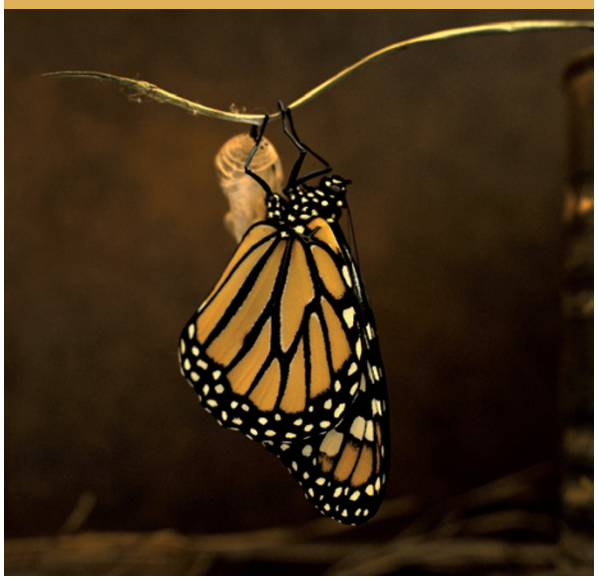
MORPHOLOGY

Oncogenic morphs of p53



The transcription factor and tumour suppressor p53 is frequently mutated in human cancers, and these missense mutations can confer oncogenic properties to the mutant protein. So, Prives and colleagues sought to determine whether p53 mutants have an oncogenic role in breast cancer.

The alteration of acinar morphology in the mammary gland is thought to contribute to breast cancer tumorigenesis. Three-dimensional (3D) culture of two metastatic breast tumour cell lines expressing either p53-R280K or p53-R273H resulted in abnormal acinar morphology. Inducible knockdown of p53-R273H almost completely reverted the disorganized acinar morphology to form acinus-like structures; whereas, inducible knockdown of p53-R280K substantially reduced the invasive morphology of these 3D cultures. This indicates that p53 mutation can alter acinar morphology. The induction of a p53-R273H variant in which the transactivation domain was mutationally inactivated was unable to prevent the reversion to acinus-like structures, indicating that transcriptional activity of this mutant causes the altered acinar morphology. To investigate further, the authors undertook genome-wide expression profiling of breast tumour cells that expressed p53-R273H grown in 3D culture. Ingenuity pathway and gene ontology analyses revealed that the expression of enzymes in the mevalonate pathway significantly correlated with p53-R273H expression.

> “protein geranylgeranylation mediates the altered morphology of mammary epithelial cells that express mutant p53”

The mevalonate pathway synthesizes various isoprenoids and cholesterol. To determine its contribution to acinar morphogenesis the authors supplemented the 3D culture medium with intermediates of the mevalonate pathway. Mevalonic acid (MVA) and MVA phosphate prevented the reversion to acinus-like structures when p53-R273H was depleted. HMG-CoA reductase catalyses the synthesis of MVA and is inhibited by statins, which are used to lower cholesterol levels in patients with hypercholesterolaemia. Treating the p53-mutant breast cancer cells (cultured in 3D) with simvastatin or mevastatin reduced their growth, induced cell death in p53-R273H cells and reduced the invasive morphology of the p53-R280K cells; these effects were reversed when the cell cultures were supplemented with MVA. Importantly, the growth of p53-R273H-expressing breast cancer cell xenografts was significantly reduced by treatment with simvastatin.

Next, the authors used inhibitors to determine which downstream mevalonate pathway products — farnesyl isoprenoid, geranylgeranyl isoprenoid or cholesterol — were important for acinar morphogenesis. They found that GGTI-2133, a geranylgeranyl transferase inhibitor, reduced the growth and invasive morphology of p53-R280K 3D cell cultures. Supplementing the 3D culture medium with geranylgeranyl pyrophosphate — the geranylgeranyl transferase substrate — restored the invasive morphology of p53-R280K 3D cell cultures in which p53-R280K was knocked down or which were also treated with simvastatin. Thus, protein geranylgeranylation mediates the altered morphology of mammary epithelial cells that express mutant p53.

The expression of mevalonate pathway enzymes is regulated by sterol regulatory element-binding proteins (SREBPs). These transcriptional activators co-immunoprecipitated with the p53 mutants; the p53 mutants were found at the promoters of genes that encoded mevalonate pathway enzymes; and SREBP1 and SREBP2 were required for the recruitment of mutant p53 to the HMG-CoA reductase promoter. Together, this indicates that the p53 mutants are recruited to genes that encode mevalonate pathway enzymes by SREBPs to upregulate their expression, and that this increases protein geranylgeranylation, which in turn alters acinar morphogenesis and promotes tumorigenesis.

Finally, the authors showed that some mevalonate pathway genes are overexpressed in human breast tumours with p53 mutations, and increased expression of nine genes that encoded enzymes in the mevalonate pathway correlated with poor prognosis. Therefore, targeting the mevalonate pathway — through the use of statins or geranylgeranyl transferase inhibitors — could be used to treat patients with p53-mutant breast tumours.

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