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VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR-3 IN HYPOXIA-INDUCED VASCULAR DEVELOPMENT: A REVIEW

[1]Obeagu, Emmanuel Ifeanyi*, [2]Okoroiwu,I.L., [3]Ijioma, Solomon Nnah, [4]Daniel-Igwe,Gloria

[1]Diagnostic Laboratory Unit, University Health Services, Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria.

[2]Department of Medical Laboratory Science, Imo State University

[3]Department of Veterinary Physiology and Pharmacology,Michael Okpara University of Agriculture,Umudike,Abia State,Nigeria.

[4]Department of Veterinary Pathology,College of Veterinary Medicine, Michael Okpara University of Agriculture,Umudike,Abia State,Nigeria.

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***Correspondence for Author**
Obeagu, Emmanuel Ifeanyi
Diagnostic Laboratory Unit,University Health Services,Michael Okpara University of Agriculture,Umudike,Abia State,Nigeria.

ABSTRACT

Vascular development is controlled by two processes: vasculogenesis and angiogenesis.Vascular development is regulated by various growth factors especially the vascular endothelial growth factor (VEGF). Hypoxia stimulates vascular development.The most important cellular response to hypoxia is transcriptional activation of a number of genes.The protein products of thes genes,of which VEGF-A is one of the best characterised,regulate metabolic adaptation and cell survival as improve oxygenation through erythropoiesis and neovascularisation.

KEYWORDS: Hypoxia, Vascular Endothelia Growth Factor (VEGF), Vascular Development.

INTRODUCTION

Formation of The Cardiovascular System is governed by two fundamental processes. The first, denoted vasculogenesis, occurs during gastrulation and involves differentiation of primitive mesodermal cells into (hem) angioblasts, the precursors of endothelial and hematopoietic cells (Risau and Flamme, 1995). In the mouse yolk sac, the (hem) angioblasts form foci, called blood islands, composed of immature hematopoietic cells surrounded by primitive endothelial cells on embryonal day 6.5 (E6.5). Subsequent fusion of blood islands

and differentiation result in formation of a primitive vascular plexus during mouse E8.0–8.5. In the embryo proper, migratory endothelial precursors aggregate into solid endothelial strands, which develop further to form the dorsal aorta, cardinal veins, and other vascular structures (. In a second process, denoted angiogenesis, a functional network is formed through sprouting and pruning of new blood vessels from preexisting capillaries and by formation and insertion of tissue folds and columns of interstitial tissue into vessel lumen (intussuception) (Burri and Tarek, 1990).

Formation of the vascular system is regulated by various growth factors. Among the most important components are members belonging to the vascular endothelial growth factor (VEGF) family. In addition to VEGF-A, the founding member, the VEGF family includes four other mammalian ligands, VEGF-B, -C, -D and placental growth factor (PlGF). The VEGF ligands bind in a specific manner to three receptor tyrosine kinases, VEGFR-1 (also known as Flt-1), VEGFR-2 (Flk-1/KDR), and VEGFR-3 (Flt-4), which are expressed preferentially on blood and lymphatic endothelial cells. The importance of VEGF activity for proper vascular development has been thoroughly underscored in several gene deletion studies. For instance, heterozygous Vegf-a$^{+/-}$ mice exhibited embryonic lethality due to deficient intra- and extraembryonal vessel formation, indicating a dose-dependent regulation of embryonic vascularization by this factor. Furthermore, targeted disruption of the three Vegf receptor genes each resulted in various degrees of vascular abnormalities. In addition to VEGFs, several other factors play important roles in vascular development. Vital components for vessel remodeling and maturation are the angiopoietins and Tie receptors, ephrins and Eph receptors, and platelet-derived growth factors and their receptors (Betsholtz et al., 2001). The mammalian embryo develops in a relatively hypoxic environment; before implantation it relies on simple diffusion of oxygen, glucose, and nutrients. After onset of vascularization, the circulatory system still has to continuously evolve in order to satisfy the increasing oxygen and nutrient demand from rapidly expanding embryonic tissues. The developing embryo therefore experiences conditions in or close to the hypoxic range for most of the time prior to parturition. The most striking cellular response to hypoxia is transcriptional activation of a number of genes. The protein products of these genes, of which VEGF-A is one of the best characterized, regulate metabolic adaptation and cell survival as well as improve oxygenation, via erythropoiesis, and neovascularization. Although hypoxia-induced transcription has recently been elucidated at the molecular level (Push and Ratcliffe,2003),

our understanding of how oxygen tension affects biological processes, such as embryonal development, is only beginning to emerge.

CONCLUSION

Hypoxia induces vascular development to compensate the low oxygen tension.This involves vasculogenesis and angiogenesis.This adaptation of the body to hypoxia stimulates the release of vascular endothelial growth factor(VEGF) which helps in the vascular development.

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