RESEARCH HIGHLIGHTS

The mitochondrial Parkin receptor identified

Damaged or senescent mitochondria are removed by mitophagy, an organelle quality control mechanism that, if disrupted, causes degenerative disease. The serine–threonine kinase PINK1 directs the E3 ubiquitin ligase Parkin to damaged mitochondria to promote their elimination, but exactly how Parkin is targeted to mitochondria has been unknown.

Now Chen and Dorn (*Science* **340,** 471–475; 2013) have identified the mitochondrial receptor for Parkin. They focused on mitofusins (Mfn), known substrates for Parkin ubiquitylation. Mfn2, but not Mfn1, was shown to bind Parkin and mediate its recruitment to mitochondria. In the absence of Mfn2 in cardiomyocytes, mitochondrial protein ubiquitylation was decreased after mitophagic stimulation. PINK1 was shown to enhance the interaction between Mfn2 and Parkin, owing to its ability to phosphorylate Mfn2. Deletion of Mfn2, but not Mfn1, in cardiomyocytes caused mitochondrial enlargement and respiratory impairment. In mice, cardiomyocyte-specific deletion of Mfn2 led to dilatation of the ageing hearts and impaired contractile performance. Cardiomyocytes and heart tubes of Parkin-deficient flies recapitulated the phenotype of the cardiac-specific Mfn2-deficient mice, indicating that in both models the impairment in ubiquitylation of damaged mitochondrial proteins contributes to accumulation of abnormal mitochondria that impede cellular respiration and cardiac function. MT

No need for centromere-localized Aurora B

The chromosomal passenger complex (CPC), consisting of INCENP, survivin, borealin and the kinase Aurora B, has multiple roles in mitosis. It is believed that the localization of Aurora B to the inner centromere is essential for its role in correcting erroneous kinetochore–microtubule attachments. However, Campbell and Desai have discovered that in budding yeast, accurate chromosome biorientation occurs in the absence of centromere-localized CPC (*Nature* **497,** 118–121; 2013).

The authors found that an INCENP (Sli15) mutant with a truncated N-terminus (Sli15(ΔNT)) that is unable to bind survivin, known to target the CPC to centromeres, did not affect viability. The Sli15(ΔNT) cells failed to show defects in several assays for chromosome segregation and biorientation despite the lack of Sli15(ΔNT) and Aurora B (Ipl1) between sister kinetochore clusters (the localization corresponding to the inner centromere in other species). However, the Sli15(ΔNT)–Ipl1 complex accumulated prematurely at spindle microtubules. As microtubules can activate Aurora B, the authors suggest that this premature clustering on microtubules is sufficient for its role in biorientation, an idea they confirm by prematurely localizing Sli15 on microtubules by other means. This could also explain how truncated Sli15 can suppress the phenotypes of mutations in genes whose products are known to target the CPC to centromeres.

These data, together with previous findings by the Earnshaw group (*J. Cell Biol.* **183,** 279–296; 2008) demonstrating viability of chicken DT40 cells in the absence of centromere-localized CPC, may call for a revised view on how Aurora B exerts its role in promoting proper attachment. CKR

p53 extends to the microenvironment

p53 is known to exert cell-intrinsic tumour suppression through cell cycle arrest, apoptosis and cellular senescence. Lujambio *et al.* now report that p53 promotes non-cell-autonomous tumour suppression, by triggering an anti-tumorigenic microenvironment that regulates macrophage function (*Cell* **11,** 449–460; 2013).

Liver tumour initiation is often linked to fibrosis caused by hepatic stellate cell (HSC) proliferation. p53 is known to limit liver fibrosis by promoting HSC senescence, production of extracellular matrix and immune response regulators that comprise the senescence-associated secretory phenotype (SASP), and senescent cell clearance by immune cells. The authors demonstrated that conditional p53 deletion in HSCs promotes liver cirrhosis and mortality in mice and also results in increased non-cell-autonomous tumour formation by epithelial cells. Gene expression analyses determined that p53 regulates the SASP, immune signalling and protein secretion components in senescent HSCs, which displayed preferential secretion of macrophage-regulating cytokines. Moreover, p53-proficient senescent HSCs promoted macrophage polarization towards the anti-tumorigenic M1 subclass, which was able to eliminate senescent HSCs in co-culture experiments and was enriched in p53-positive damaged mouse livers. In contrast, p53-deficient proliferating HSCs enhanced the prominence of the pro-tumorigenic M2 macrophages, which increased premalignant cell proliferation in culture.

These findings reveal that p53 mediates a tumour-cell-extrinsic anti-tumorigenic response by controlling the SASP and macrophage polarization to limit liver damage and subsequent tumour formation. AIZ

Death by mitochondrial Rb

The retinoblastoma protein (pRB) is a transcriptional cofactor, and the gene that encodes it is mutated in many human tumours. Lees and colleagues uncovered an unexpected transcription-independent role for mouse pRB, by showing that it potentiates mitochondria-mediated cell death (*Genes Dev.* **27,** 1003–1015; 2013). They found that pRB expression enhanced TNF-α-induced apoptosis in a manner that depends on its localization to the mitochondrial outer membrane. They demonstrated that pRB requires the pro-apoptotic factor Bax for this effect, as pRB-associated apoptosis was ablated in Bax knockout cells. The authors showed that pRB interacts directly with Bax to induce release of cytochrome C from the mitochondria, leading to mitochondrial and ultimately cell demise. They identified the pocket domain of pRB as an essential mediator of this effect, and ruled out the involvement of nuclear pRB by using cells that lack endogenous Rb but express Rb with a mutation in its nuclear localization signal. Finally, using a mouse osteosarcoma cell line lacking both endogenous Rb and p53 proteins, but expressing the pRB pocket domain fused to a mitochondrial localization signal and deleted of the nuclear localization signal, the authors demonstrated that pRB-mediated effects on cell death decrease tumour formation in xenograft assays. NLB

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