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Novel Attributions of TREMs in Immunity

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Abstract

⁴The emerging role of the TREMs (Triggering Receptors Expressed by Myeloid cells) family in inflammation makes it important to explore their molecular mechanisms governing key pathways in inflammatory diseases. The TREMs family interaction with microbial products make it a strong candidate to target inflammatory diseases and raises an important question of its potential as a useful target in inflammatory diseases caused by products other than microbes, for example psoriasis. The interaction of TREMs with various immune responses can be of key importance in handling inflammatory diseases. The well established interaction of TREM-1 with microbial products like LPS and the emerging interactions with products from different important diseases of brain, heart, lungs and skin demands its full investigation as a therapeutic target. The post translational modifications (PTMs) that might regulate the functions of genes are also discussed and its future potential is reviewed. Furthermore, its close cross talk with TLRs, NLRs and NODs is also reviewed in context of developing novel therapeutics.

Introduction

The innate inflammatory response is the first of its kind to protect the body against attacking pathogens (Khan et al., 2015). However, excessive inflammation needs to be controlled to avoid tissue damage. Pathogens are recognized by special sensors, the pathogen associated molecular patterns (PRRs) which activates innate immune responses and shapes the adaptive ¹³unity of organisms (Khan et al., 2015). A new class of cell receptors, the triggering receptors expressed on myeloid cells (TREMs) are identified (Bouchan et al., 2000) which modulates PRR-signaling by up or down regulation (Genua et al., 2014). ²⁶There are four classes of TREM family protein namely TREM-1, TREM-2, TLT-1 and TLT-2 (Bellingan, et al., 2002).

The identification of Triggering receptors expressed by myeloid cells (TREMs) on Ig superfamily that is selectively expressed on neutrophils and monocytes upregulates (TREM-1) in response to LPS suggests its important role in

inflammatory diseases (Bouchan et al., 2000; Barraud and Gibot, 2011). The latter investigations ¹⁹s its high expression level on other human immune cells including dendritic cells, granulocytes¹² and natural killer cells with T cells and B cells (Allcock et al., 2003; Matesanz-Isabel et al., 2011; Rigo et al., 2011). TREMs regulation and expression remains a topic of interest to many scientists particularly immunologists and pharmacists who consider it as an important therapeutic target in inflammatory diseases. (TREMs) are members of receptors that contain both activating and inhibitory isoforms defined (encoded) by gene cluster associated with major histocompatibility complex (MHC). Myeloid cells are activated by signaling through DAP12, one of the adaptor protein (Bouchan et al., 2001; Moyes et al., 2009). The bacterial and fungal induced inflammation is amplified through the phagocytes secreting pro-inflammatory chemokines and cytokines triggered by TREM-1 (Colana, 2003).

⁴²The earlier studies indicates neutrophils and monocytes (Medzhitov et al., 2000; Hoffman et al., 1999) are the mediators to bacterial infections that expresses pattern recognition receptors (PRRs) to interact with microorganisms having special conserved molecular structures (Aderem et al, 2000; Beuterman et al., 2000). The subsequent findings of TREM-1 mediation with inflammatory pathway to microbial products (Bouchan et al., 2001) as amplifier of inflammation, its upregulation in response to lipopolysaccharide (LPS), while its demonstrated protective ability to septic shock against *E. coli* through its blockade indicates it as one of the important therapeutic target in septic shock diseases.

One of the factor in the progression of liver cancer is chronic inflammation and liver kupffer cells are demonstrated to show crucial role in promoting liver cancer through mediating inflammatory responses (Wu et al., 2012). On the other hand, tissue hypoxia a major cause of inflammatory diseases and cancers that is controlled by hypoxia induced transcription factors (HIFs) having HIF-1 B and HIF-1 A subunits (Melillo, 2011). Several genes are up or down regulated in response to this hypoxic condition. TREM-1 is one among them that seems to be a key player in immunity related pathways as an amplifier of inflammation. The cross talk of TREM-1 with other pathways and diseases stresses the need to review the recent developments in progress on this class of receptors and further explore its journey from laboratory experiments to clinical research and therapeutics. This review will summarize these important aspects and avenues associated with this relatively new and scarcely reviewed class of receptors the TREMs.

