



REVIEW ARTICLE OPEN



Inflammation and cancer cell survival: TRAF2 as a key player

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TNF receptor-associated factor 2 (TRAF2) plays a crucial role in both physiological and pathological processes. It takes part in the regulation of cell survival and death, tissue regeneration, development, endoplasmic reticulum stress response, autophagy, homeostasis of the epithelial barrier and regulation of adaptive and innate immunity. Initially identified for its interaction with TNF receptor 2 (TNFR2), TRAF2 contains a TRAF domain that enables homo- and hetero-oligomerization, allowing it to interact with multiple receptors and signaling molecules. While best known for mediating TNFR1 and TNFR2 signaling, TRAF2 also modulates other receptor pathways, including MAPK, NF- κ B, and Wnt/ β -catenin cascades. By regulating NF- κ B-inducing kinase (NIK), TRAF2 is a key activator of the alternative NF- κ B pathway, linking it to inflammatory diseases, immune dysfunction, and tumorigenesis. In the innate immune system, TRAF2 influences macrophage differentiation, activation, and survival and stimulates natural killer cell cytotoxicity. In the adaptive immune system, it represses effector B- and T-cell activity while sustaining regulatory T-cell function, thus promoting immune suppression. The lack of fine-tuning of TRAF2 activity leads to excessive NF- κ B activation, driving chronic inflammation and autoimmunity. Although TRAF2 can act as a tumor suppressor, it is predominantly described as a tumor promoter, as its expression has been correlated with increased metastatic potential and poorer prognosis in several types of cancer. Targeting TRAF2 or TRAF2-dependent signaling pathways might represent a promising anti-cancer therapeutic strategy.

Cell Death and Disease (2025)16:292; <https://doi.org/10.1038/s41419-025-07609-w>

FACTS

- TRAF2 activates the NF- κ B pathway, driving inflammation, cell survival, and tumor progression while contributing to immune evasion and therapy resistance.
- TRAF2 stabilizes key proteins in the Wnt/ β -catenin pathway, driving tumor growth and metastasis.
- TRAF2 promotes VEGF-driven tumor angiogenesis and supports immune suppression through Tregs and MDSCs.
- TRAF2 supports tumor survival during ER stress, aiding resistance to anti-cancer therapies.
- TRAF2 mostly acts as a tumor promoter in different cancer types and contexts.
- TRAF2 inhibition could enhance anti-cancer therapies and improve tumor killing.

OPEN QUESTIONS

- How can the structural dynamics of TRAF2, such as its monomer-trimer equilibrium and domain-specific interactions, be harnessed for drug development?
- Can TRAF2 expression or activity serve as a biomarker for predicting cancer prognosis or therapy response?

INTRODUCTION

Inflammation plays a central role in different stages of cancer, including tumor development and malignant transformation [1]. TNF receptor-associated factors (TRAFs) are key mediators in the intricate interplay between cancer and inflammation, making them promising therapeutic targets. TRAFs belong to the TRAF family of signaling molecules that interact with a plethora of molecules thanks to their characteristic shape [2]. In complex with other proteins, TRAFs transduce signals upon activation of cytokine receptors, especially those belonging to the TNF receptors superfamily (TNFRs). TNFRs include death or decoy receptors [3], which bind to several types of ligands [4]. TNF- α , one of the major inflammatory cytokines, binds to TNF receptors 1 and 2 (TNFR1 and 2), triggering signaling pathways that regulate inflammation, immune responses, stress reactions, and apoptosis [5]. Despite sharing TNF- α as their primary ligand, TNFR1 and TNFR2 differ significantly in their structural features, signaling mechanisms, and biological outcomes. TNFR1 contains a death domain (DD) in its cytoplasmic region, which recruits DD-containing cytoplasmic proteins, such as TRADD and RIPK1. This leads to the activation of the transcription factor NF- κ B, as well as apoptotic and necroptotic pathways [6–8]. In contrast, TNFR2 lacks a DD and predominantly activates non-canonical NF- κ B and PI3K/Akt pathways, promoting cell survival, immune regulation, and

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 Edited by Mauro Piacentini

Received: 5 December 2024 Revised: 25 March 2025 Accepted: 31 March 2025

Published online: 14 April 2025

tissue regeneration [9–11]. While TNFR1 is widely expressed across various cell types, TNFR2 expression is more restricted, mostly found in immune cells, endothelial cells, and certain cancer cells, where it plays a key role in inflammation and immune suppression [12].

TRAF2 and TRAF5 are structurally and functionally similar, sharing redundant roles in TNF-induced NF- κ B activation. However, while TRAF2 is ubiquitously expressed, TRAF5 expression is limited to the lungs, thymus, spleen, and kidneys [13].

TRAF2, a 56 kDa trimeric protein, was initially identified for its interaction with the C-terminal portion of TNFR2 [14]. Structurally, TRAF2 consists of a globular C-terminal portion (TRAF-C) and an extended coiled-coil moiety (TRAF-N) comprising three long α -helices [15]. The combination of these two structurally different regions gives rise to the so-called “TRAF domain,” which is responsible for the assembly of the homo-oligomeric form [15], for the establishment and stabilization of the heterotrimer TRAF2:TRAF1 (with a 2:1 ratio) and for the interaction with other signaling proteins [3, 16, 17].

