In mammoth's blood: Ice Age adaptation

The woolly mammoth is an extinct species that lived in the arctic regions of northern America and Eurasia. Among the adaptations shown by woolly mammoths to survive the cold weather were small ears and tails, a thick layer of fat tissue under the skin, characteristic long shaggy hair and a fine underwool layer from which their name derives. Now, work from Campbell, Cooper and colleagues reveals yet another adaptation of this fascinating mammal. By comparing the sequences encoding the hemoglobin subunits from the woolly mammoth and the related Asian and African elephants, the authors identify three derived substitutions in the former. It is known that hemoglobin's affinity for O_2 increases as temperature decreases, which could hamper oxygen delivery to limbs or distal appendages in mammals living in arctic conditions. The mutations found in the mammoth hemoglobin are different from those seen in modern arctic mammals such as reindeer and musk oxen, whose hemoglobin mutations also have an adaptive role in the cold. To explore the consequences of the mammoth mutations, the authors introduced them into cDNA encoding Asian elephant hemoglobin, expressed the mammoth and elephant proteins in *Escherichia coli* and compared their oxygen-binding properties *in vitro*. The mutations had complex effects on hemoglobin properties, with the combined outcome that the affinity of mammoth hemoglobin for oxygen is similar to that of the Asian elephant at 37 °C in the presence of its cellular allosteric cofactors but is much less affected by lower temperatures. These results point to the adaptive value of this unique set of mammoth hemoglobin mutations. (*Nat. Genet.*, published online 2 May 2010, doi:10.1038/ng.574) *IC*

Scaffolding Ras

During times of plenty, *Dictyostelium discoideum* cells exist as free-living amoeba grazing on bacteria. Upon depletion of resources, chemotaxis, based on cyclic AMP signaling between individual cells is key to promoting the aggregation of amoeba to form a multicellular spore-forming structure. This structure facilitates dispersal to remote locations, where resources might be more plentiful. Ras is known to be a first responder involved in the control of *Dictyostelium* chemotaxis, with the orthologs RasG and RasC being activated early upon stimulation of cell-surface receptors. By tagging and pulling down Aimless, known to be the major Ras–guanine nucleotide exchange factor (GEF) needed for *Dictyostelium* chemotaxis, Firtel and colleagues now identify a complex involved in the regulation of Ras activation. Using deletion analysis, the authors found that Sca1 is a central 'scaffolding' component of this complex, with different Sca1 regions being required for the presence of PP2A and the Ras-GEFs, respectively, in the complex. By disrupting Sca1, the requirement for both the PP2A– and Ras-GEF–interacting regions in a rescuing construct was shown. Furthermore, the disruption of different complex components indicates that the Sca1 complex is needed for cell motility, chemotaxis and transmission of the signal to aggregate to other amoeba. Further analyses tied the Sca1 complex to signaling through the activation of RasC rather than a second *Dictyostelium* ortholog, RasG, and indicate that the pathway also involves "Target of rapamycin complex 2" (TORC2) and the protein kinase B, which in turn phosphorylates Sca1, outlining a negative-feedback loop that affects Ras regulation. Examination of the subcellular localization of Sca1 argues that the Sca1 complex acts at the leading edge of the cell, being recruited there upon chemotactic stimulation, and that this localization is dependent on the integrity of the actin cytoskeleton. Interestingly, some components in the complex have opposing phenotypes, suggesting that there is likely to be complexity in RasC regulation in the context of the Sca1 complex. In short, this work outlines an intriguing mechanism for controlling the activation of Ras on a scaffold that may direct its activity to the site of function at the leading edge of the cell, thus indicating how signals may be harnessed to give a directional response during *Dictyostelium* chemotaxis. (*Dev. Cell* **18**, 737–749, 2010) *SL*

BRCA2 and p53 get together

Tumor suppressor p53 is known as the guardian of the genome because it can maintain genome integrity by regulating the transcription of various target genes involved in the cell cycle, apoptosis and DNA repair. Previous studies have shown a direct role for p53 in homologous recombination by physically interacting with key proteins such as the recombinase RAD51 and replication protein A (RPA). Homologous recombination must be precisely regulated to ensure genomic stability, and misregulation can lead to chromosomal aberrations and cell death. Fersht and coworkers now show a direct interaction between p53 and BRCA2, an essential protein for the efficient repair of double-stranded DNA breaks. More specifically, they show that the C-terminal domain of BRCA2 interacts with the so-called transactivation domain of p53. They also identify a second interaction between the p53 DNA binding domain and the region of BRCA2 that contains the eight BRC repeats. Finally, they show that BRCA2 overexpression downregulates the expression of p53 target genes. Based on these findings, they propose a model of how p53 may act at multiple stages of homologous recombination through its interactions with RPA, RAD51 and BRCA2 to ensure the fidelity of DNA repair and the maintenance of genome integrity. Further studies will be required to work out how the interaction between p53 and BRCA2 affects homologous recombination. (*Proc. Natl. Acad. Sci. USA* **107**, 8587–8592, 2010) *BK*

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