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Role of interleukin-17 in acute myocardial infarction

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ABSTRACT

Acute myocardial infarction (AMI) is a leading cause of death worldwide. Myocardial necrosis generates damage signals and triggers an intense inflammatory response. Many cytokines that contribute to repair tissue can also cause adverse left ventricular remodeling and heart failure. Several studies have revealed that interleukin-17 (IL-17) is a cytokine with a potential role in AMI. IL-17 plays an important role in the immune response and affects the production of different inflammatory mediators in several types of cells, involved in the damage or scar process in myocardial tissue. In this review, we will discuss the current knowledge of the role of IL-17 in AMI and the effect of IL-17 in different cells, such as cardiomyocytes, smooth muscle cells and immune system cells, in AMI pathogenesis.

1. Introduction

Interleukin-17 (IL-17) plays an important role in the immune response. Currently, the IL-17 family includes IL-17A through IL-17F; these molecules exist as homodimers, although there is also an IL-17A/F heterodimer (Xu and Cao, 2010). Several cell types have been described as sources of IL-17, including Th17 cells, $\gamma\delta$ T cells, natural killer T (NKT) cells, CD8 T cells, macrophages, and dendritic cells (Xu and Cao, 2010; Cua and Tato, 2010). The biological effects of IL-17 are mediated by interactions with its receptor, which is widely distributed in different tissues and cells in the immune system, including monocytes, macrophages, dendritic cells, B lymphocytes, and neutrophils (Gu et al., 2013; Ge et al., 2014; Fossiez et al.,1996).

IL-17 and its target cells exert various effects related to host defense. For example, IL-17 is essential for host defense against microorganisms such as *Klebsiella pneumonia, Toxoplasma gondii,* and *Candida albicans* (Ouyang et al., 2008; Miossec and Kolls, 2012). The inflammatory response and the production of cytokines such as IL-17 are particularly important in several inflammatory diseases (Shabgah et al., 2014; Tesmer et al., 2008). Contradictory results have been found regarding the role of IL-17 and Th17 cells in the development of cardiovascular diseases (Taleb et al., 2015). However, atherosclerosis develops due to chronic inflammation, and the ischemic events triggered by atherosclerosis induce strong acute inflammatory responses (Swirski and Nahrendorf, 2013), particularly in acute myocardial infarction (AMI), in which sudden necrosis of many cardiomyocytes results in the release of their intracellular contents. In addition, the damaged extracellular matrix releases endogenous alarm signals, such as hyaluronan fragments and heat shock proteins; these signals increase the inflammatory response, which is a prerequisite for the repair and healing of cardiac tissue (Christia and Frangogiannis, 2013). It is evident that the inflammatory response is essential in AMI. However, the role of IL-17 in this cardiovascular disease is not clear. Here, we summarize the biological characteristics of IL-17 A (referred to as IL-17 in this text) and its roles in myocardial infarction.

2. History of IL-17 discovery

IL-17A was initially named CTLA-8 in 1993 after it was discovered in T cell hybridomas of mice and rats. The CTLA-8 gene was mapped to a single site on chromosome 1 A in mice and on chromosome 2q31 in humans (Rouvier et al., 1993). Later, it was found that *Herpes saimiri* gene 13 exhibits 57% identity with the predicted sequence of T cell-derived CTLA-8. Moreover, HVS13 and CTLA-8 recombinants showed a capacity to stimulate NF-kappa B (NF-κB) activity and IL-6 secretion in fibroblasts and to stimulate T cell proliferation. This evidence defined CTLA-8, HVS13 and their receptor as new molecules, and it was proposed that they be named IL-17, vIL-17, and IL-17R, respectively (Yao et al., 1995). Years later, Th17 cells were determined to be a new population of T helper lymphocytes and were characterized as the main

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producers of IL-17 (Harrington et al., 2005). However, other cell types have been described as sources of IL-17, including γδT cells, NKT cells, CD8 T cells, macrophages, and dendritic cells (Xu et al., 2010; Cua et al., 2013). The study of IL-17 has received great interest due to the biological functions of this cytokine in host defense and in pathological conditions.

3. IL-17 and receptors

There are currently 6 known molecules in the IL-17 family: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F; these molecules exist as homodimers, although the heterodimer IL-17A/F also exists (Liu et al., 2013). The biological effects of IL-17 are mediated by interactions with its receptor, which is widely distributed in different tissues and cells of the immune system, such as monocytes, macrophages, dendritic cells, B lymphocytes, and neutrophils (Ge et al., 2014; Gu et al., 2013). To date, five receptors have been described for the IL-17 family: IL-17RA, IL-17RB, IL-17RC, IL-RD, and IL-17RE (Gu et al., 2013). IL-17 induces the activation of a heterodimer complex consisting of the IL-17RA and IL-17RC receptors, which in turn activates signaling pathways involving NF-κB and mitogen-activated protein kinases and ultimately results in the expression of proinflammatory cytokines (Song and Qian, 2013). IL-17 provides a communication channel between innate and adaptive immunity in inflammatory diseases, particularly cardiovascular diseases.

