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Review / Mini-Review

Immunological Window of Myocardial Infarction

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Abstract

Acute myocardial infarction (MI) describes as an irreversible death of heart muscle which is initiated by a shortage of myocardium oxygen supply and accompanies by a complex of pro- and anti-inflammatory events. During the last decades, innate and adaptive immune responses are considered more serious for controlling myocardial infarction. As, it was confirmed that deregulated immune system which triggers excessive local and systemic inflammatory events is responsible for serious adverse effects associated with acute MI. Bone marrow activation, spleen monocytopoiesis, a remarkable increase of circulating cytokines and adhesion molecules, in addition to elevated levels of active peripheral leukocytes and platelets are playing significant roles in determining the clinical outcome of patients with MI. The previous experience demonstrated the failure of traditional harsh anti-inflammatory strategies. High mortality rate and poor quality of life observed for survivors of MI despite current progress in the field highlight the urgent need for such interdisciplinary studies in the context of molecular cardiology. Hence, unraveling the cellular and molecular events which are involved in the management of inflammatory responses post-MI is of special focus. The concept of immune regulation after myocardial infarction is not new, but our perception for dealing with the challenge has been changed during the last decades with gaining more in-depth molecular/immunological knowledge. It seems that fine-tuning the interplay between innate and adaptive immune responses and regulating their cross-talk should be in special focus to establish effective therapeutic strategies.

***Keywords*:** Cardiovascular diseases, Myocardial infarction, Innate and adaptive immune systems, Autoimmunity, Inflammation

Background

Cardiovascular diseases (CVDs) are the first cause of death in the world, count for more than 34% of the total number of death per year. In the United States of the America cardiovascular diseases take million lives in each year exclusively. According to the American Heart Association's Heart and Stroke Statistics 48% of all adults in this country develop some type of CVD (Benjamin et al., 2019). CVDs are also the leading cause of death in the European Union countries (Tadayon et al., 2019). Statistical analysis indicates that 43000 cases with CVD have been reported in Iran annually and cardiac complications take 300 lives daily. Prevalence, mortality and morbidity of CVD during recent decades in Iran were reported previously (Sarrafzadegan and Mohammmadifard, 2019). The official statistics of the Ministry of Health and Medical Education of Iran show that 33-38% of total deaths are somehow due to the cardiovascular complications. These pieces of information about CVDs worldwide have made it a universal challenge. The last revision of the World Health Organization CVD risk prediction charts from 21 global regions was published in 2019 (WHO CVD Risk Chart Working Group) and was applied for risk assessment in various populations (Babatunde et al., 2020; Islam et al., 2020; Samaniyan Bavarsad et al., 2020). Furthermore, a higher risk of coronary heart disease and stroke during the last year of worldwide Coronavirus disease (COVID-19) pandemic was reported recently (Gronewold and Hermann, 2021).

In parallel with advancements in therapeutic

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strategies, various cardio-protective strategies were also introduced and applied in pre-clinical studies and clinical settings. However, translational medicine has no success as much as the pre-clinical studies does (Hoeeg et al., 2021; Zhao et al., 2020).

This could be due to the multifactorial nature of MI which is associated with functional modification of different cell types including tissue-specific and non-specific cells such as cardiomyocytes, smooth muscle cells, fibroblasts, endothelial cells, platelets and effector cells of both innate and adaptive immune systems. Therefore, a better strategy could be a combination of therapies with synergistic effects (Davidson et al., 2019). In such strategy, the role of immune system and its modifications during the pathogenesis of MI seem to be of crucial importance (Hausenloy et al., 2017).

