The era of cardiovascular epigenetics: histone deacetylases and vascular inflammation

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This editorial refers to ‘HDAC4 regulates vascular inflammation via activation of autophagy,’ by D. Yang et al., pp. 1016–1028.

Vascular inflammation plays a crucial role in the development of vascular disease: atherosclerosis is characterized by infiltration of the vascular wall by inflammatory cells, increased local production of proinflammatory cytokines, and oxidative modifications of vascular structures. Given the importance of inflammation in vascular disease pathogenesis, new strategies have suppressed vascular inflammation (e.g. anti-interleukin-1β treatment with canakinumab) and reduced cardiovascular risk. These findings suggest that, in addition to the current state of the art provided by modern cardiovascular therapeutics, novel therapeutic strategies reducing vascular inflammation will allow for targeting the residual cardiovascular risk.

Vascular inflammation has also been associated with and suggested as a trigger for the recycling of cellular components and organelles, a process known as autophagy (or autophagic flux). This process is known to have a physiological role in endothelial cells and vascular smooth muscle cells (VSMCs), playing an integral role in the adaptive response to cellular stress and protecting against vascular calcification and apoptosis.

Despite a physiological role for autophagy in vascular biology, abnormally activated autophagy in vascular cells leads to local injury, cell death, and vascular disease pathogenesis. Autophagy contributes to atherogenesis through decreased plaque stability after autophagic death of VSMCs and is in turn stimulated by atherogenic molecules (e.g. reactive oxygen species, oxidized low-density lipoprotein, and cytokines). Important transcription factors and epigenetic modifications involved in cardiovascular disease pathogenesis, like forkhead box O (FoxO), have also been found to regulate autophagy. More specifically, histone deacetylases (HDACs), enzymes responsible for removing acetyl groups from lysine residues, regulate autophagy in cardiovascular cells in addition to regulating the expression of genes involved in inflammatory signaling, metabolic disorders and hypertrophic responses. Isocitrate dehydrogenase (IDH) has been proposed as a therapeutic strategy in cardiovascular disease. Although some isoforms of HDACs (e.g. sir-tuins, or Class III HDACs) have been shown to have anti-inflammatory effects, HDACs of Class II have been shown to promote autophagy and pro-inflammatory vascular processes. Whether Class IIa HDACs (e.g. HDAC4) promote vascular inflammation via autophagy is not known and may provide new mechanistic insight into the regulation of autophagy-related inflammation and ultimately vascular biology.

In this issue of Cardiovascular Research, Yang et al. extend our understanding of the role of HDAC4, a Class IIa HDAC, in vascular disease by critically linking increased expression of HDAC4 and autophagy to vascular inflammation. Specifically, in Ang II-induced models of vascular inflammation, it was observed that autophagic processes were activated and HDAC4 expression was increased, suggesting vascular inflammation was causally associated with high HDAC4 expression and autophagy. Furthermore, there was a reduction in FoxO3a acetylation and an increase in FoxO3a binding to autophagic promoters in Ang II models, suggesting a role for deacetylated FoxO3a in increasing autophagy. To investigate a direct role for HDAC4 in vascular inflammation and autophagy in this study, HDAC4 was silenced (by siRNA) or pharmacologically inhibited (by tasquinimod). HDAC4 was at least partially responsible for Ang II-induced inflammation and autophagic processes. Furthermore, silencing HDAC4 led to increased acetylation of FoxO3a, suggesting HDAC4 mediates deacetylation of FoxO3a in the Ang II model, and thereby increasing FoxO3a binding to autophagic promoters. Some studies have questioned whether autophagy is merely a secondary effect of vascular inflammation. To investigate a direct role for autophagy in vascular inflammation, the phosphatidylethanolamine-conjugated form of microtubule-associated protein light chain 3 (LC3-II) was silenced (by siRNA) or autophagic processes were inhibited pharmacologically (LY294002 or 3-methyladenine). Inhibiting or silencing autophagic processes both led to reduced vascular inflammation in Ang II models. Ang II-induced autophagy was also dependent on FoxO3a as silencing FoxO3a led to reduced Ang II-induced autophagic processes.

Taken together, these findings are the first to describe a unique mechanism for the important role of HDAC4 in the regulation of Ang II-induced autophagy and vascular inflammation via modification of key transcription factor FoxO3a (Figure 1). This study thus provides new avenues for exploration, including the direct regulation of autophagy-related vascular inflammation and HDAC-related targeting.

Despite the potential of HDAC inhibition in mediating autophagy-dependent vascular inflammation, this study also raises crucial questions about autophagy that need to be further explored. Although Yang et al. argue in this study that increased HDAC-mediated autophagy results in
increased vascular inflammation, a recent study has demonstrated that increasing autophagy via microRNA-100 reduces vascular inflammation. These different views demonstrate that pathophysiological autophagy may not be simply a result of increased autophagy but also a change in the type of autophagy, dependent on its stimuli (e.g. microRNA, HDAC). Further exploration will provide new insight into the different kinds of autophagic processes and then a more nuanced approach to targeting these processes may be developed accordingly.

Moreover, this study also raises exciting new questions to be explored in the future in the regulation of HDAC4 by oxidative stress. Epigenetic modifiers have been shown to be modulated by oxidative stress. Using an inhibitor of redox-sensitive transcription factor specificity protein (SP) 1 (mithramycin), the authors found that Ang II-induced increase in HDAC4 expression was suppressed with reduced activity of SP1, demonstrating inflammation-related increase in HDAC4 expression is SP1-mediated. This link of HDAC4 to redox-sensitive processes is
consistent with previous findings.\(^1\) From this study’s initial exploration of the redox-sensitivity of HDAC4, combined with previous knowledge that HDAC4 has redox-sensitive cysteine residues and is sensitive to protein kinase A and calcium/calcium-dependent protein kinase II, these new pathways may provide a crucial link between vascular oxidative stress and vascular inflammation.\(^14,15\)

Given the exciting importance of these findings together, studies examining HDAC4’s role in regulating vascular inflammation and oxidative stress in human vessels will provide further translational value. In conclusion, this study provides one crucial step forward in understanding epigenetic changes that mediate processes like inflammation in the vasculature, in this case particularly via autophagy-related pathways. Targeted inhibitors against specific Class IIa HDACs may be a very promising therapeutic approach in the future for autophagy-related vascular inflammation and disease as further research is conducted.

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**References**