4. Inflammation in AMI

Atherosclerosis is a chronic inflammatory disease (Libby, 2002) associated with cardiovascular diseases that involve acute coronary syndromes, such as AMI (Overbaugh, 2009). Initially, atherosclerotic plaques originate in the subendothelial space of medium and large arteries and are characterized by a dysfunctional endothelium, proliferation of smooth muscle cells, foam cells, a lipid nucleus, a thick fibrous layer, and moderate inflammatory activity (Halvorsen et al., 2008). However, in the final stage of the disease, thinning of the fibrous layer is caused by metalloproteinases, which causes the rupture of the atherosclerotic plaque and the subsequent formation of a thrombus that blocks blood flow to the cardiac muscle (Overbaugh, 2009; Finn et al., 2010; Christia and Frangogiannis, 2013), preventing the delivery of oxygen and nutrients to the myocardium; this blockage causes cardiac tissue necrosis (Finn et al., 2010) or the death of a portion of the cardiac muscle (Halvorsen et al., 2008; Overbaugh, 2009; Finn et al., 2010; Christia and Frangogiannis, 2013), which induces the release of the intracellular contents of cardiomyocytes; in addition, the damaged extracellular matrix releases endogenous warning signals, such as hyaluronan fragments and heat shock proteins, which cause an intense inflammatory reaction (Finn et al., 2010; Christia and Frangogiannis, 2013). The inflammatory phase is characterized by a dramatic increase in cardiac mast cell density following myocardial infarction (Engels et al., 1995). In the canine heart, in the first few hours following ischemia-reperfusion, the cardiac mast cells were the predominant source of TNF-α (Frangogiannis et al., 1998), which promotes the activation of endothelium that favor the recruitment of leukocytes. Following AMI, the number of circulating polymorphonuclears increases in AMI patients (Akpek et al., 2012) and infarcted tissue (Zidar et al., 2005). Neutrophils release myeloperoxidase, which results in tissue damage as well as neutrophil-derived lipocalin induce recruitment of Ly-6C^{hi} monocytes, which could give rise to inflammatory macrophages that predominate in the inflammatory phase (Wan et al., 2013; Nahrendorf et al., 2007). M1 macrophages secrete TNF-α, IL-1β and IL-6, which are necessary for healing (Frangogiannis, 2014). Also, these cytokines in the mouse model contributed to the activation of myofibroblasts, thereby promoting the secretion of collagen and extracellular matrix that induce fibrosis of the ventricle (Liu et al., 2015) and subsequent dysfunction due to dilatation of the ventricle; moreover, even non-infarcted areas can be affected, and this can lead to the remodeling of negative infarcted cardiac tissue, which has been reported as a cause of death in patients (Sutton and Sharpe, 2000). The inflammatory phase subsequently changes to a proliferative phase (in which fibroblasts proliferate and synthesize collagen to form a scar). The proliferation phase involves a predominance of macrophages and myofibroblasts in the infarct area (Turner, 2016). M2 macrophages increased gradually and represent the predominant macrophage subsets at 5 days post-AMI (Yan et al., 2013). Additionally, the increase in the matrix metalloproteinases activity degrades the extracellular matrix while promoting the formation of new collagen by myofibroblasts together with myocytes; these changes contribute to ventricular remodeling (Turner, 2016) and finally to a maturation phase characterized by the overexpression of fibrotic factors and anti-inflammatory substances, such as TGF-β and IL-10, as well as the proliferation of fibroblast, synthesis of collagen, formation of tissue scar (Turner, 2016), and the formation of new microvasculature, which provides nutrients and oxygen to damaged tissue in canines (Dobaczewski et al.,2004).

The different stages of AMI and periods post-AMI involve different cellular actors, such as cardiomyocytes, endothelial cells, neutrophils, monocytes, macrophages, and myofibroblasts, as well as inflammatory mediators, such as IL-17. Several cells are sources of IL-17, including natural killer cells, neutrophils and lymphoid cells (Katayama et al., 2013; Ferretti et al., 2003; Korn et al., 2009; Fahl et al., 2014). In this context, natural killer cells and neutrophils were previously reported to represent a minor proportion of IL-17A-secreting leukocytes in myocardial ischemia/reperfusion injury (Liao et al., 2012). However, neutrophils may have a relevant role in infarction. In this context, the polymorphonulear neutrophils of patients with ST-segment elevation acute myocardial infarction release neutrophil extracellular traps that contain extracellular chromatin networks decorated with granular neutrophils and proteins, such as IL-17 in the artery (de Boer et al., 2013; Stakos et al., 2015). Moreover, CD4^{+} T cells infiltrate the infarcted tissue in humans, and the Th17 cell subsets play an important role in the pathogenesis of various inflammatory diseases that involved heart tissue injury, such as myocarditis (Myers et al., 2016). Meanwhile, the presence of γδ T cells in atherosclerotic lesions in humans has been reported (Kleindienst et al., 1993). Moreover, γδ T cells are increased after the AMI (Yan et al., 2013), and they represent the major source of IL-17 in infarcted tissue (Hofmann and Frantz, 2015; Vantourout and Hayday, 2013).