TREM pathway and its interaction with diseases

TREM-1

The selectively expressed cell surface receptors on macrophages, monocytes and neutrophils of the immunoglobulin family the TREM-1 is devoid of cytoplasmic signaling motifs thus requires DAP12 a transmembrane activating enzyme to activate proinflammatory immune response (Colonna and Facchetti 2003). Janus kinase 2 (JAK2) a non receptor tyrosine kinase, PKB and ERK1/2 responds to the TREM-1 activation results in STAT3, STAT5 and NF- κ B phosphorylation (Fortin et al., 2007). The inflammatory response genes are upregulated by these transcription factors (Fortin et al., 2007). The activation of TREM-1 by its unknown ligand or Toll like receptor (TLR) through LPS makes TREM-1 and TLR pathways to associate with each other (Fortin et al., 2007) that in turn results in interleukin-1 receptor associated kinase (IRAK1) that leads to the production of proinflammatory cytokines through NF- κ B pathway (Fortin et al., 2007). The alliance of TREM-1 and TLR pathway dictates the degranulation of neutrophils. Phagocytosis, respiratory burst and large production of proinflammatory cytokines are the other outcomes of TREM-1 activation. Several of the cell surface proteins are also upregulated in response to TREM-1 examples of which include CD11, CD29, CD80 etc (Bouchon et al., 2000; Fortin et al., 2007). This hugely diverse involvement of TREM-1 in important innate and adaptive immune

responses makes it interesting candidate to study its functional role in immunity and therapeutics. The short description of TREM-1 involvement in inflammation is shown in Figure 1.

Myocardial infarction (MI) is one of the leading causes of deaths in humans (WHO, 2008). Recently the innate immune response has been implicated in cardiac response to MI where TREM-1 that is expressed by immune related cells the neutrophils, monocytes and macrophages and is a proven amplifier of innate immune response triggered by Toll like receptors (TLRs) (Fan and Malik 2009). It has been shown recently that TREM-1 deficient mice have significantly lower risks of MI seen from the reduction in infarcted size of the tissue (Boufenzar et al., 2015). Furthermore, it was demonstrated that anti-TREM-1 monoclonal antibody decreased survival rates in mice confirming its pivotal role in MI and its modulation by LR12, a synthetic TREM-1 peptide inhibitor (Lemarie et al., 2014), confers its therapeutic application for MI (Zhou et al., 2014, Boufenzar et al., 2015).

TREM-1 has been demonstrated to amplify TLR2 and TLR4 signaling (Pelham and Agarwal 2014). TREM-1 not only synergizes with TLRs but also interacts with NLRs to produce cytokines like TNF, IL-1 β , IL-6 and IL-8. Thus it is worth mentioning that TREM-1 amplifies signals from both the major pathways the TLR and the NLR which are two important pathogen recognition receptors PRRs that

