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Review

TREM-1; is It a Pivotal Target for Cardiovascular Diseases?

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Abstract: Cardiovascular Diseases (CVDs) are still menacing and killing adults worldwide, notwithstanding the tremendous effort, to decrease their related mortality and morbidity. Lately, a growing body of evidences indicated that inflammation plays a pivotal role in the pathogenesis and complications of CVDs. A receptor of the immunoglobulin superfamily, triggering receptor expressed on myeloid cells -1 (TREM-1) was shown to induce and to amplify the inflammation in both acute and chronic diseases pathogenesis and progression and hence it is one of the important factors that complicates CVDs. Thus, studies endeavored to investigate the role played by TREM-1 in CVDs with respect to their etiologies, complications and possible therapeutics. We examined here, for the first time, the most relevant studies regarding TREM-1 involvement in CVDs. We summarized the finding after critically analyzing them and made some suggestions for furtherance of the investigations with the aim to utilize TREM-1 and its pathways for diagnostic, management and prognosis of CVDs. Overall, TREM-1 was found to be involved in the pathogenesis of acute and chronic cardiovascular conditions like Acute myocardial infraction (AMI) and atherosclerosis as well. Although most therapeutic approaches are yet to be elucidated, present research outcome displays a promising future to utilize TREM-1 pathway as potential target to understand and manage CVDs.

Keywords: Triggering receptor expressed on myeloid cells, DNAX-activating protein 12, cardiovascular diseases, atherosclerosis, coronary arteries diseases, acute myocardial infract, endocarditis.

1. Introduction

Cardiovascular diseases (CVDs) still hold the first place in causing death in adults in most part of the world despite the ongoing battle against them [1-3]. It is important to know that the fight against CVDs is weakened by the continuous increase in prevalence of metabolic syndrome, which is their bedrock underlying etiology [2]. Conditions such as sedentariness, high cholesterol and high fructose diet also exact heavy toll on CVDs prevalence. The common denominator of the onset and the progression of these diseases is the chronic immunoinflammatory process that involves the up regulation of proinflammatory cytokines and chemokines such as IL-1, IL6, TNF-α and IL-8 [4-6]. TREM-1 has been found to be involved in acute [7, 8] as well as chronic inflammatory diseases owing to its role-played in innate immunological reactions [9-11]. Lately investigations have endeavored to find the implication of TREM-1 in pathogenesis and management of CVDs. Overall the findings are promising for TREM-1 pathway to be utilized for CVD biomarker or management [12-15].

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TREM-1 is a 30 kD glycoprotein surface receptor that belongs to the superfamily of immunoglobulin [16, 17]. It is initially found to be expressed on cells derived from myeloblast where it amplifies their inflammatory responses with release of cytokines and chemokine [18]. Bacterial and fungal infections stimulate TREM-1 expression [8, 19]. There are two relevant forms of TREM-1: the trans-membrane, the soluble (sTREM-1) or the secreted. While the overall expression of all TREM-1 is associated with an increased severity of infection, the trans membrane form is found to contribute to inflammation process while the soluble form plays a role of decoy receptor in amending the inflammatory process[20]. In fact, sTREM-1 hinders the TREM-1 ligand to reach the monocytes, macrophages, and neutrophils membrane [21, 22]. It has been found that sTREM is released by activity of metalloproteinase that detach the ectodomain of the transmembrane TREM-1[23].

We reviewed in this article the findings of recent publications regarding the implication of TREM-1 mainly in heart and vessel related diseases. We accessed the strength of the results and presented the relation among them. We also suggested new pathways of investigation that will corroborate with the current findings to advancing to therapeutics of CVDs utilizing TREM-1 pathway.