5. IL-17 in AMI

The role of IL-17 in cardiovascular disease is unclear, and there are conflicting reports. Some reports have demonstrated that patients with AMI present increased circulating levels of IL-17 that are associated with the clinical instability of the patients (Cheng et al., 2008; Hashmi and Zeng, 2006). Similarly, AMI studies in animal models have shown significant increases in IL-17 protein levels as well as cumulative increases in the expression of the IL-17RA, IL-1β, inducible nitric oxide synthase (iNOS), IL-6, and matrix metalloproteinase (MMP)-9 genes (Barry et al., 2013), suggesting that IL-17 may play a role in the inflammatory cascade of AMI. Moreover, IL-17 exacerbates ventricular remodeling in early and late post-AMI stages in mice (Zhou et al., 2014). In addition, blockade of the IL-23/IL-17A axis alleviates late post-AMI remodeling (Yan et al., 2013). These findings suggest that IL-17 and the IL-23/IL-17A axis have an adverse effect on ventricular structure after AMI in mice. Accordingly, other authors have reported increases in circulating IL-17 levels in patients that were associated with AMI (Simon et al., 2013). However, unlike in the other studies, in this study, the authors associated high levels of IL-17 with a better cardiovascular outcome at a 2-year follow up in a Caucasian population, as reflected by reductions in mortality and the recurrence of AMI (Simon et al., 2013). Additionally, this study reported that low levels of IL-17 and high levels of soluble vascular cell adhesion molecule-1

(VCAM-1) were associated with a poor prognosis in patients (Simon et al., 2013). It has also been reported that knockout of IL-23 involved in the IL-23/IL-17 axis induces high mortality related to ventricular rupture in the subacute phase after AMI in mice. Additionally, IL-23 deficiency triggers an increase in the expression of IL-1β and IFN-γ and a reduction in IL-10 in the infarcted area. Furthermore, cardiac fibroblasts derived from IL-23-deficient mice show decreased expression of collagen, which could lead to adverse remodeling of the left ventricle (Savvatis et al., 2014). These findings in humans suggest a protective effect of IL-17 in mediating a good cardiovascular prognosis after AMI. In addition, the results suggest a regulatory role for IL-23 in inflammation through the downregulation of inflammatory cytokines and indicate the contribution of IL-23 to tissue remodeling after AMI.

6. Effect of IL-17 on cardiomyocytes and smooth muscle cells

In the infarcted heart, sudden necrosis of a large number of cardiomyocytes results in the release of their intracellular contents and initiates an intense inflammatory reaction (inflammatory phase) that includes cytokines (Christia and Frangogiannis, 2013), such as IL-17 (Barry et al., 2013). The expression of IL-17 in the myocardial tissue suggests that it may exert effect on different cellular targets, thereby modulating the inflammatory response. In this context, *in vitro* studies have demonstrated that IL-17 directly induces apoptosis in mouse cardiomyocytes via iNOS activation in these cells, suggesting that IL-17 contributes to the deterioration of the cardiac tissue by directly contributing to the apoptosis of cardiac cells (Su et al., 2016). Other *in vitro* studies have demonstrated that IL-17 induces the activation of NADPH oxidase in a p38 MAPK-dependent manner and later induces the generation of superoxide and hydrogen peroxide, which involves the Nox2 subunit in smooth muscle cells in mice (Pietrowski et al., 2011). A biological consequence of iNOS and free radicals is the induction of adhesion molecules, such as intracellular adhesion molecule-1 (ICAM), VCAM, and platelet endothelial cell adhesion molecule (Carreau et al., 2011), which favor the recruitment and accumulation of leukocytes in an inflammatory state such as AMI. Together, these findings suggest that IL-17 induces apoptosis in cardiomyocytes, which then release free radicals such as iNOS, promoting the inflammatory process through the induction of molecules that participate in leukocyte adhesion in the damaged cardiac tissue (Fig. 1).