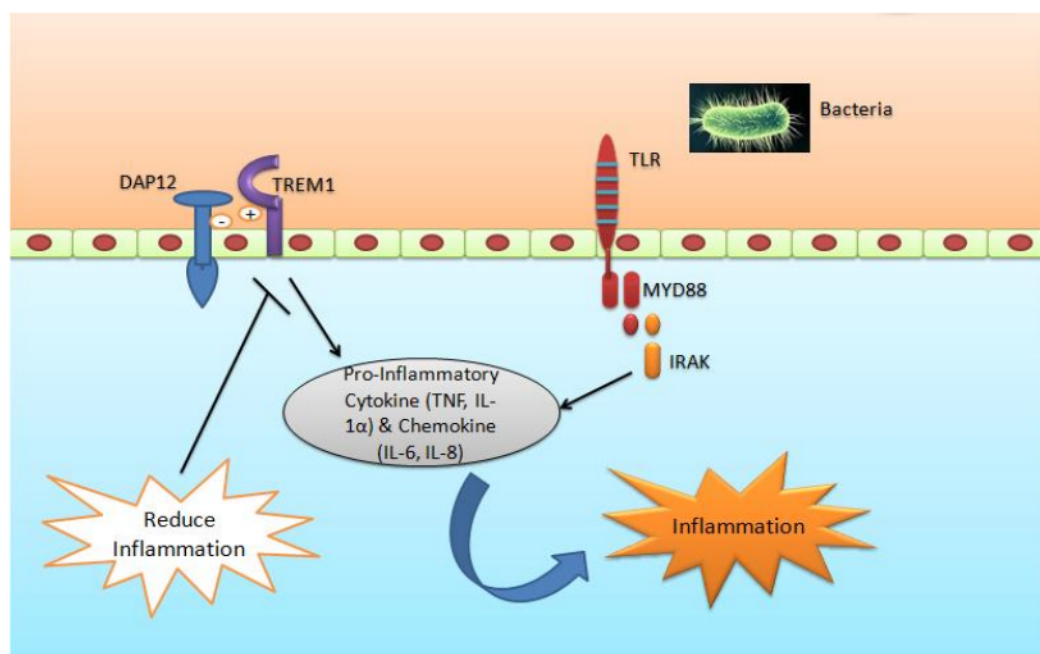


Figure 1. The TREM-1 signaling pathway where TREM-1 by microbial components or LPS results in the acute inflammatory response that causes sepsis. TREM-1 association with DAP12, TREM-1 that mediates a host of responses, including excessive release of pro-inflammatory cytokines, with increased expression of cell activation markers.

interacts with **TREM-1** (Arts et al., 2012) and have defined roles in p38, CARD9, BTK, IRAK1, and mBD2 (Neill et al., 2007). TLR2 and TLR3 show synergistic effects after stimulation of monocytes at cytokine level although it is yet not fully defined. **TREM-1 and TLR2 pathways synergistic effects** are realized through the studies where TLR2 ligands upregulate expression of TREM-1 through integrating with MYD88 (Haselmayer et al., 2009), and its synergistic effects on NF- κ B (Haselmayer et al., 2009). A slight upregulation of TREM-1 is also observed when TLR3 ligand polyinosinic:polycytidylic acid stimulate monocytes cells (Bleharski et al., 2003) while there are reports which negates the upregulation of TREM-1 (Begum et al., 2004), TNF- α production (Arts et al., 2011), or increase in neutrophils activation (Radsak et al., 2004). It has been shown that TREM-1 can increase phosphorylation of IRAK1 which could be the possible explanation for the interaction of TREM-1 and TLR4 signaling (Haselmayer et al., 2009). Moreover, a synergistic release of ROS is reported through a crosstalk of TREM-1 and TLR4 through P13K. An increase in p38 and p13K activation has been observed through TREM-1 and TLR4 stimulation in which p13K promotes ERK and Akt cascades that leads to increased production of cytokines (Yamamoto et al., 2000). These interesting interactions of TREM-1 with TLRs make it an important gene for study in disease conditions and as a target for different pharmaceutical agents to help cure inflammatory and cancerous diseases.

Pneumonia, an acute respiratory tract bacterial infection is a major cause of deaths around the globe (Mizgerd, 2006) making 35% of the mortalities caused by infectious diseases (WHO). Critically ill patients present severe sepsis that result in multiple organ failure leading to death (Russell, 2006). Polymorphonuclear neutrophils (PMNs) are the major effector cells in pneumonia that migrates to the site of inflammation and kills the bacteria in innate immune response, where migration of PMNs are regulated by the production of chemokines that in turn acts on chemokine receptors controlling the migration of PMNs ahead the concentration gradient (Baggiolini, 1998). TREM-1 has been shown to enhance PMNs activation in response to microbial products (Bouchon et al., 2000; Haselmayer et al., 2009), and soluble **TREM-1** (sTREM1) (Gibot et al., 2004) in plasma is regarded as quality indicator of sepsis both of which modulates the inflammatory response to sepsis and pneumonia.

