Editorial Commentary

Hypertension: A Novel Regulator of Adaptive Immunity in Atherosclerosis?

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Epidemiological investigations clearly point out that hypertension is a powerful cardiovascular risk factor. Elevated blood pressure levels have been found to be highly predictive of cardiovascular events, including ischemic coronary disease, stroke, and peripheral arterial disease. These ischemic cardiovascular events have a predominant vascular origin resulting from atherosclerosis.

Hypertension is known to act on the arterial wall to promote both vascular remodeling and atherosclerosis, resulting in diminished arterial wall compliance and elevated stiffness. Clinical and experimental investigations have shown that increased blood pressure is associated with exaggerated atherosclerosis. In human subjects, carotid artery intima-media thickness, measured with high-resolution B-mode ultrasound, is highly correlated with blood pressure levels and well-reflects atherosclerosis and tracks its progression. Previous experimental studies have demonstrated that hypertension increases the rate of atherosclerotic plaque development in hypercholesterolemic rabbits, monkeys, and more recently in mouse models of atherosclerosis.

Several mechanisms can account for hypertension-induced atherosclerosis. Pressure-induced stretch of the wall increases endothelial permeability to low-density lipoprotein and accentuates low-density lipoprotein accumulation in the intima, which is central to the atherogenic process. Hypertension also promotes or aggravates endothelial dysfunction, and our current understanding of the pathobiology of atherosclerosis suggests that alterations of endothelial function play a pivotal role in the development and progression of atherosclerosis and its clinical complications. Monocyte adhesion, an early hallmark of atherosclerosis, is enhanced by hypertension. Finally, inflammation associated to hypertension is of particular relevance to atherosclerosis, because it is well-accepted that atherosclerosis is an inflammatory disease of the arterial wall where interactions between vascular and inflammatory cells play critical roles in disease initiation and progression. Recent studies underline the role of hypertension in the vascular activation of the nuclear transcription factor NF-κB, which induces the transcription of a large range of inflammatory genes.

Of particular importance is the fact that clinical research has revealed that severe clinical manifestations of atherosclerosis are caused by unstable plaques prone to fibrous cap rupture, which triggers thrombus formation and vessel lumen occlusion, rather than lumen stenosis stemming from exaggerated plaque growth. Features of unstable plaques include a large lipid core with increased accumulation of activated inflammatory cells (macrophages and T lymphocytes) that infiltrate the fibrous cap and induce substantial loss in both vascular smooth muscle cells and collagen, leading to fibrous cap destabilization and disruption. Stable atherosclerotic plaques are characterized by a small lipid core, which is separated from the lumen vessel by a thick fibrous cap, composed of vascular smooth muscle cells secreting a solid collagen matrix. Other “unstable” plaques are characterized by endothelial erosion and lumen thrombosis.

Whether and how hypertension could affect the atherosclerotic plaque phenotype is totally unknown. Moreover, hypertension presents in several forms, some linked to the activation of the renin-angiotensin system and elevated circulating angiotensin (Ang) II, and some with normal Ang II levels. Whether all forms of hypertension convey similar effects on plaque development and vulnerability is a critical issue worthy of investigation. In this issue of Hypertension, Mazzolai et al specifically addressed this issue by using the apolipoprotein E (apoE) knockout model with 2-kidney, 1 clip (2K-1C) renal hypertension, resulting in activation of the renin-angiotensin system and high circulating Ang II levels, or 1-kidney, 1 clip (1K-1C) renal hypertension resulting in similar increase in blood pressure levels but with normal plasma Ang II levels. Mazzolai et al found that these 2 forms of hypertension led to similar increase in atherosclerotic plaque size compared with normotensive animals. However, interestingly those hypertensive animals with high Ang II had atherosclerotic plaques with signs of instability, including higher macrophage content, lower collagen and smooth muscle cell accumulation, and larger lipid core than hypertensive apoE−/− mice with normal Ang II, which had plaques suggestive of a stable phenotype (thicker fibrous cap, less inflammatory cell infiltration, and smaller lipid core). In addition, hypertensive apoE−/− mice with high Ang II showed enhanced systemic inflammation compared with hypertensive mice with normal Ang II, as shown by increased serum IL-6 levels and white blood cell counts.

Both innate and adaptive immune mechanisms are involved in atherosclerosis. The profile of the T helper (Th) cell response in atherosclerosis is of the Th1 type, characterized by high secretion of interferon γ (IFN-γ), and several studies have shown the important pro-atherogenic potential of Th1-related pro-inflammatory mechanisms in experimental...
models of atherosclerosis.13 Of great interest in this context, Mazzolai et al reported that splenocytes from hypertensive apoE−/− mice with high Ang II produced more IFN-γ than those from hypertensive mice with normal Ang II or normotensive apoE−/− mice, suggesting that Ang II promoted an immune switch toward a Th1 response. This is in good agreement with a recent study by Shao et al, who demonstrated a significant increase in the Th1 cytokine, IFN-γ, and a decrease in the Th2 cytokine, IL-4, in rats infused with Ang II.14 Ang II can act through AT1 receptors on immune cells and triggers the proliferation of splenocytes.15

The work of Mazzolai et al adds arguments to a substantial body of evidence that suggests an important role for Th1-mediated immune responses in the development and progression of atherosclerotic lesions in experimental models.13 Human studies also indicate a strong association between Th1-related responses and plaque instability.16 Therefore, based on observations that the immune response in atherosclerosis is switched toward Th1-mediated responses, a dogma has emerged that Th1 is deleterious and Th2 protective against atherosclerosis.17 The finding that IL-10, a Th2-related cytokine, exerts major antiatherogenic effects18 has particularly reinforced this Th1/Th2 paradigm in immunity to atherosclerosis. However, IL-10 is not specific to Th2 cells and can be secreted by both macrophages and regulatory T cells (Treg), another subtype of T cells. Treg, with cytokine profiles distinct from either Th1 or Th2 cells, has been shown to play an important role in the regulation of, and protection against, various Th1-mediated and Th2-mediated immunoinflammatory diseases.19 We have recently reported that supplementation of apoE−/− mice with antigen-specific Tr1, a subtype of Treg that produce high amounts of IL-10, lead to the induction of a regulatory immune phenotype with reduction in both Th1-mediated and Th2-mediated responses, decreased plaque development, and promoted stabilization.20 It is therefore tempting to speculate that atherosclerosis results from an imbalance between pathogenic and regulatory T-cells, and it would be of great interest to further explore the potential effect of Ang II on regulatory T cells.

In conclusion, the work by Mazzolai et al is the first to our knowledge that sheds light on the differential effects of hypertension on atherosclerotic plaque stability depending on the humoral status. Hypertension must be seen as a permissive factor that promotes atherosclerosis development, but additional humoral factors that often accompany hypertension, especially Ang II, determine the phenotype of the plaque, which ultimately determines the occurrence of clinical events.

References