7. IL-17 and neutrophils

Polymorphonuclear cells play an important role in inflammation due to their ability to perform a variety of effector functions that collectively represent one of the major mechanisms of innate immunity. Thrombus formation in the coronary artery is an essential event that triggers AMI; it has been shown that neutrophils contribute to this process through neutrophil extracellular traps (NETs) (Denny et al., 2010; Fuchs et al., 2010). Recently, the presence of IL-17 was determined in samples of coronary artery thrombi obtained from patients after AMI. In this study, IL-17 was found in NETs in fresh and lytic thrombi after AMI (Fig. 2A2), suggesting the participation of IL-17 in thrombus stabilization and growth in AMI (de Boer et al., 2013). After AMI, it has been demonstrated that IL-18, P-selectin, and ICAM-1 contribute to the accumulation of neutrophils in the ischemic area in animal models (Denny et al., 2010; Ivey et al., 1995; Briaud et al., 2001]. Moreover, IL-17 was found to induce neutrophil infiltration in the peripheral area of wild-type (WT) mice in a model of stroke, while *Il17ra*$^{-/-}$ mice showed a marked reduction in neutrophils after stroke (Gelderblom et al., 2012). Studies in humans have established that IL-17 causes the production of CXCL1 (GRO-α) and CXCL8 in human endothelial cells (Onishi and Gaffen, 2010; Yuan et al., 2015) and that these molecules induce the expression of adhesion molecules such as E-selectin, VCAM-1, p38MAPK and ICAM in endothelial cells (Roussel et al., 2010) (Fig. 2A). This response is promoted by the presence of TNF-α, which upregulates E-selectin and ICAM-1, which in turn contribute to neutrophil adhesion and the migration of neutrophils through endothelial cells (Bosteen et al., 2014). The first phase of AMI is characterized by maximum accumulation of neutrophils in the first hours in the infarcted myocardium (Christia and Frangogiannis, 2013), and elevated levels of IL-17 also circulate in patients with AMI (Liang et al., 2009). These results suggest that IL-17 is a cytokine associated with the formation of the thrombus in the coronary artery and with the induction of adhesion molecules and IL-8, which contribute to the recruitment of neutrophils to the ischemic tissue (Fig. 2A). This suggestion is reinforced by the increase in circulant neutrophils and high levels of IL-17 found in AMI patients in the first phase. One of the widely documented biological actions of neutrophils is the production of reactive oxygen species (ROS). Studies in mice have demonstrated that IL-17 activates neutrophils through IL17RC in an autocrine manner, inducing the production of ROS (Taylor et al., 2014) that activate transcription factors such as NF-κB (Hirotani et al., 2002). NF-κB in turn induces the

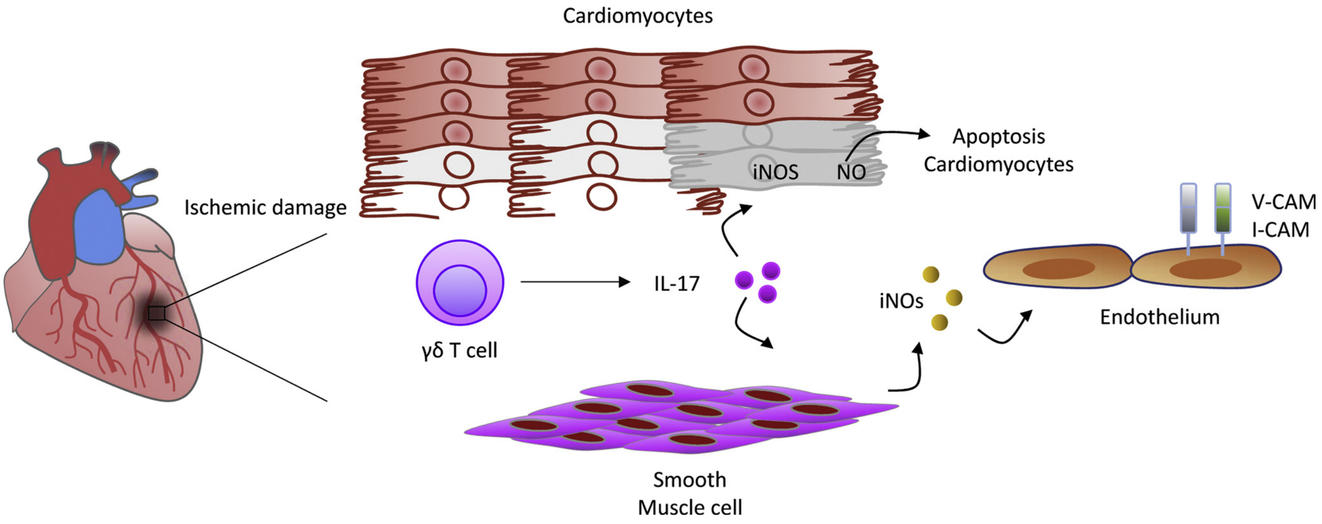

Fig. 1. IL-17 in cardiomyocytes and smooth muscle cells in AMI. After AMI, the levels of circulating IL-17 increased and the major source of IL-17 infarcted tissue were the γδ T cells. IL-17 induced cardiomyocyte apoptosis in the ischemic tissue and contributed to the deterioration of cardiac tissue function. Additionally, IL-17 induced the activation of smooth muscle cells and the release of iNOS, which induced the expression of adhesion molecules in endothelial cells (Cheng et al., 2008; Yan et al., 2013; Hofmann and Frantz, 2015; Su et al., 2016; Barry et al., 2013; Carreau et al., 2011).

