The Networks Between the Sympathetic Nervous System and Immune System in Atherosclerosis

Recently, we read with great interest a review by Libby et al. (1). In this review, they demonstrated that leukocytes act as prostaglandins in atherosclerosis and build up important neuroimmune networks. However, there are some concerns about how the sympathetic nervous system (SNS) interacts with the immune response in atherosclerosis.

The SNS exerts complex control over inflammation in atherosclerosis both on a systemic scale and at the regional level (Figure 1). SNS fibers innervate the...
primary and second lymphoid organs (bone marrow, thymus, spleen, lymph nodes) involved in immune modulation. The SNS contributes to the differentiation, maturation, recruitment, and regulation of immune cells via lymphoid organs. The SNS is also a modulator in thymus, spleen, and lymph node and can modulate the recognition, proliferation, and effector phases of the immune response. It influences immune cell migration and alters cytokine production (2,3).

What’s more, the SNS directly innervates the target lesion and plays a proinflammatory role in immune cells. First, norepinephrine released from sympathetic nerve endings binds to α- or β-adrenergic receptors expressed on immune cells (T cells, B cells, natural killer cells, and macrophages). This response gives rise to a cascade of events, including the production of proinflammatory cytokines and recruitment of leukocytes (4). Second, the SNS releases neuropeptide Y, which increases the adhesion of human leukocytes to endothelial cells. Third, the SNS might also exert an influence on vascular and lymphatic smooth muscle regulating the blood flow or lymph flow and thereby lymphocyte delivery (5).

Furthermore, peripherally secreted proinflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor-α, can signal to the brain via the circulation or through afferent fibers, which in turn leads to activation of the SNS (2). This might form a vicious circle between SNS activity and inflammation (atherosclerosis).

Mingxian Chen, MD
Qiming Liu, MD
*Shenghua Zhou, MD
*Department of Cardiology
The Second Xiangya Hospital of Central South University
No. 139 Middle Renmin Road
Furong District
Changsha City
Hunan Province 410011
China
E-mail: xyzhoushenghua@126.com
http://dx.doi.org/10.1016/j.jacc.2016.04.049

Please note: This work was supported by grants from the National Natural Science Foundation of China (No. 81270257). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

**REPLY: The Networks Between the Sympathetic Nervous System and Immune System in Atherosclerosis**

We thank Dr. Chen and colleagues for their interest in our recent paper (1). We agree completely with the importance of the sympathetic nervous system as a modulator of leukocyte functions and hematopoiesis. Indeed, similar to the diagram that they provide, the central Figure of our publication depicts explicitly the links between the central nervous system, sympathetic outflow, and beta3-adrenergic signaling as a stimulator of overproduction of leukocytes under stress conditions such as acute myocardial infarction. We described this pathway in the paper by Dutta et al. (2) cited in their letter. We thank these readers for their appreciation of this important point.

*Peter Libby, MD
Matthias Nahrendorf, MD
Filip K. Swirski, PhD
*Division of Cardiovascular Medicine
Department of Medicine
Brigham and Women’s Hospital
Harvard Medical School
77 Avenue Louis Pasteur
Boston, Massachusetts 02115
E-mail: plibby@bwh.harvard.edu
http://dx.doi.org/10.1016/j.jacc.2016.05.017

Please note: Dr. Libby is involved in consulting in clinical trials; receives sponsored research support from Novartis; and receives funding from the National Heart, Lung, and Blood Institute (R01 HL804072). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

**Percutaneous Coronary Intervention After Transcatheter Aortic Valve Replacement: Approach and Challenges**

We read with great interest the paper by Chakravarty et al. (1) regarding percutaneous coronary intervention (PCI) of the left main coronary artery (LM) in