Triggering Receptors Expressed on Myeloid Cells 1: Our New Partner in Human Oncology?

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Inflammation is recognized as one of the hallmarks of cancer. Indeed, strong evidence indicates that chronic inflammation plays a major role in oncogenesis, promoting genome instability, epigenetic alterations, proliferation and dissemination of cancer cells. Mononuclear phagocytes (MPs) have been identified as key contributors of the inflammatory infiltrate in several solid human neoplasia, promoting angiogenesis and cancer progression. One of the most described amplifiers of MPs pro-inflammatory innate immune response is the triggering receptors expressed on myeloid cells 1 (TREM-1). Growing evidence suggests TREM-1 involvement in oncogenesis through cancer related inflammation and the surrounding tumor microenvironment. In human oncology, high levels of TREM-1 and/or its soluble form have been associated with poorer survival data in several solid malignancies, especially in hepatocellular carcinoma and lung cancer. TREM-1 should be considered as a potential biomarker in human oncology and could be used as a new therapeutic target of interest in human oncology (TREM-1 inhibitors, TREM-1 agonists). More clinical studies are urgently needed to confirm TREM-1 (and TREM family) roles in the prognosis and the treatment of human solid cancers.

Keywords: inflammation, cancer, hepatocellular carcinoma, lung cancer, TREM-1

INTRODUCTION

The hallmarks of cancer include several biological abilities that are acquired during the multistep process of human tumors (ie: proliferative signaling, evading growth suppressors, angiogenesis induction, escape and metastasis activation) (1, 2). Among them, inflammation is now recognized as a defining hallmark of cancer (2). Indeed, strong evidence indicate that chronic inflammation plays a major role in oncogenesis, promoting genome instability, epigenetic alterations, proliferation and dissemination of cancer cells (3, 4). Moreover, necrotic cell death from tumors generates proinflammatory signals (ie: IL-1α) in the proximal tissue microenvironment, in opposition to apoptosis and autophagy (2). Necrotic cells are able to enroll inflammatory elements from the immune system, including mononuclear phagocytes (MPs), which contribute to angiogenesis, invasiveness and therefore cancer progression (5). MPs have been identified as key contributors of the inflammatory infiltration in several solid human cancers (6, 7).
can be actively recruited from the circulation to tumor fields by tumor-related agents as primary monocytes, which differentiate into tumor-associated macrophages (TAMs) or tumor-associated dendritic cells (TADCs) (8, 9). The most described enhancer of MPs pro-inflammatory innate immune response are the triggering receptors expressed on myeloid cells (TREM), especially TREM-1. TREM proteins are a community of cell surface receptors mostly expressed on myeloid cells (10). The most described ligands of TREM-1 are pathogen-associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs, endogenous ligands released after sterile tissue injury). More recently, heat shock protein 70-kDA (HSP70), peptidoglycan recognition receptor 1 (PGLYRP1) and platelets were also described as potential TREM-1 ligands (11).

Engagement of TREM-1 plays a crucial role in the modulation of inflammation. Indeed, it leads to an increase of tumor necrosis factor α (TNFα) secretion by monocytes, IL-8 and monocyte chemoattractant protein 1. The release of these elements induces neutrophil degranulation and the secretion of myeloperoxidase and nitric oxide (12, 13). Beside its membrane-anchored form, TREM-1 is released as a soluble protein (sTREM-1) upon its activation by proteolytic cleavage, and sTREM-1 is a useful biomarker of the activation of the TREM-1 pathway (14).

The TREM family has been mainly investigated in severe inflammation (15). However, it is now well known that TREM-1 is highly expressed in some tumoral tissues, as hepatocellular carcinoma and lung carcinoma. Growing evidence suggests TREM-1 involvement in oncogenesis through cancer-associated inflammation and the tumor microenvironment (TME) (13).

In this review, we describe current knowledge about TREM-1 in human solid tumors.

TREM-1 implications in cancer promotion are summarized in Figure 1.

Main molecular signaling of cancer promotion are summarized in Figure 2.

