RESEARCH HIGHLIGHTS

Ras upregulates autophagy to support tumorigenesis

Autophagy is induced in response to stress and allows cells to survive through recycling of cellular components. As such, autophagy enables cancer cell survival in oxygen-poor tumour regions. White and colleagues now show that oncogenic Ras upregulates basal autophagy, and that Ras-transformed cells require autophagy to maintain mitochondrial function (*Genes Dev.* **25,** 460–470; 2011).

Expression of constitutively active Ras mutants induced autophagy in an mTOR-independent manner. Intriguingly, autophagy-defective Ras-transformed cells were not able to proliferate in nutrient-poor conditions and could not form tumours efficiently *in vivo*, suggesting a critical role for autophagy in Ras-mediated tumour maintenance. Indeed, basal autophagy was upregulated in human cancer cell lines expressing mutant Ras, and mutations in key autophagy genes suppressed proliferation in several of these cell lines.

When Ras-transformed autophagy-deficient cells were examined by electron microscopy, the authors noted accumulation of abnormal mitochondria. Biochemical analyses showed that autophagy defects led to decreased production of TCA (tricarboxylic acid) cycle intermediates and impaired oxygen consumption. Together, these data suggest that autophagy has an important role in supplying the metabolites necessary to support mitochondrial metabolism in cancer cells. Ras-mediated upregulation of autophagy might therefore have a dual role in tumorigenesis: it promotes tumour initiation by enabling catabolism of cellular components to support growth, and is necessary for tumour maintenance by supporting mitochondrial homeostasis. EJC

SUMO wrestling at centromeric chromatin

Centromeric heterochromatin is defined by the accumulation of specific proteins, such as HP1. Transcription of major satellite DNA repeats at centromeres has been observed, but a functional link between these RNAs and HP1 has not been demonstrated. Almouzni and colleagues now show that SUMOylation of mammalian HP1 is required for its interaction with RNA transcribed from DNA repeats of pericentric regions and *de novo* recruitment to pericentric chromatin (*Nat. Genet.* **43,** 220–227; 2011). They found that forward transcripts of major satellite repeats were present in heterochromatin immunoprecipitated with HP1α antibodies and showed that the hinge region of HP1α interacts with centromeric RNA, whereas the full-length protein does not.

The authors reasoned that a post-translational modification may prevent interaction of the full-length HP1α protein with RNA and turned to SUMOylation, as HP1α fission yeast homologue Swi6 is known to be SUMOylated. They found that the hinge region of mammalian HP1α is SUMOylated *in vitro* and *in vivo* and that this modification is required for the full-length protein to interact with major satellite RNAs *in vitro*. SUMO–HP1α is only present at low levels *in vivo* but fusing HP1α to the E2-conjugating SUMO enzyme increased the level of the modification and promoted HP1α *de novo* recruitment to pericentric chromatin. It remains to be determined how SUMO promotes the interaction with major RNAs specifically at centromeric regions. NLB

Centrosome anchoring by Nup133

Centrosomes are tethered to the nuclear envelope during the cell cycle, possibly to facilitate the coordination of spindle assembly and nuclear envelope breakdown in mitosis. Doye and colleagues now identify a centrosome-anchoring network involving the nuclear pore protein Nup133, CENPF, NudE/EL and dynein/dynactin (*J. Cell Biol.* **192,** 855–871; 2011).

The kinetochore protein and Nup133-binding partner CENPF is known to assemble at the nuclear envelope in prophase, and the authors found that this association is dependent on the amino terminus of Nup133. As NudE and NudEL interact with both CENPF and dynein and accumulate at the nuclear envelope in prophase, they investigated whether these proteins mediate the association of dynein to the nuclear envelope. The authors found that CENPF indeed recruits dynein/dynactin to Nup133 at the nuclear envelope through NudE/EL. Moreover, time-lapse microscopy imaging of chromosomes and centrosomes revealed that disruption of any of the components in this link causes centrosomes to detach from the nuclear envelope. Doye and colleagues also found that the Nup133-mediated centrosome-tethering mechanism is separate from a previously identified RanBP2–BICD2 pathway. Assembly and positioning of the mitotic spindle is transiently perturbed in cells lacking the Nup133 N terminus or NudE/NudEL. Although these defects are eventually corrected, the authors speculate that loss of NPC-centrosome tethering could lead to chromosome missegregation and aneuploidy in cases when other spindle assembly pathways are also impaired. CKR

DNA damage: miRs on the rise

Following DNA damage, cells protect their genomic integrity by initiating repair or apoptosis. Central to these responses is the Ataxia telangiectasia mutated (ATM) kinase, which is activated by double-strand breaks (DSBs). Zhang *et al.* now show that ATM promotes microRNA (miRNA) processing following DNA damage (*Mol. Cell* **18,** 371–383; 2011).

The authors demonstrate that induction of DSBs leads to the ATM-dependent upregulation of a quarter of the total known mature miRNA population. This population includes miRNAs known to be induced by the KH-type splicing regulatory protein (KSRP), which binds pri-miRNA precursors and promotes their processing to mature miRNAs by the Drosha and Dicer complexes. Zhang *et al.* also show that KSRP is phosphorylated directly by ATM in response to DNA damage, leading to upregulation of mature miRNAs. Mechanistically, ATM phosphorylation increases the affinity of KSRP for pri-miRNAs and enhances the interaction of these precursors with Drosha to allow further processing into pre-miRNAs. Intriguingly, phosphorylated KSRP is necessary, but not sufficient for miRNA upregulation, hinting at the existence of other ATM substrates with similar roles.

These findings place KSRP in the nexus between DNA-damage signalling and miRNA biogenesis and suggest post-transcriptional miRNA processing as a potential mechanism for cells to modulate gene expression in response to DNA damage. AIZ

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