Myocardial infarction: Definition, causes and routine treatments

Myocardial infarction (MI) (also called heart attack) is the direct result of coronary artery disease (CAD) and described as the irreversible death of heart muscle. It is mainly established by exposure of the tissue to prolonged lack of oxygen supply (Zafari et al., 2017). Molecular mechanisms responsible for development and progression of the cardiac remodeling were described in great details (Ayoub et al., 2017; Qiu and Liu, 2019; Schirone et al., 2017; Schüttler et al., 2019). Recently, some genes, lipidomic markers, and microRNAs were introduced as potent biomarkers for diagnosis of the acute MI (Condrat et al., 2020; Horváth et al., 2020; Li et al., 2019; Liu et al., 2019; Samouillan et al., 2020). Furthermore, the crucial role of exosomes in modulating the micro-communications among different cell types of cardiac tissue was discussed during cardiovascular diseases, myocardial infarction and their therapeutic strategies (Chen et al., 2021; Chistiakov et al., 2016; Ma et al., 2020; Pan et al., 2019; Sahoo and Losordo, 2014; Tan et al., 2020; Wu et al., 2019; Yuan et al., 2016).

There are some classifications for myocardial infarction, among which the most famous one was released in 2007 dividing the failures to 5 groups including MI types I to V (Thygesen et al., 2007). This classification was updated 4 times and the last one was published in 2018 (Thygesen et al., 2018; Thygesen et al., 2012; Saaby et al., 2013). Pharmaceutical regimes and revascularization strategies including the application of β-blockers and angiotensin-converting enzyme inhibitors (ACEIs), percutaneous transluminal coronary angioplasty (PTCA) and stenting, or surgical strategies such as the insertion of left ventricular assist devices (LVADs), coronary artery bypass graft (CABG) and cardiac transplantation are the most common therapeutic methods applied for patients with acute myocardial infarction and congestive heart failure (CHF)(Kuo and Tseng, 2009; Panahi et al., 2018). Although routine revascularization strategies make sense to help the remained viable cells of the myocardium, it may lead to ischemia/reperfusion (I/R) injury (Braunwald and Kloner, 1985; Yellon and Hausenloy, 2007). In addition to modifying the final infarct size and left ventricular ejection fraction (LVEF), this could be extensively responsible for the clinical outcome (Hausenloy and Yellon, 2013).

Various mechanisms are associated with the lethal reperfusion injury including release of reactive oxygen species (Raedschelders et al., 2012; Saparov et al., 2017), collapse of the mitochondrial membrane potential (Griffiths and Halestrap, 1995), restoration of physiological pH (Lemasters et al., 1996), and more recently modifications in lymphocyte kinetics (Boag et al., 2015; Bodí et al., 2009). The latter one will result in microvascular obstruction (MVO) in less than 2 hours following reperfusion in animal studies (Boag et al., 2017; Hausenloy and Yellon, 2013; Reffelmann and Kloner, 2002; Yellon and Hausenloy, 2007). Consequences of MVO, unlike lethal reperfusion injury, could be visualized and quantified by different methods such as echocardiography and magnetic resonance imaging in human subjects and is accompanied with adverse clinical outcomes (Bolognese et al., 2004; Hombach et al., 2005; Ito et al., 1996; de Waha et al., 2010; Wu, 2012; Wu et al., 1998). The temporal dynamics of immune responses following prolonged myocardial ischemia/reperfusion was fully investigated in a previous study (Rusinkevich et al., 2019).

Myocardial infarction: A tolerogenic failure

Heart tissues are believed to be protected against autoimmune-based events by specialized functions of tolerogenic dendritic cells, T regulatory cells, and T cells with the expression of inhibitory molecules such as programmed cell death-1 (PD-1). They are in cross-talk with heart cells' ligands. Different antigens have been proposed for self-tolerance failure and initiating cardiac autoimmunity. Full and in detailed description of these concepts were provided in another studies (Carrillo-Salinas et al., 2019; Salaman et al., 2020).

Atherosclerosis is defined as the inflammatory disease of the arterial wall (Matsuura et al., 2014). In animal and human subjects, atherosclerosis is

responsible for different cardiovascular complications including myocardial infarction in addition to autoimmune diseases established by the activity of autoantigens and autoantibodies, in lymphoid or non-lymphoid tissues (Frostegård, 2013; Meier and Binstadt, 2018; Sattler et al., 2017; Shi, 2010). Apolipoprotein B-100, which is the core protein in the structure of low-density lipoprotein is the target of these autoantibodies (*reviewed in* Ley, 2016). It was demonstrated that the cells from both innate and adaptive immune systems are present in the arterial walls and play key functions in the development of atherosclerosis (Dieterlen et al., 2016; Lee et al., 2020).