TREM-1 IN DIGESTIVE ONCOLOGY

Hepatocellular Carcinoma

Human hepatocellular carcinoma (HCC) is a very strong example of inflammation-associated cancer. HCC quietly

![Figure 1: TREM-1 implications in cancer promotion.](https://www.frontiersin.org/)

![Figure 2: Main molecular signaling of cancer promotion.](https://www.frontiersin.org/)
occurs in the setting of chronic inflammation due to an exposition to infectious pathogens or toxic compounds (16). Indeed, in most cases (> 90%), human HCC occurs in the setting of chronic inflammation or cirrhosis. In both conditions, hepatocytes are destroyed and resident inflammatory cells [Kupffer cells (KC)], as well as other inflammatory cells (monocytes, neutrophils), are triggered to release cytokines that lead to a counterbalanced expansion of the surviving hepatocytes (17).

The role of TREM-1 has been recently studied in 3 distinct works. Ten years ago, Liao et al. (18) first investigated TREM-1 expression in human HCC. They used immunohistochemistry (IHC) to assess peritumoral and intratumoral TREM-1 expression on tissue microarray from 240 patients with HCC. They demonstrated that peritumoral TREM-1 expression was significantly associated with vascular invasion (p < 0.001), tumor size (p = 0.001) and high TNM stage (p < 0.001) (18). In addition, high density of peritumoral TREM-1 was associated with elevated risk of recurrence (p = 0.008) and poor overall survival (OS) (p < 0.001) (18). They also determined soluble TREM-1 (sTREM-1) levels (using ELISA) from the plasma of 92 patients operated on for benign or malignant liver tumor (preoperative and 5 days postoperative) (18). Soluble TREM-1 level was significantly increased in patients suffering from HCC in comparison with those with non-malignant liver tumor/disease (ie: cyst, hemangioma, focal nodular hyperplasia) (p < 0.005) (18).

Duan et al. (10) investigated TREM-1 expression through western blot/qRT-PCR/immunofluorescence analyses in archived tissues from 322 patients who have been operated on for HCC. They demonstrated that TREM-1 was found in HCC cancer cells and tumor tissues and that high TREM-1 was significantly associated with higher recurrence and lower survival in HCC patients. Recurrence-free survival and 5-year survival rates for patients with high TREM-1 expression were 51.6% and 51.3%, respectively, in comparison with 70.9% and 62.8% for patients with low TREM-1 (p = 0.060 and p = 0.007, respectively) (10). Moreover, authors performed functional experiments which supported that TREM-1 significantly mediated invasion, proliferation, and apoptosis inhibition of HCC cells. They demonstrated that a majority of
proinflammatory cytokines were significantly associated with TREM-1 level, including TNF-α, IL-1b, and MCP-1 (10).

More recently, TREM-1 expression was evaluated by IHC on 119 tissue samples from patients with HCC curative resection (19). The results they obtained are in accordance with those previously published. In their samples, the amount of TREM-1+ TAMs was significantly higher in HCC with advanced stages, which suggests that abundant TREM-1+ TAMs are engaged in malignant progression (19).

In human HCC, TREM-1 truly seems to be involved on tumor cell proliferation and invasion. Although further investigations are needed to confirm its implication in human oncology, TREM-1 could be an useful therapeutic target in human HCC.

**Inflammatory Bowel Disease-Associated Carcinoma and Colorectal Cancer**

Colorectal carcinoma (CRC) is another example of cancer that is partly promoted by chronic inflammation (20). Indeed, patients with inflammatory bowel disease (IBD) are at increased risk of CRC and the long-term use of non-steroidal anti-inflammatory drugs decreases their colon cancer risk (20). In this situation, almost all the studies have been carried out on in vivo mouse model of DSS-induced colitis leading to the conclusion that TREM-1 inhibition reduces colitis and tumor development within animal’s colon (21, 22).

In human CRC, TREM-1 expression has been studied through a nineteen gene-based risk score (TCA19) classifier in two studies (23, 24). In a first work based on 18 matched primary human CRC samples, synchronous liver metastases and normal colonic epithelium (23), authors demonstrated that the expression level of TREM-1 assessed by RNA-sequencing was significantly higher in primary CRC tissue and their metastasis than in normal colonic epithelium (23). Those results indicate that TREM-1 expression is a predominant regulator activated during CRC tumorigenesis and may be a key event associated with CRC aggressiveness (23). Another study assessed clinical implication of TCA19 in 60 patients with stage IV CRC (24). Once more, TREM-1 was expressed at significantly higher level in primary or metastatic tumor tissues than in non-tumoral colonic tissue (assessed by RT-qPCR), suggesting that TREM-1 was related to progression and metastasis in human CRC (24).

