The Healing Wound: A Case for Extracellular Matrix

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Abstract. Heart failure that accompanies chronic ischemic heart disease is a worldwide health problem of major proportions. Pathophysiologic mechanisms responsible for its onset and progressive nature pose serious challenges, while repeated hospitalizations stress health care resources. Herein the microscopic structural remodeling of the myocardium that appears at and remote to myocardial infarction is reviewed. Using a paradigm of wound healing, the involvement of chemical mediators of tissue repair generated within granulation tissue by constitutive cells is examined.

Key Words. fibrosis, infarcted myocardium, noninfarcted myocardium, angiotensin II, bradykinin, angiotensin converting enzyme, angiotensin II receptors

The Mystery Case: April 7, 1994

Seeking to collect his thoughts in the late hours of this cool and dusky Thursday evening, Dr. Nick Brown strolled now deserted arteries of what seemed an obtunded city. Particularly worrisome was his 52-year-old patient, Mr. J., recently admitted with yet another episode of advanced symptomatic heart failure. A resident in internal medicine at one of the city's university teaching hospitals, Nick had found signs and symptoms of impaired systemic perfusion, expanded intravascular and extravascular volumes, Cheyne-Stokes breathing, and pulsus alternans. An intravenous infusion of a positive inotropic agent, together with intravenous loop diuretic, were required to initiate a recovery of circulatory and volume homeostasis.

Nine months earlier, Mr. J., a previously healthy, quick-talking negotiator for a health maintenance organization, had survived a large, uneventful anterior myocardial infarction (MI). Over the ensuing months, and despite Nick's carefully formulated prescription of cost-efficient measures designed to reduce risk factors, to preserve cardiac function, and to prevent decompensation that required hospitalization, Mr. J. had gradually spiraled downward, like so many others in Nick's growing ambulatory care practice of chronic heart failure; cardiac transplantation appeared inevitable.

Nick wondered what accounted for this malignant course. Was it some mysterious defect in calcium handling that originated in a faulty sarcoplasmic reticulum because of its inadequate supply of energy? On this he was doubtful. Such biochemically driven hypotheses of impaired contractility, promulgated over the past 40 years, had not been convincingly demonstrated in the explanted, failing human heart of ischemic origin. Nick was further flummoxed why the hypertrophic growth of the overworked, remaining myocytes had proven ineffective. Perhaps not unlike giant mastodons trapped in tar, myocytes found themselves unable to properly contract or lengthen, and subject to the ravages of their adverse environment. With today's understanding that tissues elaborate peptides and polypeptides, whose autocrine and paracrine properties influence cell phenotype, and the growth and behavior of cells that govern tissue structure, Nick was convinced answers would reside in the microscopic examination of the failing myocardium. He therefore wanted to know more about this subject and decided to make his way over to the medical school library.

Microscopic Structure of the Failing Human Heart of Ischemic Origin

In a landmark morphologic study of the explanted failing human heart with previous infarction(s), Beltrami et al. [1] provided answers to several of Nick's questions. Figure 1 illustrates their findings. In both the right and left ventricles, "scattered myocyte loss leading to the formation of multiple foci of replacement fibrosis in the myocardium, in combination with interstitial fibrosis, appears to be the major cause of ventricular remodeling in the cardiomyopathic heart of ischemic origin." It was found that infarction does not represent the principal etiological factor in the accumulation of collagen in the ventricle(s) with the progression of disease. Replacement and interstitial fibrosis account for nearly 70% of the amount of fibrotic tissue in the myocardium, whereas myocardial infarction comprises approximately 30%.

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events occurring in the noninfarcted myocardium" of both ventricles. Moreover, "tissue sections of the noninfarcted myocardium demonstrated that ischemic cardiomyopathy was accompanied by multiple sites of myocardial injury across the wall of the left and right ventricles. These lesions were more numerous in the endomyocardium than in the midmyocardium and epicardium of both ventricles. Such patchy areas of replacement fibrosis consisted of collagen accumulation surrounding at times small myocyte profiles. Large fibroblasts dispersed within collagen also were present. Furthermore, the myocardial tissue, free of these foci of damage, showed diffuse interstitial fibrosis that involved the wall of the left and right ventricles. Myocytes were enlarged, although a certain variability in muscle cell size was noted. Similar structural characteristics were seen in the multiple myocardial samples included in the analysis of each heart. These morphological findings were observed in all 10 cases examined.