Another important inflammatory disease regarded as autoimmune disorder the Rheumatoid arthritis (RA) mainly affecting bone and cartilage (Chen et al., 2015), is a painful disease of elderly people with swollen joints, lungs and heart. The attacking pathogens are battled out by activation of innate immune response through polymorphonuclear cells (PMNs) and natural killer cells to clear affected tissue of pathogens. TREM-1 and DAP12 are shown to be important activators of RA pathogenesis and its involvement in PMNs suggests its therapeutic potential either through blocking DAP12 signaling pathway or inhibiting TREM-1 expression (Chen et al., 2015). Another gram-negative bacteria *Porphyromonas gingivalis* implicated in periodontal inflammation and *in vitro*

investigation shows enhanced expression of TREM-1 and sTREM-1 demonstrating its role in chronic gingivalis pain (Bostanci et al., 2013).

Apart from bacterial infections, psoriasis, an important skin disease, characterized by abnormal differentiation of keratinocytes, which can be fully cured through pertinent therapy, might reveal interesting targets for curing other inflammatory diseases as well (Lowe et al., 2007). Several of the immune related cells including dendritic cells and T-cells with different cytokines and chemokines are supposed to play important role in pathogenesis (Gibot et al., 2004). The transcriptome of psoriatic inflammatory pathway shows TREM-1 signaling which makes researchers to look for characterizing this pathway in psoriasis. The patients of psoriasis show expression of TREM-1 on circulating myeloid cells and psoriatic lesions. Furthermore, the reduction of TREM-1 positive cells in psoriatic lesions following successful treatment and TREM-1 blockade in an *in vitro* and *ex vivo* allogeneic mixed lymphocyte reaction (MLR), using peptidoglycan (PGN)-activated monocytes and psoriatic lesional dendritic cells having activated antigen caused low IL-17 production indicates its probable role in TREM-1 psoriatic pathway (Hyder et al., 2013).

Chronic inflammation provides suitable environment for different kind of cancers including liver and lungs to develop that incurs high mortality worldwide. The carcinogenic compounds damage different organs like liver to produce damage associated molecular patterns (DAMPs) that activates inflammatory associated genes that recruits monocytes, granulocytes, neutrophils etc. to site of damage. The over activation of these genes causes mutations to cells resulting in its uncontrolled mitosis ultimately resulting in cancer (Wu et al., 2012). TREM-1 is expressed in over 90% of cancers emphasizing its probable role in disease development and its modulation as an opportunity to treat inflammations caused by infectious agents or cancers. To illustrate the TREM-1 interaction with different proteins a string analysis was performed which shows its involvement with important proteins like TREM-2, TLR4, TLR2, NOD2 etc. shown in Figure 2.

TREM-2

TREM-2 like TREM-1 also expressed on myeloid cells but is confined to dendritic cells (DCs) only. There are several severe disease phenotypes associated with knockout of TREM-2 like Nasu-Halokata disease (NHD) (Xing et al., 2015) hence hampered its characterization. TREM-2 mutations or deletions cause neurodegeneration and ultimately a premature death (Sessa et al., 2004). This makes the characterization of TREM-2 focused on tissue expression pattern mostly in microglia and osteoclasts. TREM-2 expression is opposite to that of TREM-1 and the finding of stored pools of TREM-2 in microglia (Sessa et al., 2004). Other studies show downregulation of TREM-2 surface expression in response to TLR stimulation (Turnbull et al., 2006; Hamerman et al., 2006). TREM-2 is demonstrated to have a role in microglia inflammation hence can be further investigated for neuro inflammations. Recently TREM-2 has been shown to have a relationship

