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Role of molecular oxygen sensors in colorectal cancer growth

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Prolyl hydroxylase domain containing proteins (PHD1, PHD2 and PHD3) mediate cellular adaptation to altered environmental oxygen levels. These molecular adaptive responses are misguided in solid tumors, which are hallmarked by intratumoral hypoxia. Tumor hypoxia is often associated with enhanced metastasis and poor prognosis. This study addressed the significance of the PHD enzymes in colorectal cancer spread.

Expression levels of PHD1, PHD2 and PHD3 were analyzed in human primary colorectal cancer samples, and correlated to clinical tumor features. PHD3 was down-regulated in a majority of tumor samples, and downregulated PHD3 expression was associated with increased occurrence of distant metastasis, enhanced tumor cell dissemination and impaired oncologic survival. No such correlations were observed regarding the expressions of PHD1 and PHD2. Therefore, the specific role of PHD3 in colorectal cancer spread was analyzed in detail, applying gain- or loss of function approaches in colon carcinoma cells. Orthotopic and heterotopic implantation of genetically altered colon tumor cells into syngeneic mice revealed attenuated tumor growth and reduced metastasis upon over-expression of PHD3. Conversely, under-expression of PHD3 facilitated the migration, invasion and clonogenic potential of tumor cells in vivo and in vitro. Further mechanistic analysis linked the enhanced tumorigenicity of PHD3 under-expressing tumor cells to improved metabolic efficiency. Since spatial expression analyses of human colorectal cancer tissues revealed PHD3 expression in both cancer cells and stromal macrophages, we likewise studied the function of PHD3 in tumor associated macrophages (TAMs). We found that loss of PHD3 supports pro-inflammatory and tumor-repellant macrophage functions.

Taken together, these findings suggest that loss of PHD3-expression in tumor cells exerts tumor-suppressive effects, whereas its expression in innate immune cells may independently regulate pro-inflammatory and tumor-suppressive effects of tumor-associated macrophages.