Adaptation by RNA editing

Ion channels must adapt to their thermal environment in order to operate efficiently, and potassium channels are thought to be especially temperature sensitive. To identify mechanisms of temperature adaptation, Garrett and Rosenthal compared potassium channel orthologs from tropical and Antarctic octopus species and found, surprisingly, that the primary sequences encoded by the two genes differed at only four positions. Experiments on each channel expressed in *Xenopus* oocytes focused on the opening and closing kinetics, which are the most temperature-sensitive properties, and showed that the two channels are functionally virtually identical. To investigate whether temperature adaptation might be post-transcriptional, the authors looked for alanine-to-isoleucine RNA editing in the octopus channel cDNAs and found that both transcripts are extensively edited, resulting in a number of amino acid changes. Focusing on four sites that were edited almost exclusively in one species or the other, they introduced each of the four amino acid changes into the unedited channel background and found that three of them produced clear functional changes. Two exclusively tropical edits slowed channel opening and increased the rate of inactivation. However, the most pronounced effect was due to a substitution (I321V) in the channel's pore, which greatly accelerated closing kinetics by destabilizing the channel's open state. This site is extensively edited in both Antarctic and Arctic species, whereas temperate species show intermediate levels of editing and tropical species are mostly unedited, suggesting that editing of this site represents an adaptation to cold. (*Science* doi:10.1126/science.1212795, published online 5 January 2012) *AH*

Intrinsic regulation

KCNH channels, which include the EAG, ERG and ELK channel subfamilies, are voltage-gated K^+ channels involved in regulating electrical excitability in heart and nerve cells. Although related to the cyclic nucleotide–regulated HCN and CNG channels, they are not regulated by nucleotide binding. KCNH channels have an intracellular C-terminal cyclic nucleotide–binding homology domain (CNBHD) that is connected to the channel pore by a C-linker, and these regions are important for channel trafficking and function. However, there is no structural information on these C-terminal domains, so it is unclear what role they play in channel regulation. Now, Zagotta and colleagues have determined the structure of the C-linker/CNBHD from zebrafish ELK. Similarly to HCN channels, the C-linker is important for mediating intersubunit contacts, but the ELK C-linker/CNBHD forms dimers in the crystal and in solution, whereas the HCN C-linker/cyclic nucleotide binding domain (CNBD) is tetrameric. The ligand binding pocket of ELK CNBHD has a negatively charged electrostatic profile, making it an unfavorable site for binding by the negatively charged nucleotides, which may help explain its nucleotide independence. In addition, a tyrosine phenyl ring on the short C-terminal β9-strand of CNBHD sits at an equivalent position to the cAMP purine ring position in HCN CNBD. The authors find that mutating the tyrosine or deleting β9 causes a shift in ELK's voltage-dependent activation. So rather than being regulated by cyclic nucleotide–binding, the authors suggest that β9 may act as an intrinsic regulatory element. (*Nature* doi:10.1038/nature10735, published online 9 January 2012) *MM*

Written by Angela K. Eggleston, Arianne Heinrichs, Steve Mason & Michelle Montoya

Tumor-suppressive Smurf

The Smurf2 E3 ubiquitin ligase was first identified as a regulator of TGF-β signaling, but its activity and expression have since been linked to telomere attrition and cancer, respectively. However it is unclear how, or even if, Smurf2 regulation plays a role in tumorigenesis. Zhang and colleagues now report that murine *Smurf2* deletion leads to higher rates of tumor incidence and earlier oncogenic transformation of fibroblasts, suggesting that Smurf2 may regulate genomic stability. Indeed, Smurf2 colocalized with DNA damage markers in etoposide-treated cells and loss of *Smurf2* correlated with chromatin decompaction, increased histone H3 Lys4 and Lys9 trimethylation and histone H2B ubiquitination. This indicates that loss of Smurf2 relaxes chromatin structure, leading to genomic instability. Furthermore, Smurf2 was found to ubiquitinate RNF20, the E3 ligase responsible for ubiquitinating H2B, resulting in RNF20 degradation. In the absence of Smurf2, RNF20 levels increased. shRNA-mediated depletion of RNF20 resulted in reduced levels of ubiquitinated H2B and more compact chromatin. These results were corroborated by clinical samples showing an inverse correlation between nuclear Smurf2 and RNF20 levels in breast cancers and lymphomas. The authors propose that Smurf2 functions as a tumor-suppressing protein through its regulation of RNF20. How these findings relate to clinical findings correlating elevated cytoplasmic Smurf2 expression and poor clinical prognosis remains to be seen and will certainly be of interest for future study. (*Nat. Med.* doi:10.1038/nm.2596, published online 8 January 2012) *SM*

Swift, strandwise translocation

DNA glycosylases cleave the glycosidic bond of a damaged base as the first step in its removal and must be able to identify rare lesions and translocate swiftly in a vast excess of undamaged DNA. MutM glycosylase recognizes 8-oxoguanine lesions, and the structure of MutM bound to an undamaged base pair (the interrogation complex, IC) was previously solved. In a recent study, Verdine and colleagues describe an alternative IC structure, the slanted complex (SC). This complex has the same interaction with the non-target strand as the IC does, and retains the same strong bend in the duplex DNA, but the complementary target strand is moved by one nucleotide in relation to the IC, inducing a tilt in the base pairs of the helix. Mutational analysis identifies Arg112 as a residue stabilizing the IC, as a single mutation in this position can induce formation of the SC. Molecular dynamics simulations confirm that the lesion recognition process by MutM appears to involve strandwise translocation of one nucleotide, rather than single base pair steps. At this point, it is not known whether a particular undamaged base complex will adopt the IC or SC state, and it is uncertain whether strandwise translocation is the physiologically relevant mechanism. Nevertheless, these results offer an intriguing new mechanism for how proteins can move along nucleic acids. (*Proc. Natl. Acad. Sci.* doi:10.1073/pnas.1111237108, published online 4 January 2012) *AKE*

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