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Invited Review

The Triggering Receptor Expressed on Myeloid cells-1: A new player during acute myocardial infarction

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ABSTRACT

Following myocardial ischemia, an intense activation of the immune system occurs that leads to inflammatory cytokines and chemokines production and to the recruitment of neutrophils and mononuclear cells in the infarcted area. Although pro-inflammatory signals initiate the cellular events necessary for scar formation, excessive and prolonged inflammation promotes deleterious cardiac remodeling and dysfunction. The triggering receptor expressed on myeloid cells-1 (TREM-1) is a highly conserved immune-receptor expressed by neutrophils and monocytes that acts as an amplifier of the innate immune response. Blockade of TREM-1 activation protects from hyper-responsiveness and death during severe infections.

Here we review the role of TREM-1 in orchestrating the inflammatory response that follows MI. TREM-1 deletion (*Trem-1*$^{-/-}$) or modulation by the use of a short inhibitory peptide (LR12) dampens myocardial inflammation, limits leukocyte recruitment, and improves heart function and survival in mice or pigs. Moreover, the soluble form of TREM-1 (sTREM-1) is found in the plasma of patients suffering from an acute MI and its concentration is an independent predictor of death. This suggests that TREM-1 may constitute a new therapeutic target during acute MI.

Contents

1. Introduction

1.1. The triggering receptor expressed on myeloid cells 1

A new family of receptors expressed on myeloid cells has been recently described: the Triggering Receptor Expressed on Myeloid Cells (TREM) family. The TREMs isoforms share low sequence homology with each other or with other immunoglobin

Abbreviations: IL, Interleukin; MI, Myocardial Infarction; TLR, Toll Like Receptor; (s)TREM, (soluble) Triggering Receptor Expressed on Myeloid cells; TREML, TREM-like.

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superfamily members and are characterized by having only one immunoglobulin-like domain. The six identified *trem* genes (Trem1, Trem2, Treml1-4) are clustered on human chromosome 6 (and mouse chromosome 17). TREM-1, TREM-2, TREML-3, and TREML-4 associate with the adaptor protein DNAX activating 12 (DAP12, also called KARAP) for signaling [1]. Engagement of TREMs triggers a signaling pathway involving ZAP70 (ζ-chain-associated protein 70) and SYK (spleen tyrosine kinase) and an ensuing recruitment and tyrosine phosphorylation of adaptor molecules such as GRB2 (growth factor receptor binding protein 2), the activation of PI3K (phosphatidylinositol 3-kinase), PLC-γ (phospholipase C-γ), ERK-1, -2 (extracellular-signal-regulated kinase) and p38 MAPK (p38 mitogen-associated protein kinase), Akt serine/threonine kinase, STAT5 (signal transducer and activator of transcription 5) and CARD9-MALT1-BCL10 complex formation [2,3]. The activation of these pathways ultimately leads to a mobilization of intracellular calcium, a rearrangement of the actin cytoskeleton and activation of transcriptional factors such as NFκB. This finally results in production of metalloproteases, pro-inflammatory cytokines and chemokines, including monocyte chemoattractant proteins 1 and 3 (MCP-1, MCP-3), macrophage inflammatory protein 1α (MIP1-α), interleukin 1β (IL-1β), IL-6, IL-8, TNFα, along with rapid neutrophil degranulation and oxidative burst, with a parallel negative regulation of anti-inflammatory IL-10 [4,5].

Among the TREM family, TREM-1 has been identified on both human and murine neutrophils, mature monocytes and macrophages. Its expression by these effector cells is dramatically increased in skin, biological fluids and tissues infected by Gram-positive or Gram-negative bacteria as well as by fungi [6]. The activation of TREM-1 by its yet unknown ligand in the presence of Toll-like receptor 2 (TLR2) or TLR4 ligands amplifies the production of proinflammatory cytokines [tumor necrosis factor alpha (TNFα), IL-1β, granulocyte-macrophage colony stimulating factor], together with the inhibition of IL-10 release. In addition, activation of these TLRs upregulates TREM-1 expression [4]. Thus, TREM-1 and TLRs appear to cooperate in mounting an inflammatory response.

1.2. Soluble TREM-1

Besides its membrane-anchored form, a soluble form of TREM-1 (sTREM-1) is liberated by proteolytic cleavage of its extracellular domain [7]. sTREM-1 acts as a decoy receptor, sequestering the TREM-1 ligand, which may exist in soluble form in the sera of septic patients [8], and dampening TREM-1 activation [6,9]. Thus, sTREM-1 concentration can be used as a surrogate marker of TREM-1 activation.

