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STATE-OF-THE-ART PAPER

Repair After Myocardial Infarction, Between Fantasy and Reality

The Role of Chemokines

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Despite considerable progress over the last decades, acute myocardial infarction continues to remain the major cause of morbidity and mortality worldwide. The present therapies include only cause-dependent interventions, which are not able to reduce myocardial necrosis and optimize cardiac repair following infarction. This review highlights the cellular and molecular processes after myocardial injury and focuses on chemokines, the main modulators of the inflammatory and reparatory events, as the most valuable drug targets. (J Am Coll Cardiol 2011;58:2357–62) © 2011 by the American College of Cardiology Foundation

Modern cardiology has made considerable advances in the diagnosis and management of acute myocardial infarction (MI), but there still remains the need to design strategies to regain the affected tissue and to re-establish the organ function entirely.

To accomplish this, sustained effort must be made to understand the cellular and molecular mechanisms following MI (1). It is known that hypoxia induces death of cardiomyocytes and triggers an inflammatory response (1,2). The recruited inflammatory cells clean the wound of tissue debris, whereas fibroblasts and endothelial cells infiltrate, proliferate, remodel the extracellular matrix, and determine scar formation (1).

Beyond their crucial role in coordinating leukocyte recruitment (3), chemokines interfere with all phases of MI (4) (Fig. 1, Online Appendix, Online Table 1), contributing to inflammatory and reparatory processes.

Heart: the "motor" of life. Myocardium is built from long chains of striated muscle, and because of its increased mitochondrial content, exhibits remarkable resistance to fatigue, sustaining all vital functions of the organism.

Despite what was hitherto believed, new evidence demonstrates the regeneration of heart muscle cells after birth (5). But how is that possible? Although several studies have reported a possible fusion of stem cells with cardiomyocytes followed by mitochondria and genetic material transfer (6), discussion regarding this subject is purely speculative.

However, it is generally accepted that Lin^{-}/c-kit^{+} cardiac progenitor cells must exist (7) and could be localized beneath epicardium, or near the origin of the coronary arteries and aorta, in a so-called cardiac stem cell niche (8). On the other hand, mesenchymal stem cells (MSCs) were also described as cardiac precursors and are mostly found in bone marrow (9). We do not know their role in physiological cardiac renewal; however, they have an important role in cardiac regeneration after injury (10) and were broadly used as a source for stem cell therapy after MI (9).

Recently, a network of interstitial cells with exceptionally long cellular processes, called telocytes, which assure the long-distance signaling in myocardium, has been described (8). These cells seem to play a significant role in cardiac development, physiology, renewal, and repair (11).

A dramatic scenario occurs when, for various reasons, the blood supply to the heart cells is interrupted. Without oxygen, most of the cardiomyocytes will die. Therefore, a rapid repair and renewal of the injured area is of critical importance.

Inflammatory phase: danger or necessity. Despite the cardioprotective effects of some secreted cytokines (TNFα, HIF) and chemokines (CCL2, CXCL12, macrophage inhibitory factor) (12–17), along with permanent damaging of the cardiomyocyte, the local repair capacity of the heart is limited, and prompt external cellular help at this moment becomes essential.

The initial inflammation is modulated through several molecular steps involving selectins, integrins, cell adhesion molecules (1), and various endogenous ligands, called danger-associated molecular patterns (DAMPs) or "danger signals" (18). Moreover, several Toll-like receptors (TLRs) recog-

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Abbreviations and Acronyms

EPC = endothelial progenitor cell

MI = myocardial infarction

MSC = mesenchymal stem cell

nize pathogen-associated molecular patterns (PAMPs), the basis of the innate immune system (19), but are also endogenous markers of tissue damage (20).

The first cells recruited within hours for a short time to the injured site are neutrophils. When arriving, they release proteolytic enzymes and reactive oxygen species, and directly injure surrounding cells (1,21). Neutrophil depletion in animals undergoing MI led to a marked decrease in infarct size (22,23). All successful experimental interventions of blocking complement (24), reactive oxygen species (25), or NF-kB pathway (26) reduce neutrophil infiltration. CXCR2-binding chemokines, including CXCL8, CXCL2, CXCL1 and CXCL6, as well as CCL3 and CCL5 (23,27), are also critical for neutrophil recruitment (4). Blocking these chemokines and their receptors dramatically reduces infarction size and preserves cardiac function.