Patho-physiologically different cells of the immune system, including T cells, monocytes and dendritic cells are induced by different stimuli (Benagiano et al., 2005; McNiel et al., 1990), leading to secretion of pro-inflammatory cytokines in the atherosclerotic lesions (George et al., 2000). So, atherosclerosis shares many of its aspects with chronic autoimmune diseases accompanied by increased level of inflammatory cytokines, modified T helper 1 to T helper 2 cells ratio, and enhanced macrophage and lymphocyte activity (Shi, 2010). It was previously proposed that unbalanced T- and B-cell dependent adaptive immune responses are in close relationship with cardiomyocytes death and tissue fibrosis (Kino et al., 2020; Sánchez-Trujillo et al., 2017). Progressive form of atherosclerosis is observed in patients with rheumatoid arthritis (Sherer and Shoenfeld, 2006). Also, more than 50 times higher chance of inflammatory coronary events was reported for young female patients with systemic lupus erythematosus (SLE) in comparison to healthy individuals (Asanuma et al., 2003; Manzi et al., 1997).

Considering these facts, proper regimes of autoantigen mucosal immunization via recruiting antigen-specific T regulatory and adaptive immune cells are among effective strategies for inhibition of atherosclerosis progression, plaque inflammation and reactivity of lymph node lymphocytes against autoantigens (George, 2008). Important role of T regulatory cells in plaque instability during atherosclerosis and their stimulation by rapamycin, anti-CD3 antibodies, and indirect activation by dendritic cells were previously demonstrated (Yang et al., 2006; Ait-Oufella et al., 2006). According to pre-clinical studies tolerogenic dendritic cells have a favorable capacity for immune-based regulation of the hostile environment following the myocardial infarction. These cells, as a novel anti-remodeling therapy, following their migration to local lymph nodes, induce infarct-specific T regulatory cells and affect polarization of macrophage populations (Choo et al., 2017; Švajger and Rožman, 2018). Also, the induction of cardiomyocyte proliferation by regulatory T cells was reported following MI (Zacchigna et al., 2018).

Myocardial infarction: Interplay between innate and adaptive immune responses

Myocardial infarction is a complex of metabolic, inflammatory and immunological events (Hausenloy et al., 2009; Jung et al., 2019; Kuroki et al., 1993; Prabhu, 2018; Vinten-Johansen et al., 2004) which is accompanied by strong inflammation, cell death and fibrosis as helper mechanisms for tissue repair. These events are triggered by various mechanisms such as aldosterone- mineralocorticoid receptor (MR) signaling (Boag et al., 2017; Rafatian et al., 2014). However, continued activity of these events may lead to cardiac degeneration and heart failure (Burchfield et al., 2013; Frangogiannis et al., 2002; Frangogiannis, 2014). A rise in programmed cell death (PCD), mostly determined with caspase 3 activity, is observed in the first days following MI (Odörfer et al., 2008; Palojoke et al., 2001; Cheng et al., 1996). Moreover, during the first week strong accumulation of macrophages reported in both infarct and peri-infarct zones, which gradually decreases (Nahrendorf et al., 2013).

Pro-inflammatory and inflammatory resolution/reparative phases were proposed as key immune responses following the MI. These responses are mediated by the effector cells of both innate and adaptive immune cells (Fang et al., 2015; Lai et al., 2019). However, the role of effector cells of adaptive immune system (Lymphocytes) is less clear in comparison to monocytes and neutrophils (Horckman et al., 2018). Unlike previous trend, it is now evident that the presence and function of B and T lymphocytes play a critical role in the sequential events triggered following the myocardial infarction (Lee et al., 2020; Santos-Zas et al., 2019). These effects with either constructive or destructive consequences are time- and subset- dependent (Figure 1)(Boag et al., 2017, Hofmann and Frantz, 2015; Hofmann and Frantz, 2016).