Although those two studies have some limitations (retrospective, small number of patients), they are in accordance with a pro-tumoral role in human CRC. Further investigations are needed to confirm such observations, especially in prospective works.

Studies assessing TREM-1 and/or soluble TREM-1 (sTREM-1) expression in human digestive cancers are summarized in Table 1.

**TREM-1 IN LUNG CANCER**

Lung cancer is the most common cause of cancer-related deaths worldwide with a 5-year survival rate for all stages of only 17% (26). TREM-1 and sTREM-1 expression were recently studied in human lung cancer, especially in human non-small cell lung cancer (NSCLC), which represents over 80% of all lung cancers (26).

TREM-1 was first investigated in lung cancer fifteen years ago, using IHC on primary NSCLC specimen from 68 surgically resected patients (27). Authors demonstrated that disease-free survival (DFS) and OS were significantly shorter in patients with high TREM-1 expression than in those with low TREM-1 level (DFS: median of 22 months versus not reached; OS: 29 months versus not reached) (27).

They also assessed sTREM-1 levels by ELISA in 4 distinct panels of pleural effusions of 65 patients (i.e., transudative pleural effusions due to congestive heart failure or postoperative reactive effusion; parapneumonic pleural effusions; tumor pleural effusions with tumoral cells and without infection; exudative pleural effusions due to neoplasia but without infection and no detectable tumoral cells) (27). They found that TREM-1 levels were significantly higher in tumoral pleural effusions than in transudate (p = 0.017) (27).

In 2014, Yuan et al. worked on NSCLC specimen and paracarcinoma tissue from 3 patients (28). They demonstrated that TREM-1–positive cells were TAMs (28). They also performed RT-PCR and RT-qPCR on pulmonary samples from individuals with NSCLC and identified excess TREM-1 expression in human pulmonary adenocarcinoma tissues. On the contrary, TREM-1 expression was not found in normal pulmonary tissue (28).

A recent study focused on sTREM-1 levels in 164 people with lung cancer, at any stage (NSCLC: n = 137; SCLC: n = 27) (29). In patients with NSCLC, stage and sTREM-1 were prognostic values (stage: p < 0.0001, sTREM-1: p = 0.011) (29). Regarding stage IV patients (n = 75), high sTREM-1 level was a critical indicator of poorer survival (median OS: 4.8 versus 11.4 months,

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**Table 1** Studies assessing TREM-1 and/or soluble TREM-1 (sTREM-1) expression in human digestive cancers and the correlation with survival data.

| Cancer type                  | Reference          | Number of patients | Studied parameter | Statistical significance               |
|------------------------------|--------------------|--------------------|-------------------|----------------------------------------|
| Hepatocellular carcinoma     | Liao et al., 2012 (17) | 240                | TREM-1            | significantly associated with poorer OS (HR = 2.25) |
|                              | Liao et al., 2012 (17) | 92                 | sTREM1            | significantly associated with poorer OS |
|                              | Duan et al., 2014 (10) | 322                | TREM-1            | significantly associated with increased |
|                              | Wu et al., 2019 (25)  | 119                | TREM-1            | recurrence and poorer OS (HR = 1.6)      |
| Colorectal Carcinoma         | Kim et al., 2014 (23) | 18                 | TREM-1            | significantly associated with poorer DFS |
|                              | Lee et al., 2019 (23) | 60                 | TREM-1            | significantly higher in tumoral tissues than in non-tumoral tissues |

DFS, disease free survival; HR, hazard ratio; NS, not significant; OS, overall survival.
p = 0.009) (29). In the subgroup of SCLC patients, those observations were not confirmed (p = 0.07) (29).

Finally, an interesting work suggested there is different degrees of TREM-1 expression along NSCLC development (30). Based on analyses made of fresh tumor tissues and the matching non-tumoral tissue samples from 40 non-treated patients with NSCLC, it was shown that TREM-1 rates on tumor tissue-derived monocytes/macrophages were decreased in comparison to TREM-1 levels detected on monocytes from peripheral blood of patients suffering from NSCLC (30). Authors demonstrated that TREM-1 rates on monocytes/macrophages progressively decreased with the advancement of tumor stage and tumor invasion of lymph nodes, which suggests that weak TREM-1 expression on TAMs could be a new feature of advanced lung cancer stage (30).