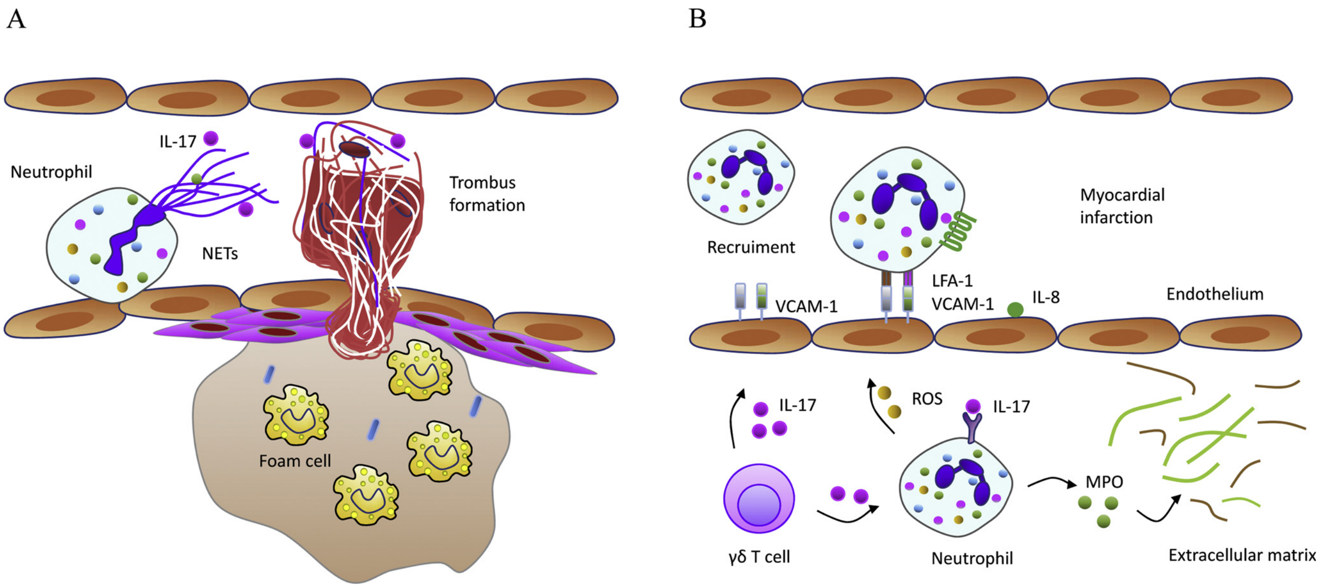

Fig. 2. IL-17 and neutrophils in AMI. (A) Neutrophils are among the major effectors of innate immunity and contain several mediators, including IL-17. Neutrophils are also susceptible to NETosis, or the release of NETs with IL-17, which can contribute to thrombus formation-induced AMI. (B) Neutrophils can be activated by IL-17 derived from $\gamma\delta$ T cells, and activated neutrophils secrete ROS that induce the expression of VCAM on endothelial cells, thus allowing the recruitment of leukocytes. Additionally, matrix metalloproteinases induce extracellular matrix degradation in ischemic tissue, which is a prerequisite for cardiac remodeling (de Boer et al., 2013; Roussel et al., 2010; Cheng et al., 2008; Yan et al., 2013; Hofmann and Frantz, 2015; Liang et al., 2009; Mocatta et al., 2007).

production of TNF-α (Youle and Strasser, 2008), which plays a key role in apoptotic and necrotic events in cardiomyocytes that may induce the remodeling of the left ventricle after AMI (Hori and Nishida, 2009). Another molecule involved in this process is myeloperoxidase (MPO) (Vasilyev et al., 2005), and polymorphonuclears are the most abundant source of MPO (van Leeuwen et al., 2008). High levels of MPO and IL-17 are considered to be indicators of inflammation in patients with AMI (Cheng et al., 2008; Liang et al., 2009; Mocatta et al., 2007), suggesting that a biological action of IL-17 in cardiac neutrophils is the induction of ROS and MPO, which induce damage in the tissue and thus exacerbate the inflammatory response in the infarcted myocardium (Fig. 2B). In an ischemia/reperfusion rat model, IL-17 has also been reported to promote the expression of CXCL1 in myocytes, which may contribute to the recruitment of neutrophils (Barry et al., 2013); in the same context, in mouse kidney ischemia/reperfusion, IL-17A derived from GR-1^{+} neutrophils has been found to contribute to IFN-γ production, neutrophil infiltration, and kidney tissue damage, demonstrating an essential role for neutrophils in the inflammatory response in kidney ischemia and reperfusion injury (Li et al., 2010).