TREM-1 Signaling

The membrane bound TREM-1 has a short intracellular domain. It requires to be associated to the immunoreceptor tyrosine-based activation motif (ITAM) containing signaling adaptor protein, DNAX-activating protein 12 (DAP-12) as well as to interact with MyD88 to carry out its intracellular signaling (figure 1a). It is established that TREM-1 and toll like receptors (TLRs) interact synergistically to promote inflammation by inducing the production of inflammatory cytokines and chemokines. TLRs are most preeminent pathogen recognition receptors (PRRs) that carryout inflammatory reactions upon stimulation by pathogen-associated molecular patterns (PAMPS) or damage-associated molecular patterns (DAMPs) [22, 24-27 27]. TREM-1 in fact, interacts with TLR-4 to induce more cytokines production by myeloid cells upon exposure to LPS [28, 29]. The process involves the recruitment of inflammation mediators such as Phosphatidylinositol-4,5 bisphosphate 3-kinase (PI3K), extracellular signal–regulated kinases (ERKs), interleukin-1 receptor associated kinase 1 (IRAK-1), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [30]. Moreover, it has been found that the activation of TREM-1 alone does not induce a consistent inflammation process. This suggests that TREM-1 relies on its interaction with other pathways such as of TLRs to fully carryout its downstream reactions as far as inflammation is concerned. In the cytoplasm, nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) play similar synergistic role with TREM-1 [31]. As PRRs, they recognize both PAMPs and DAMPs in microbial infection as well as sterile tissues injuries. They induce upon stimulation the recruitment of innate immune cells that in turn initiate the adaptive immune response. NOD-1/2 activation in conjunction with TLRs and TREM-1 induce NF-κB up regulation and other pro inflammatory cytokines. It is yet to be elucidated if NLRs and TREM-1 can react synergistically but independently from TLRs.

TREM-1 ligands

The putative ligands of TREM-1 were evasive earlier in this decade [29, 32] but lately light started to shine on them. High mobility group box-1 (HMGB-1) also known as amphoterin, was the earlier targeted

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ligand for its role in inducing TREM-1 signaling in activation of Kupffer cell in hepatocellular carcinoma [33-35] [36]. It plays a very significant role as chromatin proteins that like histones are involved in DNA stabilization and gene transcription control. It is regularly upregulated in macrophages and neutrophils recruited during inflammation process especially in tissue injury [37, 38]. HMGB-1 also activates PRRs like DAMPs. It is found to up regulate NF-kB and it translocation to the nucleus for pro inflammatory cytokines and chemokines production. Also, in inflammation HMGB-1 works in concert with receptor of advanced glycation end products (RAGE) or TLRs to form a complex with CXCL-12 (HMGB-1-CXCL-12) in synergy with stromal cell-derived factor-1 (SDF-1) to enhance CXCR-4 signaling and inflammatory cells migration[39].

Peptidoglycan recognition protein -1 (PGRP-1) only or linked to its ligand -peptidoglycans (PG) [40] - was found to induce TREM-1 signaling and the synergetic interaction with TLRs [41, 42]. PGs are glycopeptide polymers containing N-acetylmuramic acid or N-glycolylmuramic acid and D-amino acids. They are found in bacterial wall, where they play key role of keeping bacterial morphology. Unlike the endotoxins that are exclusively found in gram-negative bacteria wall, PG is found in both Gram-negative and Gram-positive bacterial wall. Contrariwise, eukaryotes cells do not contain PG in their cells walls. PGRPs are recognized as types of PRR. They are actively involved in innate immune response including pathogen recognition, induction of phagocytosis and degradation of the amidase activity of PG[43-45].

Actin was also found to trigger TREM-1 with direct interaction with the extracellular portion of the receptor and to induce the downstream signaling in platelets and macrophages. Briefly, TREM-1 interaction with its ligand induces a series of production of intermediary reactions leading ultimately to upregulation of pro inflammatory cytokines such as IL-1β, IL-2, IL-12, and TNF-α [46].

TREM-1 in inflammatory processes

TREM- 1 upregulates the cell surface activation markers myeloid cells. It was also found to be increased during septic shock. It is over expressed in number of infective diseases such as pneumonia and suppurated cholangitis [47-49]. Lately, several studies showed that TREM-1 up regulation on parenchymal cells are associated with the development of chronic disease in the organs they belong to [50] [10, 51, 52]. In fact TREM-1 was found upregulated in obstructive nephropathies [53], and chronic kidney diseases [9, 54]. In chronic inflammatory bowel disease, TREM-1 has been found to be constantly up regulated and specially during flaring episodes [55]. TREM-1 has been found to be implicated in glenohumeral arthritis development and in its progression [56]. Macrophages in lungs cancers were shown to increase TREM-1 expression with subsequent inflammatory response to induce complications and early death [8].

TREM-1 in Cardiovascular Diseases

Out of the most recent studies pulled out of Medline with key words TREM-1, cardiovascular diseases, myocardial infarcts, endocarditis, atherosclerosis, and pericarditis, we found that most relevant studies are those summarized in Table 1. It is remarkable how all of them approach the cardiovascular disease involving TREM-1 in its role played in inflammation either in acute setting

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like endocarditis and AMI, or in chronic condition such as in atherosclerosis (Table 1). In atherosclerosis, the role TREM-1 is found to be in chronic inflammation leading to macrophages and leucocytes apoptosis and necrosis, which contribute to build up fatty streak [57, 58]. It has also been found to induce the vulnerability of the plaque by TREM-1 expression of vascular smooth muscle cells (VSMCs) and dendritic cells [59, 60].

