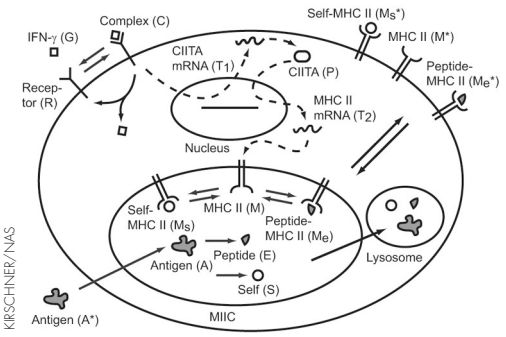
Research Roundup



KIRSCHNER/NAS

There are multiple TB resistance pathways in the cell.

TB bug inhibits any which way

Each new study of *Mycobacterium tuberculosis* (*Mtb*), the causative agent of tuberculosis (TB), seems to come up with a new resistance mechanism, and fails to see evidence for the mechanisms claimed by others. Now Stewart Chang, Jennifer Linderman, and Denise Kirschner (University of Michigan, Ann Arbor, MI) use a mathematical model to conclude that multiple mechanisms operate. Different mechanisms are best suited to protection under different conditions, and some are masked by experimental protocols used in previous studies.

Mtb prevents macrophages from doing their job primarily by inhibiting antigen presentation by MHC class II. The Michigan group included four parts of this process (identified by others) that could be inhibited: MHC transcription; MHC protein maturation; antigen processing; and peptide loading onto MHC. IFN-γ and antigen got things going, and surface expression of peptide-loaded MHC was the readout.

Two inhibition classes served distinct time frames: effects were immediate for inhibition of antigen processing or peptide loading but delayed for inhibition of MHC transcription or maturation. The long pulses of IFN-γ used by two previous groups resulted in inhibition mediated primarily by effects on either maturation or transcription, respectively, with some part of the effect unexplained.

To suggest candidates for these unexplained effects, Kirschner and colleagues identified a number of processes whose inhibition in silico has major effects on antigen presentation efficiency. In vitro time series will allow many of the model's predictions to be tested. JCB

Reference: Chang, S.T., et al. 2005. *Proc. Natl. Acad. Sci. USA*. doi:10.1073/pnas0500362102

Split motifs

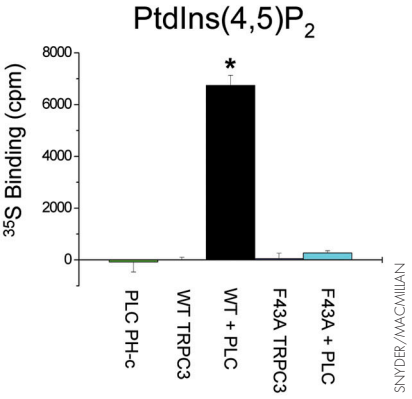
Many more motifs may be lurking in proteins than previously expected. Randen Patterson (Pennsylvania State University, State College, PA), Damian van Rossum, Solomon Snyder (Johns Hopkins University, Baltimore, MD), and colleagues report that functional protein–lipid interaction motifs can be formed when partial motifs from two proteins unite.

The group's initial example of a split domain comes in the context of a Ca^{2+} entry system. In this system, neurotransmitters bind receptors that trigger production of inositol 1,4,5-trisphosphate (IP3), which in turn prompts release of intracellular Ca^{2+} stores and entry of extracellular Ca^{2+} through TRPC3 channels. Snyder and colleagues previously established that phospholipase Cγ1 (PLC-γ1) was needed for this latter TRPC3 action, independent of PLC-γ1's enzymatic activity in generating IP3.

They now report that the binding of TRPC3 and PLC-γ1 to each other brings together two halves of a split PH domain, a motif associated with the binding of lipids and other proteins. Mutation of the partial PH domains changes the lipid-binding profile of the TRPC3–PLC-γ1 complex, and reduces the amount of TRPC3 at the plasma membrane 24 h after stimulation.

The phenomenon of split domains may be widespread. A modified search algorithm spotted not only the half-domains in TRPC3 and PLC-γ1 but also split domains in additional proteins. "It has opened up a whole new world," says Snyder. "It will amplify perhaps many-fold the number of protein recognition motifs." This profusion of motifs, he says, allows the cell to deliver on a promise: "Everything is hand delivered." JCB

Reference: van Rossum, D.B., et al. 2005. *Nature*. 434:99–104.



SNYDER/MACMILIAN

Only TRPC3 (WT) combined with PLC-γ1 generates a PH domain that binds lipids.

PML goes to the centrosome

The promyelocytic leukemia gene (PML) has "too many things it is involved in," says Kun-Sang Chang (University of Texas MD Anderson Cancer Center, Houston, TX). But now Chang, Zhi-Xiang Xu, and colleagues have added another function: the PML3 isoform prevents centrosome reduplication.

PML has at least 7 isoforms but most studies have used only one (PML4). Chang developed isoform-specific antibodies and saw that PML3 antibodies gave staining that coincided with that of centrosome proteins. Knock-down by siRNA of PML3, but not of other PML isoforms, resulted in centrosome amplification. And only PML3 interacted with and, when overexpressed, reduced the phosphorylation of Aurora A kinase.

It is known that in cells with activated Aurora A kinase there is a failure to inhibit Cdk2/cyclin E, leading to reduplication of centrosomes. Cells lacking PML had higher levels of Cdk2 kinase activity, which could explain the centrosome reduplication. What is signaling to PML from upstream is still mysterious, but the new findings certainly provide one possible explanation for why PML is lost in so many tumor types. JCB

Reference: Xu, Z.-X., et al. 2005. *Mol. Cell.* 17:721–732.