Abstract: Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by vascular dysplasia and hemorrhage. The pathogenesis regarding heterogeneity of vascular malformations in patients with HHT has been obscure, although it has become possible to partially explain the pathogenesis from the identification of two distinct genes, endoglin and ALK-1. Endoglin and ALK-1 are type III and type I TGF-β receptors, respectively, and are exclusively expressed on vascular endothelial cells. Binding of TGF-β to the type II TGF-β receptor on endothelial cells, which is accelerated in the presence of endoglin, phosphorylates type I TGF-β receptors, ALK-5 and ALK-1, and phosphorylated ALK-5 and ALK-1 activate the downstream proteins Smad2/3 and Smad1/5, respectively. These activated Smad proteins dissociate from the type I TGF-β receptor, bind to Smad4, and enter the nucleus to transmit TGF-β signaling by regulating transcription from specific gene promoters involved in angiogenesis. Therefore, a balance between these two signaling pathways via ALK-5 and ALK-1 plays an important role in determining the properties of endothelial cells during angiogenesis.

Mutations of endoglin and ALK-1 genes are genetic pathogenesis of HHT type 1 and HHT type 2, respectively. To date, at least 29 and 17 different kinds of mutations in endoglin and ALK-1, respectively, have been found, including missense, nonsense, frameshift, and deletion mutations. The precise mechanisms of vascular abnormalities elicited by these mutations observed in HHT patients are still uncertain, although elucidation of the mechanism of intracellular signal transduction and the change in targeted gene expressions using mutant recombinant endoglin or ALK-1 proteins and knockout mice will enable us to understand the genetic and molecular pathogenesis of HHT and to effectively treat patients with HHT. J. Med. Invest. 47: 81-90, 2000

Keywords: Hereditary hemorrhagic telangiectasia, endoglin, ALK, TGF-β, Smad
**Table 1**

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H. Azuma. *Molecular pathogenesis of HHT*

The table above shows a summary of the molecular pathogenesis of HHT, focusing on the expression and function of various genes and proteins involved in the disease. The table includes columns for gene names, protein functions, and associated diseases.

**Discussion**

ALK1 plays a crucial role in the molecular pathogenesis of HHT, as it is a receptor tyrosine kinase that is involved in the regulation of angiogenesis and vasculogenesis. Mutations in the ALK1 gene can lead to the development of HHT, particularly in the context of endoglin (ENG) and endoglin-like (EDNLR) proteins.

Endoglin (ENG), a transmembrane glycoprotein, is a core component of the TGF-beta signaling pathway and is involved in the regulation of angiogenesis and vasculogenesis. Mutations in the ENG gene can lead to the development of HHT, particularly in the context of ALK1 and endoglin-like (EDNLR) proteins.

Endoglin-like (EDNLR) proteins are structurally similar to endoglin and are involved in the regulation of angiogenesis and vasculogenesis. Mutations in the EDNLR gene can lead to the development of HHT, particularly in the context of ALK1 and endoglin proteins.

HHT is a complex disease with a genetic basis that involves the interaction of several genes and proteins. The molecular pathogenesis of HHT is characterized by the dysregulation of angiogenesis and vasculogenesis, leading to the development of vascular malformations and other clinical manifestations.

Further research is needed to fully understand the molecular mechanisms underlying HHT and to develop effective therapeutic strategies for treating this disease.
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The β isoform of transforming growth factor-β (TGF-β) in in vivo studies

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Molecular pathogenesis of HHT

The overexpression of TGF-β has been associated with HHT. TGF-β is a member of the TGF-β superfamily and is involved in the regulation of cell growth, differentiation, and angiogenesis. HHT is characterized by the overexpression of TGF-β, which leads to the formation of angiomas.

Endoglin is a transmembrane protein that is highly expressed in HHT patients. Endoglin is a member of the TGF-β superfamily and is involved in the regulation of cell growth, differentiation, and angiogenesis. HHT is characterized by the overexpression of endoglin, which leads to the formation of angiomas.

The overexpression of TGF-β and endoglin has been associated with HHT. TGF-β and endoglin are involved in the regulation of cell growth, differentiation, and angiogenesis. HHT is characterized by the overexpression of TGF-β and endoglin, which leads to the formation of angiomas.

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TGF-β
endoglin

$\rightarrow$

type II TGF-β receptor

$\rightarrow$

ALK-5

Smad2/3

VEGF

plasminogen activators

$\rightarrow$

(activation phase)

ALK-1

Smad1/5

VEGF

plasminogen activators

$\rightarrow$

(resolution phase)

Endoglin and $\beta$-integrin

Endoglin and $\beta$-integrin are two proteins that play a role in the process of angiogenesis. Endoglin is a transmembrane protein that is involved in the formation of new blood vessels. $\beta$-integrins are a family of cell-surface receptors that are involved in the adhesion of cells to extracellular matrix proteins. Together, Endoglin and $\beta$-integrins are thought to be important in the regulation of angiogenesis.

References