The monomer-trimer equilibrium plays a pivotal role in the control of TRAF2 functions [18], being also crucial for membrane binding [19]. *In silico* simulations suggest that the length of the coiled-coil region strongly influences the structural dynamics at the three interfaces present in the globular, C-terminal domain [20]. In particular, the reciprocal interaction of the long α -helices reduces the asymmetric motions of the three subunits, indicating strong communication between the two protein domains. Like other TRAF family members, TRAF2 also contains within the N-terminal region a predicted RING motif, displaying a ubiquitin E3 ligase activity connected to the coiled-coil section of the TRAF domain via five zinc finger motifs [15].

By linking the receptors to their downstream effectors, TRAF2 tightly regulates signaling pathways implied in many physiological and pathological processes, from inflammation to cancer [3]. However, the molecular mechanisms behind the TRAF2 multiple activities are still poorly understood due to the limited information about its molecular structure. The knowledge about TRAF2 dynamics and its role in membrane association and membrane vesicle trafficking is, in fact, generally limited to some TRAF2 fragments [18–23] because the equilibrium between TRAF2 monomeric and oligomeric forms and the presence of the long-coiled coil (TRAF-N) domain have hindered its purification. Despite these challenges, an expanding body of literature highlights this molecule’s pivotal role in unraveling the mechanisms underlying various physiological and pathological phenomena [7]. Under physiological conditions, TRAF2 modulates immune responses by supporting macrophage activation, T-cell differentiation, and the stability of regulatory T cells (Tregs) [24]. It also influences cell survival [25], maintains epithelial barrier integrity [26], and governs autophagy and the ER stress response [27–29]. TRAF2 enhances proinflammatory signaling, positioning it as a key driver of cancer-associated inflammation. An extensive review has been written by Siegmund et al. in 2022 on TRAF2 signaling and roles [3]. Our present work updates and expands upon key insights into TRAF2’s structural, molecular and mechanistic roles and its functions on the immune system. We elucidate how TRAF2’s signaling contributes to physiological functions as well as to cancer progression through direct mechanisms, inflammation, and the tumor microenvironment (TME), providing examples across cancer types. Additionally, we outline potential therapeutic strategies, including candidate inhibitors and combination approaches, and highlight future research directions to deepen the knowledge on TRAF2’s pivotal role in cancer biology.

TRAF2 STRUCTURE AND FUNCTION

Insights on TRAF2 structural features and conformational dynamics

The C-terminal portion (TRAF-C) and the coiled-coil tail (TRAF-N) are the most studied TRAF2 domains, regulating its oligomerization [18] and membrane binding [19]. These domains exhibit distinct

structural and dynamic properties. TRAF-N has a typical elongated, sticky coiled-coil shape (Fig. 1) with a single secondary structure, while each TRAF-C subunit features a β -sandwich motif [4] and two monomer-monomer interfaces. Interactions at these interfaces, involving H-bonds and hydrophobic contacts, display dynamic behavior, enabling continuous subunit rearrangements in *in silico* simulations [30]. These movements, largely asymmetric, cause transient clustering of two monomers while the third remains independent, affecting protein surface shape and receptor peptide binding, as shown by molecular docking [18, 30]. Molecular dynamics simulations [20] further suggest that the coiled-coil section strongly influences C-terminal dynamics, indicating interdomain communication. Specifically, interactions among the three long α -helices reduce subunit asymmetry and surface roughness. Overall, these findings highlight the crucial role of TRAF2’s oligomeric structure in receptor and ligand recognition, as well as interaction regulation.

Overview of TRAF2 signaling pathways

Germline- and cell-specific TRAF knock-out models have provided insight into the essential roles of TRAFs in several signal transduction cascades [30]. TRAF2 is a principal mediator of TNF- α signaling, acting downstream of its receptors, TNFR1 and 2 [31], thus triggering the activation of NF- κ B, the major transcription factor of inflammatory molecules [7]. Mitogen-activated protein kinases (MAPKs), such as c-Jun N-terminal kinases (JNKs), are also activated, inhibiting apoptosis and promoting cell survival and inflammation [17]. Beyond its role in cytokine signaling, TRAF2 controls key cellular processes through ubiquitination of many substrates and, in this way, regulates their stability and, thus, their functions [32]. TRAF2 is also the target of ubiquitination/deubiquitination, which, by regulating its subcellular localization, dictates the cell fate between survival and death [21]. The activation of NF- κ B relies on the recruitment of TRAF2 to plasma membrane lipid rafts, a process disrupted when TRAF2 is ubiquitinated, thereby impairing its signaling ability [33].

TRAF2-mediated TNFR1 and TNFR2 signaling pathways

TRAF2 acts downstream of TNFR1, which is involved in innate and adaptive immunity responses, inflammation, apoptosis, and necroptosis (Fig. 2) [34]. TNF- α triggers TNFR1 activation in either membrane-bound (mTNF- α) or soluble (sTNF- α) forms and initiates TNFR1 trimerization and the assembly of complex I, which recruits RIPK1 and TRADD, both containing a death domain (DD) [35]. There is further recruitment of the ubiquitin ligases cellular inhibitors of apoptosis proteins 1 and 2 (cIAP1 and cIAP2), which stabilize RIPK1 [36].