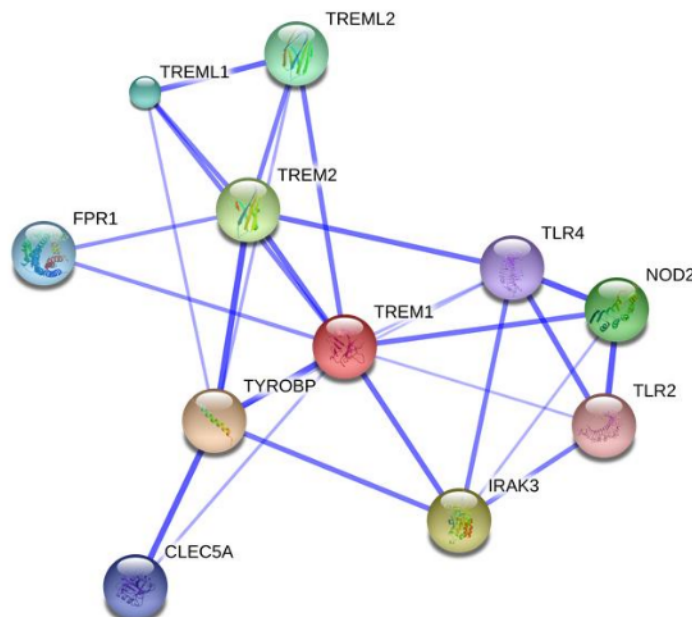


Figure 2. TREM-1 interaction with different important proteins that play role in important cellular processes. Several proteins including TREM-2, TLR4, NOD2, IRAK3 shows strong association with TREM-1.

39 with Parkinson's disease (Rayaprolu et al., 2013) and Alzheimer's disease (Finelli, et al. 2015).

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TLT-1

TREM like transcript 1 is another member of the TREMs family responsible for augmenting platelet cells to aggregate and promote leukocyte interactions (Ferrer-Acosta et al. 2014). Platelets mediate homeostasis, thrombosis and inflammation (George, 2000). As TREM-1, TLT-1 is also considered a possible modulator of sepsis (Ferrer-Acosta et al. 2014) where platelet count or thrombocytopenia is considered a possible indicator of patient death. Lupus, an autoimmune disorder has recently been linked to TLT-1 (Morales-Ortiz et al. 2014).

TLT-2

TREM like transcript 2 is unique to other TREMs in terms of its distribution as it is present on both myeloid and lymphoid cells (King et al., 2006) with conserved expression pattern both in human and mouse modulated by an inflammatory stimuli. TLT-2 is localized intracellularly in neutrophils and translocates rapidly to cell surface upon degranulation. These observations enhances the canvas of TLT-2 and will be useful in understanding of the immune responses mediated by TLT-2. A recent finding explores that TLT-2 clear apoptotic cells by binding to phosphatidylserine, a major phagocytotic signal on apoptotic cells, that indicates further involvement of TREM receptors in inflammation and autoimmune responses (De Freitas et al., 2012). A short list of diseases and its interaction with TREMs is given in Table 1.

The above examples depict TREMs importance in a range of diseases from infectious and carcinogenic to autoimmune disorders. Hence a detailed investigation of the TREMs regulation including its post translational modifications and its induction in therapeutic models might improve the available treatments against wide range of diseases. This article will mainly focus on TREM-1 and its ability as a therapeutic target.

TREM-1 and its epigenetic regulation

Epigenetics, the modifications of cytosine and guanine dinucleotides (CpG) through DNA methylation (Robertson, 2005; Baylin and Jones, 2011) and histone alterations like phosphorylation, acetylation, ubiquitination, miRNA and SUMOylation making up the epigenome have been implicated in several diseases and is now considered an important target for epigenetic medicine and therapies (Dowson et al., 2012). The highly dynamic epigenetic status of genomes that varies among different tissues involving multiple enzymes collectively and coherently work to methylate DNA and bring post transcriptional histone modifications (Kouzarides, 2007). There are several important diseases that are suggested to be under epigenetic control including cancer (Esteller, 2007), autism (Schanen, 2006), depression (McGowan et al., 2009), asthma (Adcock, et al., 2005), multiple sclerosis (Mastroratti, et al., 2007), chronic obstructive pulmonary disease (Adcock, et al., 2005), hence underpinning its crucial role in disease development and prognosis. TREM-1 as is described above has been implicated in several inflammatory diseases hence its epigenetic

