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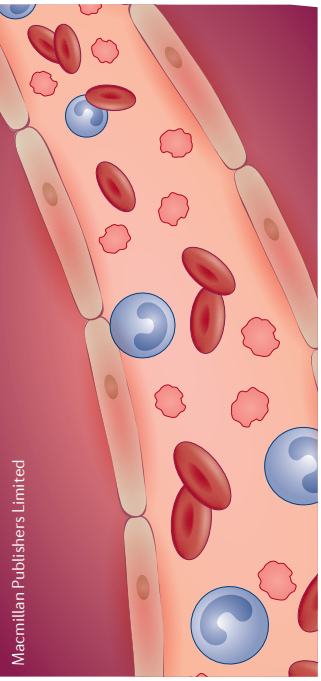
HYPERTENSION

# Thrombin amplification loop in hypertension



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Inflammatory cells are important for the development of hypertension, and coagulation factors are known to promote vascular inflammation in models of atherosclerosis. However, the degree to which platelets, coagulation factors and leukocytes interact to regulate vascular inflammation in hypertension is not known. Now, researchers have revealed an amplification loop in which angiotensin II (Ang II) induces the production of thrombin by platelets, leading to leukocyte adhesion and vascular inflammation in the setting of hypertension — a series of events that can be blocked by inhibitors of factor XI (FXI).

"We explain this finding through the phenomenon of thrombin–FXI feedback activation," explains researcher Philip Wenzel. "This amplification of thrombin generation has been described *in vitro* and in models of thrombosis, but never before in arterial hypertension or in any other vascular disease that is not a clotting disease."

Previous research demonstrating a role for inflammation in hypertension and interaction between inflammatory and coagulation factors in models of arterial injury led Wenzel and colleagues to explore the potential interplay between platelets, leukocytes and coagulation factors in arterial hypertension. Administration of Ang II to mice led to adhesion of leukocytes to the endothelium in the carotid artery. Depletion of thrombin or platelets inhibited Ang II-induced leukocyte adhesion and endothelial dysfunction, suggesting a role for platelets in thrombin generation or in mediating its effects. Mice lacking functional GPIbα thrombin receptors on platelets were also protected from Ang II-induced vascular dysfunction.

As thrombin can promote coagulation by activating FXI, and FXI can bind to GPIbα on platelets, Wenzel and colleagues looked at the effects of blocking FXI on Ang II-induced vascular dysfunction. Genetic or pharmacologic inhibition of FXI led to reduced endothelial dysfunction and leukocyte adhesion in response to Ang II; these effects were restored by administration of FXI, leading to the proposal that platelets are key to thrombin–FXI feedback activation in Ang II-induced vascular inflammation. Reducing FXI levels also significantly attenuated hypertension induced by Ang II in mice or by 5/6 nephrectomy in rats, an effect that was associated with decreased vascular oxidative stress, reduced thrombin formation, and reduced parameters of kidney damage.

The researchers plan to further investigate the mechanisms and clinical applications of their findings. "As FXI inhibitors will soon be in clinical use as anticoagulants, it will be important to measure their effect on blood pressure," notes Wenzel.

*Susan J. Allison*

**ORIGINAL ARTICLE** Kossmann, S. *et al.* Platelet-localized FXI promotes a vascular coagulation-inflammatory circuit in arterial hypertension. *Sci. Transl. Med.* http://dx.doi.org/10.1126/scitranslmed.aah4923 (2017)