As TREM-1 was originally thought to be specifically involved during infectious processes, the usefulness of sTREM-1 concentration in diagnosing sepsis and in discriminating between sterile and septic inflammatory disorders has been the focus of several studies during the last decade. This topic has been recently reviewed elsewhere [10]. Briefly, sTREM-1 has been evaluated in three main situations: (1) as a biomarker of systemic sepsis, (2) as a diagnostic tool for localized infections and (3) as a prognostic biomarker of infection. Most studies have included critically ill patients and/or patients from the emergency room. The situation in which measurements of sTREM-1 concentration appears the most useful is in diagnosing localized infection, especially in the setting of pleural effusions or ascitis [11–13]. In the other side, the measurement of plasma sTREM-1concentrations does not seem to hold its initial promises in discriminating between septic and sterile inflammation [14].

Indeed, a growing body of evidence suggests that sTREM-1 concentrations increase in biologic fluids even in the absence of infection. TREM-1 expression depends on the activation of several Toll-like receptors (TLRs) or NOD-like receptors, and it has become clear that many danger-associated molecular patterns (or alarmins, such as high mobility group box nuclear protein, heat shock proteins, free cyclic AMP) that activate these receptors may be produced during aseptic inflammatory conditions such as hemorrhagic shock, ischemia-reperfusion, or inflammatory intestinal diseases.

1.3. Experimental inhibition of the TREM-1 pathway

Since the synthesis of LR12, a TREM-1 antagonist peptide, the therapeutic modulation of TREM-1 pathway has been the subject of many experimental studies. LR12 is a dodecapeptide which has been designed to mimick a highly conserved sequence across various species (human, monkey, porcine and murine sequences) and across two genes belonging to the TREM family (*trem-1 a*nd *treml1*) [15]. Most of these studies are related to sepsis or endotoxinemia in rodents. For example, in a rat model of *Pseudomonas Aeruginosa* -induced pneumonia as well as during melioidosis, TREM-1 antagonist administration was associated with hemodynamic improvement, a dampening of the tissular and systemic inflammatory responses, and a decrease in coagulation activation. In fine, antagonist administration improved survival [16,17]. Similar encouraging results have been reported during experimental hemorrhagic shock, ischemia-reperfusion or severe acute pancreatitis [18–20].

Recently, relevant pre-clinical data have been obtained in a resuscitated model of septic shock in pigs, as well as in LPS challenged nonhuman primates [21,22].

2. TREM-1 and myocardial infarction

2.1. Rationale for a pharmacological modulation of TREM-1

Similarities exist between septic shock and myocardial infarction (MI). First, during these two conditions, the role of the immune system is ambivalent as it can act like a double-edged sword. Indeed, after coronary occlusion, immune response appears crucial for debridement of the infarcted myocardium and the strengthening of the scar. However, delayed resolution of inflammation is known to lead to increased infarct size and detrimental ventricular remodeling. In the same way, immune response is essential for bacterial clearance during sepsis. However, the dysregulated inflammatory response that characterizes septic shock states results in organ dysfunction and death. Second, during these two conditions, priming of the immune response is triggered by pattern recognition receptors (PRRs) activation. PRRs recognize exogenous (pathogen-associated molecular patterns, PAMPs) or endogenous (damage-associated molecular patterns, DAMPs) molecules. PAMPs are conserved microbial motifs among microbial species, whereas DAMPS are endogenous molecules released from damaged cells [23]. During myocardial ischemia, necrotic cells and damaged extracellular matrix components produce large amounts of DAMPs, which in turn activate PRRs signaling. TREM-1 is known to cooperate with numerous PRRs, especially TLR2 and TLR4 [3]. Yet, among the TLRs present in the heart, TLR2 and TLR4 have the highest expression levels and have been most investigated in the context of cardiac ischemia [24]. In this context, it seemed relevant to evaluate TREM-1 modulation during myocardial infarction.

2.2. Role of TREM-1 during experimental myocardial infarction

Until recently, little was known about the role of TREM-1 in the heart. The first description of *trem-1*expression in heart tissue dates back to 2002 but it was not the main topic of the study [25]. From 2002 to 2013, no studies evaluated TREM-1 involvement during any kind of cardiac condition. Then, last year, TREM-1

engagement was shown to be involved in septic-induced myocardial dysfunction [26]. And in the field of cardiovascular diseases, a recent genetic association study reported that various TREM-1 gene polymorphisms were associated with the onset of coronary artery disease [27]. However, no data were available about the mechanisms by which TREM-1 participates in the development and/or the acute phase of coronary events. We thus conducted two experimental studies aiming at evaluating TREM-1 role during chronic coronary ligation [28] and during transient myocardial ischemia [29].