Wound Healing and the Myocardium

In addressing factors responsible for the accumulation of collagen in noninfarcted myocardium, it is useful to focus on the fibrogenic component of healing because it ordinarily is responsible for fibrous tissue formation. Healing is a property of all vascularized tissues.

Fundamental aspects of tissue repair

The heart is composed of parenchyma and stroma. Parenchyma consists of highly differentiated cardiac myocytes that provide very specialized functions and distinctive morphologic features. Myocytes have lost their functional and phenotypic diversity. This contrasts with cellular elements of stroma, which include fibroblasts and macrophages. These cells are bathed by a tissue fluid that contains signals that regulate their behavior and phenotype. Signals gain access to the interstitial space from plasma, parenchymal cells, fibroblasts, macrophages, or invading inflammatory cells. The extracellular space, therefore, has broad-ranging functions that regulate cell migration, differentiation, and gene expression [2].

Fibroblasts have an extensive clonal heterogeneity; phenotypically transformed fibroblast-like cells have considerable diversity with respect to structural protein synthesis, expression of receptors, response to regulatory molecules, rates of cell turnover, and distinctive morphologic features [3,4]. In the heart, different clonal subsets contribute to early fibrinolytic and subsequent fibrogenic responses that lead to fibrous tissue formation [5]. Genes that govern phenotypic expression and the behavior of interstitial cells involved in tissue repair and their subsequent expression of fibrillar collagen are therefore of considerable interest.

Disproportionate stromal growth, relative to cardiac myocytes, accounts for an inappropriate increase in myocardial collagen concentration. Described as fibrosis, the abnormal accumulation of fibrous tissue can appear around intramural coronary arteries and arterioles (a perivascular fibrosis) and within the interstitial space (an interstitial fibrosis). Each of these fibrous tissue responses is considered a reactive fibrosis, which can accompany such diverse provocation as tissue irritation or invasion by a foreign substance or protein. Microscopic scarring (a reparative fibrosis), occurs in response to parenchymal cell necrosis irrespective of its etiologic basis. Either form creates a pathologic remodeling of myocardium. When fibrosis occurs in the presence of myocyte growth, it accounts for pathologic hypertrophy. In the absence of myocyte growth, fibrosis produces a pathologic remodeling of tissue.

These reactive and reparative responses are confined to the site of foreign material or myocyte loss, provided the degree of parenchymal and microvascular damage is minor and thereby regulatory signals are limited to involved tissue. On the other hand, the entire organ may be involved in the disproportionate accumulation of stroma when the insult evokes an extensive, healing response. This is the case with large transmural myocardial infarction (MI). Here a reparative fibrosis (i.e., a macroscopic scar) appears at the site of necrosis, while a reactive fibrosis appears in the noninfarcted portion of the infarcted ventricle and the noninfarcted ventricle and interventricular septum [6-9]. The formation of stroma at these remote sites, albeit of uncertain pathophysiologic origins, may be caused by a dispersion of fibrogenic signals within tissue fluid of the interstitial space that is common to both ventricles and septum. These signals, however, do not provoke unwanted repair in systemic organs. When fibrogenic signals gain access to the circulation and are not neutralized, systemic organs can be involved in an unwanted accumulation of stroma. This represents a wound healing response gone awry.

Regulation of tissue repair

Endothelial cells are central to the initiation of the early exudative and subsequent inflammatory phases of wound healing. For example, vascular hyperpermeability with interstitial edema accompanies the elaboration of such chemical mediators as bradykinin and prostaglandins. Fibroblast-like cells are pivotal to the tissue repair that follows inflammation. Such cells appear at the site of cardiac myocyte necrosis and repair several days after MI or freeze-thaw injury [5,9]. They are larger than usual interstitial fibroblasts, have a prominent endoplasmic reticulum, and have a large nucleus that can be indented in keeping with cell contraction. Contractile behavior of these cells is conferred by α-smooth muscle actin microfilaments acquired during phenotypic transformation. Because of their appearance and contractile nature, they have been termed myofibroblasts (MyoFb). Despite their smooth muscle cell–like appearance, these cells arise from interstitial fibroblasts and/or pericytes [10,11]. Myofibroblast contraction governs the retraction of granulation tissue, a contractile response promoted by their having cell–cell (desmosome and