Transfer of lymphocytes between healthy inbred rats is harmless to the myocardium. If, however, the lymphocytes are donated by a rat that has survived a myocardial infarction (MI), the healthy myocardium of the recipient rat is attacked and myocytes are executed by the transferred lymphocytes, and the damage caused by the infiltrating lymphocytes seems to be directly related to the size of the infarct in the donors. Furthermore, cytotoxic CD8 + T lymphocytes obtained after MI are able to recognize and kill healthy cardiomyocytes in vitro. These observations indicate that MI may immunize the victim against its own myocardium, resulting in subsequent autoimmune-mediated damage of the surviving myocytes. Whether such friendly fire by lymphocytes against viable myocardium does occur in humans after MI is not known but is not unlikely.

MI Development and Healing
A wealth of information exists on the role of inflammation and friendly fire in myocardial ischemia-reperfusion injury. Myocardial necrosis induces inflammation mediated by the nonspecific (innate) immune system, involving endothelial activation and leakage (expression of adhesion molecules and complement), and recruitment of neutrophils followed by monocytes/macrophages, lymphocytes, plasma cells, eosinophils, and mast cells. How and why cells belonging to the adaptive immune system (lymphocytes and plasma cells), specialized to handle foreign microbial invaders, participate remains a mystery. T cells by far outnumbered B cells in a canine model of myocardial ischemia and reperfusion, but virtually no data exist on the phenotypes of the infiltrating lymphocytes in human MI. The purpose of the short-lived presence of neutrophils early after MI is also difficult to grasp; wound healing proceeds on schedule or even faster in animals depleted of neutrophils. Repair of the damage is carried out by local and blood-derived fibroblasts (collagen synthesis) and endothelial cells (angiogenesis and vasculogenesis). Ultimately, the recruited cells commit suicide by apoptosis, and only a memorial scar is left on the previous battlefield.

Timely reperfusion saves endangered myocytes, but it comes at a price; badly wounded myocytes at the brink of the grave are given the kiss of death by the otherwise lifesaving oxygen (via formation of oxygen-derived free radicals) and mediators of inflammation (complement and neutrophils). After short-term myocardial ischemia in animals (<1 hour in mice, rats, rabbits, and pigs; <1.5 hour in dogs), this friendly fire can be fought back by antiinflammatory interventions. However, myocardial ischemia usually lasts much longer in human MI, and reperfusion, when it at last occurs, often arrives too late to save a meaningful number of myocytes at imminent danger of dying. Reperfusion may, however, still rescue the local cells needed for rapid healing and repair, fibroblasts and endothelial cells. With further delay of reperfusion, these cells will also vanish, and with them, the lines of supply within the infarcted myocardium, making reflow impossible (no-reflow) and increasing the risk of infarct thinning and expansion, myocardial rupture, and late aneurysm formation. Even at this point, where the acute damage is completed, reperfusion may still be beneficial by reestablishing sufficient forward flow to the surviving but starving myocytes bordering the infarct. These ischemic myocytes are surviving only because of a collateral but not optimal blood supply. If forward flow is not reestablished by reopening the infarct-related artery, myocytes in this ischemic penumbra tend to commit suicide (apoptosis) for a long time after MI because of chronic malnutrition. They may be saved by late reperfusion.

Remote Viable Myocardium After MI
Much less information exists on a possible role of inflammation and friendly fire in the nons ischemic remote myocardium in MI. In the present issue of Circulation, Abbate et al6 describe for the first time widespread myocardial inflammation in about two thirds of patients dying 1 to 12 weeks after acute MI. T cells and activated cells were identified by immunohistochemical staining for the T cell receptor (CD3) and human leukocyte antigen (HLA) class II (type DR), respectively. Many activated cells were present in hearts with infarction, both in infarcted and in remote viable areas (versus none in control hearts). In the remote myocardium, virtually all T cells were activated (CD3+/DR+), representing approximately 70% of all DR+ cells. HLA class II molecules are normally present on antigen-presenting cells (monocytes/macrophages, dendritic cells, B cells), but their expression may be induced on other cells by interferon-γ secreted by activated T cells, and HLA-DR positivity is an accepted marker of T-cell activation. The T cells in the remote viable
Coronary Arteries in ACS

Atherosclerosis, the major underlying cause of ACS, is a chronic and widespread immunoinflammatory disease of large and medium-sized arteries fueled by atherogenic lipoproteins, in particular modified low-density lipoprotein (LDL). If proatherogenic friendly fire occurs, the most likely cause is autoantigens derived from LDL oxidation and leading to T-cell stimulation and cytokine secretion (eg, interferon-γ). Heat-shock proteins also constitute plausible targets for autoimmune attacks based on molecular mimicry.7