2.3. TREM-1 during chronic experimental model of MI

In mice, TREM-1 is upregulated in the ischemic myocardium - and at a lower rate in the non-ischemic remote myocardium-, both at the mRNA and proteins levels. In humans, TREM-1 is expressed in the heart after MI, and colocalizes with leukocyte infiltrate (neutrophils, monocytes and macrophages). After MI, several leukocytes subset sequentially infiltrate the heart. First, neutrophils reach a peak within the first day and decline shortly, replaced by inflammatory monocytes and then by macrophages [30]. Among various chemokines implicated in leukocyte recruitment, CCL2 (monocyte chemoattractant protein-1, MCP-1) plays a major role in monocyte recruitment after neutrophils have infiltrated the myocardium. Indeed, MCP-$1^{-/-}$ mice show the same time-course and density of neutrophil infiltration than wild-type controls, while monocytes and macrophages recruitment is greatly reduced in KO strain [31]. TREM-1 is crucially involved in leukocytes recruitment, especially neutrophils. Indeed, we have found that pharmacological inhibition of TREM-1 or genetic invalidation led to a five-fold decrease in the number of recruited neutrophils. Interestingly, when neutrophils do not infiltrate the myocardium (by TREM-1 pathway modulation or by specific monoclonal antibody-mediated depletion of neutrophils before coronary ligation), the second wave of leukocytes recruitment (*i.e.* monocytes) does not occur. It parallels with a drop in CCL2 expression in heart tissue. In addition to the decrease in the absolute count of leukocytes recruited into the heart, we also found that leukocytes activation was dampened. For example, neutrophils from *Trem-1*$^{-/-}$ mice showed lower migratory abilities (*in vitro* trans-well assay), produced lower amount of myeloperoxidase or TNF-α. Within the first week after MI, proinflammatory leukocytes subsets give way to anti-inflammatory, reparative subsets. This phenotypic switch is well illustrated by proteases activity, which is tightly regulated to balance wound debridement with ventricular wall weakening. Sustained protease activity depends on TREM-1 activation, and TREM-1 inhibition is associated with a more favorable balance between proteases and their inhibitors. Ultimately, we observed that TREM-1 inhibition was associated with smaller infarct size (Fig. 1) and better survival through preventing from myocardial rupture.

Leukocytes also invade the non-ischemic remote myocardium and may contribute to various deleterious processes such as promotion of interstitial myocardial fibrosis that leads to contractile dysfunction and heart failure. We have found that TREM-1 participated in this harmful phenomenon. Indeed, fibrosis of the remote myocardium was higher in control mice than in *Trem-1*$^{-/-}$ or pharmacologically TREM-1-inhibited mice (Fig. 1).

Human data suggests that results obtained in rodent models are likely to be translated to the clinic [30]. However, we designed a clinically relevant pig model of MI.

2.4. TREM-1 during acute myocardial ischemia/reperfusion injury model

Infarct size after MI correlates with mortality and onset of heart failure. Limitation of infarct size, and thus limitation of ischemia/reperfusion injury, is a major therapeutic target after MI, as reperfusion injury could be responsible for up to half the final

