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Angiogenic Stimuli and Endoglin Absence Induces Brain Arteriovenous Malformations: Are Local Endoglin Deletion and Angiogenesis the 'Second Hit' That Is Necessary for Arteriovenous Malformations Formation in HHT-1?

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Arteriovenous malformations (AVMs) occur in less than 1% of the general population and can appear anywhere in the body, but brain AVMs are of special concern because their bleeding may result in a stroke. The risk of brain AVM bleeding is about 4% per year, and approximately 50% of the bleeds have severe consequences: permanent disability in half of these cases and death in the other half. AVMs may also produce headaches, seizures and progressive paralysis. Over 95% of brain AVMs are sporadic and the familial cases are mainly seen in patients with hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber syndrome, an autosomal dominant hereditary disease affecting 1 in 5,000–8,000 people [1].

HHT is caused by mutations and the consequent functional haploinsufficiency in genes related with the signaling mechanisms of the transforming growth factor- β (TGF- β) superfamily of proteins, namely endoglin (HHT-1), activin receptor-like kinase (ALK-1) (HHT-2) and Smad4 (HHT in association with juvenile polyposis (JPHT)). Further genes are predicted at loci identified by linkage analyses on chromosomes 5 (HHT-3) and 7 (HHT-4). HHT-1 and HHT-2 are the most common forms, and HHT-1 patients have ten times more risk to develop brain AVMs than HHT-2 patients [1].

The mechanism involved in HHT-associated AVMs formation has been largely discussed, and, although several hypotheses have been published, it is not fully clarified. AVMs are thought to occur in the presence of endoglin or ALK-1 haploinsufficiency and a 'second hit', presumably a local angiogenic stimulus and/or a further reduction in endoglin or ALK-1 expression that could be related with a local inflammatory process [2, 3]. It should be noted that both endoglin and ALK-1 participate in TGF- β -dependent angiogenesis [2], and that in endothelial cells, endoglin activates the TGF- β -ALK-1 signaling pathway leading to endothelial

cell activation and proliferation [4]. However, there are evidences that local absence of endoglin, either attributable to somatic mutation or to a transient lack of endoglin in endothelial cells, in the presence of angiogenic stimuli, would lead to endothelial cell proliferation and AVM formation [3].

In the present issue of *Cerebrovascular Diseases*, Choi et al. [5] assessed the relative roles of endoglin and ALK-1 insufficiency in brain malformations induced by the local deletion of endoglin or ALK-1 using the Cre/loxP system in mice and the injection into the basal ganglia of adenoviral vectors with cytomegalovirus promoter-driving Cre recombinase and the simultaneous activation of focal angiogenesis by injecting adeno-associated viral vectors with cytomegalovirus promoter-driving VEGF. Using this ingenious approach, they obtained focal areas of irregularly dilated vessels, arteriovenous shunting, and inflammatory cell infiltration, aspects resembling human brain AVM [5]. Interestingly, there were more dysplastic vessels formed per copy of endoglin deletion than that of ALK-1, thus suggesting that more severe brain dysplasia is associated to endoglin insufficiency. This is in clear agreement with the higher frequency of brain AVMs observed in HHT-1 patients as compared to HHT-2 patients.

In addition, the study of Choi et al. [5] gives a new support to the concept that HHT-related AVMs formation requires a second hit, probably an angiogenic stimulus. These studies also reveal that complete deletion of endoglin in a small number of endothelial cells is sufficient to cause brain AVMs after angiogenic stimulation. This is in agreement with the hypothesis that an additional local endoglin loss in some endothelial cells of HHT patients (for instance by a local inflammatory process) could also play a role in the appearance of brain AVMs in this disease [3]. These results also open new perspectives for the use of antiangiogenic therapies for the treatment or even the prevention of the appearance of brain AVMs in HHT patients.

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