ORIGINAL ARTICLE

Circulating fibrocytes as predictors of adverse events in unstable angina

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Half of the patients who present with unstable angina (UA) develop recurrent symptoms over the subsequent year. Identification of patients destined to develop such adverse events would be clinically valuable, but current tools do not allow for this discrimination. Fibrocytes are bone marrow–derived progenitor cells that co-express markers of leukocytes and fibroblasts and are released into the circulation in the context of tissue injury. We hypothesized that, in patients with UA, the number of circulating fibrocytes predicts subsequent adverse events. We enrolled 55 subjects with UA, 18 with chronic stable angina, and 22 controls and correlated their concentration of circulating fibrocytes to clinical events (recurrent angina, myocardial infarction, revascularization, or death) over the subsequent year. Subjects with UA had a >2-fold higher median concentration of both total and activated fibrocytes compared with subjects with chronic stable angina and controls. In UA subjects, the concentration of total fibrocytes identified those who developed recurrent angina requiring revascularization (time-dependent area under the curve 0.85) and was superior to risk stratification using thrombolysis in myocardial infarction risk score and N-terminal pro B-type natriuretic peptide levels (area under the curve, 0.53 and 0.56, respectively, $P < 0.001$). After multivariable adjustment for thrombolysis in myocardial infarction predicted death, MI, or recurrent ischemia, total fibrocyte level was associated with recurrent angina (hazard ratio, 1.016 per 10,000 cells/mL increase; 95% confidence interval, 1.007–1.024; $P < 0.001$). Circulating fibrocytes are elevated in patients with UA and successfully risk stratify them for adverse clinical outcomes. Fibrocytes may represent a novel biomarker of outcome in this population. (Translational Research 2016;■:1–11)

Abbreviations: AUC = area under the curve; CABG = coronary artery bypass surgery; CAD = coronary artery disease; CSA = chronic stable angina; DDR = discoidin domain receptor; FACS = fluorescence-activated cell sorting; PCI = percutaneous coronary intervention; SMA = smooth muscle actin; SMAD = mothers against decapentaplegic homolog; TGF = transforming growth factor; TIMI = thrombolysis in myocardial infarction; UA = unstable angina

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AT A GLANCE COMMENTARY

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Background

Unstable angina (UA) is among the most common presentations of acute coronary syndrome, but our current ability to identify patients at high risk of recurrent ischemic events is very limited. Fibrocytes are circulating bone marrow–derived cells that home to sites of tissue injury, differentiate into fibroblasts and myofibroblasts, and contribute to scar formation. We hypothesized that in patients with UA, the number of circulating fibrocytes correlates with subsequent adverse events.

Translational Significance

This study found that fibrocytes and their activated subsets were significantly elevated in the peripheral blood of subjects with UA compared with those with stable angina and controls. Moreover, in subjects with UA, elevated fibrocyte levels during the index presentation were associated with recurrent angina over the subsequent year. Circulating fibrocytes may represent a novel biomarker of prognosis in patients with UA and may be involved in atherosclerotic plaque growth.

INTRODUCTION

Patients who present under the umbrella term of acute coronary syndrome have a wide range of clinical outcomes, including recurrent ischemia, need for revascularization, and death. Although prognostic factors are well established for patients with ST elevation myocardial infarction and non–ST elevation myocardial infarction,[1] identification of patients with unstable angina (UA) who are at increased risk of adverse outcomes has proven more elusive. Risk stratification of UA patients is clinically important because this population has high rates of recurrent cardiovascular events over the year after their initial presentation.[2] Compared with their troponin-positive counterparts, patients with UA have lower rates of death and myocardial infarction (MI) at 1 year, but half develop recurrent ischemia requiring revascularization,[3] resulting in substantial morbidity and cost. The ability to identify UA patients during the index hospitalization who are at increased risk for adverse events has the potential to improve the outcomes of this subgroup, for example, by targeting them for more aggressive therapy. Several biomarkers have been assessed in this population including brain natriuretic peptide (BNP), high sensitivity cardiac troponin T, and C-reactive protein.[3-6] These biomarkers have been associated with increased short-[3,4] and long-term[5,6] mortality, but not predictive of recurrent ischemic events.

Fibrocytes are circulating bone marrow–derived progenitor cells that are identified by the co-expression of the common leukocyte antigen CD45 and the fibroblast marker collagen-1. Fibrocytes can home to injured tissues, differentiate into fibroblasts and myofibroblasts, and contribute to fibrogenesis. Fibrocytes represent $<0.5\%$ of nucleated cells in the peripheral blood of healthy individuals, but in fibrotic diseases, blood concentrations can increase up to 100-fold and correlate with severity of tissue injury.[7-10] As fibrocytes differentiate into fibroblasts and myofibroblasts under the influence of the fibrogenic cytokine transforming growth factor (TGF)-β, they progressively lose the progenitor markers CD34 and CD45, retain the expression of collagens-1 and -3, and gain the expression of the myofibroblast marker, α-smooth muscle actin (α-SMA).[11-14] Activated subsets of fibrocytes can, thus, be identified on the basis of expression of phosphorylated SMAD-2 and -3 downstream of the TGF-β receptor,[15] α-SMA, and discoidin domain receptor (DDR)-2, a cell surface receptor for extracellular fibrillar collagens that mediates upregulation of matrix metalloproteinases and collagen turnover.[16]

In the context of coronary artery disease (CAD), fibrocytes have been detected in the fibrous cap of atherosclerotic plaques,[17] areas of intimal hyperplasia,[18] postmortem myocardial samples taken from the infarct zone of patients with MI,[19] and the circulation of patients with acute MI.[20] Given that the release of fibrocytes from the bone marrow to the peripheral blood is a conserved response to tissue injury, we reasoned that the extent of myocardial ischemia in UA may be reflected in the expansion and activation of the pool of circulating fibrocytes. We, therefore, tested the hypothesis that in patients with UA, the number and phenotype of circulating fibrocytes predict subsequent development of adverse clinical events.

METHODS

Patient recruitment and blood collection. Adult patients referred for coronary angiography were recruited into an observational cohort study at the University of Virginia between May 2010 and June 2012. Exclusion criteria were (1) inability to provide informed consent; (2) known fibrotic disease; (3) active infection or malignancy; (4) trauma or a surgical procedure in the prior 6 weeks; and (5) expected survival <1 year. The research was carried out according to the principles of