Targeting Resolution of Inflammation Following Myocardial Infarction

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Myocardial Infarction: Orchestral interplay of Immune Cells

Heart failure accounts for more than 34% of deaths in the US [1]. The pathogenesis of heart failure after myocardial infarction (MI) is served by changes in left ventricle size, shape and function, which are associated with molecular and functional changes in myocardium [2,3]. Multiples risk factors including obesity, diabetes and hypertension contribute in the development of MI. These risk factors are subsequently associated with heart failure related mortality and morbidity. MI initiates a rapid inflammatory response with both time and cell-type dependent entry of heterogeneous immune cells into the infarcted area, as well as remote areas. Collectively, the immune response and subsequent tissue remodeling leads to left ventricle dilatation [4].

The post-MI inflammatory response is composed of two phases. The first phase is characterized by entry of leukocytes into the infarcted area to phagocytose necrotic myocytes. The second phase of the post-MI inflammatory response comprises effecrocytosis, a function mainly performed by macrophages to resolve the inflammation. Neutrophil entry is guided through inherent signaling system (adhesion, rolling, arrest, dialedesis, transmigration) and entry limiting resolvents that are activated during the wound healing process, chemokines (CCL2, CCL5), cytokines (IL-1β, IL-6, TNF-α) and adhesion molecules (ICAM-1 and VCAM-1) to maintain homeostasis. Overall, the range of inflammation and the consequent resolution of inflammation are overlapping that is critical for repair and wound healing. Inflammation and the consequent resolution of inflammation with aspirin therapy.

Inflammation is an inner impairment to free activity or something that restricts or forbids the inflammation. Perhaps to some extent the biphasic inflammatory response overlaps with subsequent post-MI extracellular matrix deposition. In the early post-MI wound healing phase, i.e., within the first week, the normal extracellular matrix structure virtually disappears [7]. The level of collagen determines the extent of post-MI infarct expansion. A prolonged and uncontrolled post-MI inflammatory response leads to cardiac remodeling and progression towards heart failure [8]. Adamek and colleagues have demonstrated that aspirin can be used to resolve post-MI inflammation caused by pro-inflammatory cytokines. Aspirin reduces inflammatory cytokines (TNF-α and IL-1β) successfully. However, there was no improvement in left ventricle function [9]. Additional research warrants to determine the cell types, receptors and mechanism involved in controlling post-MI resolution of inflammation with aspirin therapy.

Resolution, not inhibition, of Inflammation is Important Post-MI

Resolution can be defined as the decomposition, absorption or breakdown of the products of inflammation or cessation of inflammation. The compounds that promote the disappearance (resolution) of inflammation or causes dispersion of inflammation are termed as resolvents [10]. In contrast, inhibition of inflammation is an inner impairment to free activity or something that restricts or forbids the inflammation.

Inhibition of polymorphonuclear leukocytes using anti-inflammatory therapy with a high dose of prednisolone or methylprednisolone in patients with acute MI results in cases of cardiac rupture [11]. This clinical evidence indicates that impairment of post-MI inflammation adversely affects myocyte repair and wound healing. Inflammation and the consequent resolution of inflammation are overlapping that is critical for post-MI ventricular remodeling (Figure 1). In the post-MI sterile wound healing process, chemokines (CCL2, CCL5), cytokines (IL-1β, IL-6, TNF-α) and adhesion molecules (ICAM-1 and VCAM-1) ease neutrophil extravasation into the infarcted area [12]. The early inflammatory response is characterized by neutrophil
influx which is necessary to clear necrotic cardiomyocytes; this phase overlaps with resolution of the inflammation. Following MI, the time neutrophils spend in the infarcted area as well as the density of neutrophils in the infarcted are stimulates potent inflammatory response to surrounding cells. After engulfment of ischemic or injury related debris neutrophils activate a ‘find me and eat me’ signal to promote their clearance [13]. Macrophages drive this resolution by mediating the efferocytosis of neutrophils [14].

Resolvents: Bioactive Lipid Pro-Resolving Agents

Resolvin E1 is an n-3 polyunsaturated fatty (fish oil) acid-derived endogenous oxidation product. Resolvin E1 has direct protective effect on cardiomyocytes against ischemia-reperfusion injury, thus limiting the infarct area when administered just before reperfusion. The putative protective effect is by transactivation of the epidermal growth factor receptor (EGFR), which activates prosurvival pathways (Akt and ERK1/2) and inhibits apoptosis [15]. A number of bioactive lipid mediators with specialized pro-resolving functions such as the lipoxins (LX A, 15-epi-LX A), resolvins (from eicosapentaenoic acid (EPA); RvE1, and from docosahexaenoic acid; RvD1, RvD2), protectins (protectin D1; PD1) and maresins (MaR1) have been implicated in resolution of inflammation [10,16-18], however, their potential role in the post-MI setting and heart failure remains unknown.

Indeed, Birnbaum and colleagues demonstrated anti-inflammatory properties of the EPA derived resolvins, lipoxin-A4 (LXA4) and 15 (R)-epi-lipoxinA4 (15-epi-LXA4), in the myocardium following atorvastatin and pioglitazone treatment in rats [19]. Particularly, simultaneous treatment of selective cyclooxygenase (COX)-2 inhibitor valdecoxib with atorvastatin or pioglitazone limits production of 15-epi-LXA4 [19]. These studies show that atorvastatin promotes the myocardial generation of 15-epi-LXA4 via S-nitrosylation of COX-2. This is akin to the acetylation of COX-2 by aspirin, as S-nitrosylated COX-2 produces 15-epi-LXA4. Certainly, Serhan’s laboratory has demonstrated lipoxigenase interaction products such as LXA4 and 15-epi-LXA4 have pro-resolving and anti-inflammatory properties in the resolution of acute inflammation. Both of these bioactive lipid mediators inhibit chemotaxis, adherence, and transmigration of neutrophils [20].

CONCLUSION

Prolonged uncontrollable inflammation is the fundamental component in post-MI cardiac remodeling and heart failure pathology, thus development of therapeutics that support post-MI resolution of inflammation are of translational interest. Considering the promising pro-resolving and anti-inflammatory properties of resolvins, a wide array of n-3 immunoresolvons are under trial for the treatment of cardiovascular disease. The proper dose, stable formulation, delivery method and timing of treatment required to achieve optimum therapeutic and pharmacological effect in resolution of post-MI inflammation. Timely resolution of post-MI inflammation will reduce deleterious effects on cardiomyocytes that survived after initial infarct. Additionally, timely resolution helps to attenuate the ventilicular remodeling that is important in the sequelae of heart failur. Thus, as shown in Figure 1, resolvents or substances that polarize macrophages from their classical (M1) role in inflammation towards a pro-resolving alternative (M2) activation, or rapid clearance of inflammation, will be of special interest; agents that can resolve inflammation or enhance clearance of inflammation should limit post-MI ventricular dilation, and prevent progression towards heart failure.

ACKNOWLEDGEMENT

Author acknowledges support from NIH-NCCAM R00AT006704 and the editorial assistance of Benjamin Everett, PhD. Figure 1 was produced using Servier Medical Art.

REFERENCES


