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Id-1 Induces Tumor Angiogenesis in Human Breast Cancers by Stabilizing HIF-1α protein

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We have previously reported that overexpression of Id-1 is significantly associated with tumor angiogenesis in human pancreas cancer (Br. J. Cancer (2004) 90:1198). In order to delineate the molecular mechanism of Id-1 action and its correlation with tumor angiogenesis in human breast cancers, Id-1 was ectopically expressed in human umbilical vein endothelial cell (HUVEC) and human breast cancer cell line, MCF7, and its effect on the expression of angiogenesis-related genes was investigated. We also investigated its association with tumor angiogenesis in 263 human primary breast cancers. In HUVEC, ectopic expression of Id-1 resulted in enhanced proliferation and tube formation, particularly under hypoxic condition. Vascular endothelial growth factor (VEGF) showed augmented expression both at the mRNA and protein levels in the presence of ectopic Id-1 expression. But for hypoxia-inducible factor 1 alpha (HIF-1α), the mRNA level remained constant despite increased protein level in the presence of ectopic Id-1 expression. Similar expression patterns of VEGF and HIF-1α were observed in MCF7. In the presence of ectopic Id-1 expression, both the VEGF promoter and the extracellular signal-regulated protein kinase (ERK) activities were enhanced as assessed by reporter assay and immunoblotting, respectively. In addition, treatment with the protein synthesis inhibitor, cycloheximide, showed sustained protein level of HIF-1α in the presence of ectopic Id-1 expression. In human primary human breast cancers, we examined the relationship between Id-1 expression and tumor angiogenesis by immunohistochemistry and quantification of microvessel density (MVD), respectively. Statistically significant correlation was found between the Id-1 overexpression (moderate/strong expression) and tumor angiogenesis, MVD ($p = 0.014$). In conclusion, Id-1 induced tumor angiogenesis in human breast cancers by stabilizing the pivotal HIF-1α protein from degradation via the activation of the ERK pathway, and by subsequently enhancing VEGF expression and vascular tube formation. Our results

strongly suggest Id-1 as a possible target molecule for anti-angiogenic drug design in breast cancer treatment.

Keyword: Id-1, breast cancers, angiogenesis, HIF-1