LOCAL ANGIOTENSIN II AND MYOCARDIAL FIBROSIS

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1. INTRODUCTION

A wound healing response that eventuates in fibrous tissue formation appears at the site of myocardial infarction (MI). Fibrosis can also appear remote to the MI where it can cause an extensive structural remodeling of viable myocardium. Fibrosis, an abnormal increase in tissue collagen concentration, can adversely affect organ function.

Cells responsible for fibrous tissue formation at sites of repair consist principally of phenotypically transformed fibroblast-like cells having distinctive morphologic features and phenotypic characteristics termed myofibroblasts (myoFb), because they express alpha-smooth muscle actin microfilaments and are contractile (1). These cells are abundant at sites of tissue repair (1, 2). Interstitial fibroblasts are responsible for normal collagen turnover and are considered a source of myoFb. Signals responsible for this transformation in cell phenotype are under investigation. Recent in vivo and in vitro studies indicate that fibroblast-like cells are metabolically active — activity that extends beyond their synthesis and degradation of collagen. This includes their ability to generate substances such as AngII (3). It therefore is no longer tenable to consider metabolic activity of fibroblast-like cells as confined solely to the secretion of matrix components. The healing response is mediated by substances produced within infarcted tissue. The purpose of this manuscript will be to address the elaboration of AngII by myoFb in the infarcted heart and its contribution to fibrous tissue formation.

2. CARDIAC REPAIR POSTINFARCTION

Myocardial infarction in rats was created by left coronary artery ligation. Fibrosis of infarcted rat heart included: a) extensive myocardial infarction (MI) of the left ventricular

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free wall; b) noninfarcted sites remote to MI; c) the visceral pericardium after opening of the parietal pericardium and manual handling of the heart; and d) placement of a foreign body (silk suture) into the myocardium around the left coronary artery (4). In the infarcted heart, type I collagen gene expression was determined by in situ hybridization; its fibrillar collagen composition by the collagen-specific stain picrosirius red; and its cellular elements using hematoxylin and eosin and/or specific immunohistochemistry for detection of cell phenotype (vide infra).

2.1 Collagen Gene Expression

By quantitative in situ hybridization, type I collagen gene expression is normally low in the myocardium of both ventricles. It is markedly increased at the site of infarction on day 3, remains elevated at week 1, 2, 4 and persists for as long as 3 months (5). Transcript for type I collagen is also increased at sites of pericardial fibrosis and endocardial fibrosis of intraventricular septum. Markedly increased type I collagen expression is further seen in noninfarcted myocardium of the septum and right ventricles at week 1, but not day 3, and remains high as long as week 4.

2.2 Collagen Accumulation

Type I collagen makes up about 80% of total collagen found in scar tissue and is therefore the most important collagen in repairing tissue. Microscopic evidence of early fibrillar collagen formation is seen at the site of MI at week 1. A fibrillar assembly of collagen that borders on necrotic tissue to represent early scar formation is seen at week 2. Continued collagen accumulation is evident at week 4 (Figure 1, panel A) and 8 (4). Necrotic cells have been completely replaced by fibrous tissue on week 4 and it is at this point in time that thinning of the infarct scar begins becoming more advanced at wk 8. Detailed aspects of scar remodeling has been reported by others (6, 7).

Increased fibrous tissue, evidenced by hydroxyproline assay and histochemistry, is observed by week 2 at remote sites in hearts with extensive MI. This likewise has been observed in the human myocardium (8). At these remote sites involving the right ventricular free wall and septum microscopic scars replace myocytes lost. Increased interstitial collagen formation is observed at these sites in the absence of myocyte necrosis. A perivascular fibrosis of intramyocardial coronary arteries is also seen at these sites (4). An endocardial fibrosis of the left ventricular aspect of the interventricular septum represents another aspect of the structural remodeling of the heart by fibrous tissue that appears remote to MI (4). In rats with or without MI, fibrosis of the visceral pericardium (Figure 1, panel B) and myocardium surrounding the silk ligature is evident at postoperative wk 2. Markedly increased type I collagen mRNA is colocalized with collagen accumulation in both infarcted and noninfarcted myocardium.

3. CELLS PRODUCING COLLAGEN AT SITES OF INJURY IN THE INFARCTED HEART

Cells responsible for type I collagen gene expression at the site of MI were identified by in situ hybridization (5) and found to be fibroblast-like cells, not cardiac myocytes, endothelial cells or vascular smooth muscle cells. These fibroblast-like cells, together with macrophages, surround necrotic myocytes. These cells were identified as myoFb by immu-