RIPK1 then recruits TAB1/2 and MAP3K, activating the kinase TAK1, which in turn triggers NF- κ B, p38, AP-1, and JNK signaling pathways, promoting inflammation, cell survival, and proliferation [37–40]. TAK1 also activates the kinase NIK that, by phosphorylating IKK, activates the alternative NF- κ B pathway [41].

When TNFRs are unstimulated, the cIAP-TRAF2 complex inhibits the alternative NF- κ B pathway by promoting the degradation of NIK [42]. If complex I fails to assemble, complex II, composed of FADD, TRADD, and STAT1, forms and mediates TNF- α -induced apoptosis via TNFR1 through activation of caspases 8 and 3 [43]. TRAF2 prevents excessive apoptosis by facilitating the proteasomal degradation of activated caspase-8 [44]. If caspase activity is insufficient, an alternative complex II forms with RIPK1 and RIPK3, activating the pseudokinase MLKL and leading to necroptotic cell death. This pathway eliminates damaged or infected cells, while its dysregulation can result in uncontrolled cell death or viral infection [45].

TNFR2, primarily expressed in immune cells [46], lacks a DD and promotes anti-inflammatory functions, neuroprotection and remyelination [9]. Upon activation by TNF- α , TNFR2 weakly associates with the TRAF2-cIAP1-cIAP2 complex, which activates noncanonical NF- κ B signaling by inhibiting NIK degradation [10]. TNFR2 also enhances cell survival and proliferation by forming a complex with the tyrosine kinase Etk/Bmx and VEGFR2, activating the PI3K/Akt pathway and downstream STAT5 signaling [11].

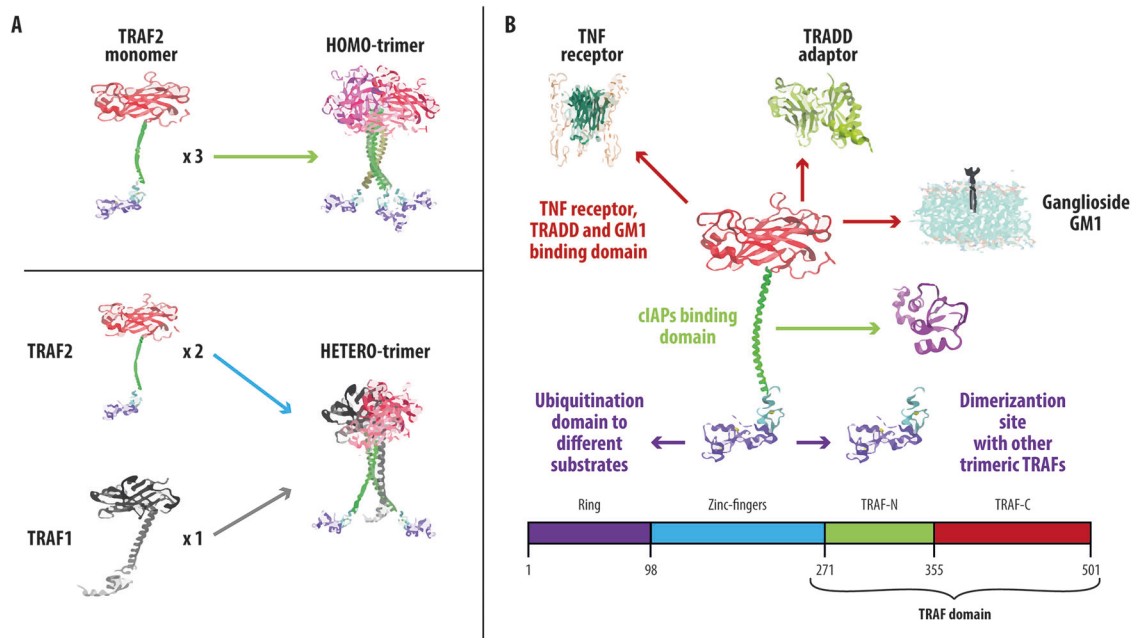


Fig. 1 Structure-to-function relationship of TRAF2. **A** Self-oligomerization of TRAF2 (upper panel) and heterotrimer (TRAF2:TRAF1) formation (lower panel). The (partial) available structures of monomeric TRAF2 domains are represented in different colors: purple and cyan = RING domain + first zinc finger motif (PDB file: 3knv); green = TRAF-N (PDB: 3m06); red = TRAF-C (PDB: 1ca4). **B** The structure of selected partners of TRAF2 is shown (extracted from the following PDB files: receptor, 1tnr; TRADD, 1f3v; clAPs, 3m0a). TRAF2 partners are correlated to the corresponding interacting regions of TRAF2 (red, green and purple arrows). At the bottom, the position of the four TRAF2 domains in the sequence is represented in the corresponding colors. The union of the TRAF-N and TRAF-C is referred to as the “TRAF domain,” following the traditional nomenclature reported in the literature.