TREM-1 expression in TAMs from tumoral tissues of human NSCLC was correlated with reduced DFS and OS. TREM-1 level is an independent predictor of survival in NSCLC, and might be a component of human lung cancer progression. Further investigations are needed to better understand its role in tumor immunomodulation in thoracic oncology, especially for NSCLC tumors.

Studies assessing TREM-1 and/or soluble TREM-1 (sTREM-1) expression in human lung cancer are summarized in Table 2.

**TREM-1 IN OTHER HUMAN MALIGNANCIES**

Except for lung, liver and colon cancers, TREM-1 has been poorly studied in humans malignancies. Very recently, TREM-1 expression has been studied in other human solid tumors (Table 3).

Based on data coming from The Cancer Genome Atlas (TCGA), TREM-1 expression was compared between papillary thyroid carcinoma (n = 512) and normal thyroid tissues (n = 58) (31). TREM-1 mRNA expression was significantly higher in human papillary thyroid carcinoma tissues in comparison to non-tumoral thyroid tissues (p<0.0001) (31). The immunohistochemical results (achieved using Human Protein Atlas immunohistochemical images) demonstrated that TREM-1 protein expression was significantly upregulated in papillary thyroid carcinoma tissue compared with non-malignant tissues (31). Additionally, high TREM-1 expression was significantly associated with lymph node metastasis and with advanced T status (31).

| TABLE 2 | Studies assessing TREM-1 and/or soluble TREM-1 (sTREM-1) expression in human lung cancer and the correlation with survival data. |
|---------|-------------------------------------------------------------------------------------------------------------------------------|
| Reference | Number of patients | Studied parameter | Statistical significance |
| Ho et al., 2008 (26) | 68 | TREM-1 | significantly associated with reduced DFS and poorer OS (HR = 2.72) |
| Ho et al., 2008 (26) | 65 | sTREM1 | NS |
| Yuan et al., 2014 (27) | 3 | sTREM1 | upregulated in NSCLC |
| Kuemmel et al., 2018 (28) | 164 | sTREM-1 | significantly associated with poorer OS in NSCLC (median survival 8.5 vs. 13.3 months) |

DFS, disease free survival; HR, hazard ratio; NS, not significant; NSCLC, non-small cell lung carcinoma; OS, overall survival.
cohort of 63 untreated patients diagnosed with clear cell RCC (ccRCC). In comparison to healthy controls, sTREM-1 levels were significantly higher in patients suffering from ccRCC (mean = 265.3 pg/mL in ccRCC patients versus mean = 110.04 pg/mL in controls, p < 0.001) (36). Based on data coming from The Cancer Genome Atlas (TCGA, n = 531 ccRCC), authors also found that high TREM-1 expression was significantly correlated with worse OS and high disease stage (36).

Although TREM-1 and sTREM-1 requires further elucidation in human oncology, they might be implicated in diverse human solid malignancies and might be used as a potential biomarker for diagnosis and also disease progression. TREM-1 could also provide a new therapeutic target in different kind of human solid tumors.

### DISCUSSION AND PERSPECTIVES

Nowadays, inflammation is recognized as an essential component in cancer, playing a crucial role in cancer induction and promotion. This is largely influenced by immune cells from TME, notably TAMs. TREM-1, which is one of the most described amplifiers of MPs pro-inflammatory innate immune response, could assume a significant role in such interplay.

In this review, we summarized all the current clinical knowledge about TREM-1 in human oncology. In that situation, we may notice that TREM-1 has mainly been studied in colon, hepatocellular and lung (NSCLC) carcinoma tissues that highly expressed TREM-1 (as well as sTREM-1). Although TREM-1 has not been yet extensively studied in all kind of tumor types (ie: solid as hematological malignancies), TREM-1 should be consider as a potential biomarker in human oncology and could be used as a new therapeutic target of interest. Since the interaction between TREM-1 and DAP12 is critical for the stabilization and multimerization of TREM-1, finding TREM-1 inhibitors was a complicated process. Different TREM-1 inhibitors have been designed and studied in different murine models of malignancies associated with chronic inflammation. It was demonstrated it might confer protection against tumor progression and thus provide advantages in terms of survival through the reduction of MP inflammatory reactions. The power of this design is that it lowers, but does not fully abolish, inflammatory answers, which is crucial for tumor management. A recent Phase IIa clinical trial was conducted to assess the safety, tolerance and pharmacokinetics of the synthesized peptide nangibotide (LR12), the first pharmaceutical candidate targeting TREM-1 to be in clinical development in patients with septic shock (25). Future investigations of this agent for the treatment of cancer are pending, but this therapeutic option appears promising.

