Neuronal switch

Type IIa receptor protein tyrosine phosphatases (RPTPs), such as RPTPσ, LAR and RPTPδ, are cell-surface receptors with important roles in neuronal development, function and repair. Their ectodomains interact with heparan sulfate proteoglycans (HSPGs) and chondroitin sulfate proteoglycans (CSPGs), which typically have opposing effects on cell function. How these effects are mediated at the molecular level has until now been unknown. The CSPG neurocan was previously shown to reduce outgrowth of dorsal root ganglion neurons, and this inhibitory effect is decreased in *RPTPσ*$^{-/-}$ (*Ptprs*$^{-/-}$) neurons. Now Aricescu, Flanagan, Jones and colleagues show that the HSPG glypican-2 strongly promotes outgrowth of the same neuronal population, also in an RPTPσ-dependent manner. The glycosaminoglycan (GAG) chains of neurocan and glypican-2 are involved in these opposing activities, through a common receptor, RPTPσ. Crystallographic analysis of a shared GAG-binding site in RPTPσ reveals a V-shaped arrangement of immunoglobulin domains 1 and 2 (Ig1 and Ig2), which is stabilized by conserved interactions. Residues of RPTPσ known to mediate GAG binding lie on loops between Ig1 β-strands C–D and E–F, forming an extended positively charged surface. The crystal structure of human LAR Ig1-2 in complex with a synthetic heparin mimic reveals a conformational plasticity of the C–D loop. The modified topology of the GAG-binding site maintains an overall positive charge, suggesting that the combination of basic side chains used by the GAG-binding site may vary to accommodate chemically diverse GAGs. Heparan sulfate and heparin analogs were shown to induce RPTPσ clustering, whereas excess chondroitin sulfate inhibited heparan sulfate–induced RPTPσ clustering, suggesting that the HSPG:CSPG ratio and its effect on receptor clustering may influence neuronal function. Indeed, exogenous addition of HSPG or CSPG shifts the HSPG:CSPG ratio, thereby switching the cellular response. The authors propose a model in which high levels of HSPG promote clustering of RPTPσ molecules, causing an uneven distribution of phosphatase activity on the cell surface and the formation of microdomains with high phosphotyrosine levels that support neuronal extension. Conversely, increasing the CSPG:HSPG ratio shifts the balance away from growth-promoting RPTPσ clusters and results in stalled axon growth. (*Science* doi:10.1126/science.1200840, published online 31 Mar 2011) *AH*

A tale of parasitic tails

Production of functional mRNAs in the mitochondria of trypanosomes involves several steps after transcription of the kinetoplastid DNA. The initial polycistronic precursor mRNAs are cleaved to yield pre-mRNAs and rRNAs. Most pre-mRNAs require editing (either insertion or deletion of U residues) to generate usable transcripts. Before editing, the pre-mRNAs possess a short (20–40 nt) polyadenylated tail, but the fully edited version contains a much longer extension (200–300 nt) composed of both A and U nucleotides. The mitochondrial poly(A) polymerase KPAP1 adds the initial short tail, and it was speculated that the post-editing formation of the A/U tail involved KPAP1 and the TUTase RET1. It was not clear how these enzymes collaborated to make the A/U tail or what its physiological role was. Aphasizheva and colleagues have now investigated A/U addition by looking for factors that interact with KPAP1. This led to the isolation of two pentatricopeptide repeat (PPR) proteins, KPAF1 and KPAF2, that form a heterodimer; a small amount of RET1 was also found to bind KPAF1. In the absence of KPAF1, the short poly(A) tail is formed, but the long A/U tail is not, and this compromises parasite viability. A/U tail formation is able to be reconstituted *in vitro* when KPAFs are added to KPAP1 and RET1. KPAFs change the activity of both enzymes: in its presence, RET1 UMP addition is limited to ~18 nt, whereas the addition of poly(A) by KPAP1 is stimulated. The long A/U tail promotes the association of fully edited mRNAs with translating mitochondrial ribosomal complexes, specifically through an interaction with the small ribosome subunit. Functionally, loss of the A/U tails due to knockdown of KPAF1 results in inhibition of mitochondrial translation. Therefore, KPAF1–2 heterodimer-dependent extension of the short poly(A) tail into a full A/U heteropolymer constitutes a rate-limiting, possibly regulatory step that additionally discriminates which mRNAs are fully edited and can form productive translation complexes. (*Mol. Cell* **42**, 106–117, 2011) *AKE*

BAD to the bone

The enzyme-catalyzed addition of a methyl group to the side chain of an amino acid residue is a well-known post-translational modification, of which the most prominent example is the methylation of lysine and arginine residues on histones. The methylation of arginine residues is carried out by members of the protein arginine methyltransferase (PRMT) family. Fukamizu and colleagues report that a PRMT catalyzes the methylation of two arginines that are in close proximity on the BCL-2 antagonist of cell death (BAD), a proapoptotic protein. The authors previously showed that PRMT1 methylates two arginines within the Akt phosphorylation motif of a Forkhead box O protein, preventing its phosphorylation by Akt. Now they have investigated whether this occurs on other proteins with an Akt consensus motif. The authors performed an *in vitro* screen of several other proteins containing the RxRxxS/T motif and determined that arginine methylation at that site in BAD prevented Akt-mediated phosphorylation from occurring. siRNA knockdown of PRMT1 in human cells led to a decrease in the mitochondrial localization of BAD and reduced the amount of BAD bound to BCL-X_L, an anti-apoptotic protein. Because PRMT1 knockdown also reduced the amount of activated caspase-3 that could be detected under conditions known to stimulate apoptosis, the authors concluded that this methyltransferase is an important regulator of BAD-mediated apoptosis. Additional studies are needed to determine exactly what external stimuli lead to BAD-methylation *in vivo*, which will help clarify whether PRMT1 plays a role in tumorigenesis. (*Proc. Natl. Acad. Sci. USA* **108**, 6085–6090, 2011) *JMF*

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