Interleukin-4, Oxidative Stress, Vascular Inflammation and Atherosclerosis

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Abstract — The pro-oxidative and pro-inflammatory pathways in vascular endothelium have been implicated in the initiation and progression of atherosclerosis. In fact, inflammatory responses in vascular endothelium are primarily regulated through oxidative stress-mediated signaling pathways leading to overexpression of pro-inflammatory mediators. Enhanced expression of cytokines, chemokines and adhesion molecules in endothelial cells and their close interactions facilitate recruiting and adhering blood leukocytes to vessel wall, and subsequently stimulate transendothelial migration, which are thought to be critical early pathologic events in atherogenesis. Although interleukin-4 (IL-4) was traditionally considered as an anti-inflammatory cytokine, recent in vitro and in vivo studies have provided robust evidence that IL-4 exerts pro-inflammatory effects on vascular endothelium and may play a critical role in the development of atherosclerosis. The cellular and molecular mechanisms responsible for IL-4-induced atherosclerosis, however, remain largely unknown. The present review focuses on the distinct sources of IL-4-mediated reactive oxygen species (ROS) generation as well as the pivotal role of ROS in IL-4-induced vascular inflammation. These studies will provide novel insights into a clear delineation of the oxidative mechanisms of IL-4-mediated stimulation of vascular inflammation and subsequent development of atherosclerosis. It will also contribute to novel therapeutic approaches for atherosclerosis specifically targeted against pro-oxidative and pro-inflammatory pathways in vascular endothelium.

Keywords: IL-4, Reactive oxygen species, Inflammation, Vascular endothelium, Atherosclerosis

IL-4 AND ATHEROSCLEROSIS

Cardiovascular disease (CVD) including atherosclerosis is one of the leading causes of illness and death worldwide. In the United States, an estimated 81,100,000 American adults have one or more types of CVD and the estimated cost of CVD for 2010 is $503.2 billion (American Heart Association Statistics Committee and Stroke Statistics Subcommittee, 2010). Although the exact cause of this disease remains unsolved, the pro-oxidative and pro-inflammatory vascular environments are fundamental contributors to the initiation and progression of CVD (Hennig and Chow, 1988; Ylä-Herttuala, 1992; Ross, 1993; Hennig et al., 1996; Bouloumie et al., 1999; Heitzer et al., 2001; Sorescu et al., 2002; Guzik et al., 2006; Thomas et al., 2008).

Although the contribution of T-helper 1 (Th1) and T-helper 2 (Th2) cell responses to the development of atherosclerosis remains unclear, pro-inflammatory cytokines secreted by Th1 cells (Th1 cytokines) have been implicated in atherogenesis. It is commonly believed that interferon-γ (INF-γ), a typical Th1 cytokine, exerts pro-inflammatory and pro-atherogenic action (Tedgui and Mallat, 2006). However, the development of atherosclerosis was not completely abolished even though disruption of INF-γ gene diminished the severity of this disease in low density lipoprotein receptor (LDLR)-deficient mice (Buono et al., 2003). These studies raise the possibility that other pathways may also contribute to the disease progression. Indeed, there is increasing evidence that Th2 cells might...