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Unusual $CD4^+CD28^{null}$ T Lymphocytes and Recurrence of Acute Coronary Events

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Objectives We hypothesized that the expansion of unusual T lymphocytes, $CD4^+CD28^{null}$ T cells, might represent a key pathogenetic mechanism of recurrent instability.

Background Clinical presentation of acute coronary syndromes (ACS) is variable. Some patients have recurrent episodes of instability, despite optimal treatment, whereas others have a single acute event in their life. The $CD4^+CD28^{null}$ T cells, with a functional profile that favors vascular injury, have recently been found both in peripheral blood and in unstable coronary plaques of patients with ACS.

Methods Peripheral blood T cells from 120 consecutive unstable angina (UA) patients were analyzed for the distribution of T-cell subsets by flow cytometry. Patients were subgrouped according to the occurrence of prior (during the 24 months before the study enrollment) and subsequent (during the 24 months of follow-up) acute coronary events. For 51 patients, the index event was the first ever (G1); 30 patients had prior events (G2); and 39 patients had further events at follow-up (death, myocardial infarction, or UA) or both before and after the index event (G3).

Results The $CD4^+CD28^{null}$ T-cell frequency was higher in G3 than in G2 and G1 (median 9.5% [range 2.4% to 48.0%] vs. 5.1% [range 0.4% to 27.8%] and 2.3% [range 0.2% to 22.8%], respectively; $p < 0.001$). The expansion of these unusual T lymphocytes was higher in patients with elevated C-reactive protein levels, and it was reduced by statin therapy. On multivariate logistic regression analysis, $CD4^+CD28^{null}$ T-cell frequency was an independent predictor of future acute coronary events (odds ratio 3.01, 95% confidence interval 1.1 to 8.25; $p = 0.023$).

Conclusions A perturbation of T-cell repertoire is strongly associated with the recurrence of acute coronary events, conceivably playing a key pathogenetic role. (J Am Coll Cardiol 2007;50:1450–8) © 2007 by the American College of Cardiology Foundation

The spectrum of clinical presentation of acute coronary syndromes (ACS) is extremely varied. At one extreme end of the spectrum, some patients have several acute coronary events (either myocardial infarction or unstable angina [UA]) over a period of years, despite the use of the more advanced and costly pharmaceutical strategies and invasive procedures. At the other end of the spectrum, some patients have a single acute event, such as an acute myocardial infarction not preceded by anginal symptoms and, after this event, remain totally asymptomatic for years (1). The mechanisms of the occasional transition from stable to unstable atherosclerosis may not be the same in these 2 extreme groups (2). We have recently demonstrated that patients with recurrent acute coronary events have persistently high levels of C-reactive protein (CRP) and enhanced in vivo and in vitro monocyte response to proinflammatory stimuli (3–6).

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Activated inflammatory cells have been found in the coronary plaques as well as in the peripheral blood of patients with ACS (7–14). In particular, patients with UA have an increased frequency of $CD4^+$ T lymphocytes characterized by defective cell surface expression of CD28, a major costimulatory molecule critically involved in determining the outcome of antigen recognition by T lymphocytes. $CD4^+CD28^{null}$ T cells are expanded in the

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peripheral blood of patients with UA and infiltrate unstable coronary plaques, where they undergo clonal expansion, probably triggered by specific antigens (12,13). These cells are capable of releasing large amounts of interferon (IFN)-γ and they are the dominant population of IFN-γ producing cells in the peripheral blood of patients with UA (12). Because of the increased IFN-γ production, one of their functions is the activation of monocytes and macrophages; indeed, monocytes from patients with UA display a molecular fingerprint of ongoing IFN-γ stimulation (14). Therefore, $CD4^+CD28^{null}$ T cells might be involved in the control of plaque-infiltrating macrophages.

$CD4^+CD28^{null}$ T cells are distinct from classic helper T cells in several additional aspects (15). In particular, they express killer immunoglobulin-like receptors, a characteristic of natural killer cells, and have killer cell functions (16,17). Endothelial cells are susceptible to this T-cell–mediated injury (16). Furthermore, in the presence of CRP at concentrations frequently found in patients at risk for coronary events, susceptibility of endothelial cells to T-cell–mediated cytotoxicity is increased (16).

