C3 or Not C3: That Is the Question
Stephanie W. Watts

Hypertension. 2004;44:25-26; originally published online May 3, 2004;
doi: 10.1161/01.HYP.0000129538.65075.6b

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/44/1/25

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Hypertension 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 Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/
Numerous investigators have studied the potential genetic causes of essential hypertension, and several genes have been described as candidates. These genes may contribute to the inappropriate and exaggerated growth of arterial smooth muscle cells in genetically hypertensive individuals and thus ultimately contribute to the disease by supporting creation of stronger, more muscular, and sometimes narrowed arteries. The article by Lin et al in this issue of *Hypertension* describes selective expression of the complement protein complement 3 (C3) in arterial cells from the spontaneously hypertensive rat (SHR) and clear involvement of this protein in mediating enhanced arterial smooth muscle growth in the SHR.

**Complement 3**

The complement system is a major effector of humoral immunity and innate immunity. Complement proteins, normally found in the plasma, are inactive and become active through classical stimulation (antibody-activated) pathways or alternative (cell surface–activated) pathways. Proteolysis of C3 represents an early and essential event in complement activation through either pathway. Cleavage of C3 by spontaneous breakdown, binding to a microbial surface, or through binding a C3 convertase leads to generation of 2 proteolytic proteins called C3a and C3b. These effectors act ultimately to cause phagocytosis of opsonized particles, activate later stages of complement (through formation of C5 convertase), and induce inflammation.

The possible role of C3 or complement in hypertension has largely been studied in the kidney, where C3 or complement plays a role in IgA nephropathy, and is deposited in small arteries and arterioles of SHRs given deoxycorticosterone acetate (DOCA) and salt, and is necessary for renal injury in DOCA–salt mice. C5-deficient mice administered DOCA and salt do not develop as severe a renal injury as wild-type mice treated with DOCA and salt. C3 has been implicated in the left ventricular perivascular inflammation found in renovascular hypertensive rats and as a stimulus of pulmonary vascular constriction. In the human, elevated levels of C3 have been associated with the hypertension of systemic lupus erythematosus and essential hypertension with concomitant left ventricular hypertrophy. However, to this point, C3 had not been described as playing a role in or as a cause of arterial smooth muscle cell growth in hypertensive disease.

The article by Lin et al in this issue describes an important finding of a differential expression of the complement protein C3 in the exaggerated growth of arterial smooth muscle cells from SHRs of an age (3 weeks) that precedes measurable increases in blood pressure. The authors first study medial tissues from whole arteries and, using gene chip analyses, demonstrate that several genes are expressed in SHR tissues but not Wistar–Kyoto rat (WKY) tissues; other genes are expressed in both but at either lower or higher levels in SHRs versus WKYS. Preprocomplement C3 is an mRNA species expressed in SHRs but not in WKYS, and the authors were able to demonstrate that this “all or none” expression was faithfully continued in cells that were cultured from WKYS and SHRs. This was different from the other mRNA species (sodium-dependent neurotransmitter transporter, epidermal growth factor precursor, etc.) for which expression was upregulated in WKY cells once put into culture; cells from WKYS continued to not express C3. The authors followed this lead to demonstrate that exogenous C3 could change the phenotype of smooth muscle, could stimulate a higher level of growth in the SHR versus WKY cultured myocytes, and was necessary for the enhanced growth/synthetic phenotype of the SHR cells. This was based on the observations that reduction of C3 expression by antisense oligonucleotide administration altered the phenotype and growth of these cells. The authors conclude that C3 might be the gene that enables the synthetic phenotype of arterial smooth muscle cells from SHRs at a prehypertensive stage and thus may represent a new target for hypertensive treatment. An article by Schaadt et al described an increased frequency of the C3 gene in hypertensive patients compared with control, with a relative risk of 1.90. These findings, published nearly a quarter of a century ago, complement (pun-intended) the work discussed here. The present studies raise the idea that complement plays roles other than that strictly in inflammation, and this opens up exciting avenues for understanding this now more complex role of complement in vascular function. Lin et al reference articles that describe the production of C3 by some vascular smooth muscle lines, and thus the effect of C3 could be immediate to the vasculature.

**Questions and Perspectives**

These studies bring up several questions. First is the question as to relative levels of circulating and activated C3 (C3a,
C3b) in WKYs versus SHRs and why the growth curve in cells from SHRs would be higher in response to exogenous C3. The authors demonstrated that cells from SHRs but not WKYs are making C3. Exogenous C3 would then be completely “new” to cells from WKYs but not new to cells from SHRs, which are presumably expressing C3 already. Because the cells from SHRs are already exposed to C3, these findings suggest that it is the elements downstream of C3 and their activity that may be different between SHRs and WKYs. It will be intriguing to understand the downstream targets of C3 in the vascular smooth muscle cell. Second, what governs the expression of C3 in the SHR versus WKY cell? There must be elements that allow or promote C3 expression in SHR that are not activated in cells of the WKY. This could include differences in the preprocomplement C3 promoter, level of transcriptional activation, stability of mRNA, etc. Another larger question raised is the role of the inflammatory system in hypertension, both experimental and human. In what other target organs might complement or C3 play a role?

In summary, the finding of Lin et al. suggests that the complement system is critical for the exaggerated growth and altered phenotype observed in arterial smooth muscle cells from the SHR. This represents a new function for complement in hypertension and is important and exciting for this reason.

References