The pivotal role of chronic inflammation in the pathogenesis of atherosclerosis and aortic aneurysm is now firmly established. Atherosclerotic lesions usually develop at branch points in arteries with abnormal shear stress. Risk factors such as hypercholesterolemia, hypertension, and cigarette smoke, among others, promote injury to the vascular endothelium, resulting in the infiltration of leukocytes to initiate an inflammatory response. Monocytes infiltrating the lesion area accumulate lipids and become foam cells. Meanwhile, T lymphocytes populating the intimal area of the lesion secrete inflammatory cytokines such as γ-interferon (INF) and tumor necrosis factors (TNF) that further stimulate macrophages and activate vascular endothelial and smooth muscle cells. Chronic inflammation of the vessel wall attributable to repetitive endothelial injury advances lesion development with the deposition of extracellular matrix in forming a fibrous cap.

The coordinated regulation of extracellular matrix synthesis and degradation is essential for the maintenance of vascular homeostasis and plaque stability. Matrix metalloproteinases (MMPs) that degrade extracellular matrix promote atherosclerotic lesion formation by increasing smooth muscle cell migration and angiogenesis. Lesions with thin fibrous cap covering a necrotic core of dead cells are prone to fissures and rupture resulting in myocardial infarction. Likewise, the increase in MMP activities in the abdominal aorta also leads to the development of abdominal aortic aneurysm (AAA) and rupture.2,3 The mechanism by which JNK activation modulates the expression of genes governing extracellular matrix biosynthesis and degradation has not been defined.

In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Zhang et al studying TNF-α suppression of prolyl-4-hydroxylase expression have identified a novel mechanism by which JNK inhibits extracellular matrix synthesis.8 They identified a TNF-α responsive suppressor element in the promoter region of the human prolyl-4-hydroxylase 1(PIH4E1) gene. The search for transcription factor interacting with this suppressor element sequence revealed several proteins, including the 55-kDa transcription factor NonO. Significantly, the binding of NonO to the suppressor element sequence was much higher when nuclear extracts from TNF-α-treated cells were included in the assay, indicating that NonO may participate with other TNF-α induced nuclear proteins in a complex in suppressing P4H1 expression. The pivotal role of NonO was confirmed by experiments showing the silencing of NonO expression with siRNA also dramatically reduced TNF-α suppression of P4H1 gene expression. Based on data showing that JNK-specific inhibitor and the ASK-1 specific inhibitor thioredoxin also blocks TNF-α-mediated P4H1 suppression in smooth muscle cells, these authors concluded that NonO participates in this pathway and that TNF-α activation of the ASK1-JNK-NonO pathway directly suppresses P4H1 expression. A schematic model showing TNF-α suppression of P4H1 synthesis via ASK1, JNK, and NonO is shown in the Figure.

The observation that TNF-α effectively inhibits P4H1 expression, and thus collagen synthesis, in smooth muscle cells is an important finding with therapeutic implications. As TNF-α has dual effects on extracellular matrix homeostasis, including the induction of metalloproteinases responsible for matrix degradation and the suppression of synthesis of matrix proteins, TNF-α contributes directly to the pathology of
Atherosclerotic plaque rupture and abdominal aortic aneurysm. Therefore, the inhibition of these TNF-α-mediated changes in vascular structure may be beneficial in preventing catastrophic outcome associated with these events. However, basal TNF-α activity may also be necessary for normal tissue repair, thus global inhibition of TNF-α activity may not be entirely desirable. Identifying a TNF-α-responsive element in the promoter region of the P4H1 gene, and uncovering the importance of ASK1-JNK-NonO pathway in mediating the TNF-α effects, offer a unique opportunity to modulate inflammation-induced alterations of extracellular matrix homeostasis in the vasculature without changing basal TNF-α activity. Novel therapeutics aimed at inhibiting ASK1-JNK-NonO activation in the vessel wall, particularly through NonO inhibition, may increase plaque stability and reduce incidence of fatal cardiovascular events. Although it remains uncertain whether such an approach can specifically improve cardiovascular outcome without any undesirable side effects, the Zhang study provided another novel target that is worthwhile of additional pursue.

Disclosures
None.

References
A No-No for NonO and JNK in Extracellular Matrix Homeostasis and Vascular Stability
David Y. Hui

Arterioscler Thromb Vasc Biol. 2007;27:1677-1678
doi: 10.1161/ATVBAHA.107.146894

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://atvb.ahajournals.org/content/27/8/1677

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the
Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for
which permission is being requested is located, click Request Permissions in the middle column of the Web
page under Services. Further information about this process is available in the Permissions and Rights
Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online
at:
http://atvb.ahajournals.org//subscriptions/