Two others TREM-1 inhibitors are also under study: LP17 peptide (a synthetic peptide blocker of TREM-1) and the GF9 peptide (a ligand-independent human TREM-1 inhibitory peptide). TREM-1 inhibition by LP17 have been studied in vivo, in mouse models of IBD-associated colorectal carcinoma (21). LP17 has been shown to improve the development of inflammation and tumors in the colon by providing anti-inflammatory actions. In addition, LP17 impaired intestinal epithelial growth in DSS-induced colitis (21). Blockade of TREM-1 by the delivery of the inhibitor peptide GF9 significantly abolished tumor progression in human xenograft models of non-small cell lung cancer (37). The GF9 peptide has also demonstrated therapeutic relevance in pancreatic cancer (38, 39). Its use in human pancreatic cancer xenograft mouse models caused a significant antitumoral action, which was associated with the abolition of TAM infiltrate, decreasing of serum levels of pro-inflammatory cytokines and an improvement in the animals’ survival. Moreover, GF9 therapy also significantly altered the resistance to PD-L1 inhibition, thereby enhancing its therapeutic efficiency in orthotopic HCC-bearing models (19). Those results support that specific TREM-1 inhibitors could be used as single therapy or as part of a combinatory treatment for many human solid malignancies.

**Table 3** | Studies assessing TREM-1 and/or soluble TREM-1 (sTREM-1) expression in human solid malignancies (except digestive and lung cancers).

| Reference         | Cancer                      | Number of patients | Studied parameter | Statistical significance |
|-------------------|-----------------------------|--------------------|-------------------|--------------------------|
| Xie et al., 2017  | Papillary thyroid carcinoma | 512 (from The Cancer Genome Atlas) | TREM-1             | significantly associated with reduced PFS. |
| Kluckova et al., 2020 | Glioma                  | 63                 | sTREM1             | sTREM-1 levels in the group of all glioma patients were significantly weaker than in the healthy group of patients |
| Pullikuth et al., 2021 | Breast cancer            | 701                | TREM-1             | Not significant |
| Ford et al., 2022  | Renal cell carcinoma       | 63 untreated patients + 531 from The Cancer Genome Atlas | TREM-1             | Significantly associated with worse OS and high disease stage |

PFS, progression free survival; NS, not significant; OS, overall survival.
malignancies (NCT04682431: an open-label, multicenter, First-In-Human, Phase 1a/1b study of PY159 in subjects with locally advanced (unresectable) and/or metastatic solid tumors that are refractory or relapsed to standard of care (including checkpoint inhibitors, if approved for that indication).

Moreover, levels on monocytes/macrophages have been shown to progressively decrease with the advancement of tumor stage and tumor invasion of lymph nodes in NSCLC, supporting that low TREM-1 expression on TAMs may be a new characteristic of late stage pulmonary carcinoma. This observation provides an additional degree of complicity to the expression of TREM-1 on other myeloid and non-myeloid cells that are implicated in anti-tumor responses.

Furthermore, other TREM were found on human chromosome 6p21 (15), especially TREM-2 which is thought for developing clinical applications of TREM2-targeted therapies (15). Although few clinical studies of TREM2 targeting in cancer are currently being conducted, the potential for developing clinical applications of TREM2-targeted therapies remains high in the short-term future (41). Indeed, some fundamental research has identified TREM-2 as a valuable therapeutic target for cancer immunotherapy (41). Another potential role of TREM-1 concerns the regulation of apoptosis and autophagy (42), which play a double role in the regulation of senescence in normal and cancer stem cells, and of cellular responses to different therapeutical approaches (43).

More clinical studies are urgently needed to confirm TREM-1 (and TREM family) roles in the prognosis and the treatment of human cancer.

**CONCLUSION**

Although the therapeutical application of TREM-1 inhibitors is mainly restricted to preclinical studies, modulation of the TREM-1 receptor could be a useful therapeutical application for the management of some human solid malignancies. More extensive investigations are necessary before immunotherapeutical approaches targeting TREM-1 may be developed in human oncology.

**AUTHOR CONTRIBUTIONS**

Manuscript writing and editing: MM, VH, AL, AT, SR, MD, and JPB. Figures design: MM. Review and approval of the manuscript: all of the authors.

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