Table 1. Involvement of TREM-1 in Cardiovascular Disease.

CVD	Approach	Outcome	Model Ref
Atherosclerosis	Effect of oxLDL on TREM-1 expression in macrophages during atherogenesis	oxLDL increased TREM-1 expression and its interaction with TLR-4 to amplify inflammation. This action is reduced by TREM-1 silencing or inhibition	M [66]
Atherosclerosis	Role played by TREM-1 in macrophages involvement in atherosclerosis	TREM-1 in association with TLR-4 contribute to formation of foam cell derived from macrophages through inflammatory response	M [67]
Atherosclerosis	TERM-1 polymorphism is associated arthrosclerosis severity	rs4711668 polymorphism within TREM-1 gene and TLR-2 are associated coronary atherosclerosis, TLR-1,4,6 with mild coronary atherosclerosis.	H [61]
Atherosclerosis	TREM-1 expression on dendritic cells (DC) in atherosclerotic plaques	TREM-1 was up regulated in DCs of atherosclerotic plaque and was positively correlated with plaque destabilization	H [59]
Atherosclerosis	TREM-1 expression in vulnerability of atheroma plaque	Increased expression of TREM-1 in VSMCs is associated with plaque vulnerability	H [60, 68]
Acute myocardial infraction	sTREM-1 level regulation by its polymorphism and plasma sL-selectins level	SNP (rs2234246) is associated with increased plasma sTREM-1 and L-selectin	H [69]
Acute myocardial infraction	Role played by TREM-1 in inflammatory response after AMI	TREM-1 deletion or inhibition decreases the inflammation after AMI	M [70]

Acute myocardial infraction	TREM-1 inhibition by LR12 effect on reperfusion injury after MI	TREM-1 inhibition by LR-12 amends the reperfusion injury of the myocardia	S [71]
Acute myocardial infraction	TREM-1 expression in causing innate immune and inflammatory response after myocardial infracts	TREM-1 genetic inhibition reduced inflammation and sTREM-1 level. TREM-1 is positively correlated with the AMI severity	M [15]
Coronary artery diseases	TREM-1 and TLR polymorphisms in CAD	Polymorphisms in TREM-1 and in TLRs were robustly associated to CAD	H [61]
In-stent restenosis	Association of sTREM-1 with in-stent restenosis and expression of TREM-1 in VSMCs	sTREM-1 was elevated in patient with stent restenosis and TREM-1 induce VSCMs inflammation, migration, and proliferation	H [64]
Myocardial dysfunction in septicemia	Association of level of sTREM-1 and severity of myocardial dysfunction in septicemia	sTREM level predicts myocardial dysfunction in septicemia	H [72]
Myocardial dysfunction	Association of TREM-1 with LPS-induced ventricular dysfunction	TREM-1 plays a significant role in LPS-induced ventricular dysfunction	M [73]
Infective Endocarditis	How polymorphism in TREM-1 and TLRs affects the outcome of IE	No association was found between SNPs within TREM-1 genes and the outcome of IE	H [54]
Infective Endocarditis	How heredity of TREM-1 variation could affect the susceptibility and outcome of EI	Only rs1817537 polymorphism is associated high susceptibility to IE	H [74]
Cardiac transplant	How TREM-1and antigen presenting cells affects alloreactive CD4 and lymphocytes	TREM-1 contribute to the differentiation and the proliferation of CD-4 positive lymphocytes	M [65]
Cardiac arrest after heart Surgery	sTREM-1 level after cardiac event without Infection	TREM-1 along with Procalcitonin increase during cardiac event and are not specific to infection but to inflammation	H [7]

H: human; M: mouse, S: swine;

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The destabilization of the plaque leads to artery occlusion and when it occurs in coronary artery, it causes acute myocardial infarction (AMI). TREM-1 was also found to amplify the inflammation following myocardial infraction and its modulation provides better outcome for post AMI in both short and long term [15]. Studies endeavored to find any polymorphism in TREM-1 gene expression associated with atherosclerosis remains elusive on their conclusion, however, it has been found that sTREM-1 is increased in AMI is associated with SNP polymorphism [61, 62]). Elevated levels of serum sTREM-1 is associated with incidence of in stent-restenosis (ISR) and also TREM-1 expression is seen more in the VSCMs of the neointimal and medial region of the stenotic artery, TREM-1 inhibition could play a modulating role in this phenomenon [63, 64]. In endocarditis, several TREM-1 SNP [54] polymorphisms have been reported to be associated with endocarditis susceptibility in Caucasians, and it does not have any effect on endocarditis outcome. In heart surgery TREM-1 expression is found to be associated with post-operative inflammation. In heart transplant rejection, TREM-1 has been found to play key role in lymphocytes CD4+ recruitment [65].

