldoni et al. wondered whether decorin might be even more promiscuous, and bind to other receptor tyrosine kinases as well.

The researchers screened 42 different receptors, and found that decorin also targeted Met—the receptor for the growth factor HGF, which promotes proliferation and invasion when constitutively activated in cancer cells. Although binding to decorin briefly activated Met, this only led to the receptor’s rapid down-regulation via two different pathways—by degradation inside the cell and by the cleavage and release of its extracellular domain. According to senior author Renato Iozzo, decorin is therefore the first known antagonist of Met signaling.

Treating cells with decorin also caused the destruction of a downstream effector of Met called β-catenin, stimulated apoptosis, and reduced cell motility. This latter effect relied on decorin’s ability to inhibit the EGF receptor as well as Met. Iozzo thinks that decorin could be a new way to treat cancers, which often have increased levels of multiple growth factor receptors and can survive therapies that only target a single pathway.

Goldoni, S., et al. 2009. J. Cell Biol. doi:10.1083/jcb.200901129.