A schematic representation of the TNFR1 and TNFR2 pathways mediated by TRAF2 is depicted in Fig. 2.

Roles of the TRADD–TRAF2 interaction

TRADD is essential in determining the downstream effects of TNF signaling by connecting TRAF2 to TNFR1 and recruiting RIPK and FADD. The high-affinity interaction between TRAF2 and TRADD ensures the TNFR1-dependent activation of NF- κ B and JNK, resulting in apoptosis inhibition and inflammatory response [47]. Conversely, TRADD binds to FADD to trigger the apoptotic cascade when NF- κ B activation is inhibited. TRADD also binds RIPK3 and promotes its activation, eliciting TNF-mediated necroptotic signal transduction [48]. The rapid NF- κ B response upon TNFR1 activation prevails over the slow activation of caspase 8 and apoptosis, which, on the contrary, is enhanced in situations of TRADD deficiency [49]. TRADD also inhibits the ubiquitination by TRAF2/clAP1/clAP2 of the autophagy mediator, beclin 1, thereby reducing autophagy [27, 50].

TRAF2 in the regulation of the Wnt- β -catenin signaling pathways

TRAF2 regulates canonical Wnt- β -catenin signaling pathways (Fig. 3). By stimulating its G-protein coupled receptor, Frizzled (FZD), Wnt triggers the recruitment of the scaffold protein Disheveled (DVL), leading to cytosolic accumulation of β -catenin and its subsequent translocation to the nucleus, where it activates the transcription factors TCF (T-cell factor)/lymphoid enhancing factor (LEF), driving Wnt target genes transcription [51]. One of the pathways triggered by Wnt involves the kinase TNIK (TRAF2 and Nck-interacting kinase), which interacts with TRAF2 and β -catenin and binds, phosphorylates and activates TCF4 [52]. A recent study demonstrated that the engagement of TNIK/ β -catenin in cytoplasm and nucleus is TRAF2-dependent and regulates cytoskeletal organization [53] (Fig. 3A). By sustaining the Wnt- β -catenin signaling [54], TRAF2 may also contribute to wound healing.

TRAF2 modulates the β -catenin-independent noncanonical Wnt signaling pathway, mediated by Wnt5a through the complex between the receptor tyrosine kinase-like orphan receptor 1 (ROR1), Frizzled 5 (FZD5) and DVL [55, 56]. TRAF2 was shown to be essential for the Wnt5a-driven inflammatory cytokine secretion via NF- κ B activation (Fig. 3B) [57].

TRAF2 PHYSIOLOGICAL FUNCTIONS

TRAF2 roles in ER stress-induced autophagy, cell death and epithelial barrier homeostasis

TRAF2 plays a critical role in the ER stress pathway by interacting with the stress sensor inositol-requiring enzyme 1 (IRE1), activating JNK signaling. TRAF2 can either prevent apoptosis triggered by excessive ER stress [58] or, through IRE1, can also induce cell death, activating caspase-12 [28, 59]. Additionally, TRAF2 promotes autophagy, including mitophagy in cardiac myocytes, which is crucial for cytoprotection during ischemia-reperfusion injury [29]. TRAF2 supports epithelial barrier integrity by regulating reactive oxygen species (ROS) production, JNK signaling, and autophagy in response to oxidative stress. TRAF2 downregulation attenuates the TNF- α /JNK pathway, enhancing E-cadherin expression, which maintains the apical–basal polarity in differentiated epithelia and strengthens epithelial barrier integrity [26]. Furthermore, TRAF2 supports intestinal cell protection, regulates epithelial–mesenchymal transition (EMT), promotes wound healing [60] and influences cell cycle progression [61].

Figure 4 illustrates TRAF2’s roles in ER stress and epithelial barrier homeostasis.

TRAF2 roles in inflammatory and immune system cells

TRAF2 plays a critical role in maintaining immune system homeostasis by regulating the activation, proliferation, and differentiation of immune cells, such as macrophages, NK cells, T and B cells, Tregs,