TREM-1 in Pathogenesis of Atherosclerosis

Atherosclerotic plaque constitutes the hallmark etiology of cardiac, cerebrovascular, and other embolismic events in individual with metabolic syndrome, genetic abnormalities, smoking, male sex, or old age. It is led by increased blood low-density lipoprotein (LDL) concentration and possibly triggered by viral or bacterial infection[75-77]. Its pathogenesis is multifactorial and a progressive chronic inflammatory process over decades. The inflammation starts in endothelial cell wall. LDL particles once in contact with the vessel wall trigger a proliferation and migration of myeloid cells such as neutrophil and monocyte /macrophages toward the lumen. Innate immune response has been found to induce myeloid cells proliferations, which contribute to the formation of the plaque. In the beginning of plaque formation, there is flux of blood neutrophil and maturation of resident monocytes into macrophages in media and endothelium of cholesterol rich area of the vessel. Their scavenger receptors recognize the oxidized low-density lipoprotein (oxLDL) engulf and digest them. The excess accumulation of lipid turns them into cells occupied with large droplet of fat called foam cells [5]. They contribute and maintain an environment of chronic inflammation with release of cytokines and chemokines. If there is no reversion of the condition leading to this initial chronic inflammation stage, the recruitment of inflammatory cells will continue and will produce more foam cells which latter will undergo apoptosis, and calcification [78]. This process will continue and build the lipid streak and calcified plaque. If the endothelium is intact, the plaque remains stable. The destabilization is found to be a normal complication of growing plaques especially vulnerable plaques [68]. The vulnerable plaque has been found to be the cause of diseases such as myocardial infracts if they are in coronary arteries or stroke if they are in carotid arteries.

TREM-1 has been found to be up regulated in athermanous arthrosclerosis plaque compared to fibrotic plaque. Moreover, TREM-1 was found promoting the destabilization of athermanous plaque in association with an up regulation of matrix metalloproteinase (MMP) [79]. In a study comparing symptomatic and asymptomatic plaques it has been found that TREM-1, DAP-12 is up regulated in symptomatic compared to asymptomatic. Furthermore, the stimulation of VSMCs derived from symptomatic plaque with the potent inflammatory cytokines TNF-α induced a higher expression of TREM-1 compared to the ones from asymptomatic plaques. This suggests that VSMCs from an unstable plaque are prone to inflammation and TREM-1 plays a major role to this pathogenesis. The

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up regulation of TREM-1 in atherosclerotic plaque contribute to plaque destabilization via its up regulation in macrophages and vascular smooth cells by inducing the secretion of MMP-1 and MMP-9 that hydrolyze the gelatin and collagen leading to the vulnerability of the plaque [68]. Interestingly, it is lately found that MMP-9 has pivotal role to cleave the membrane bound TREM-1 inducing increased circulation of sTREM-1 above threshold that it is used as important biomarker in sepsis [20]. These finding suggest that TREM-1 and MMP-9 share a positive correlation which needs to be elucidated. However, these studies implicate the significant role of this tandem in the pathogenesis of atherosclerosis. Moreover, E-selectin, Vascular cell adhesion molecule -1 (VCAM-1) and Intercellular adhesion molecule-1 (ICAM-1) molecules were found to be key role players in building up of atheroma plaque [80, 81]. They are up regulated by increased expression of TNF-α, IL-4.

One of dilemma to overcome in treatment of arteriosclerotic caused diseases is the restenosis of in-stent implant. In fact, the in-stent restenosis [64] limit significantly the hope offered by peripheral angioplasty after artery occlusion (Table1). Several drugs have been suggested to reduce the chance of the demoralizing event without any significant success. A recruitment of monocytes and low-grade inflammation has been found to play a key role in the proliferation of VSMCs [82]. sTREM-1 is shown to be increased in patients with in-stent restenosis (ISR) and VSMCs isolated from the neo-intima express increased TREM-1 compared to control [63, 64].

