PPARα AND ATHEROSCLEROSIS

Jorge Plutzky

Introduction

Over the past five years, several groups, including ours, began pursuing the hypothesis that peroxisome proliferator activated receptors (PPARs) might be expressed in the vasculature, directly influencing important vascular responses. Certainly such notions were well-based, given established roles for PPARs in regulating metabolic processes, such as lipids, glucose homeostasis, and adipogenesis, known to critically influence the vessel wall. Furthermore, the use of PPAR agonists, like thiazolidinediones and fibric acid derivatives in clinical situations with increased cardiovascular risk, like diabetes and dyslipidemia (high triglycerides/low HDL), underscored the potential involvement of PPARs in vascular biology and specifically atherosclerosis. Such issues are of particular relevance in regards to PPAR alpha (PPARα), given putative natural ligands such as certain fatty acids, and the existence of clinical trials utilizing PPARα ligands that focus on cardiovascular endpoints. In fact, our interest in PPARα grew out of prior observations from our group that certain fatty acids, like docosahexanoic acid (DHA), inhibit the induction of adhesion molecules like VCAM-1, although the mechanism for this response remained unclear [1].

PPARα, Expressed in the Vasculature, a Possible Anti-inflammatory Mediator?

PPAR-α is expressed throughout the vasculature, with evidence for its presence in monocytes (mo)/macrophages (MP) [2], vascular smooth muscle cells (VSMC) [3], and endothelial cells (EC) [4,5]. In order to address the potential role of PPAR-α in vascular responses, one must demonstrate regulation of relevant gene targets in the vasculature. Given our prior observations that putative PPARα ligands like DHA could alter adhesion molecule expression [1], we investigated the potential transcriptional regulation of adhesion molecules through PPARα.

Adhesion molecule expression may be one among the earliest steps in atherogenesis [6-9]. This process depends upon the interaction between adhesion molecules on the endothelial cell (EC) surface and their counterligands on leukocytes. These EC adhesion molecules include vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), E-selectin, or P-selectin [10,11]. The increased adhesion molecule expression seen in EC in human atherosclerotic lesions may contribute to further leukocyte
recruitment to sites of atherosclerosis [10,12,13]. Recent work suggests serum levels of circulating adhesion molecules may predict cardiovascular risk.

We found that in human EC, PPARα activators inhibited the induction of VCAM-1 expression by inflammatory cytokines like TNFα [5] (Figure 1). This response, in our hands, was demonstrable on Northern and western blotting analysis, with apparent specificity for VCAM-1, with no effect demonstrable on E-selection nor ICAM-1. Similarly, the response seemed restricted to PPARα, with no changes after PPARγ agonists. The inhibition of VCAM-1 was not due to changes in message stability in response to these agonists, as shown by mRNA half-life studies. Consistent with the anticipated effects of a transcription factor, VCAM-1 promoter analysis also revealed PPARα-mediated inhibition through a likely NFκB mechanism. A functional impact could also been seen in a leukocyte adhesion assay. More recently, we have used in vitro microscopy to analyze adhesion of leukocytes to venules in the mesentery of wild-type and PPARα-deficient mice [14]. Those results are also consistent with an inhibition of leukocyte adhesion through PPARα. Thus, PPARα-mediated inhibition of VCAM-1 expression may represent a significant anti-inflammatory effect in the endothelium.

Interestingly, and importantly, others have reported broader, as well as contrasting, responses regarding PPARs and adhesion molecule responses. In some, PPARγ agonists were able to at least partially decrease VCAM-1 expression, although BRL49653 (rosiglitazone), a canonical PPARγ agonist did not; ICAM-1 was not effected [15]. Other reports found that troglitazone, which in addition to known anti-oxidant properties may also be a partial agonist for PPARγ, as well as 15d-prostaglandin J2 (15d-PGJ2), which has non-PPARγ effects, could decrease VCAM-1 and ICAM-1 in EC, with evidence in a labeled macrophage infusion model, that troglitazone could decrease Mo integration into the vessel wall [16].

PPARα inhibition of VCAM-1 has been generally consistently reported. Also noteworthy are reports that certain oxidized phospholipids, like PAPC, may increase inflammatory responses through a PPARα mechanism [17]. These various results may highlight the influence of subtle parameters such as cell type, differing agonists and agonist concentrations, as well as experimental protocols in determining results seen. Of note, PPARγ agonist treatment of LDL-receptor-deficient mouse failed to show any change in VCAM-1 expression [18], consistent with our in vitro findings.

**PPARα in Monocytes – Modulator of Plaque Thrombogenicity?**

The majority of myocardial infarctions derive from plaque rupture, a process in which the fibrous cap is breached, exposing blood to the highly thrombogenic necrotic lipid core of the arterial atherosclerotic lesion [19]. The resulting thrombus can lead to myocardial infarction and even sudden death, or if only partially occluding, might precipitate an episode of unstable angina. The primary contributor to the thrombogenicity of the lipid core of plaque appears to be tissue factor (TF), an integral membrane protein expressed on Mo, MP, and foam cells that initiates coagulation by binding to factor VII/VIIα [20,21]. The plaque from patients with unstable angina or complex lesions contain more TF than plaques