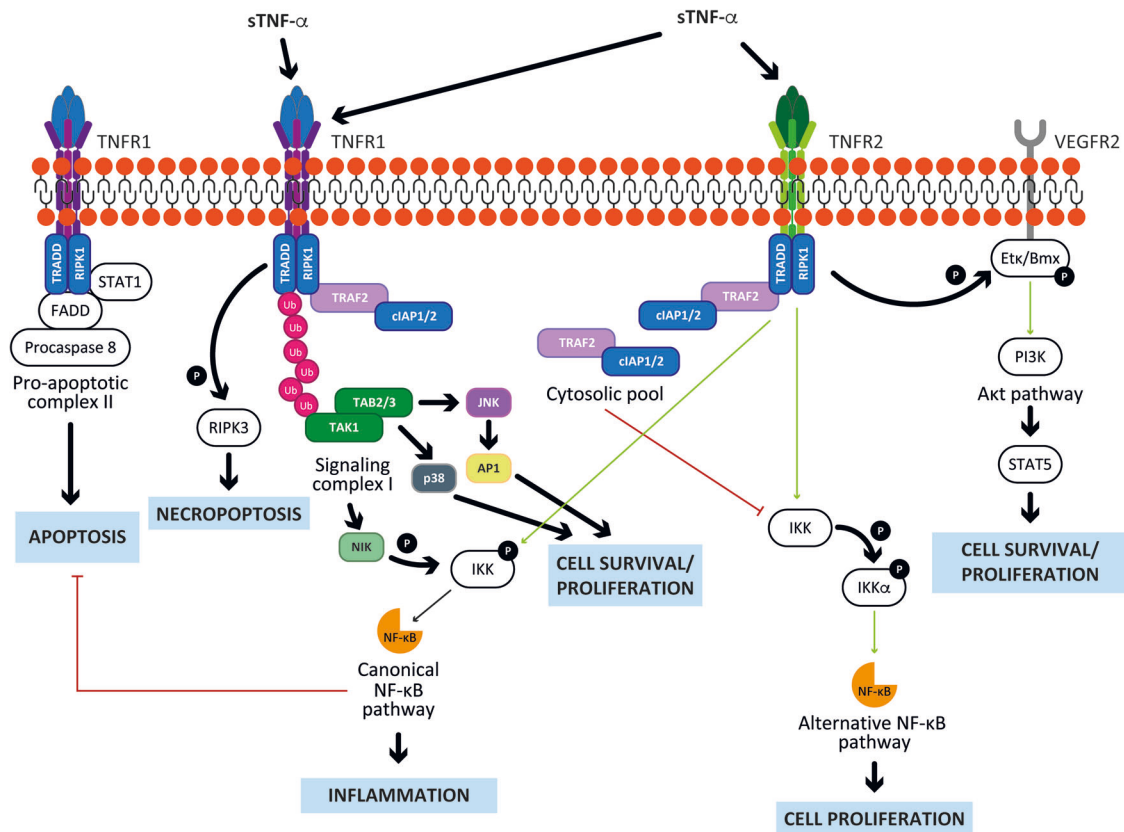


Fig. 2 TRAF2 role in the TNFR1 and TNFR2 signaling pathways. TNFR1 is activated either by mTNF- α or sTNF- α and recruits TRADD, RIPK1, TRAF2 and cIAP1/2, forming Complex I. cIAP1/2 ubiquitinates RIPK1 creating a platform for the recruitment of TAB2/3 and TAK1 which, in turn, activate JNK, AP-1 and p38 resulting in cell survival and activates NIK, which triggers NF- κ B activation promoting inflammation. When RIPK1 is deubiquitinated, cell death is triggered either through apoptosis, which is activated by the formation of the FADD/pro-caspase 8 complex, or through necroptosis, which is induced by the interaction between RIPK1 and RIPK3. TNFR2 is activated by mTNF- α and recruits TRAF2 and cIAP1/2 and, in this way, activates the noncanonical NF- κ B pathway and cell proliferation. TNFR2 also activates Etk/Bmx, which, by forming a complex with VEGFR2, activates the PI3K/Akt/STAT5 axis.

Th17 cells, dendritic cells (DCs) and mesenchymal stem cells (MSCs) [24]. TRAF2 degradation by cIAP1 is necessary for monocyte differentiation into active macrophages [62], while its signaling via TNFR1/2 promotes inflammatory and survival pathways in macrophages (Fig. 5) [22]. Moreover, TRAF2 supports type I IFN expression either in macrophages or DCs and is, therefore, crucial for infection defense [63]. TRAF2 enhances NF- κ B signaling, mediating processes like Fas expression in NK cells [64], TNFR2-driven IL-2 production, and, through the PI3K/Akt pathway, supports the expansion and stability of Tregs and suppression of Th17 [65, 66]. TRAF2 can also influence MSC immunosuppressive functions through its activity in supporting the TNF- α signaling pathway [67] and modulating regulatory B cell (Breg) activity [68]. Also, TRAF2 is involved in the activation of NF- κ B downstream of CD40 and sustains B-cell activation and the isotype switch [69]. It has also been shown that TRAF2 inhibits DC cell apoptosis induced by TNF- α by activating NF- κ B and the expression of IL-12 and anti-apoptotic genes [70].

The functions of TRAF2 in the immune system are summarized in Table 1 [32, 62–75].

TRAF2 ROLE IN CANCER

TRAF2 expression in cancer

TRAF2 has been identified as an oncogene frequently mutated in cancer [76]. TRAF2 represents a negative prognostic factor, which is required for the malignant phenotype, anchorage-independent growth and increased resistance to chemotherapy and radiotherapy of several cancers [77]. Suppression of TRAF2 in these

cancer cells results in NF- κ B downregulation [76] and apoptosis [78]. Among the rare paradoxical effects of TRAF2, TRAF2 inactivating mutations increase alternative NF- κ B pathway activation in mantle cell lymphoma, diffuse large B-cell lymphoma and multiple myeloma [79, 80].