Table 1: TREMs signaling pathways and its interaction with diseases

| TREMs | Related immune Cell | Signaling pathway and effector | Disease | Tissue | Reference |
|--------|---|--|--------------------------|--------|--|
| TREM-1 | Neutrophils, mature monocytes and macrophages | Toll like receptors (TLRs) /NLRs TNF, IL-1B, IL-6 and IL-8. | Myocardial infarction | Heart | Boufenzar, et al., 2015 |
| | Tumor associated dendritic cells | Cyclo-oxygenase pathway | Lung Cancer | Lungs | Yuan et al., 2014 |
| | Polymorphonuclear neutrophils (PMNs) | TREM-1 pathway | Pneumonia | Lungs | Russel, 2006 |
| | Polymorpho nuclear cells (PMNs) | TREM-1 pathway | Rheumatoid arthritis | Joints | Chen et al., 2015 |
| | dendritic cells and T-cells | IL17 signaling | Psoriasis | Skin | 43 yes et al., 2007 |
| TREM-2 | Microglia inflammation | TREM-2/DAP12 pathway | Parkinson's, Alzheimer's | Brain | Rayaprolu et al., 2013; Finelli, et al. 2015 |
| | Microglia | TREM-2/DAP12 pathway | Nasu-Hakola | Brain | Xing et al., 2015 |

regulation might have prime importance in its use as therapeutic target.

One of the major protein produced by hepatocytes during acute phase, the serum amyloid A (SAA) (Hoffman et al., 1982; Uhlar et al., 1999) which is also released during several inflammatory diseases caused by microbes, tissue injury or dysfunction of immune response (Ferrero-Miliani et al., 2007). The clinical diagnosis of the important inflammatory diseases like atherosclerosis, rheumatoid arthritis, and diabetes is made by determining the elevated level of SAA in blood plasma level (Yan et al., 2014). Recently, jmj3d3 a histone H3 lysine 27 (H3K27) demethylase is shown to overexpress in SAA stimulated macrophages and is responsible for induction of cytokine genes. The observations of inhibition of proinflammatory cytokines, the G-CSF, IL-23-p19 and TREM-1 and the upregulation of trimethylation at promoter of H3K27 on silencing of jmj3d3 suggests the epigenetic regulation of proinflammatory cytokines in SAA stimulated cytokines (Yan et al., 2014).

Recently a group of scientists demonstrated that TREM-1 knockout macrophages shows high cell apoptotic activity in response to lipopolysaccharide (LPS) marks its role in macrophage cell survival (Yuan et al., 2014). B cell lymphoma 2 (Bcl2) induction was hampered with knock out of TREM-1 and increased activation of caspase-3 in response to LPS (Yuan et al., 2014). This study reflects the role of TREM-1 in inflammatory cells by increasing its longevity and survival. In another study, curcumin was shown to modulate the epigenetic control of TREM-1 through methylation/de-methylation of DNA or acetylation/de-acetylation of histones (Yuan et al., 2012).

TREM-1 undergoes multiple post translational modifications, each of which is bringing tangible change in its function and puts it as one of the major target for developing epigenetic drugs that might provide a remedy to several inflammatory and cancerous diseases of the

present era. It is hence very important to further investigate the in-depth role of the post translational modifications of TREM-1 to translate laboratory findings to clinics where patients can seek relief from chronic ailments.

TREM-1 modulation as therapeutic target

The expression of TREM-1 and its dependence on TLRs (Fortin et al., 2007, Zheng et al., 2010) and NO like receptors (Fortin et al., 2007), and many of the danger associated molecular patterns (DAMPs) such as heat shock proteins (HSPs), high mobility group box protein (HMGP) and free cyclic AMP that are responsible for the activation of these receptors are produced in different aseptic shock conditions including hemorrhage, ischemia and cancers. Recently, several clinical studies demonstrates high levels of sTREM-1 in blood plasma level in several disease conditions including cardiac dysfunction (Ford and McVicar, 2009, Zhou et al., 2014), inflammatory bowel disease (IBD) (Genua et al., 2014) and multi-organ failure patients (Ford and McVicar, 2009). The sTREM-1 which has an association with several inflammatory diseases including sepsis, chronic obstructive pulmonary disease (COPD) and severe pneumonia (Rohde et al., 2012) as diagnostic and prognostic marker make its pathway important for therapeutic modulation. It was initiated when a TREM-1 antagonist was developed hence pushed the TREM-1 characterization and its application in inflammatory disease therapies which shows promising results in rodents and other model animals.

