Editorial

TIMPing the Aorta

Smooth Muscle Cell–Specific Deletion of BMAL1 Limits Murine Abdominal Aortic Aneurysm Development

Carla Winter, Oliver Soehnlein, Lars Maegdefessel

Abdominal aortic aneurysms (AAAs) are defined as enlargements of the abdominal aorta to >1.5-fold of their normal size (usually around 3 cm).[1] The overall AAA prevalence is estimated to be 6% in men and 1.6% in women.[2] The asymptomatic and silent nature of an aneurysm makes their diagnosis extremely challenging, whereas ruptured AAAs account for ≈15 000 deaths in the United States annually.[3] Until now only surgical (open or endovascular) repair exist as treatment options for patients. A better understanding of the subcellular deregulations and regulatory networks triggering aneurysm expansion seem of essential importance for the discovery of novel therapeutic targets.

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Homeostasis of vascular smooth muscle cells (VSMCs), being the major component of the vasculature, plays a crucial—but controversial—role in AAA development and disease progression. Although VSMCs contribute to aortic inflammation and synthesis of MMPs (matrix metalloproteinases), their proliferation and production of matrix proteins has stabilizing effects.[4] Loss of VSMCs through apoptosis is overall considered detrimental for aneurysm progression.

In this current issue of *ATVB*, Lutshumba et al[5] describe a novel mechanism through which VSMCs trigger AAA development and progression using 2 independent experimental murine models.[5] VSMC-specific deletion of the basic helix-loop-helix transcription factor BMAL1 (Brain and Muscle ARNT-Like Protein-1; or MOP3 in human or Arnt3 in mouse) shielded mice from aneurysm disease on deoxycorticosterone acetate or aldosterone (Aldo) plus high salt stimulation, as well as Ang II (angiotensin II) infusion (using hypercholesterolemic mice). Importantly, the authors were able to unravel a connection between the protective deletion of BMAL1 in VSMCs and an upregulation of the TIMP4 (tissue inhibitor of metalloproteinase 4), which suppressed deoxycorticosterone acetate-salt–induced MMP activation and consequential elastin degradation.

The authors have discovered and describe elegantly a molecular functional circuit through which BMAL1 binds to the *Timp4* promoter, and thus blocks its transcription. Hence, deletion or inhibition of BMAL1 induces Timp4 expression. TIMP4 can limit the detrimental activity of MMPs and elastin degradation, which are key processes during aneurysm expansion.[6] Other TIMPs, such as TIMP1 and TIMP3 have been previously linked with AAA disease,[7] however, the role of TIMP4 has not been thoroughly investigated in aneurysms. Thus, BMAL1-controlled regulation of TIMP4 expression represents a novel circuit exerting protective effects on aortic dilation.

Furthermore, the protective effect of *Bmal1* deletion in smooth muscle cells was associated with hampered aortic neutrophil infiltration and reduced apoptosis. Both aspects play a pivotal role in aortic aneurysm but also in many other disease models. In recent years, evidence on the importance of neutrophils in atherosclerosis and its complications has been accumulating. Mechanistically, neutrophils may facilitate influx of inflammatory monocytes, activate these and orchestrate the remodeling of diseased vessels.[8] However, in the context of AAA, the relevance of neutrophils is less understood, and hence the association of lower neutrophil accumulation and overall improved AAA made in this study raises the question to what degree there is a causal connection between these 2 observations. In addition, it should be important to study how smooth muscle cell–specific deletion of *Bmal1* relates to the expression of neutrophil-attracting chemokines, as this could explain some of the discrepancies discovered for the protective role of *Bmal1* loss in AAAs and its detrimental effects in other forms of vascular disease as discussed below (Figure).

BMAL1 has previously been recognized for its function as core clock protein being essential for controlling circadian rhythmicity on a cellular level.[9] Bioinformatics analyses have revealed that a large variety of genes is regulated in a circadian fashion in the aorta and intriguingly aortic ruptures and dissections seem to follow a circadian pattern.[10] Intriguingly, and in contrast with the current finding, systemic BMAL1 deletion was previously linked with an acceleration of vascular disease development, such as an impaired vascular remodeling in response to blood flow reduction,[11] an overall increase in MMP2/9 activity,[12] and endothelial dysfunction relating to nitric oxide (NO) synthase uncoupling.[13] Furthermore, aortic grafts from *Bmal1*$^{-/-}$ mice transplanted into littermate wild-type mice developed

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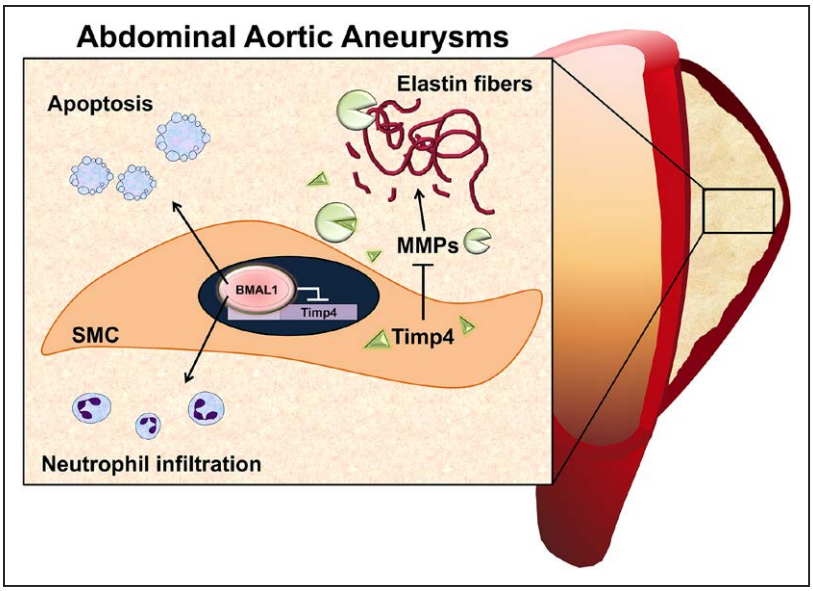

Figure. BMAL1 (brain and muscle ARNT-like protein-1) expressed by smooth muscle cells (SMCs) contributes to development and progression of abdominal aortic aneurysms (AAAs). BMAL1 regulates TIMP4 (tissue inhibitor of metalloproteinase 4) expression by binding to its promoter. TIMP4 inhibits MMPs (matrix metalloproteinases) and finally elastin breakdown leading to aortic dilation and AAA formation. In addition, cell-specific deletion of BMAL1 in smooth muscle cells reduced apoptosis and neutrophil infiltration.

robust arteriosclerotic disease.[14] All of these findings stand in contrast to the recent discovery for VSMC-specific deletion of BMAL1 exhibiting protective effects in aneurysm disease. The discordant results could reflect the differences and obstacles when utilizing a global knockout model with systemic disruption versus a conditional deletion strategy. In addition, VSMC-specific mechanisms being beneficial in limiting aortic dilatation might exert opposing (or no) effects in triggering the progression of other vascular pathologies, in which atherosclerotic processes and thrombotic events are of central importance.[14,15]

Taken together, the here presented study reveals an important regulatory circuit of Bmal1-controlled expression of TIMP4. In the context of AAA, this loop centered on smooth muscle cells seems beneficial. It remains to be studied how exactly the connection to hampered neutrophil recruitment and vessel wall apoptosis can be explained.

Disclosures

None.

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