Effect of TRAF2 in cancer cells and the establishment of an immunosuppressed tumor microenvironment

TNF and its receptors are essential components of the tumor microenvironment (TME). TNFR1 drives inflammation, apoptosis, or necrosis, depending on the cell type, while TNFR2 promotes cell proliferation. TNFR1's role in the TME is well-studied, whereas TNFR2 has only recently gained attention. While TNFR2 is rarely expressed in normal tissues, it is frequently overexpressed in cancer cells and other TME cellular components [81]. In cancers, TRAF2 overexpression inhibits the apoptotic process while promoting angiogenesis, tumorigenesis [82, 83] and tumor progression [84].

TRAF2 has a prominent role in activating NF- κ B, whose activity is detrimental in the context of chronic inflammation or tumorigenesis [85]. Persistent NF- κ B activation by TRAF2-dependent signaling pathways triggers the production of pro-inflammatory cytokines, which contribute to the survival and progression of cancer cells and are a hallmark of many inflammatory diseases. Inflammation promotes tumorigenesis, suppresses anti-tumor immunity, and drives an immunosuppressive TME [86, 87]. Recruited immune cells release cytokines and reactive oxygen species (ROS), which induce DNA damage, impair

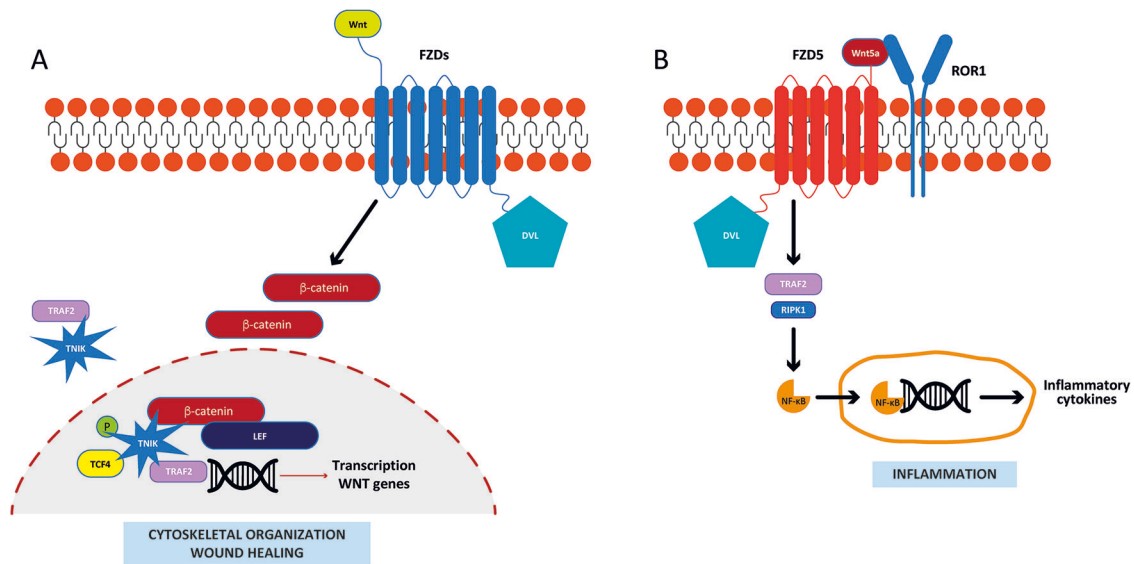


Fig. 3 TRAF2 role in the canonical and noncanonical Wnt signaling pathways. **A** In the canonical pathway, Wnt activates its receptor, FZD, and results in the recruitment of the scaffold protein, DVL, and to the cytoplasmic accumulation of β -catenin. TRAF2 participates in the TNIK-dependent activation of TCF-4/LEF, which forms a complex with β -catenin and activates the transcription of Wnt target genes involved in cytoskeletal organization and wound healing. **B** The noncanonical pathway is triggered by the interaction of Wnt5a to FZD5 and ROR1, which promotes the formation of the TRAF2/RIPK1 complex and results in the activation of NF- κ B and the promotion of inflammation.