In general, one may propose that lymphocyte activation and secretion of cytokines by these cells, following the myocardial infarction, recruits the active players of innate immune responses to the damaged cardiac tissue in the first 24 hours. Through the induction of inflammatory status this leads to a remarkable activity of macrophages with phagocytic behavior to remove cell remnants

and debris, which reaches its peak in 72 hours (Cheng et al., 2017; Frangogiannis et al., 2002; van den Akker et al., 2013).

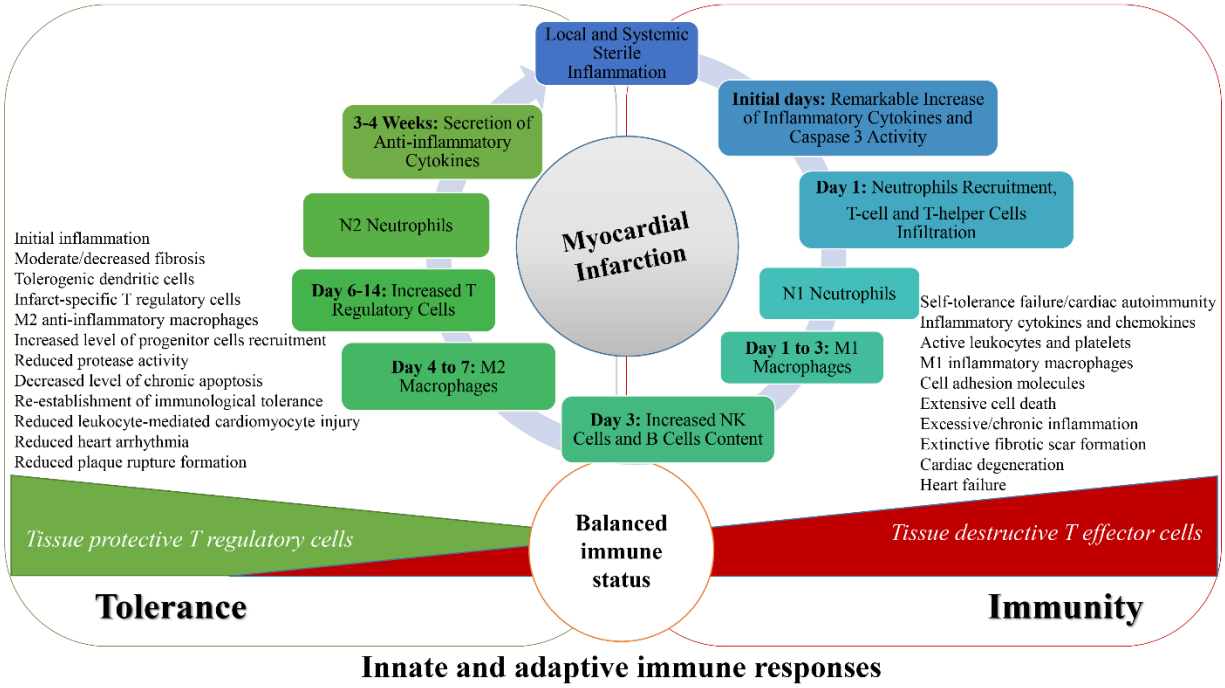

Figure 1. Time-dependent manner of immune cells recruitment to the cardiac tissue following myocardial infarction (MI). The homeostatic activity of innate and adaptive immune cells is crucial for management of local and systemic inflammations in the benefit of tissue regeneration and reparative mechanisms.

These post-MI events are mediated by mobilization of the bone marrow resident hematopoietic progenitor cells into the spleen leading to production of monocyte and neutrophil populations (Gentek and Hoeffel, 2017). Strong adhesive interactions between endothelial cells and leukocytes, induced by different cytokines, chemokines and components of complement system, are responsible for recruitment of inflammatory cells with cytotoxic activities to the infract zone (Nah and Rhee, 2009).