8. IL-17 and monocytes

Monocytes are currently understood to be a heterogeneous population in humans and in mice, and they differentiate into tissue macrophages (Swirski et al., 2007; Auffray et al., 2007; Sheel and Engwerda, 2012; Weber et al., 2000). In mice, two types of monocytes have been identified: those with the Gr1^{+}Ly6C^{high}CCR2^{+}CX3CR1^{low} phenotype (Swirski et al., 2007; Auffray et al., 2007; Sheel and Engwerda, 2012) and those with the Gr1–Ly6C^{low}CCR2–CX3CR1^{high} phenotype (Swirski et al., 2007; Auffray et al., 2007; Sheel and Engwerda, 2012). Ly6C^{hi} (inflammatory) monocytes extravasate into the blood in a CCR2 − CCL2-dependent manner and are essential in inflammation. Ly6C^{low} (patrolling) monocytes emigrate into the blood via CX3CR1-CX3CL1, signaling and monitoring the luminal face of the small blood vessel endothelium under homeostatic and inflammatory conditions (Swirski et al., 2007; Auffray et al., 2007; Sheel and Engwerda, 2012). A few hours after reperfusion in AMI, chemoattractant factors such as C5a and CCL2 cause the infiltration of mononuclear cells, including monocytes, to the infarcted myocardial tissue (Frangogiannis, 2014; van Leeuwen et al., 2008). Recent research has shown that IL-17 induces the expression of E-selectin, ICAM1, VCAM1, and CCL2 transcripts in human umbilical cord endothelial cells (Erbel et al., 2014), which contributes to the adhesion and rolling of monocytes along endothelial cells (Erbel et al., 2009). This finding suggests that the activation of the endothelium through IL-17 facilitates the adhesion, rolling, migration, and accumulation of monocytes in the inflammatory process (Fig. 3A-3B). This evidence was reinforced by an in vivo study in animal models demonstrating that IL-17 knockout reduces CCL2, IL-1β and IL-6, which notably decreases monocyte/macrophage infiltration in the inflammatory process (Usui et al., 2012). In a murine model of AMI, the predominant population in the first days post infarction was that of Ly6C^{+} monocytes (equivalent to CD14^{++} CD16^{-} monocytes in humans), which was associated with the inflammatory process taking place at that moment (Auffray et al., 2007). Interestingly, Ly6C^{+} monocytes express high levels of the IL-17 receptor (Gu et al., 2013), suggesting that the IL-17 receptor may play a biological role in Ly6C^{+} monocytes. In experimental autoimmune myocarditis a decrease in Ly6C^{hi} monocytes has been reported in the heart in Il17ra$^{-/-}$ mice (Wu et al., 2014), suggesting an activation of the IL-17 receptor; thus, IL-17 is essential for the infiltration of Ly6C^{hi} monocytes into sites of inflammation.

9. IL-17 and macrophages

An environment rich in cytokines and growth factors prevails in AMI, and these factors play an important role in the differentiation of monocytes, which can adopt a variety of macrophage phenotypes with different functional properties, including the M1 macrophage phenotype (Martinez and Gordon, 2014). Classically activated (M1) macrophages are induced in the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) or in the presence of both lipopolysaccharide (LPS) and IFN-γ. These macrophages are characterized by an inflammatory profile and are efficient producers of free radicals, nitrogen intermediates, and proinflammatory cytokines such as IL-1β and TNF (Martinez and Gordon, 2014; Glezeva et al., 2015). In contrast, macrophage colony-stimulating factor (M-CSF), IL-4 and IL-13 induce

