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The "*Sharp*" blade against HIF-mediated metastasis

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Hypoxia-inducible factors (HIFs) control cellular adaptation to oxygen deprivation. Cancer cells engage HIFs to sustain their growth in adverse conditions, thus promoting a cellular reprograming that includes metabolism, proliferation, survival and mobility. HIFs overexpression in human cancer biopsies correlates with high metastasis and mortality. A recent report has elucidated a novel mechanism for HIFs regulation in triple-negative breast cancer. Specifically, the basic helix-loop-helix (bHLH), Sharp-1, serves HIF1α to the proteasome and promotes its O_2-indendpendet degradation, counteracting HIF-mediated metastasis. These findings shed light on how HIFs are manipulated during cancer pathogenesis.

Keywords: HIF, Sharp1, hypoxia, metastasis, cancer metabolism, breast cancer, angiogenesis, VHL, p63

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Metastasis dissemination is the main determinant for cancer-related deaths.[1-4] The molecular basis to acquire ability to colonize other organs by cancer cells has been long studied, but it is still poorly understood.[5] Hypoxia-inducible factors (HIFs) play a key role in different aspects of cancer biology, including angiogenesis,[6-13] metabolic reprograming,[14-20] drug resistance,[21-24] epithelial-mesenchymal transition (EMT)[25-29] and metastasis.[30-33] A recent paper reports novel data, elucidating novel aspects of the molecular basis of HIFs' regulation in metastasization of human breast cancer.[34]

The hypoxia-inducible factors 1 and 2 (HIF1 and HIF2, together referred to as HIFs) mediate physiological functions in cellular adaptation to hypoxic stress, modulating O_2-dependent transcriptional responses.[35-44] HIFs are heterodimeric transcriptional factors composed by the O_2-labile α-subunits (HIF1α and HIF2α) and the stable β-subunits (HIF1β and HIF2β). HIFs activity, hence, is primarily controlled by intracellular oxygen level. In normoxia condition, high O_2 concentration (20% O_2) confers to specific prolyl-hydroxilases (PHDs)[45] the ability to modify two proline residues on HIFs α-subunits, promoting their ubiquitin-dependent protesomal degradation, mainly mediated by Von Hippel-Lindau E3 ubiquitin-ligase (VHL).[46-51] When intracellular oxygen concentration falls down to hypoxia (less than 2% O_2), unhydroxylated status of prolines impairs VHL recognition, resulting in HIFs intracellular accumulation.[45,52-54] HIFs activation has the ability to widely modify the cell transcriptional profile.[55,56] HIFs, indeed, mediate expression of several genes related to metabolism (GLUT1, GLUT3, ALDOA, ENO1, GAPDH, HK1, HK2, PFKL, PGK1, PKM2, LDHA),[57-61] proliferation (IGF-2, TGFA, VEGFA),[12,62-64] survival (TERT, NANOG, OCT4)[65-71] and cell migration-invasion (ZEB1, ZEB2, SNAI2, MMP14, MMP9, AMF, MET, PTHrP)[72-74] (for review, Keith et al.[35]). Thus, HIFs support the adaptation to cell growth in oxygen deprivation.[35,41,75-79] Upregulation of HIF α-subunits has been reported in a wide range of human cancers and is often associated with poor prognosis.[80-85] Ability to adapt to hypoxia, indeed, has long been correlated to cancer progression, metastasis and bad prognosis in human cancers.[57,61,75,86-88] Multiple animal cancer models sustain a role for HIFs in these processes.[42,89-94] For example, conditional deletion of HIF-1α in

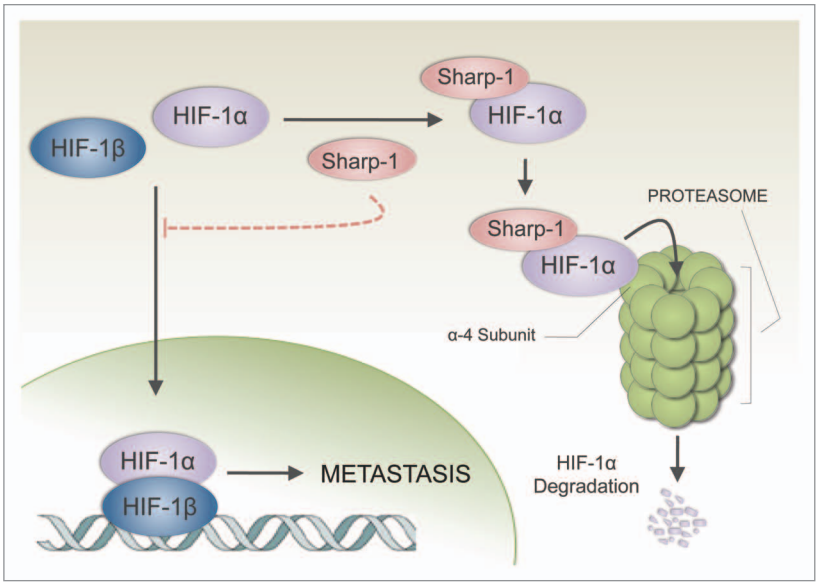

Figure 1. Sharp-1 counteracts metastasis promoting HIF-1α degradation. HIF-1α and HIF-1β form an active heterodimer able to regulate expression of several genes required by cancer cells for acquisition of metastasis propensity. Upon physical interaction, Sharp-1 drives HIF-1α on the α4 subunit of 20 S proteasome, promoting its ubiquitin-independent degradation.