Yolk sac, fetal liver-derived, and monocyte-derived macrophages are main populations of macrophages playing crucial roles during pre- and post-MI events. They are involved in normal and disease situations for maintaining tissue homeostasis and accelerating the reparative process (Engelbertsen et al., 2013; Gomez et al., 2015; Hoeffel et al., 2012; Munshi, 2017; Pinto et al., 2016; Wynn, 2015). M1 macrophages, with cell remnant clearance and extracellular matrix degenerative -capacities, are the dominant population of macrophages in the first 3 days following the MI. Ly-6Clow monocyte-derived M2 macrophages, with wound healing properties, substitute this population during day 4 to 7 following the MI (Yan et al., 2013). M2 macrophages mediate these events through the secretion of anti-inflammatory cytokines, induction of angiogenesis, and collagen deposition (Cheng et al., 2017). Three main interventional methods including drug treatments, cell transplantations, and genetic modifications, were proposed to manage macrophage population switch (Xu et al., 2019).

Innate immune responses are triggered following the MI in order to switch on the tissue repair mechanisms (Aurora et al., 2014; Huang et al., 2013; Lai et al., 2017; Lavine et al., 2014). Similar to other inflammatory conditions, a minimal amount of pro-inflammatory cytokines is necessary for recruiting the main players of the immune system. A contradictory problem occurs when the level of inflammatory cytokines rises above the proper level. In this state, similar to other autoimmune conditions, instead of recruiting the progenitor cells to the damaged sites, the inflammatory mechanisms play as enemies and destroy the tissue structure (Frangogiannis et al., 2002; van den Akker et al., 2013). The roles of inflammatory agents in the pathogenesis of different cardiovascular diseases have been discussed previously (Caligiuri et al., 2000; Hansson, 2005; Hansson and Libby, 2006; Hansson and Hermansson, 2011; Huber et al., 2001; Liuzzo et al., 1999; Liuzzo et al., 2000; Robertson and Hansson, 2006; Song et al., 2001;

Zhou et al., 2000). It should be noticed that during myocardial infarction, unlike pathogen-induced inflammation, we are exposed with a sterile inflammatory status initiated by damage associated molecular patterns (DAMPs) or alarmins (Chen and Nuñez, 2010; Lee et al., 2018). It was proposed that inflammasomes recognize danger signals and mediate sterile inflammatory responses following acute myocardial infarction (AMI) (Fang et al., 2015).

The sequential role of different effector cells of the immune system depicted by van den Akker and colleagues, demonstrated that switching between pro- and anti- inflammatory status happens on day 5 to 7 post MI (van den Akker et al., 2013). B cells, T cells and natural killer (NK) cells are the main players of adaptive immune system with specialized functions (Boag et al., 2017; Boehm, 2011; Iwasaki and Medzhitov, 2015; Nutt et al., 2015; Owen et al., 2013; Pieper et al., 2013; Vivier et al., 2008). It was described by Horckmans and colleagues that the creation and functional properties of fat-associated lymphoid clusters (FALCs) can be modified upon the release of inflammatory cytokines following the MI (Horckmans et al., 2018). These secondary lymphoid organs which contain populations of B and T cells could be found with high frequencies in the pericardium (Bénézech et al., 2015). Based on recent findings they could be considered as the regulation sites for rapid immune responses following acute MI.

The role of T-cells in the pathogenesis of acute coronary syndrome was fully discussed previously (Yu et al., 2014). Furthermore, the importance of a subpopulation of cytotoxic T-cells (CD8+CD57+ cells) following myocardial infarction was confirmed which propose its prognostic features. Moreover, it was demonstrated that Foxp3+ CD4+ T cells are responsible for differentiation of monocytes and macrophages following MI (Weirather et al., 2014). Also, in a separate review paper, the detailed roles of lymphocytes and T regulatory cells during post MI events were fully described (Hofmann and Frantz, 2015), including the concept of tolerance and its important role in the pathogenesis and consequences of MI. Based on available information, the existence of T regulatory cells is necessary for proper healing of the damaged tissue following MI.

