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Editorial

C-reactive protein: A potential new molecular link between inflammation, thrombosis and vascular cell proliferation?

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See article by Cirillo et al. [9] (pages 47–55) in this issue.

C-reactive protein (CRP), a pentraxin synthesized in the liver, is a highly conserved pentameric plasma protein that participates in the systemic response to inflammation. In humans, plasma levels of CRP may rise rapidly and markedly (>1000-fold) after an acute inflammatory stimulus and presumably contribute to host defence [1]. On the other hand, although CRP may exert pleiotropic effects, both "pro-inflammatory" [2] and "anti-inflammatory" (reviewed in Ref. [1]), a large number of studies have demonstrated an association between slightly elevated CRP plasma levels (3–10 μg/ml) and increased risk of developing cardiovascular disease in apparently healthy individuals [2]. This suggests that CRP might be not only a simple downstream marker of inflammation but may have a direct role in atherothrombosis.

Accumulating evidence suggests that CRP may directly elicit a variety of pro-atherogenic effects in vascular tissue. In particular, it has been reported that CRP stimulates production of interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1), intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin in vascular endothelial cells [3]. Also, CRP attenuates endothelial progenitor cell survival, differentiation, and function via inhibition of nitric oxide (NO) [4]. Vascular smooth muscle cells (vSMC) may be also a target of the pro-inflammatory and pro-atherogenic actions of CRP. In fact, it increases angiotensin II-induced vSMC proliferation, migration and reactive oxygen species (ROS) production. In addition, CRP up-regulates inducible NO production and increases nuclear transcription factor, NF-κB, and mitogen-activated protein kinase (MAPK) activities in vSMC [5].

In monocyte-macrophages, CRP stimulates increased uptake of oxidized low-density lipoprotein (ox-LDL), production of cytokines, and expression of matrix metalloproteinase-1 (MMP-1) [3]. Interestingly, in these cells, recent reports show that CRP also up-regulates expression of tissue factor (TF) [6], thus linking inflammation, coagulation, and thrombosis [7].

Tissue factor is a transmembrane glycoprotein that is not normally exposed to the circulation or is not normally in contact with it. Upon vascular injury, TF is exposed to circulating blood, where it becomes available for binding to Factor VIIa. The resulting complex leads to initiation of the serine protease cascade of the coagulation system. Strong evidence assigning a central role to TF in inflammation- and thrombosis-associated atherosclerosis has also been reported. Thus, TF can be found in the atheromatous plaque and its exposure after plaque disruption may lead to thrombosis, vascular occlusion, and myocardial infarction (reviewed in Ref. [8]).

Although it is generally assumed that CRP induces TF expression in human monocytes ([6]), it remains to be determined whether CRP modulates TF levels and activity on vascular wall cells. In the study published in the current issue of *Cardiovascular Research*, Cirillo, et al. show for the first time that CRP increases TF activity and antigen both in human umbilical vein endothelial cells (HUVEC) and vSMC in a concentration-dependent manner. TF up-regulation by CRP occurs at the transcriptional level via activation of the transcription factor NF-κB ([9]). The authors hypothesize a direct interaction between CRP and endothelial cells, in accordance with recently published results by Devaraj et al.

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[10] showing that CRP mediates its biological effects on endothelial cells via binding and internalisation through Fcgamma receptors CD32 and CD64.

The study by Cirillo et al. is particularly interesting because it confirms the existence of a molecular link between vascular inflammation and clotting activation previously proposed by Napoleone et al., who demonstrated that long pentraxin PTX3 (structurally related to classic pentraxins, such as CRP) enhanced the expression of TF on endothelial cells previously exposed to endotoxin (lipopolysaccharide) or interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α) [11].

Furthermore, although previous studies indicated a controversial role of CRP in endothelial and vSMC proliferation (reviewed in Ref. [3]), another interesting finding of this paper is that CRP, besides to induce TF, stimulates proliferation of both HUVEC and vSMC in a dose-dependent manner by ERK1/2 activation. This suggests that CRP might play a role in thrombosis and vascular remodelling associated with neointimal formation and vascular disease. Thus, CRP may regulate proliferation and migration of vascular cells either directly (results from this study) and/or indirectly through induction of TF. In fact, cell culture studies have demonstrated that the TF:VIIa complex is critical for vSMC migration [12] and, interestingly, TF:VIIa-mediated vSMC migration can be inhibited by intravascular adenoviral delivery of TF pathway inhibitor (TFPI) in a murine model of vascular remodelling [13]. The relative pathophysiological relevance of these two CRP-controlled mechanisms might be better tested in vivo using the low-TF mice model in which a human minigene directs a low level of both constitutive and induced TF expression in transgenic mice [14].

Since transgenic mice that over-express CRP are more likely to have arterial thrombosis following vascular injury [15], it would be interesting to determine in this model the impact of CRP over-expression on vascular damage-induced thrombosis.

Results presented by Cirillo et al. in this issue of *Cardiovascular Research* lend further support to the view that CRP might be not only a risk marker but it may indeed be a participant and culprit in atherogenesis. Moreover, the recent observation by Bisoendial et al. that infusion of CRP into humans induces endothelial cell activation and release of inflammatory mediators and coagulation factors [16] is consistent with this scenario.

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