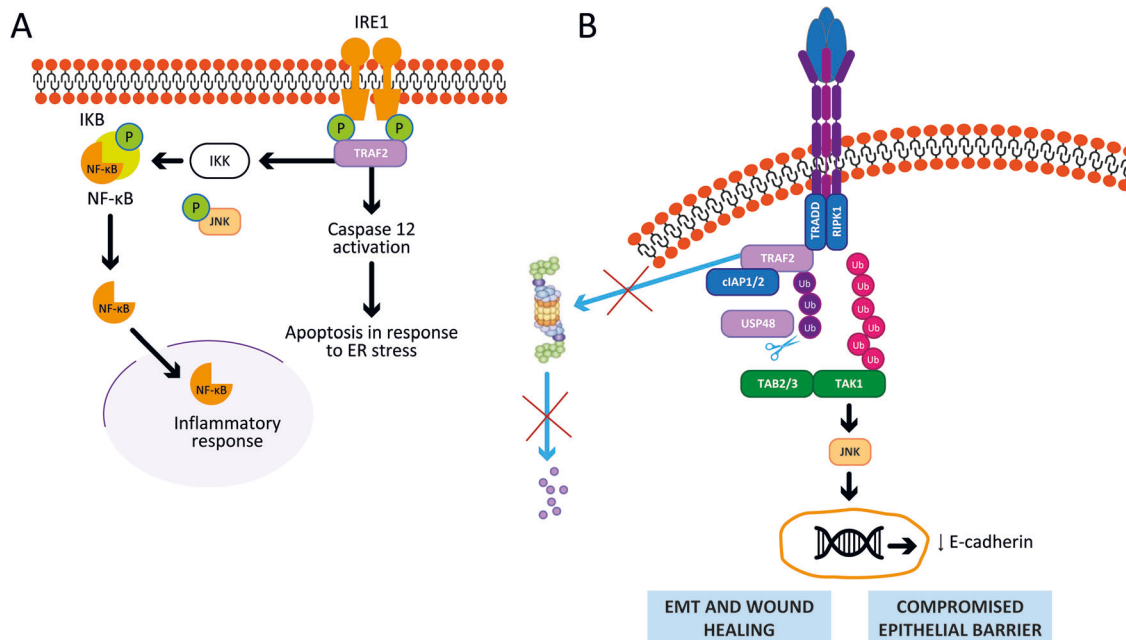


Fig. 4 TRAF2 roles in ER stress response and epithelial barrier homeostasis. **A** TRAF2 interacts with the cytoplasmic portion of IRE1 and promotes the activation of JNK and NF- κ B, thus inducing an inflammatory response. Conversely, TRAF2 induces the activation of caspase 12 and the apoptotic process. **B** Downstream of TNFR1, USP48 promotes the stabilization of TRAF2, leading to the activation of JNK and downregulation of E-cadherin. In this way, TRAF2 contributes to the decreased epithelial barrier.

repair, and contribute to cellular transformation and tumorigenesis [88]. TRAF2 seems to promote malignant transformation by driving EMT [89–91] as its degradation increases the expression of epithelial markers, such as E-cadherin, and decreased expression of the mesenchymal marker, vimentin [84]. In this way, TRAF2 also disrupts the E-cadherin- β -catenin complex, leading to uncontrolled β -catenin signaling. Consequently, cancer cells lose adhesion, gain motility, and exhibit increased infiltration and metastatic potentials [92–94]. The TRAF2-dependent EMT induction may result from Wnt5a-mediated NF- κ B activation and

subsequent IL-6 secretion [47, 95]. Since persistent stress conditions typically characterize the TME, the TRAF2-sustained ER stress response aids cancer cells and other TME components adapt to ER stress induced by chemotherapeutic agents, thus avoiding apoptosis and promoting chemoresistance [96].

TRAF2 is recruited by IRE1, where it forms a complex that activates the NF- κ B pathway and the subsequent transcription of anti-apoptotic genes, which help tumor cells resist ER stress-induced cell death [97]. By interacting with IRE1, TRAF2 also leads to prolonged activation of the JNK pathway [98]. By inducing

