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p53 cuts off invading cells

The tumor suppressor limits cell invasion by inducing a mitochondrial protease to cleave the actin cytoskeleton.

The tumor suppressor p53 does all it can to prevent oncogenes from inducing tumorigenesis, killing defective cells or pushing them into senescence. Sometimes, oncogenes manage to initiate tumor development in the presence of p53, but, even then, the tumor suppressor doesn't give up and focuses its efforts instead on limiting the tumor's ability to invade and metastasize (1). Yamauchi et al. reveal that one way p53 accomplishes this is by activating a mitochondrial protease to cleave β-actin and restrict the formation of invasive membrane protrusions (2).

"Most research has focused on how p53 prevents metastasis by regulating epithelial-to-mesenchymal transitions," explains Keiko Kawauchi from the Mechanobiology Institute at the National University of Singapore. In contrast, she says, little is known about how p53 affects the cytoskeletal processes that drive cell invasion. Kawauchi and colleagues, led by Shota Yamauchi, therefore compared Ras-transformed fibroblasts with and without wild-type p53 (2). Compared with p53-null cells, transformed fibroblasts expressing p53 were less invasive and formed fewer focal adhesions to the extracellular matrix. p130Cas, a focal adhesion signaling protein that promotes the formation of lamellipodial membrane protrusions and cancer cell invasion (3), was less phosphorylated in p53-positive cells, indicating that the tumor suppressor limits invasion by down-regulating the activity of this protein. Indeed, knocking down p130Cas suppressed the invasion of Ras-transformed fibroblasts lacking p53.

Yamauchi et al. found that, as for other focal adhesion proteins (4), p130Cas phosphorylation was enhanced by actin polymerization. The actin-depolymerizing drug cytochalasin D reduced p130Cas phosphorylation, whereas stabilizing actin filaments with jasplakinolide had the opposite effect. In the presence of wild-type p53, oncogenic Ras lowered F-actin levels by inducing the proteolytic cleavage of β-actin, thereby reducing p130Cas phosphorylation. Ras-transformed fibroblasts that either lacked p53 or expressed a dominant-negative version of the tumor suppressor showed no such decrease in F-actin levels or p130Cas phosphorylation.

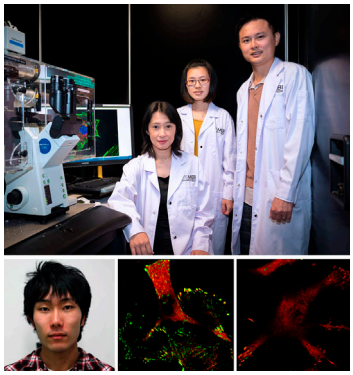
The researchers then investigated which protease was targeting β-actin. "Caspase-3 and the mitochondrial protease HtrA2 have been shown to cleave β-actin," says Kawauchi. "Caspase-3 wasn't activated by Ras transformation, so we focused on HtrA2. Knocking down or inhibiting this protease suppressed β-actin cleavage and enhanced the invasion of Ras-transformed, p53-positive fibroblasts."

> "Actin remodeling is a signal that prevents cell invasion."

HtrA2 normally resides in the intermembrane space of mitochondria, but p53 overexpression can induce the protease's release into the cytosol (5). By stimulating mitochondrial fission, however, oncogenic Ras induced HtrA2's release even in cells lacking p53. What then is the role of p53? The researchers found that the tumor suppressor lowers actin levels and inhibits cell invasion by promoting HtrA2's activation inside mitochondria so that the protease can efficiently cleave β-actin upon its release into the cytosol after mitochondrial fragmentation. The MAP kinase p38 is critical to this activation step. "p53 promotes the translocation of p38 into mitochondria so that the MAP kinase can phosphorylate and activate HtrA2," Kawauchi explains.

p53 promoted p38's translocation into mitochondria by reducing the inner membrane potential of mitochondria near the periphery of Ras-transformed fibroblasts. Ras induced p53's accumulation in the cytoplasm, allowing the tumor suppressor to stimulate p38 import, HtrA2 activation and, after Ras-induced mitochondrial fission, β-actin cleavage. "The decrease in F-actin suppresses p130Cas signaling," says Kawauchi, "so actin remodeling is a signal that prevents cell invasion."

Kawauchi and colleagues now want to investigate how p53 reduces the membrane potential of peripheral mitochondria. "How does p53 regulate local changes in mitochondrial potential? It will be important for us to find out," she says.



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Focal Point

(Bottom left) Shota Yamauchi, (top row, left to right) Keiko Kawauchi, Yan Yan Hou, Alvin Kunyao Guo, and colleagues (not pictured) investigate how the tumor suppressor p53 limits cancer cell invasion. In the absence of p53 (bottom center), fibroblasts expressing oncogenic Ras form numerous focal adhesions (red) containing phosphorylated p130Cas (green), which stimulates lamellipodial protrusion and cell invasion. In contrast, transformed fibroblasts expressing p53 (bottom right) have few focal adhesions and low levels of p130Cas phosphorylation and therefore limited invasiveness. p53 down-regulates p130Cas phosphorylation by promoting the activation of a mitochondrial protease, HtrA2, that, upon its release into the cytosol, cleaves β-actin to lower F-actin levels and inhibit p130Cas signaling.

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