The bacterial sepsis is the major cause of mortality in newborns (Sanchez et al., 2011). In a recent study the therapeutic potential of TREM-1 is evaluated in neonatal sepsis. It was shown that blocking of TREM-1 results in lower secretion of pro-inflammatory cytokines that might be a new therapy to fight neonatal infections (Qian et al., 2014). The painful journey of elderly people because of rheumatoid arthritis (RA); and several other chronic inflammatory disorders like ulcerative colitis and Crohn's disease in humans which has been shown to have a close

connection with TREM-1 expression can be treated through modulation of TREM-1 pathway (Chen et al., 2015). The use of dominant negative vectors of DAP-12 (Chen et al., 2013) on rheumatoid arthritis primary specimens demonstrates reduction in pro-inflammatory signaling protein ERK1/2 (Chen et al., 2013) which have a complementary effect on reduction of pro-inflammatory cytokines. On the other hand, an important chemokine IL-8 that is responsible to attract neutrophils and basophils to the site of infection that might have a role in rheumatoid arthritis (Kasama et al., 2005) and provides an opportunity to use DAP-12 as a drug target against rheumatoid arthritis that will affect the expression of TREM-1.

Chronic inflammation is the main cause of cancer pathogenesis and metastasis. The liver kupffer cells have an important role in chronic inflammation and promotion of liver cancer. It has been demonstrated that a diethylnitrosamine (DEN) induced hepatocellular carcinogenesis was faded by the deletion of murine homolog of TREM-1 in mice (Wu et al., 2012). This study further elaborates that kupffer cells deplete on deletion of TREM-1 that downregulates the expression of several pro-inflammatory cytokines and chemokines including IL-6, TNF, CXCL10 determined by PCR and western blotting. It has also been shown that TREM-1 is highly expressed in cancerous tissues of colon, lung (Liao et al, 2012; Ho et al, 2008). Furthermore, TREM-1 expression is also implicated in patients with NSCLC with higher recurrence and poor survival of cancer patients suggesting that TREM-1 may play an important role in cancer progression (Ho et al., 2008). Mechanistically TREM-1 deletion for liver cancer was suggested by Wu et al., 2012 showing the attenuation of p38, MAPK, ERK1/2 and NF- κ B pathways in kupffer cells resulted in lower liver injury while re-introduction of TREM-1 resulted in bringing the cancerous phenotype back (Wu et al., 2012).

These studies provide important grounds for exploring the mechanistic understanding of TREM-1 pathway and its modulation for making it as a drug target that can be used in many important infectious and cancerous diseases.

Conclusion

The family of TREM proteins plays critical roles in immune responses by interacting with several important processes including cytokine production and phagocytosis. The presence of soluble TREMs in patients' fluids can be used as biomarkers against inflammatory diseases. Among TREMs, TREM-1 is emerging as an interesting gene modulating various functions especially in inflammatory diseases. The studies performed in past since its discovery underpins its important role in acute and chronic inflammatory diseases. Its responsiveness is not only limited to bacterial toxins but are also to the chemicals produced by danger associated molecular patterns (DAMPs) that enhances its applicability as therapeutic target in many of the important inflammatory diseases. The future research which identifies miRNAs that control the expression of TREM-1 and its carriers will be of high interest to pharmaceutical companies desiring of making TREM-1 related drugs and therapeutics.

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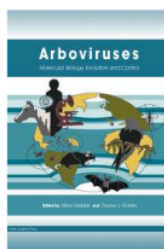
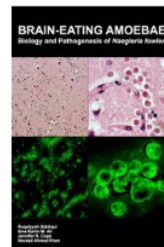
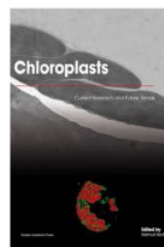
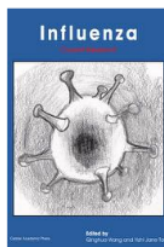
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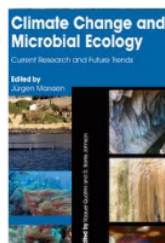
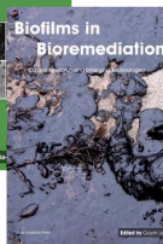
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