Atherosclerosis is induced by chronic inflammation, suggesting that the onset of detrimental cardiovascular events could be associated with failure to control inflammatory mechanisms. Pathological characteristics of vulnerable plaque, which causes acute coronary syndrome (ACS), include infiltration of inflammatory cells such as macrophages, T cells, and dendritic cells; large lipid core; neovascularization; intraplaque hematoma; apoptosis of vascular smooth muscle and endothelial cells; and a thin fibrous cap covering the atheroma. To understand the development of atherosclerosis and plaque instability, it is important to discern the role of T cells in acquired immunity. Recently, it has been demonstrated that CD4+ helper T cells (Th cells) can be classified into several subsets: Th1 cells secreting proinflammatory cytokines interferon (IFN)-γ, interleukin (IL)-2, and tumor necrosis factor-α; Th2 cells secreting antiinflammatory cytokines IL-4, IL-5, IL-10, and IL-13; Th17 cells secreting IL-17, IL-21, and IL-22; regulatory T cells (Tregs); Th9 cells producing IL-9 and IL-10; Th22 cells producing IL-22; and follicular helper T cells involved in class switching of B cells (Figure). CD4+ T cells are the dominant phenotype observed in atherosclerotic lesions, and CD4+ Th cells such as Th1, Th2, Th17, and inducible Treg cells regulated by cytokines, chemokines, dendritic cells, and macrophages are deeply involved in the progression of atherosclerosis.

Treg cells suppress immune response and provide immunotolerance; they are classified as natural Tregs (nTregs) or inducible Tregs (iTregs). Treg cells express IL-2 receptor (CD25) and cytotoxic T lymphocyte (CTL)-associated antigen-4, which...
function as negative regulators of T-cell immune responses via binding to CD80/CD86 on antigen-presenting cells and competitively suppressing CD28 signals. The nTregs are characterized by expression of forkhead box P3 (Foxp3), a master gene required for the development and differentiation of nTregs in the thymus, irrespective of external antigen sensitization; these cells secrete IL-10, transforming growth factor (TGF)-β, and IL-35, which are related to immunosuppression and self-tolerance. On the other hand, iTregs are induced by naive T cells (Th0) in the peripheral lymphoid organs in response to exogenous antigens; TGF-β and IL-2 are vital for the differentiation of iTregs, which in turn secrete TGF-β and IL-10, and provide immunosuppression and immunotolerance (Figure). Recently, it has been reported that human FoxP3/FoxP3<sup>+</sup> T cells can be separated into 3 subsets based on function and phenotype: CD45RA<sup>-</sup>/FoxP3<sup>+</sup> resting Treg cells (Fr1), CD45RA<sup>-</sup>/FoxP3<sup>+</sup> effector Treg cells (Fr2), and cytokine-secreting CD45RA<sup>-</sup>/FoxP3<sup>+</sup> non-Treg cells (Fr3). The Fr3 population produces higher levels of IL-17 than naive FoxP3/CD45RA<sup>+</sup> or memory-like FoxP3<sup>-</sup>CD45RA<sup>-</sup> CD4<sup>+</sup> non-Treg cells (Fr4+5) and contains FoxP3<sup>+</sup>ROR<sup>+</sup> double-positive cells, suggesting Th17 potential; in addition, Fr3 cells express large amounts of IL-2 and IFN-γ. Fr3 and Fr4+5 are considered the effector T cells (Teff). All these findings demonstrate the diversity and plasticity within each Treg fraction, which may contribute to the progression of cardiovascular disease.

In this issue of the Journal, Emoto et al<sup>6</sup> report the frequency of Tregs and the Treg/Teff ratio in patients with coronary artery disease (CAD), including stable angina and old myocardial infarction. Their findings demonstrate that the population of Tregs decreased but that of Fr3 cells increased in CAD patients, who also had lower Treg/Teff ratio (Fr1+2/Fr3+4+5) compared with healthy controls.

TGF-β and IL-10-producing Treg cells have an anti-atherosclerotic function, suppressing the development of atherosclerotic plaques. Treg number decreases with progression of atherosclerosis in human atherosclerotic atheroma,<sup>7</sup> and Th1 or Th17 populations are increased in ACS compared with stable angina patients and healthy controls.<sup>8</sup> The study of Emoto et al<sup>6</sup> raises several questions: whether inflammatory cytokines IL-2, IFN-γ, and IL-17 are secreted by Fr3 cells and whether CD4<sup>+</sup>CD28<sup>+</sup> T cells are included in the Fr3 population. In addition, the level of plasticity among CD45RA<sup>-</sup>/FoxP3<sup>+</sup> non-Treg (Fr3) in cardiovascular disease remains unclear, and whether or not the increase in the Fr3 population and decrease in the Treg/Teff ratio (Fr1+2/Fr3+4+5) is more pronounced in ACS than in CAD. In ACS, there is an abundance of senescent CD4<sup>+</sup> CTLs, which promote vulnerable plaque formation. These cells express TRAIL and induce apoptosis of endothelial and vascular smooth cells through TRAIL/DR5 signaling. On the other hand, CD4<sup>+</sup> CTLs have lost the costimulatory CD28 molecule and have expanded as a monoclonal population;<sup>11</sup> furthermore, in ACS, they express killer immunoglobulin-like receptors (KIRs), which recognize HLA class I molecules, rendering the cells cytolytically independent of T-cell receptor triggering.<sup>12,13</sup> In addition, in ACS, the CD4<sup>+</sup>CD28<sup>+</sup> T cells actively express perforin and kill endothelial cells more effectively than in stable angina patients and healthy controls.<sup>14</sup> Reduction in FoxP3<sup>+</sup> Treg cells and progression of arteriosclerotic lesions were observed in CD80/CD86<sup>+</sup>LDLR<sup>+</sup> mice after transplantation of bone marrow from CD28<sup>-</sup> mice;<sup>15</sup> the co-stimulatory signal was also considered important for Treg function. Emoto et al show that the Treg/Teff ratio negatively correlates with the number of CD4<sup>+</sup>CD28<sup>+</sup> T cells and expression of high-sensitivity C-reactive protein in CAD.<sup>6</sup> Recently, it was shown that CRP dose-dependently enhances CD4<sup>+</sup>CD28<sup>+</sup> mediated cytotoxicity in ACS.<sup>14</sup> However, it is unclear whether CD4<sup>+</sup>CD28<sup>+</sup> T cells from patients with stable cardiovascular disease represent potent killer cells expressing KIRs and perforin, and if CRP enhances CD4<sup>+</sup>CD28<sup>+</sup> CTL function.

Deeper understanding of the role of CD4<sup>+</sup> T cell diversity and plasticity in atherosclerosis and cardiovascular disease could lead to the development of new therapeutic approaches and contribute to a reduction in the morbidity and mortality of ACS.

Acknowledgments

Open Research grant from the Japan Research Promotion Foundation for Cardiovascular Disease and Grant-in-Aid for Scientific Research (C).

Disclosures

None.

References