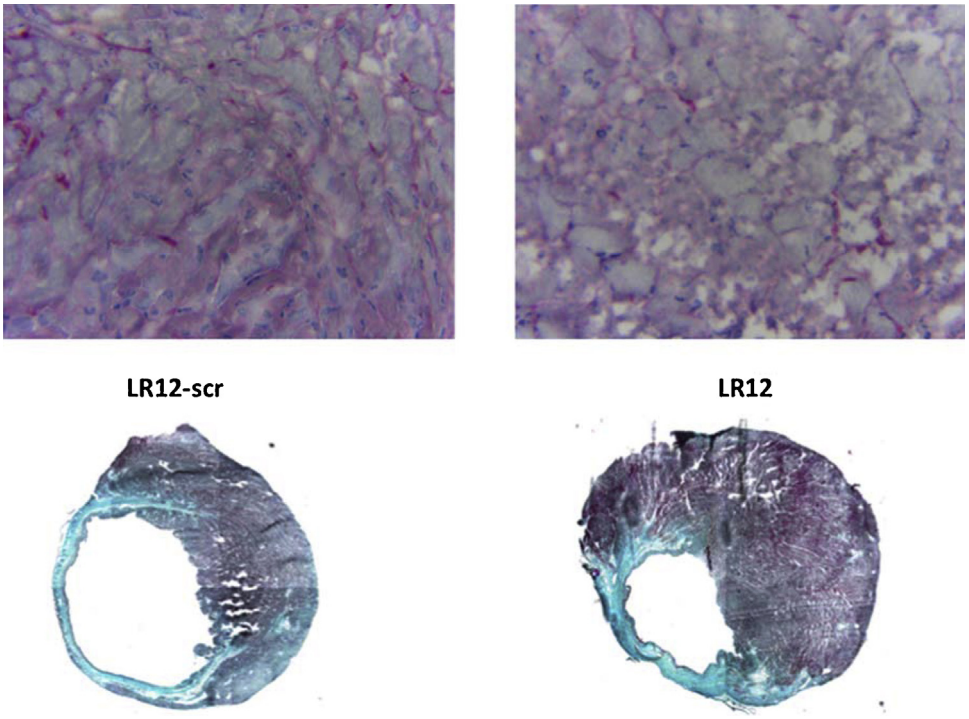

Fig. 1. Pharmacologic inhibition of TREM-1 by LR12 reduces infarct size and myocardial fibrosis in mice. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Upper panels: red sirius staining highlighting myocardial fibrosis 2 weeks after MI. Lower panels: infarct size evaluation by TTC staining 2 weeks after MI. LR12-scr is a scrambled control peptide.

infarct size [32]. The unmet need for novel cardioprotective therapies have been recently reviewed [33].

To investigate TREM-1 role during myocardial reperfusion injury, we used a clinically relevant low-invasive closed-chest MI model in pigs, and tried to mimic what could be the use of TREM-1 inhibitory peptide in the clinic (intravenous administration just before reperfusion) [29]. We found that TREM-1 engagement associated with hemodynamics compromise, decreased cardiac contractility, larger infarct size and more remote organs dysfunction (*i.e.* pulmonary and renal failure). These damages were prevented by pharmacological inhibition of TREM-1 just prior to reperfusion. Considering the evaluated time-lapse (*i.e.* first eighteen hours after coronary occlusion), several hypothetical mechanisms involving neutrophils may be suspected: (1) TREM-1 is involved in neutrophil transmigration and could worsen the no reflow phenomenon by facilitating neutrophils entrapment into the microvasculature through expression of adhesion molecules [34]; (2) activated neutrophils can directly injure surrounding cardiomyocytes by release of toxic products such as reactive oxygen species, a critical mediator of myocardial reperfusion injury; (3) activation of the TLR4 pathway on circulating leukocytes, which is amplified by TREM-1 signaling, results in decreased cardiomyocytes contractility [35].

3. Prognostic value of sTREM-1 levels after myocardial infarction

As discussed above, there is growing evidence that TREM-1 activation is a critical mediator of the inflammatory response that follows MI. The soluble form of TREM-1 is a biomarker of TREM-1 activation, and high concentration after MI should therefore be associated with worse outcome. Relevance of TREM-1 activation after MI was assessed by evaluating the relationship between circulating sTREM-1 plasma concentration at presentation and survival in a cohort of 1015 patients enrolled in the French prospective multicenter FAST-MI 2005 (NCT00673036) [36]. Briefly, this nationwide survey included all patients admitted for acute MI (whether ST-segment elevation or not) with symptom onset less than 48 h, during a one-month period. High sTREM-1 concentration at the time of presentation was associated with higher risk of death after 2 years of follow-up, even after adjustment for several multivariable cardiovascular risk factors. This relationship between high plasma levels of sTREM-1 and increased mortality was also replicated in another similar nationwide survey that used the same methodology five years later, the FAST-MI 2010 (NCT01237418) [37] (unpublished data) [38].

4. Conclusion

TREM-1 is up-regulated in the myocardial tissue following infarction and participates to the deleterious amplification of the inflammatory process that leads to cardiac remodeling and dysfunction. Its pharmacological inhibition appears protective during several experimental models of MI. Moreover, measurement of plasma concentration of sTREM-1 is of prognostic interest in patients suffering from MI. Whether such a measurement may be used in the clinic to guide/reassess therapeutic options remains to be evaluated.

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