On the other hand, neutrophils release chemotactic factors (28) and induce accumulation of splenic monocytes in injured tissue (29). Blocking this splenic monocytes exodus by angiotensin-converting enzyme inhibition has a beneficial effect on cardiac function (30). Two monocyte populations have been identified, the inflammatory monocytes: Gr1(+)CCR2(+)CX3CR1(lo)($Gr1^{high}$), and the resident monocytes: Gr1(−)CCR2(−)CX3CR1(hi)($Gr1^{low}$) (31). The first population of murine monocytes shares the same characteristics with the classical human $CD14hiCD16^{-}$ monocytes, dominates the early phase of MI, and exhibits phagocytic, proteolytic, and inflammatory functions. They digest damaged tissue and clear the wound of cellular debris. The murine resident monocytes correspond to human $CD14^{lo}CD16^{+}$ nonclassical monocytes (32) and dominate the later phase, have attenuated inflammatory properties, and promote healing via myofibroblast accumulation, angiogenesis, and deposition of collagen (33). Neutrophils seem to sustain the extravasation of inflammatory monocytes, in a CCR2-dependent manner, but not the recruitment of resident monocytes (34).

Recent data have shown that Ly-6C(hi) monocytosis (35), as well as $CD14hiCD16^{-}$, but not resident monocytes, negatively correlated with preservation of left ventricular function (36). Indeed, inhibiting CCL2 with a neutralizing antibody or competitive peptide leads to pathological defects in infarcted mice, such as decreased macrophage infiltration, delayed replacement of dead cardiomyocytes with granulation tissue, and decreased myofibroblasts accumulation (37,38). However, delayed phagocytosis of injured cardiomyocytes may increase the arrhythmogenic potential or predisposition to mechanical complications, such as heart rupture (37). Therefore, the potential use of CCL2 as a clinical therapeutic target should be carefully scrutinized.

In conclusion, until proven otherwise, short and limited presence of neutrophils is needed to initiate inflammatory reaction and pave the way for monocytes. However, the explosion of inflammatory mediators leads to a self-maintaining cycle, increasing myocardial damage. Therefore, specific reduction of neutrophil infiltration could have a favorable clinical impact on the evolution of an MI.

Besides the cellular external help, the inflammatory response can also have another important task: preparing the surrounding unaffected cardiomyocytes for stress conditions. It is known that chemokines and cytokines are synthesized, not only in infarcted tissue, but also in unaffected regions (4), triggering initiation of defending mechanisms, such as activating HIF (39) and NF-kB (40), and place cardiomyocytes in a "pre-conditioning" state, increasing resistance to a new hypoxic event. HIF induces specific synthesis of some chemokines, such as CXCL12 (41) and MIF (42), with demonstrated cardioprotective effects. Impairing HIF activation by hypoxic condition, as in diabetic hearts, interferes with ATP production and induces metabolic, energetic abnormalities, disturbing vessel development (43).

In conclusion, the inflammatory response after MI deserves special attention and may provide therapeutic key targets to control the entire wound healing and scar formation (33).

Proliferation phase: when it starts and why it stops. The transition between the inflammatory and proliferation phases is decisive. The heart wall, cleaned of dead cardiomyocytes and matrix debris, without new supporting structures, will inevitably break under the high blood pressure and high mechanical force. The incidence of experimental heart rupture occurs at a later time, after a hypoxic insult (44), and coincides with the passage between the 2 phases.

As soon as the necrotic cells and matrix debris are removed, the rapid inhibition of inflammation by TGF-β and IL10 (45) is essential for the optimal infarct healing. Inflammatory cells are replaced by resident or recruited $Gr1^{low}$ monocytes, lymphocytes, and mast cells that initiate healing.

Resident monocytes, a heterogenic group of cells, patrol between the cardiomyocytes using CX3CR1 receptors (34), maturate into macrophages, and maintain the homeostasis of the normal tissue. After MI, they are recruited to the site of injury by CX3CR1-dependent (46) or CCR5-dependent (47) mechanisms. Recent studies demonstrate the existence of 2 distinct types of macrophages, M1 and M2, with similar behavior as $Gr1^{high}$ and $Gr1^{low}$ monocytes, respectively (48). However, it is not known whether the differentiation is determined by monocyte maturation or later macrophage polarization.

Because the appropriate blood supply is crucial for heart survival and function, angiogenesis is considered an optimal therapeutic target. VEGF and CXCL12 control and modulate the recruitment of endothelial progenitor cells (EPCs) and proper formation of blood vessels (49). Although this occurs continuously, EPCs are not continuously recruited. Earlier transplantation of EPCs seems to have maximal beneficial effects, whereas later systemic transplantation of EPCs failed to influence cardiac remodeling and function.