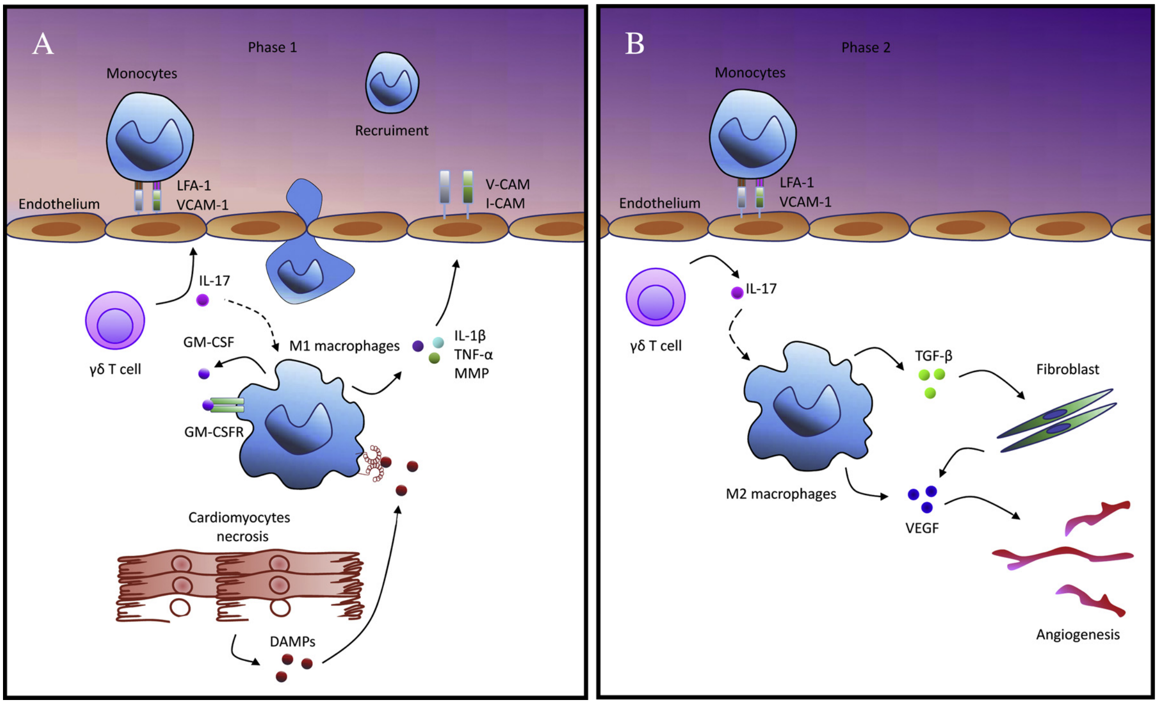

Fig. 3. Monocytes and macrophages in AMI.
γδ T cells secrete IL-17 in the ischemic tissue and participate in the different phases of the infarct. (A) IL-17 contributes to the recruitment of monocytes through the activation of endothelial cells. Tissue monocytes can differentiate into M1 macrophages through the action of IL-17 (phase I), which induces the production of GM-CSF and the expression of its receptor. Macrophages differentiated by IL-17 probably recognize DAMPs and secrete inflammatory cytokines. (B) Furthermore, after AMI, IL-17 participates in the differentiation of M2 macrophages (phase II) and the secretion of TGF-β and VEGF, contributing to tissue regeneration (Yan et al., 2013; Hofmann and Frantz, 2015; Vantourout and Hayday, 2013; Erbel et al., 2014, 2009; de la Paz Sánchez-Martínez et al., 2017; Li et al., 2014; Nakai et al., 2017; Zizzo and Cohen, 2013; Silverpil et al., 2011).

alternatively activated or regulatory (M2) macrophages, which secrete high levels of IL-10 and low levels of proinflammatory cytokines such as TNF-α (Murray and Wynn, 2011; Gordon and Martinez, 2010).

Macrophages can respond to the prevailing microenvironment of cytokines that can influence their differentiation or activation, such as IL-17. In this sense, IL-17 is able to increase the GM-CSF receptor expression, GM-CSF secretion and GM-CSF-mediated differentiation (Isailovic et al., 2015; Starnes et al., 2001; Cua and Tato, 2010); GM-CSF can be produced in part by cardiac fibroblasts through IL-17 stimulation (Wu et al., 2014). The positive regulation of the production of GM-CSF and its receptor could favor the production of M1 macrophages, as GM-CSF is essential for their differentiation (Martinez and Gordon, 2014).

Studies *in vitro* have demonstrated that IL-17 does not affect the expression levels of characteristic markers of M1, such as CD80 and CD86, which suggests that IL-17 does not affect the expression of M1-related markers in general (Erbel et al., 2009; de la Paz Sánchez-Martínez et al., 2017). However, mature macrophages increase TNF-α and IL-6 expression in response to IL-17 (Erbel et al., 2009; de la Paz Sánchez-Martínez et al., 2017); moreover, differentiation with IL-17 induces expression levels of TLR2 and TLR4 on macrophages similar to those of M1 (de la Paz Sánchez-Martínez et al., 2017), suggesting that macrophages differentiated with IL-17 can be activated by damage-associated molecular patterns (DAMPs) derived from dead cells in the cardiac tissue, increasing the inflammatory response. It has also been demonstrated that mouse macrophages isolated from postinfarcted heart tissue express gene signatures such as TNF-α, IL-6, IL-1β, CCL2, and CXCL1 as well as MMP1, MMP9 and TGF-β, the expression of which is dramatically suppressed in IL-17A knockout mice compared with WT mice (Yan et al., 2013).

This evidence suggests that IL-17 induces the production of GM-CSF, which could contribute to the differentiation of M1 macrophages. Additionally, IL-17 induces TLR expression in macrophages, allowing their activation by DAMPs derived from cardiac tissue and the secretion of inflammatory cytokines such as TNF-α and MMP (Fig. 3A).

After AMI, suppression and resolution of the inflammatory phase depends on anti-inflammatory mediators that induce arrest signals in cells of the immune system; however, in many cases, the inflammatory response is prolonged, resulting in significant cardiac damage (Frangogiannis, 2006). Days after an AMI, macrophages comprise the most abundant cells in the infarcted heart (Frangogiannis, 2012; Yan et al., 2013) and adopt an M2 phenotype (Prabhu, 2014). One of the functions of these macrophages in cardiac damage is to remove the damaged extracellular matrix as well as apoptotic and necrotic cells in cardiac tissue; they also secrete cytokines and promote inflammatory resolution, healing, angiogenesis, and tissue remodeling (Zhang et al., 2014).