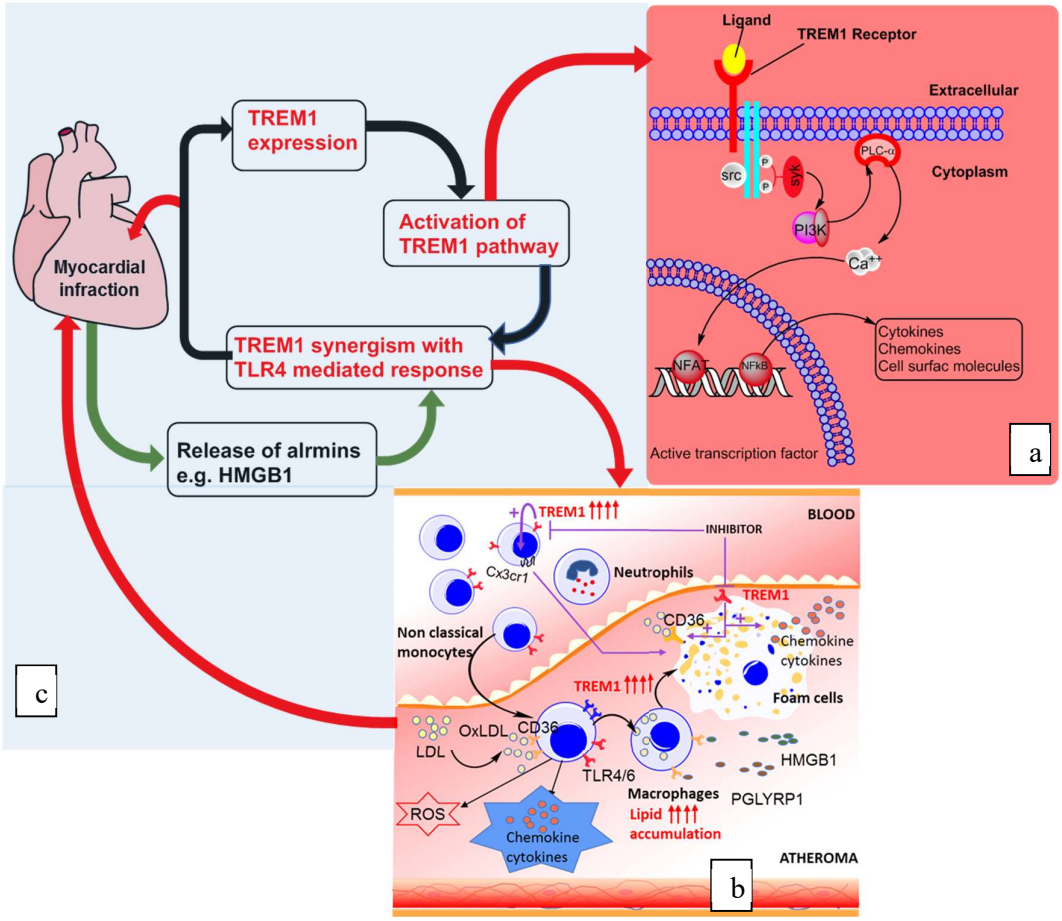

Figure 1. TREM-1 in pathogenesis of atherosclerosis leading to acute myocardial infraction: (**a**) oxLDL concentration elevation in the plasma induces TREM-1 upregulation and its ligand interaction leading to the downstream signaling. TREM-1 interacts with DAP-12 to induce proinflammatory

cytokines, chemokines and cells surface molecules transcription through PI3K and PLC-α and nuclear factors NFAT and NFκB. (**b**) The chronic inflammation condition induces the proliferation, the recruitment, and differentiation of monocytes to macrophages which in turn uptake the oxLDL to form foam cells. It also induces the proliferation of SMCs that play the similar role. Altogether they form the atheroma. **(c)** The destabilization of the atheroma plaque causes coronary artery clog. It results into AMI. During AMI, TREM-1 upregulation induces deleterious cardiac wall scar, source of a heart failure.

TREM-1 in Coronary Artery Disease (CAD) and Acute Myocardial Infracts (AMI)

