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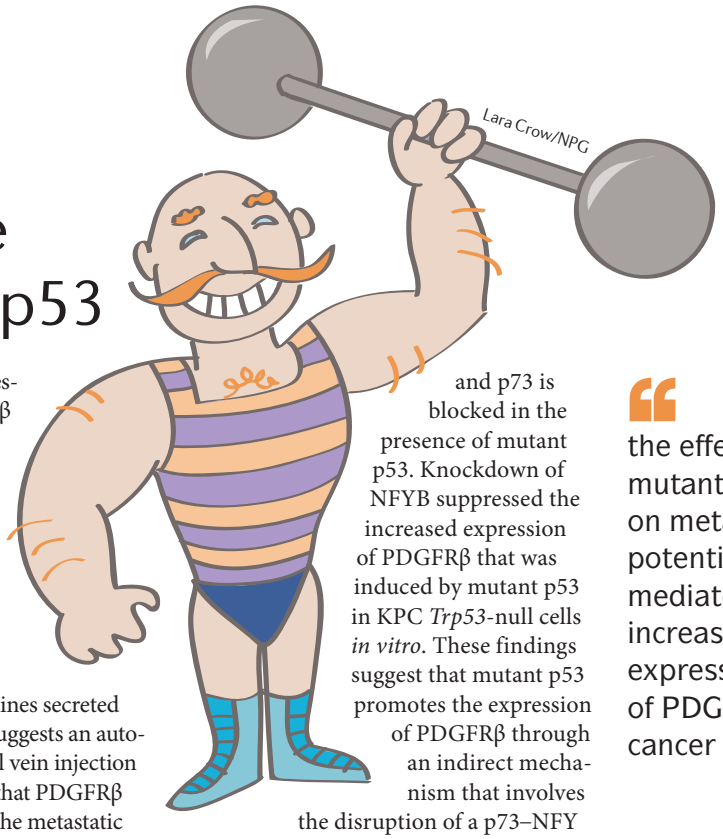
METASTASIS

# Understanding the prowess of mutant p53




Mutations in the tumour suppressor gene *TP53* are common in human tumours and there is also evidence that some mutant p53 proteins are oncogenic in addition to simply being loss-of-function mutants. Scott Lowe and colleagues have found that increased expression of platelet-derived growth factor receptor-β (PDGFRβ) in pancreatic cancer cells is mediated by DNA binding and structural mutants of p53 and that this contributes to metastasis.

*TP53* is commonly mutated in pancreatic ductal adenocarcinoma (PDAC), and this has been mimicked in Cre–Lox conditional mouse models in which one oncogenic allele of $Kras^{G12D}$ and one allele of $Trp53^{R172H}$ (a p53 structural mutant) are expressed in the exocrine pancreas (known as 'KPC mice'). To assess the biological effect of knocking down mutant p53 using short hairpin RNAs (shRNAs), the authors used a cell line derived from a tumour arising in KPC mice in which the remaining wild-type *Trp53* allele was lost during disease progression. Orthotopic injection of these KPC cells expressing a control shRNA into nude mice indicated that mutant p53 had no effect on the size of the primary tumour but substantially increased the number of metastases that developed in the lungs and the liver compared with KPC cells expressing shRNAs that targeted the mutant p53. Genome-wide transcription profiling and an shRNA approach identified *PDGFRB* as one of the genes that, when knocked down, significantly reduced the invasive capacity of KPC cells *in vitro*. PDGFRβ expression was increased in cells expressing mutant p53, and increased expression of PDGFRβ increased the invasiveness of *Trp53*-null cells. Importantly, the authors also showed that KPC cells and human pancreatic cell lines secreted PDGF, which suggests an autocrine effect. Tail vein injection assays showed that PDGFRβ is required for the metastatic effect of mutant p53 *in vivo*. Moreover, pretreatment of KPC cells with crenolanib or imatinib, two receptor tyrosine kinase inhibitors that target PDGFRβ, reduced the formation of metastases *in vivo*, and treatment of KPC mice with early pancreatic lesions with imatinib also reduced metastasis to the lungs, liver and peritoneum.

The oncogenic effects of mutant p53 have been previously shown to involve interactions with p73 and p63. p63 is not expressed in KPC cells, so the authors looked at p73 and established that the interaction between p73 and mutant p53 is important for the expression of *PDGFRB*, which is known to be repressed by p73. Several different experiments indicated that *PDGFRB* transcription involves nuclear transcription factor Y (NFY), a heterotrimeric transcriptional activator, and that p73 binds to NFYB, one of the NFY subunits. This interaction is required for the repression of *PDGFRB* by p73, and the interaction between NFYB and p73 is blocked in the presence of mutant p53. Knockdown of NFYB suppressed the increased expression of PDGFRβ that was induced by mutant p53 in KPC *Trp53*-null cells *in vitro*. These findings suggest that mutant p53 promotes the expression of PDGFRβ through an indirect mechanism that involves the disruption of a p73–NFY complex, thereby enabling NFY to promote *PDGFRB* expression.

> "the effect of mutant p53 on metastatic potential is mediated by increased expression of PDGFRβ in cancer cells"

The authors also verified that PDGFRβ expression is regulated by various mutant p53 proteins in human cancer cell lines and that an increased expression of PDGFRβ in human PDAC samples is associated with a poorer outcome. High levels of PDGFRβ in colorectal and ovarian tumours, which often have *TP53* mutations, were also associated with an increased risk of metastasis.

Overall, these results indicate that the effect of mutant p53 on metastatic potential is mediated by increased expression of PDGFRβ in cancer cells, through a mechanism that involves a loss of transcriptional repression by p73. These findings indicate that if pancreatic tumours can be detected early enough, inhibition of the PDGF–PDGFRβ signalling axis could limit metastatic potential.

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**ORIGINAL RESEARCH PAPER** Weissmueller, S. *et al.* Mutant p53 drives pancreatic cancer metastasis through cell-autonomous PDGF receptor β signaling. *Cell* **157**, 382–394 (2014)