Angiogenesis and c-Jun

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A new pathway for tumor angiogenesis, and possibly for other forms of pathologic angiogenesis, is reported in this issue of the Journal by Zhang et al. (1). They showed that when expression of the basic region-leucine zipper protein c-Jun was suppressed in human endothelial cells by transfection with a DNAzyme targeting the c-Jun mRNA, the cells could no longer form new blood vessels in vitro or in vivo. Endothelial cell proliferation, migration, invasion through collagen, tubule formation, and production of metalloproteinase-2 were all substantially inhibited in vitro in cells that expressed the c-Jun-targeting DNAzyme. A single local injection of the DNAzyme together with a transfection reagent coincident with inoculation of tumor cells in mice inhibited tumor growth by 60% and statistically significantly reduced microvessel density in the tumors. There was no toxicity. Conneal neovascularization stimulated by vascular endothelial growth factor (VEGF) was similarly inhibited by DNAzyme-mediated suppression of c-Jun. The authors established the sequence specificity of this inhibition.

This is an important advance in the field of angiogenesis research because these results have several implications. Endostatin, an endogenous angiogenesis inhibitor (2), has been demonstrated to decrease the expression of c-Jun by twofold in human microvascular endothelial cells compared with untreated cells (3). Expression of activator protein-1 (AP-1), a dimeric protein of basic region-leucine zipper proteins that belongs to the Jun, Fos, and other subfamilies of proteins, is also strongly inhibited by endostatin (3). In fact, induction of AP-1 by pro-inflammatory cytokines and genotoxic stress is mostly mediated by the c-Jun NH2-terminal kinase (JNK) and p38 mitogen-activated protein kinase cascades (4). JNK and p38 RNA levels in endothelial cells are strongly decreased by endostatin compared with levels in untreated cells (i.e., fivefold reduction in JNK RNA; fourfold reduction in p38 RNA) (3). The findings reported by Zhang et al. (1) therefore provide a putative mechanism for this activity of endostatin and suggest an additional pathway by which endostatin inhibits angiogenesis. There are at least 12 known endogenous angiogenesis inhibitors (5), which include angiostatin, tumstatin, thrombospondin-1, interferon beta, and platelet factor 4. The article by Zhang et al. raises the possibility that in the body, angiogenesis inhibitor proteins other than endostatin may also operate through a c-Jun pathway.

Another interesting finding of the Zhang et al. study is that decreased expression of c-Jun inhibited endothelial cell production of metalloproteinase-2. This enzyme is constitutively produced by endothelial cells and is required for the switch to the angiogenic phenotype in tumor models (6). Metalloproteinase-2 is also critical for the remodeling of the extracellular matrix that occurs during angiogenesis.

When c-Jun itself is overexpressed, it can act as an oncogene (7). A variety of different oncogenes have been shown to increase the angiogenic activity of tumor cells, by increasing expression of a positive regulator of angiogenesis, such as VEGF, by decreasing expression of an angiogenesis inhibitor, such as thrombospondin-1, or by both mechanisms (8,9). We may now need to add angiogenic activity to the list of functions of the Jun oncogene.

Zhang et al. note the potential important clinical implications of their findings, namely, that DNAzymes targeting c-Jun could be candidates for novel angiogenesis inhibitors for use in cancer or in other angiogenesis-dependent diseases, such as macular degeneration or psoriasis. On the basis of the experimental results reported by Zhang et al., such inhibitors may target tumor-associated endothelial cells as well as the tumor cells themselves, thus preventing the production of angiogenic activity by tumor cells and inhibiting the endothelial cell response. Therefore, DNAzymes targeting c-Jun could act as both direct and indirect inhibitors of angiogenesis (3,5).

REFERENCES


NOTE

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