Coronary artery disease and acute myocardial infraction are most common reasons of medical emergency admission in United State. In fact, every AMI occur in US every 40 seconds. Every year 525,000 new cases of AMI occur while 210,000 happen in people who have already had a heart attack. AMI occurs when a coronary artery is occluded significantly and is unable to supply sufficient oxygenated blood to area of the heart it irrigates. It is caused by the indwelling atheroma plaque overgrowth, rupture, or by severe sudden vasoconstriction. This leads to occlusion by blood clot where platelets activation and aggregation constitute the key role player. The hypoxia resulted from this event induces myocardial tissue damage with cardiomyocytes necrosis and apoptosis. The release of DAMPS from this event has been found to trigger an inflammatory cascade that studies have found TREM-1 to be involved (Fig.1) [14, 70]. After myocardial event, there is a release of inflammatory cytokine and chemokines that cause myeloid cells such as monocytes and neutrophils influx to the ischemic lesions area. They contribute to the normal myocardial repair with a fibrotic tissue [14, 15]. TREM-1 excessive up regulation may induce, after long period of time a deleterious cardiac wall remodeling that will impair the cardiac morphology and function. Cardiac failure will occur with reduced heart output and contractility. Cardiac arrhythmia may also follow when the cardiac septum is affected[83, 84].

TREM-1 is found to be implicated in AMI, where to ischemic area, it recruits monocytes that differentiate into macrophages. It also causes proliferation on neutrophils and their migration like it does in bacterial lung infection [85]. Soluble TREM-1 is increased during the onset of MI and is a predictor negative outcome. Its increase correlates positively with immediate overall death outcome. It also has been found to determine late-onset heart failure following ST- segment elevation myocardial infraction (STEMI) in human [15]. In mice the inhibition of TREM-1 by LR-12 reduces monocytes and neutrophils recruitment, and inflammation in affected myocardium. Also, inhibition of TREM-1 in its downstream signaling protect against heart failure post AMI. sTREM-1 is found elevated in the blood during AMI and its level is correlated with the death outcome. Altogether TREM-1 up regulation suggests complicated AMI and while early its inhibition protects against the detrimental outcome[15, 71, 86]. The myocardial infract healing involve majorly leucocytes recruitment that can cause damages if it not well modulated. TREM-1 inhibition has shown to eliminate neutrophils migration to ischemic site thus avoid uncontrolled healing into deleterious scar. TREM-1 suppression should be explored as a preventive approach for AMI and for the management of post AMI.

TREM-1 in endocarditis.

Endocarditis is the inflammation of the inner layer of the heart. It most commonly involves the cardiac valves. Usually its etiology is non-infective with chronic progression. This form is called nonbacterial thrombotic endocarditis (NBTE), because it does not involve bacterial infection in its development, and it clinically manifests by the release of thrombus proceeding from the vegetation's breakout. NBTE does not induce on its own a general inflammatory process, but only when complicated by bacterial infection, or by heart or brain thrombotic events. At time it can also be complicated by bacterial infestation, thus causing infective endocarditis [87].

Infective endocarditis is life threatening condition in acute onset and very debilitating cardiovascular condition in the long run. TREM-1 was found to predispose Caucasian individual to infective endocarditis. In fact, TREM-1 and its interaction with TLRs were consistently involved in others acute infective disease such as pneumonia, septicemia, and gingivitis. Also, the blockage of TREM-1 in this condition has shown in decrease of immune inflammatory reactions. In endocarditis among TLRs, rs3775073 polymorphism within TLR-6 gene is the only actually reported to be associated with the decrease endocarditis onset among a Caucasian population [54, 74]. The application of these finding may lead therapeutics approaches to amend the remodeling scar that follows the IE. Sepsis and hyper coagulation are the most common cause of NBTE. It is well defined that membrane bound TREM-1 played an important role in implication of immune response during sepsis and there is an increase of sTREM-1 in blood during sepsis.

Therapeutics of cardiovascular diseases targeting TREM1 pathway

There has not been a specific therapeutic approach developed targeting TREM-1 pathways to our knowledge. Therapeutic approaches suggested by most studies are yet to be endeavored. Indeed TREM-1 knockout mice have shown reduced inflammatory reaction when they were exposed to LPS or other inflammatory agent such PG, in acute as well in chronic diseases settings. Trem-1$^{-/-}$ mice were found to be resistant to severe form pneumonia, peritonitis, or septic shock [19, 88, 89]. The resistance that they developed is associated with down regulation of pro inflammatory cytokines and chemokines and in some cases with an increased expression of anti-inflammatory proteins. In CVD related diseases, it was demonstrated that genetic inhibition of TREM-1 resulted into the reduction of inflammation and the severity of AMI in mouse model [70]. Also, TREM-1 inhibition attenuates the inflammation underling the atheroma building up by decreasing the TREM-1 and TLR interaction and downstream signaling [67].