IL-17 plays an important role in the inflammation phase in AMI; however, there is also evidence of its biological effects on M2 macrophages after infarction. IL-17 is involved in the induction (Li et al., 2014) and activation of M2 macrophages (Nakai et al., 2017). *in vitro* studies in human cells have shown that IL-17 prevents apoptosis in macrophages and increases the expression of markers related to the M2 phenotype, such as CD163 and CD14 (Isailovic et al., 2015; Zizzo et al., 2013). In addition, IL-17 promotes the phagocytosis of apoptotic neutrophils via M2 macrophages (Zizzo and Cohen, 2013; Silverpil et al., 2011) and stimulates the production of mediators of angiogenesis such as VEGF, which, in addition to having angiogenic properties, mediates the removal of debris by macrophages together with TGF-β (Fujiu et al., 2014). This process is essential for the future repair and regeneration of tissue (Frantz and Nahrendorf, 2014). Additionally, TGF-β derived from macrophages can contribute to the activation of fibroblasts, favoring the formation of new extracellular matrix components in the damaged tissue (Pakyari et al., 2013). These data suggest a relevant role of IL-17 in the repair process of ischemic heart tissue through the induction of M2 macrophages. The effect of IL-17 on damaged tissue would mediate a higher survival rate and contribute to the removal of apoptotic cells, which is an essential event for tissue repair (Fig. 3B).

10. Th17 and AMI

CD4 + T cells contribute to the inflammatory process in acute coronary syndromes. Recent studies have explored the Th17 lymphocyte lineage in AMI (Cheng et al., 2008; Gao et al., 2010; Eid et al., 2009; Liu et al., 2012). Th17 cells express the RORγ and RORα nuclear factors, which makes it possible to distinguish Th17 cells from other Th lymphocyte lineages (Ivanov et al., 2007); they also produce IL-17A, IL-17F, and IL-22, among other cytokines (Dong, 2008; Bettelli et al., 2007). Increases in the number of Th17 cells in peripheral blood have been demonstrated in patients with AMI, and the IL-17, IL-6, and IL-23 cytokines are connected to the Th17 profile; in addition, these increases are associated with increases in the transcription factor RORγt (Cheng et al., 2008; Zhang et al., 2013), which directs the proinflammatory cell differentiation program of IL-17-producing T helper cells (Ivanov et al., 2006).

The direct role of Th17 in AMI is not yet clear, but we suggest that Th17 cells could be a source of inflammatory cytokines that contribute to the activation of macrophages and endothelial cells. More studies should be performed to identify the role of Th17 cells in AMI and/or its relationship with other cell types.

11. Conclusions

AMI is triggered by a thrombus that is generated by the rupture or erosion of an atherosclerotic plaque. Ischemic damage in myocardial tissue induces a strong inflammatory response that involves increased levels of several inflammatory cytokines, including IL-17, which is primarily sourced from $\gamma\delta$ T cells in cardiac tissue. IL-17 is a molecule with a wide variety of biological actions on a broad spectrum of cells, including cardiomyocytes, endothelial cells, neutrophils, monocytes and macrophages, that plays an important role in the inflammatory response in AMI. After AMI, IL-17 in the circulation contributes to the activation of endothelial cells, which express adhesion molecules and chemokines for the recruitment of cells such as neutrophils and monocytes. IL-17 is found in NETs, and its presence is associated with the formation of coronary artery thrombi and the induction of MPO production in neutrophils that contributes to tissue damage during inflammation in AMI. After the recruitment of neutrophils, monocytes also infiltrate the ischemic tissue; IL-17 deficiency induces a reduction in the population of Ly6C^{+} monocytes, which are considered essential in the inflammatory response. Additionally, IL-17 favors the differentiation of monocytes, as it induces the production of GM-CSF, which is essential in the differentiation of M1 macrophages; furthermore, IL-17 induces the expression of TLRs, which trigger inflammatory responses by recognizing DAMPs derived from apoptotic cardiomyocytes. In addition to contributing to the inflammation stage, IL-17 also participates in the activation of M2 macrophages, mainly in the phagocytosis processes that are essential for tissue repair. Although there is evidence for a role of Th17 cells in AMI, their biological role in myocardial ischemic tissue is unknown. Overall, the available evidence suggests that IL-17 contributes to endothelial cell activation and leukocyte recruitment, which facilitates the inflammatory response in ischemic tissue. IL-17 may even contribute to regulating the differentiation of the M2 macrophages that participate in the remodeling and reorganization of damaged myocardial tissue.

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Competing interests

The authors declare that they have no competing interests.

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