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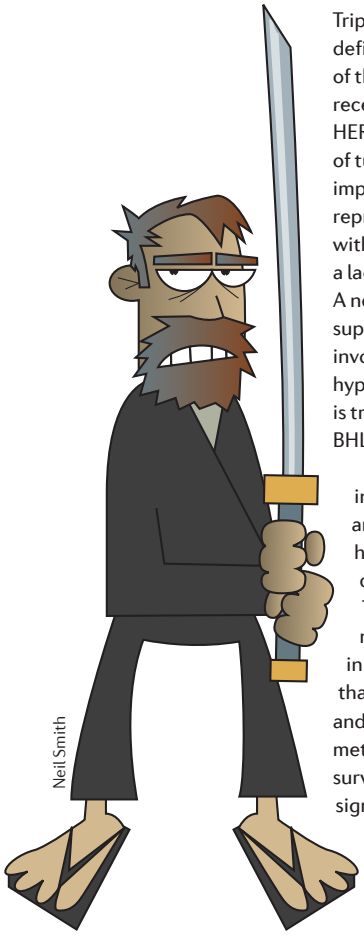
TUMOUR SUPPRESSORS

At the SHARP end of metastasis



Neil Smith

Triple-negative breast cancer (TNBC) is defined by the absence of expression of the oestrogen and progesterone receptors and ERBB2 (also known as HER2). Characterizing the mechanisms of tumour progression is particularly important for TNBC, as these cancers represent a breast cancer subtype with particularly poor prognosis and a lack of effective targeted therapies. A new study identifies a tumour suppressor mechanism in TNBC that involves an unusual degradation of hypoxia-inducible factors (HIFs) that is triggered by SHARP1 (also known as BHLHE41).

Stefano Piccolo and colleagues investigated the roles of SHARP1 and cyclin G2 (CCNG2), which they had previously identified as being downstream from the p63 isoform TAp63α, a known suppressor of metastasis. Expression analyses in primary TNBC samples indicated that low expression levels of SHARP1 and CCNG2 correlated with increased metastasis and decreased patient survival. These samples also hinted at signalling wiring: low SHARP1 and CCNG2 levels correlated with increased transforming growth factor-β (TGFβ) activity and mutation of p53 (both of which were previously known to regulate SHARP1 and CCNG2), as well as high HIF activity.

The authors then tested whether SHARP1 or CCNG2 have direct functional links to HIF signalling. They found that whereas overexpression of CCNG2 did not disrupt the transcriptional induction of HIF target genes in hypoxic conditions, both overexpression and knockdown experiments showed that SHARP1 antagonizes the protein levels and transcriptional activity of HIF1α and HIF2α in the presence of hypoxia. Thus, SHARP1 may function to regulate HIF stabilization under hypoxic conditions.

What is the molecular mechanism for the antagonism of HIF signalling by SHARP1? Co-immunoprecipitation experiments revealed a physical association between HIF1α and SHARP1. Although the canonical mechanism of HIF1α degradation occurs selectively under normoxic conditions and involves its ubiquitylation by a von Hippel–Lindau (VHL)-containing E3 ubiquitin ligase complex, the degradation of HIF1α triggered by SHARP1 overexpression occurred regardless of oxygen levels, and also in cells deficient for VHL or ubiquitin ligase activity. This indicates a novel route to HIF1α degradation; indeed, crosslinking experiments suggested that SHARP1 presents HIF1α directly to the proteasome for ubiquitin-independent degradation. This degradation was blocked by proteasome inhibitors and required the basic helix–loop–helix (bHLH) DNA-binding domain of SHARP1, although whether HIF1α degradation occurs through a DNA-bound complex is currently unclear.

What is the biological relevance of this SHARP1–HIF1α interaction? Manipulating SHARP1 levels in various TNBC cell lines that were then subjected to *in vitro* migration or *in vivo* metastasis assays showed that SHARP1 suppresses tumours by inhibiting migration and metastasis. Moreover, the tumour-suppressive effects of SHARP1 overexpression were negated by the overexpression of HIF1α.

Given the importance of metastatic spread for the lethality of many cancers, it will be interesting to investigate the importance of SHARP1 beyond TNBC, and to determine whether enhancing SHARP1 activity could be a useful therapeutic strategy.

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ORIGINAL RESEARCH PAPER Montagner, M. *et al.* SHARP1 suppresses breast cancer metastasis by promoting degradation of hypoxia-inducible factors. *Nature* **487**, 380–384 (2012)