The consideration of TREM-1 reactions pathways for biomarkers for CVDs is one of the wide venue studies should endeavor delve in, since it remains a challenge for healthcare providers to predict cardiovascular events. In fact, atherosclerosis, which is the cause AMI and stroke, is very difficult to detect by imaging [90]. A discovery of unstable atheroma at subclinical stage will be very lifesaving. Angiography is the most accurate and often used but is very invasive. Echography and MRI as today cannot detect sub-symptomatic plaque. These difficulties call for a simpler and more effective way of finding plaque presence in blood vessel and treat them early. High sensitivity C-reactive protein level was suggested earlier but it remains not convincing since it is not specific. As TREM-1 is key player in pathogenesis of atherosclerosis, it is worthy to venture to find out how it could be used as biomarker of atherosclerosis susceptibility with patient at risk. Works already showed the trend, evidencing that sTREM-1 level is associated with complications of AMI. sTREM-

1 level was shown to be correlated with the severity of AMI and heart dysfunction during sepsis but, it has not yet a robust study to make it a maker of those aforementioned condition [15]. We suggest that a large scale and multi-centric investigation of these findings are worth to be endeavored since they will help to manage efficiently CVD and diminish by the way its mortality.

In pursuit of finding therapeutic approaches to CVD utilizing TREM-1, newer TREM-1 inhibitors are being developed. LP-17 is designed peptide to fit the extracellular Fc component of TREM-1. It is considered to play a role of weakening the dimerization of TREM-1 or it competes at the ligands binding site of the receptor [27, 91]. LP-17 is 17 amino acid peptide derived from extracellular part of TLT-1. LP-17 was shown to down regulate the expression of TNF-α and IL-1β in monocytes treated with LPS. Another is the triggering receptor express on myeloid cells like transcript-1 [92, 93] and its peptide motif LP-17 were shown to mitigate the dysfunctional downstream signaling of TREM-1. Upon exposure of human neutrophils and monocytes to LPS, the addition of LP-17 induced lower expression and activity of most pro inflammatory cytokines and chemokines. Interestingly, the LR17 reduced TREM-1 expression in both initial and later stage of sepsis, and the detrimental effects of the chronic inflammation in mice model of sepsis with increase of their survival [66, 94]. Another dodecapeptide TREM-1 antagonist, LR12 (LQEEDAGEYGCM) was found beneficial in atherosclerotic plaque. LR-12 is shown to block TREM-1 and reduces its activation of monocyte/macrophage to form foam cells in atherosclerosis pathogenesis [67, 95]. Furthermore, recently been found the multimerization of TREM-1 that causes its activation is inhibited by LR12 [96]. Also, curcumin extracted from yellow pigment of turmeric has been shown to inhibit TREM-1 down streaming signaling. The diferuloylmethane has shown to modulate inflammation through inhibition of TREM-1 expression in macrophages, and the lung of septic mice [97]. Endogenous prostaglandin E2 has been found to modulate TREM-1 expression in LPS rich environment in vitro as well in vivo [98]. Recently, TREM-1 inhibition has benefited of signaling chain homooligomerization (SCHOOL) model that targeted the interaction of TREM-1 with DAP-12. In experimental pancreatic or pulmonary cancers, peptides engineered by SCHOOL technics has reduce tumor growth and increased survival rate [99]. In fact TREM-1 SCHOOL peptide GF9 in free and HDL-bound form has shown antitumor and has been able to amend sepsis in experimental model[100]. All this advancement in targeting TREM-1 inhibition as therapeutics approach will benefit CVDs search for cure.

In Dyslipidemic conditions, TREM 1 expression is upregulated in the circulating myeloid cells. In addition to this, TREM 1 also synergizes with high-cholesterol diet (HFCD)-induced monocytosis to promote pro-inflammatory and atherogenic cytokine production and foam cell formation of macrophages[101]. In a study of renal tissues from diabetic nephropathy rats, vitamin D supplementation has shown to suppress TREM-1 expression, macrophage adhesion and migration [102]. The effect of vitamin D and its immunomodulatory role in the coronary artery atherosclerosis has been already established in various study models. In our previously published study, we have demonstrated the protective nature of vitamin D against atherosclerosis in hypercholesterolemic swine via controlling cholesterol efflux and macrophage polarization via increased CYP27A1 activation [103]. This signals an interesting venue in exploring the influence of epigenetic on the expression of TREM-1and its actions.

Over all these findings need to be more elaborated with CVD specific animal model, preferentially with humanoid model such swine model. We predict that acute disease such AMI and

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endocarditis will be easier to attain than chronic disease like atherosclerosis that requires months even year to develop.

