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HIF1 α in aortic aneurysms and beyond

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Abstract

Abdominal aortic aneurysm (AAA) is a permanent expansion of the vessel wall with a high prevalence in those 65 years of age and older. Aneurysms are prone to dissection and rupture that carry a mortality rate of over 85%. Currently, surgical repair is the only option to treat this disease. The need to intervene prior to these events has set off a flurry of basic studies in an effort to understand the cellular and molecular mechanisms that govern AAA formation, progression and rupture. In the present study, the role of myeloid cells in contributing to AAA development has been confirmed. More specifically, the transcription factor, hypoxia-inducible factor-1 α (HIF1 α), was demonstrated to be a necessary component for regulating the expression of extracellular matrix modifying enzymes and their endogenous inhibitors in these cells. This new discovery may lead to therapeutic targets to prohibit the degradation and weakening of the vessel wall with the hope of limiting AAA formation and/or growth.

Commentary

Since the publication of the seminal papers by Dr Alan Daugherty that described the formation of aortic aneurysm in apolipoprotein E (ApoE)-deficient mice (ApoE KO mice) and low-density lipoprotein receptor knockout mice,^{1, 2} this field has accumulated a vast amount of data that shed light on the pathophysiology of aortic aneurysms. Unruptured aortic aneurysms are often found in a routine abdominal ultrasound. Although the prevention of future rupture can be achieved by endovascular or open surgery, the adverse outcome rates from these invasive procedures are not negligible. With the aging population, the prevalence of aortic aneurysm is expected to rise; a higher utilization of ultrasound may lead to a higher detection rate of aortic aneurysm. Thus, there is an increasing interest in the development of pharmacological therapies to slow the growth and ultimately prevent the rupture of aortic aneurysm.

To understand the pathophysiology of aortic aneurysms and, more importantly, to identify potential therapeutic targets, many researchers applied Dr Daugherty's model with or

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Competing interests

The authors declare that there are no competing interests associated with the manuscript.

without modifications to various knockout and transgenic mice.^{3–5} Collectively, the new knowledge points to the contributions of many molecular pathways that are associated with tissue injury, remodelling, repair and inflammation.

Activation of endothelial cells caused or accentuated by smoking, aging and hypertension recruits immune cells to the aortic wall. At the same time, endothelial cells may act as gatekeepers to control these initial processes that eventually lead to the formation of aortic aneurysms. Vascular smooth muscle cells' physiological or sometimes dysfunctional response to immune cell signals leads to the production of matrix degrading enzymes and pro-inflammatory cytokines. Adventitial cells, including fibroblasts, can produce cytokines/chemokines for immune cell recruitment into the vessel wall as well as communicate phenotype changes to VSMC. Immune cell infiltration can home to lesion sites for further elaboration of matrix degradation, establishing a vicious cycle of sustained inflammation and excessive tissue remodelling. These events weaken the vessel wall. Again molecular events that regulate the phenotype of each cell-type during initiation and propagation of AAA are not fully understood.

In this issue of *Clinical Science*, Takahara⁶ successfully applied Daugherty's model with the addition of a high-fat diet and a higher dose of angiotensin II to ApoE knockout mice lacking hypoxia-inducible factor-1 α (HIF1 α) in myeloid lineage cells. They found a lack of HIF1 α in myeloid lineage cells resulted in the smaller diameter of aortic aneurysm and higher macrophage infiltration into aortic wall. The authors' data suggest a potential contribution of HIF1 α in myeloid lineage cells to the formation and growth of aortic aneurysm. These findings are consistent with the authors' previous finding that activation of HIF1 α in myeloid lineage cells protects against hypertension-induced vascular remodelling. This is not too surprising when we consider the fact that hypertension is a potential risk factors of aortic aneurysm. HIF1 α in myeloid lineage cells may protect against the growth of aortic aneurysm by suppressing hypertension-induced vascular remodelling. Using a mouse model that utilizes the co-administration of angiotensin II and β -aminopropionitrile,⁷ another study found that vascular smooth muscle-specific HIF1 α knockout mice had a lower incidence of abdominal aortic aneurysm (AAA).⁸ A recent study showed that treatment with digoxin or 2-methoxyestradiol, both of which can inhibit HIF1 α , reduced the incidence of aortic aneurysm in angiotensin II-treated low-density lipoprotein receptor knockout mice.⁹ Collectively, these studies highlight the importance of HIF1 α as a key transcriptional factor to regulate complex and interacting biological processes involving many cell types in the development and growth of aortic aneurysm.

There are several caveats when interpreting the authors' data. Although the authors suggest the tissue degradation controlled by matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs) as a potential mechanism by which HIF1 α affect this pathology, no direct evidence was provided. Future studies should determine the exact means by which HIF1 α regulates TIMPs, if it does. In addition, future studies should explore how aneurysms form and expand in this model in the face of reduced cytokine expression, as both interleukin 6 (IL6) and interleukin 1 beta (IL1 β), which were down-regulated in the current studies, play a prominent role in the pathophysiology of aortic

aneurysm. At the same time, one has to verify that HIF1 α expression and/or activity levels are indeed altered in human aortic aneurysms.

Another important caveat is the authors' modifications, namely the addition of high-fat diet and the higher dose of angiotensin II, that were applied to this widely replicated model. These modifications make it difficult to compare the authors' findings with the already existing data using the unmodified model by others.

Perhaps, more importantly, one must ask how this ever-increasing number of studies that are focusing on the roles of various molecular pathways in the formation and size of aortic aneurysms in animals will help us to develop a new pharmacological therapy for the prevention of rupture. In the general population, the prevention of aortic aneurysm formation would probably be achieved by managing modifiable risk factors such as smoking, hypertension and hypercholesterolaemia. A question remains of how we can manage an aortic aneurysm once it is detected. As the field matures, it may be a time for us to directly focus on the understanding of the mechanism that leads to aortic aneurysm rupture and its pharmacological prevention.

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Abbreviations:

AAA	abdominal aortic aneurysm
ApoE	apolipoprotein E
HIF1α	hypoxia-inducible factor-1 α
IL6	interleukin 6
IL1β	interleukin 1 beta
MMP	matrix metalloproteinase
TIMP	tissue inhibitor of metalloproteinase

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