CD105 (Endoglin), Apoptosis, and Stroke

To the Editor:

The recent paper by Zhu et al.1 in this journal provides an insight into the possible mechanism of hypoxia-induced upregulation of CD105 (endoglin). The following 3 points are relevant to their paper.

Suitability of Endothelial Cell Culture and Animals as Models for Human Stroke

Lately there has been a major debate regarding the relevance of cell culture/animal models for human stroke in general and for angiogenesis in particular. Some authors maintain that the failure of current therapies for stroke in humans based on the use of animal models is possibly owing to the fact that the pathobiology of human stroke is not mirrored by experimentally-induced stroke in animal models. If true, it would limit the value findings of Zhu et al.,1 which are based on the use of murine endothelial cell culture and an in vivo mouse model of focal cerebral ischemia. However, there is strong evidence to discount this possibility. First, CD105 has been found to be highly expressed in the penumbra region of human stroke. Second, soluble CD105 levels in plasma have been found to be high in patients with stroke (our unpublished data, 2004). Furthermore, human vascular, like murine, endothelial cells showed an upregulation of CD105 expression when cultured under hypoxic conditions, although there were some notable differences in the 2 studies.1,3

Hypoxia and Apoptosis

Li et al.3 reported that hypoxia-induced upregulation of CD105 prevented vascular endothelial cells from undergoing TGF-β-induced cell apoptosis. The overexpression of CD105 in hypoxic cells ameliorated cell apoptosis either with or without TGF-β1, the conclusion being that CD105 functions via TGF-β1 signaling plus another independent pathway, as yet unknown. Since only 1% of CD105 binds to TGF-β1, the function of the remaining 99% remains unknown.4 Protection against apoptosis by CD105 could be one of its new functions.

Schematic model illustrates the possible role of CD105 in hypoxia mediated angiogenesis. Hypoxia increases the expression and transcriptional activity of HIF-1α which enhances the expression of CD105 by binding with a hypoxia response element (HRE) in the CD105 promoter. Augmented CD105 indirectly through integrin or other adaptor proteins (?), phosphorylates and activates JNK. After translocation into the nucleus, phosphorylated JNK (p-JNK) in turn phosphorylates and activates c-Jun (p-c-Jun) which promotes proliferation of endothelial cells (angiogenesis) by increasing the expression of Cdk/s/cyclins. In addition, c-Jun, by physical interaction with HIF-1, promotes transcriptional activity of the latter, leading to enhanced expression of CD105. Under hypoxic conditions, through p-JNK, CD105 forms a positive feedback regulatory loop. As above, hypoxia enhanced expression of VEGF by HIF-1α through binding to its receptor, KDR, activates ERK1/2 which through JNK, c-Jun and Cdk/s/cyclin, ultimately leads to angiogenesis. HIF-1α activated by interaction with c-Jun, increases the expression of VEGF. VEGF forms another positive feedback regulation loop through JNK under hypoxic conditions. Both positive feedback regulation loops are joined together through JNK to mediate maximum angiogenesis. Activated P38 induced by hypoxia on the one hand increase CD105 expression through a SP1 site in the CD105 promoter; on the other hand it may exert its effect through activation of HIF-1α.
The Mechanism of CD105 Induction

CD105 expression induced by hypoxia has been reported to be due to hypoxia-inducible factor-1α (HIF-1α), which directly binds to the hypoxia response element in the CD105 promoter. It has also been reported that small mothers against decapentaplegic (Smad3) and promoter-specific transcription factor 1 (SP1) interact with HIF to upregulate the expression of CD105. Hypoxia is a complicated biological process, and the expression of CD105 regulated by hypoxia is possibly involved in several pathways which may cross-talk (Figure 1). Hypoxic upregulation of gene expression involves extracellular signal-regulated kinase, which is associated with cell survival, as well as p38 and Jun N-terminal kinase (JNK), which are implicated in cell death. Zhu et al demonstrated that hypoxia-induced expression of CD105 was regulated by p38, but the role of JNK remained unresolved. In an attempt to understand the molecular mechanism by which CD105 exerts its effect on angiogenesis by TGF-β signaling, CD105 transfectants were utilized in an in vitro model, wherein overexpression of CD105 antagonised (CAGA)12-luc luciferase activity. The latter sequence is specific for TGF-β–induced Smad3 signaling. CD105 overexpression reduced serine phosphorylation of Smad3 and its intranuclear translocation and resulted in high phosphorylation of JNK1 that was able to activate c-Jun. The latter is known to inhibit Smad3 transcriptional activity on CAGA sites, suggesting that CD105 blunts Smad3 signaling through JNK1. Figure 1 summarizes the current understanding of this field. Knowledge of CD105 signaling would have practical implications for the discovery of novel therapies in a host of angiogenic diseases.

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