breast epithelium of a transgenic model for metastatic mammary tumor (mouse mammary tumor virus, MMTV) reduced initial growth of primary tumors and significantly repressed pulmonary metastasis.[95] Moreover, HIFs also support cancer progression in tumor-associated cells.[96-101] Indeed, endothelial-specific deletion of HIF1α or HIF2α in recipient mice reduced tumor expansion in xenograft experiments.[102] However, very often HIFs regulation in cancer cells appears to exempt from the control exerted by O_2 level.[103]

In a recent *Nature* letter, Montagner et al., in Piccolo's lab, elucidated a novel mechanism for O_2-independent degradation of HIFs, mediated by Sharp-1, a rising relevant implications for invasiveness and metastatic ability of human triple-negative breast cancers (TNBC).[34] TNBC includes a heterogeneous subset of breast cancers, carrying negative expression for three clinical parameters: estrogen receptor (ER), progesterone receptor (PR) and epithelial receptor B2 (ERBB2, also known as HER2).[104-108] This subset is generally identified with an aggressive phonotype, with short periods of disease-free, high propensity for visceral or central nervous system metastases and poor overall survival. Moreover, this hormonal status (ER^-, PR^-, $HER2^-$) drastically limits the therapeutic chances.[109-112]

Sharp-1 is a basic helix-loop-helix (bHLH) transcription factor involved in different cellular processes, including proliferation, differentiation and regulation of circadian rhythm.[113] Sharp-1 has also been proposed as a metastatic suppressor candidate implicated in mutant p53-mediated metastasis.[114-123] Mutant-p53, indeed, promotes TGFβ-dependent migration by repressing transcriptional ability of the metastatic suppressor TAp63,[124-131] resulting in a downstream Sharp-1 downregulation.[115,132-136] Knockdown of Sharp-1 resembled mutant-p53 overexpression, increasing migration ability and metastasis propensity of different breast cancer cell lines.[137] Montagner and colleagues identified a significant association between HIFs activity and Sharp-1 signature in a cohort of TNBC patients. Low Sharp-1 expression, indeed, associated with high HIF activity and with low metastasis-free survival. Moreover, HIF-1α physically interacts with Sharp-1 in different cellular contexts. In a previous report, overexpressed HIF-1α and Sharp-1 co-immunoprecipitated in Cos7 cells, and Sharp-1 overexpression repressed HIF-1α-dependent control of VEGF-A promoter.[138] In Montagner's paper, authors showed physical interaction between endogenous HIF-1α and Sharp-1 in different TNBC cell lines (MDA-231, Hs578T and SUM159). Upon this interaction, HIF-1α protein level was proved to be reduced and HIF's targets inhibited in an O_2-indenpendet manner. Interestingly, HIF-1α protein reduction was a consequence of proteasome-dependent degradation: Sharp-1, indeed, led to HIF-1α direct interaction with 20 S α4 subunit of proteasome with an ubiquitin-independent mechanism, promoting HIF-1α degradation (**Fig. 1**). Therefore, according to this model, Sharp-1 represents a determinant for HIFs stability that, alternative to VHL, acts in both normoxic and hypoxic cells, promoting ubiquitin-independent HIFs' proteosomal degradation. This pathway holds a high clinical relevance. Montagner et al. performed a genome-wide analysis on TNBC cell line after Sharp-1 overexpression or HIF-1α and HIF-2α stable depletion. The two independent lists of genes obtained from this experiment showed a highly statistically significant overlap (Fisher test, $p < 10^{-73}$). This leads to the hypothesis that Sharp-1 acts as a global inhibitor of HIFs activity. Interestingly, from these lists of genes, authors obtained a signature with prognostic value for TNBC: low Sharp-1 signature displayed high propensity to metastasis formation. Moreover, multivariate analysis showed that signature for Sharp-1-repressed genes did not add any prognostic information if combined with high HIFs activity signature. This supported the idea that the prognostic value of Sharp-1 signature is completely contained in the prognostic value of HIFs signature. In addition to clinical data, authors also performed elegant in vivo experiments. Both overexpression of Sharp-1 and depletion of HIFs in TNBC cell line MDA-231 comparably abolished the ability of lung colonization after tail vein injection in mice. On the contrary, contextual overexpression of a constitutive active form of HIF-1α partially rescued the effect of Sharp-1 overexpression.

HIFs represent a key determinant for cancer pathogenesis. Altered control of HIFs stabilization and activation involves different mechanisms that together contribute to pathologic engagement of HIFs

in cancer cell reprogramming to sustain adverse growth condition. In this scenario, the novel findings about Sharp/HIFs axis contribute to the elucidation of HIFs' regulation in human disease. Sharp-1, as potential biomarker or therapeutic target, opens alternative chances for human cancer diagnosis and treatments.[139-141]

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