Therefore, alongside other proinflammatory mechanisms, we hypothesized that the expansion of T lymphocytes with the functional profile of $CD4^+CD28^{null}$ T cells might represent a key pathogenetic mechanism of recurrent instability.

In this study we specifically tested this hypothesis by measuring $CD4^+CD28^{null}$ T-cell frequencies and CRP levels in a consecutive series of unstable and stable angina patients admitted to our institution. The UA patients were carefully selected on the basis of the presence or absence of recurrent episodes of instability (and/or infarction) in the 24 months before the study enrollment, and they were followed for a further period of 24 months to assess the occurrence of further acute coronary events. Moreover, because we have recently observed a relation between statin use and frequency of $CD4^+CD28^{null}$ T cells (18), we also analyzed the influence of statin therapy in this cohort of UA patients.

Abbreviations and Acronyms

ACS = acute coronary syndrome
CCU = coronary care unit
CRP = C-reactive protein
CSA = chronic stable effort angina
cTnT = cardiac troponin T
IFN-γ = interferon-γ
UA = unstable angina

Methods

Population. The UA patient selection and study design are presented in Figure 1. We prospectively evaluated 218 consecutive patients admitted to our coronary care unit (CCU) with a diagnosis of Braunwald class IIIB UA between September 2000 and September 2002. Patients with UA were considered to have recurrent acute coronary events if they had at least 2 CCU admissions with diagnosis of Braunwald class IIIB UA other than the index event and/or myocardial infarction during the 24 months before the study enrollment. Patients without any previous episode

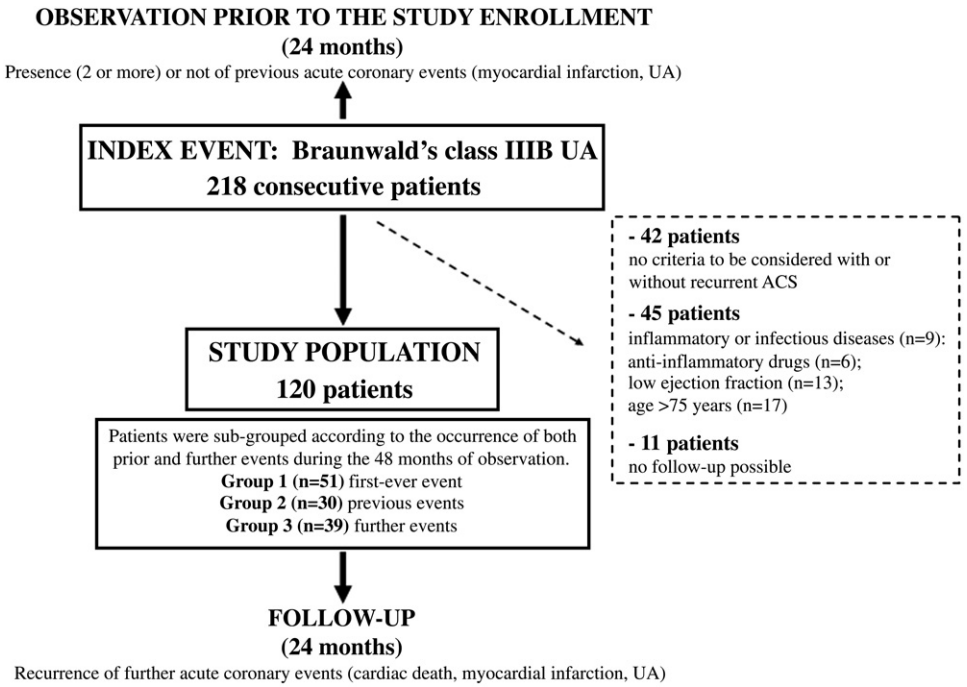

Figure 1 Patient Selection and Study Design

ACS = acute coronary syndrome; UA = unstable angina.