Recently, the relationship between epicardial adipose tissue (EAT) lymphocytes and coronary artery disease (CAD) was reported and confirmed that a higher amount of lymphocytes is present in the epicardial adipose tissue (EAT) of both CAD and non-CAD human subjects, in comparison to subcutaneous adipose tissue (SAT). However, the number of CD3 positive T cells indicates remarkable increase in epicardial adipose tissue of CAD subjects in comparison to non- CAD individuals. This is accompanied with decreased number of NK cells. Development of local inflammation and coronary atherosclerosis could be considered as main downstream events of such changes (Mráz et al., 2019).

It was indicated by Boag and colleagues that in human cases in less than one hour and half following the reperfusion, T cells and B cells are recruited to the myocardium with considerable decrease in peripheral levels of the cells. It was proposed that these cells may be accumulated in the epicardial adipose tissue, due to the shared microcirculation (Boag et al., 2015). In fact, epicardial adipose tissue could act as the central compartment to regulate post MI events via players of both adaptive and innate immune systems (Horckmans et al., 2018).

Although myocardial infarction has its own physiological reasons (Francis, 2001; Oerlemans et al., 2012; Roubille and Barrere-Lemaire, 2013) and routine therapeutic methods, the application of immunomodulatory agents such as standard immunosuppressive drugs and stem/progenitor cells will be also effective due to the critical role of T lymphocytes during MI (van den Akker et al., 2013). Cyclosporine, an immunosuppressive drug prescribed for patients with MI, triggers the function and viability of T-cells (Piot et al., 2008). It is noteworthy that replacement of the immunosuppressive drugs with cell based therapies or their cell-free counterparts would be a significant step to introduce novel clinical approaches (Guo et al., 2020; Lee and Kang, 2020).

The therapeutic modulation of inflammatory events following the MI, could lead to the reduced leukocyte-mediated cardiomyocyte injury in the border zone, decreased level of chronic apoptosis in the remodeling area, reduced protease activation, lower inflammation-driven fibrogenic signaling, increased level of progenitor cells recruitment, reduced heart arrhythmia, and reduced plaque rupture formation. These interventions are classified to broad and targeted anti- inflammatory strategies. They are encountered with some challenges including the overlap between the function of some effector molecules during different phases and heterogeneous post-infarction remodeling process in different patients (Huang and Frangogiannis, 2018). In addition, attempts to rejuvenate the aging immune system was recently proposed as another anti-inflammatory therapeutic strategy in the benefit of

effective heart regeneration following myocardial infarction (Tobin et al., 2020).

Myocardial infarction and cardiac regeneration as evolutionary and developmentally dependent traits

From developmental perspective, myocardial infarction is completely different in adult mammals in comparison to neonates as strong cardiac regenerative capacities have been reported during neonatal life. However, this ability is diminished upon the development of the immune system (Fan et al., 2020; Haubner et al., 2018; Santos et al., 2021). It was also demonstrated that the multi-potential ability of epicardial resident cells reduced after birth (Cai et al., 2019). The functional recovery of injured neonatal cardiac tissue is the result of preexisting cardiomyocyte proliferation and is mediated by various immunological, metabolic and environmental factors. As described by Lai and colleagues, in adult cardiac tissue monocyte derived macrophages are found following MI, which promote fibrosis. These data highlighted the importance of immune-modulating therapeutic strategies for treating patient with MI (Lai et al., 2019; Lam and Sadek, 2018).

Conclusion

In conclusion, to introduce better therapeutic strategies which reduce the progressive events following the MI in the benefit of tissue regeneration, multi-target methods are proposed. Among these strategies, the ones which restore immune tolerance to cardiac tissue could be more effective. These strategies will reduce complications for patients with cardiovascular disease.

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Conflict of Interest

The authors have no conflicts of interest.

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