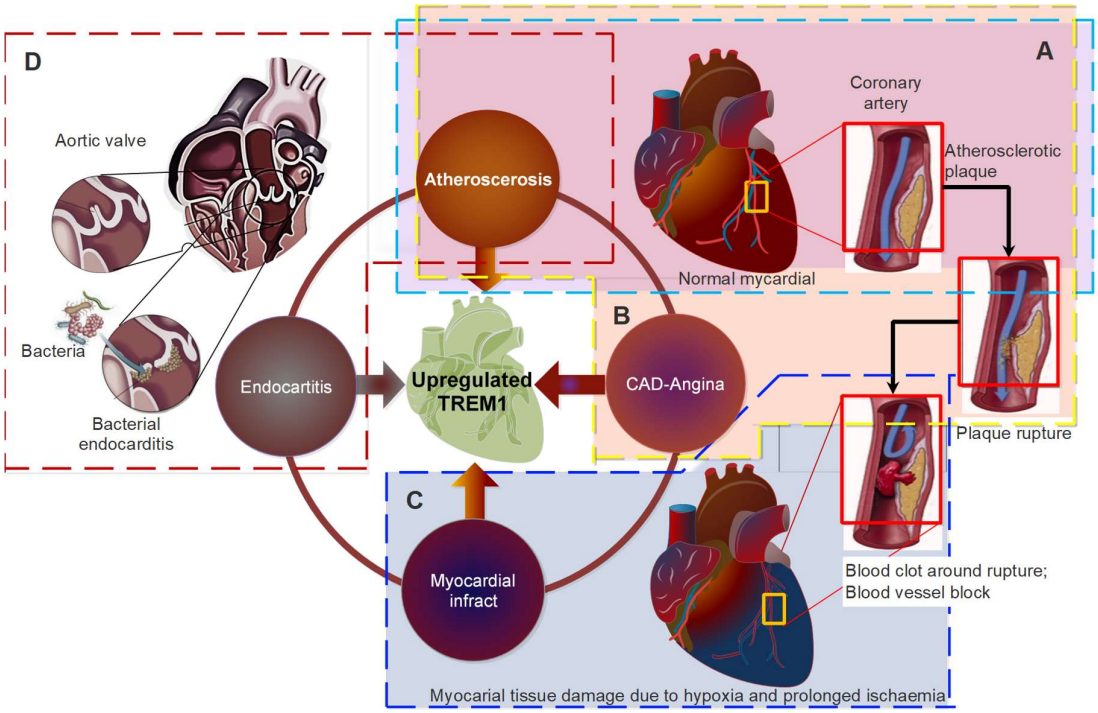

Figure 2. Role of TREM-1 in cardiovascular diseases and potential: (**a**) TREM-1 up regulation is implicated in atheroma formation in artery and its destabilization. TREM-1 modulation will reduce arthrosclerosis(b) TREM-1 play role in the atherosclerotic plaque enlargement and instability, which manifests clinically by either coronary artery disease (CAD) or angina- when the coronary is partially clogged- or (c) AMI when it is completely blocked. TREM-1 inhibition will reduce AMI events in patient at risk. (d) TREM-1 is also link to the proclivity to develop endocarditis. In patient at risk TREM-1 inhibition can protect.

Conclusion

TREM-1 is an important inflammatory role player as orchestrator and player. It achieves its functions by interacting with PRRs and their putative DAMPS and PAMPS. We believed in CVD, PGLYRP-1 alone or linked to PG is the putative ligand of TREM-1 implicated in atherosclerosis. Our insinuation is because bacteria were found to play part in pro inflammatory reaction leading to atherosclerosis and LPS component of the bacteria act as DAMPS to activate TLRs that are found to interact in synergy with TREM-1. We foresee that any intervention that will down play the role of TREM-1 on long run basis will be beneficial to prevent atherosclerosis and its detrimental outcome of AMI, stroke, or ischemia of the extremities.

Since TREM-1 contributes to the complications following AMI to complicate the immediate and future outcome, we predict that any modulation of TREM-1 during the management of AMI will be beneficial for the patient. Still this progress owes to the discovery of the ligand that is involved in interplay leading to various step of AMI pathogenesis and complications.

Overall TREM-1 in CVDs study is at its beginning. The pathogenesis as well as the therapeutic mechanistic approaches warrant focus. There are other CVDs that are not yet studied in respect of TREM-1. Because its role-played in chronic inflammation, which is the hallmark of CVDs such as hypertension, valvular diseases, peripheral artery diseases, cardiomyopathy, and heart failure should investigate for TREM-1 implication their development and complications. Their treatments should neither be left out.

Conflicts of Interest: The authors declare no conflict of interest.

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