Activated macrophages and T cells are present in human atherosclerotic lesions at all stages of development from fatty streaks to advanced plaques.7,8 Macrophages dominate by number, but T cells control their behavior by secreting cytokines. The memory T helper phenotype (CD4+) prevails, and the cytokine response is mainly of the Th1 type, favoring a proinflammatory cell-mediated immune reaction. B cells and natural killer cells are rare in intimal plaques, but prominent B cell infiltrates may occur in adventitia and the periadventitial tissue.7 Ruptured plaques responsible for ACS are particularly inflamed with signs of recent T-cell activation.7,8 Antigens may, of course, activate the adaptive immune system (T and B cells) specifically and elicit a specific immune response, and some T cells isolated from culprit and nonculprit coronary arteries and found to be diffusely activated in unstable angina in an ischemia-mimetic myocardium. HLA-DR, IL-2 receptor, CD40L, and interferon-γ, does not necessarily indicate antigen stimulation. T cell–stimulating cytokines may originate locally from cells within the plaque (eg, activated macrophages) or be brought to the plaque with the circulating blood. Systemic aggravation of the chronic smoldering inflammatory process of atherosclerosis may give rise to panarterial activation and precipitate acute ischemic events if rupture-prone plaques are present. C-reactive protein and other nonspecific systemic markers of inflammation possess prognostic information, and signs of multifocal disease activity, including multiple ruptured coronary plaques, are not uncommon in ACS.11

In unstable angina, Neri Serneri et al12 observed a transient increase in activated T cells in the peripheral blood, and Buffon et al13 found widespread activation of neutrophils across the coronary vascular bed, regardless of the location of the culprit stenosis and thus unrelated to myocardial ischemia, which is an indication that inflammation is not confined to a single culprit lesion in ACS. In acute MI, Spagnoli et al14 performed a systematic flow cytometric study of cells obtained from culprit and nonculprit coronary arteries and found evidence of widespread cell activation evaluated by HLA-DR expression. Most of the cells, including activated cells, were smooth muscle cells. Activated T cells constituted only a small fraction of all activated cells, but they were assumed to be responsible for cell activation through the release of interferon-γ and other cytokines after being triggered by unknown stimuli.

Myocardial Microcirculation in ACS

Widespread inflammation in ACS is not confined to epicardial arteries but may also involve the myocardial microcirculation.15 In troponin-negative unstable angina with pain at rest, immunostaining of left ventricular biopsies obtained from patients undergoing coronary artery bypass grafting revealed numerous activated (HLA-DR+) endothelial cells (versus few in stable angina), in both ischemic and nonischemic myocardium. HLA-DR+ T cells and macrophages were also identified. Thus, the myocardial microvasculature seems to be diffusely activated in unstable angina in an ischemia-independent manner.

Occluded Artery, Ventricular Remodeling, and Heart Failure

Rapid, complete, and sustained reperfusion is important for survival in acute MI. Although relatively few patients present within a time window during which meaningful myocardial salvage can be expected acutely by reperfusion, patients surviving with an open infarct-related artery fare better than those possessing an occluded artery. The reasons are not entirely clear, but an occluded artery is associated with higher risk of the following: (1) transmural infarction, predisposing to acute myocardial rupture, wall thinning, infarct expansion, and late aneurysm formation, (2) slow healing of the infarct, (3) chronic residual ischemia (arrhythmogenic substrate) and ongoing cell death (apoptosis) in the collateral-dependent border zone, and (4) unfavorable and progressive left ventricular remodeling of the remote nonischemic myocardium after MI. The last factor is also related to infarct size.

Heart failure after MI can result from the acute loss of myocytes in the infarct zone but more often is precipitated by the delayed and progressive pathological remodeling of the
left ventricle.\textsuperscript{16} Cell death in the infarct zone is large in magnitude but short in duration. Left ventricular remodeling begins within hours to days and continues for months. Initially, remodeling may involve side-to-side slippage of myocytes, resulting in infarct expansion. Later, in response to volume overload and neurohumoral signals, the noninfarcted remote myocardium undergoes hypertrophy, which initially helps to decrease wall stress. Ultimately, however, the left ventricle dilates, wall thinning occurs, and contractile function deteriorates. Although the precise cellular and molecular bases of left ventricular remodeling after MI are not known, myocyte apoptosis in the noninfarcted remote myocardium seems to be involved.\textsuperscript{16,17} Overstretching (abnormal tension) is able to activate the suicidal program in cultured cardiomyocytes.

Recently, Abbate et al\textsuperscript{18,19} published pertinent data on apoptosis in hearts with infarction, its relation to the patency of the infarct-related artery, and the development of heart failure. Myocyte apoptosis, both in infarcted (ischemia-driven) and in noninfarcted remote areas, was increased when the infarct-related artery was occluded (versus open at autopsy), and apoptosis was particularly frequent in hearts with unfavorable left ventricular remodeling after MI. The causes of apoptosis in the remote viable myocardium were not identified but assumed to be the conventional ones, namely high load (overstretch) and/or stimulation with neurohormones.\textsuperscript{18,19} To return to the lymphocyte data reported by Abbate et al in this issue of \textit{Circulation},\textsuperscript{6} it is tempting to speculate that these data might offer a plausible alternative explanation: diffuse T cell–mediated killing of myocytes after MI in susceptible individuals. Scattered myocyte dropout in remote myocardium seems to be much more detrimental to myocardial function than regional loss (infarction) of a similar number of myocytes.\textsuperscript{17} Phenotypic characterization of the invading lymphocytes (autoactive cytotoxic T cells?) may provide a clue. As mentioned initially in this editorial, there is sparse but fascinating experimental evidence for such a mechanism, but it needs to be validated.

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Widespread Targets for Friendly Fire in Acute Coronary Syndromes
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