Mutp53 & TAp73 regulates tumour microenvironment via hypoxia-inducible factor-1α

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TAp73 opposes HIF-1 activity through a non-transcriptional mechanism, thus affecting tumour angiogenesis. TAp73-deficient mice have an increased incidence of spontaneous and chemically induced tumours that also display enhanced vascularisation. Mechanistically, TAp73 interacts with HIF-1α, promoting HIF-1α polyubiquitination and consequent proteasomal degradation. In human lung cancer, TAp73 strongly predicts good patient prognosis, and its expression is associated with low HIF-1 activation and angiogenesis. These findings demonstrate a novel mechanism for HIF-1 regulation and provide an additional explanation for the molecular basis of the growth, progression, and invasiveness of human cancers.

p53 mutants influence the tumour microenvironment by synergistically acting with HIF-1 to promote cancer progression and metastasis. In hypoxic non-small cell lung cancer (NSCLC), p53 mutants exert a gain-of-function (GOF) effect on HIF-1, thus regulating a selective gene expression signature involved in pro-tumourigenic non-cell-autonomous functions. Hypoxia triggers p53 mutant accumulation on specific genomic DNA elements in a HIF-dependent manner, and depletion of p53 mutants impairs the hypoxia-mediated upregulation of extracellular matrix (ECM) components. Hypoxia leads to the formation of a p53 mutant/HIF-1 complex that physically binds to selective DNA response elements. Analysis of clinical NSCLC revealed that expression of an ECM gene signature was highly correlated with hypoxic tumours exclusively in patients carrying p53 mutations and was associated with poor prognosis. Our data reveal a novel GOF effect of p53 mutants in hypoxic tumours and suggest synergistic activities of p53 and HIF-1. These findings have important implications for cancer staging and might provide innovative last-line treatment options for advanced NSCLC.