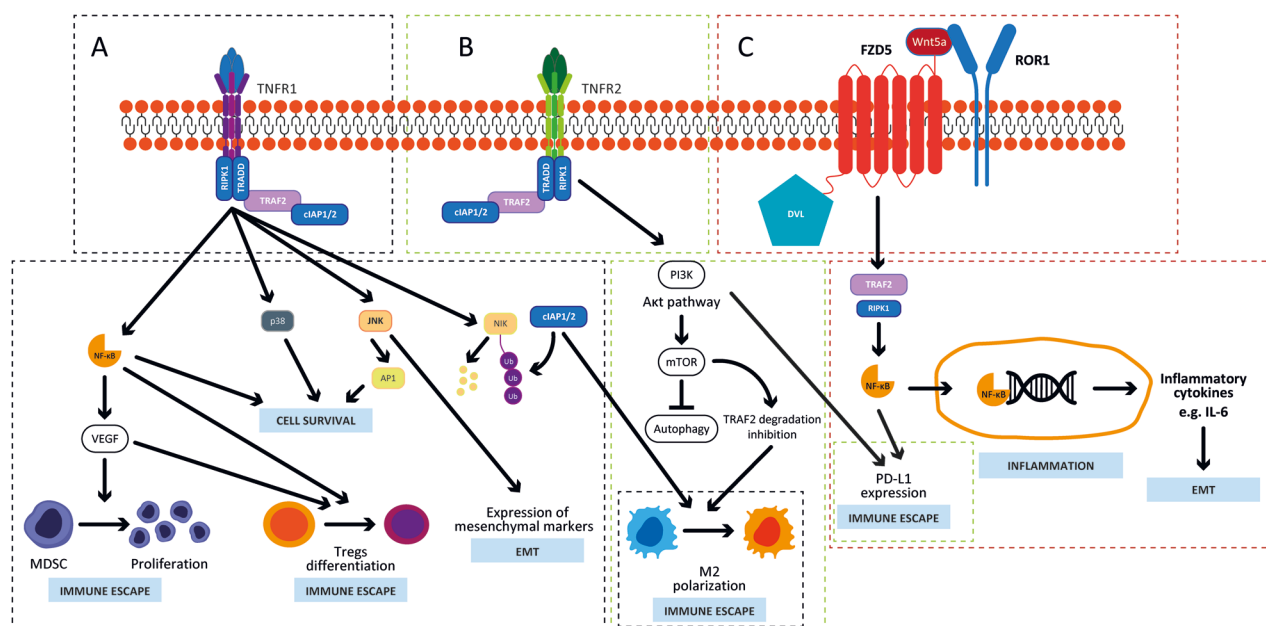


Fig. 5 TRAF2 roles in cancer. **A** TRAF2 forms a complex downstream of TNFR1 with RIPK1, TRADD, and cIAP1/2, which inhibits apoptosis and activates NF- κ B, JNK and p38. NF- κ B, in turn, increases the expression of VEGF, thus sustaining angiogenesis. Also, both VEGF and NF- κ B promote the differentiation of Tregs, thus sustaining immune escape. VEGF contributes to immune suppression by stimulating the proliferation of MDSCs. p38 and JNK promotes cell survival, and, in addition, JNK sustains EMT and, therefore, cancer aggressiveness. By promoting NIK degradation, the TRAF2-mediated TNFR1 signaling seems to play a role in the polarization of macrophages towards an M2 pro-tumoral phenotype. **B** TRAF2 stimulates cancer aggressiveness by activating the PI3K/Akt/mTOR signaling pathway downstream of TNFR2. This pathway inhibits autophagy and, by suppressing TRAF2 degradation, promotes the M2 macrophage polarization. **C** TRAF2 sustains the noncanonical Wnt signaling mediated by Wnt5a, which activates NF- κ B and triggers inflammation. The dotted squares indicate the molecules or cellular events activated by each of the three receptors (purple dotted squares: TNFR1 pathway; green dotted squares: TNFR2 pathway; red dotted squares: Wnt5a pathway). DVL Disheveled, EMT epithelial–mesenchymal transition, FZD Frizzled.

ER-stress-mediated autophagy and EMT, JNK promotes aggressiveness and resistance to anti-tumoral drugs [99].

Since TRAF2 promotes the expansion and tumor infiltration of immune suppressive cells, favoring immune escape [100], it might also shape the TME immunological characteristics. Considering the activity of TRAF2 in keeping the balance between Tregs and effector T cells (Teffs) [46], TRAF2 could display a role in facilitating cancer immune evasion. It has been shown that TRAF2-dependent inhibition of apoptosis downstream of TNFRs is exploited by several cancers to escape from the T-cell killing [3]. TRAF2 also seems to induce VEGF expression that, in turn, besides promoting angiogenesis [100], induces immune tolerance by suppressing T-cell and APCs functions and activating Tregs and MDSCs [101]. Moreover, it is possible to suggest a role of the TRAF2-dependent TNFR2 signaling in the protection of MDSC from apoptosis and their accumulation during tumor growth [102]. TRAF2 could have a role in the development and aggressiveness of cancer cells by influencing the differentiation into Th17 cells [103, 104], which exerts immunosuppressive functions and stimulates angiogenesis by secreting IL-17 [105].

TRAF2 role in specific cancers

In **gastric cancer** cell lines, TRAF2 silencing diminished the proliferation, migration and invasion [106]. Of note, in hereditary diffuse gastric cancer, the role of TRAF2 in promoting EMT could be particularly important since this tumor displays E-cadherin gene (*CDH1*) germline [92, 93] or somatic mutations, which correlate with increased aggressiveness and poor prognosis [94]. In **hepatocellular carcinoma (HCC)**, the ubiquitin-specific peptidase 24 (USP24) deubiquitinates and stabilizes TRAF2, which, in turn, promotes cell proliferation and metastasis [107, 108]. USP24 expression in HCC positively correlated with the expression of the immune evasion molecule, programmed cell death ligand 1

(PD-L1) [107]. Therefore, TRAF2 inhibition might be crucial for increasing the effectiveness of immunotherapy in HCC. In HCC, TRAF2 also promotes tumor growth by preventing ROS production, mitochondrial dysfunction [109] and autophagy [110] and contributes to drug resistance by supporting ER stress response [111]. By promoting the activation of the noncanonical NF- κ B pathway, TRAF2 supports cell proliferation [110, 112], resistance to apoptosis in both hepatitis B virus-derived HCC and spontaneous HCC [113] and macrophage polarization toward a pro-tumoral M2 phenotype [114]. In **non-small-cell lung cancer cells (NSCLC)**, TRAF2 confers resistance to TNF-mediated apoptosis [76, 82] and resistance to therapies [115, 116]. In **ovarian cancer** cells the DUB, UCHL3, is responsible for activating NF- κ B signaling by stabilizing TRAF2 thus facilitating tumorigenesis [117]. Also, TRAF2 over-expression was described to be associated with resistance to radiotherapy in **nasopharyngeal carcinoma** cells [118]. Moreover, TRAF2 has been described as being a dominant oncogenic driver of **colon cancer** development supporting the Wnt- β -catenin signaling pathway [53]. Besides this, TRAF2 seems to mediate EMT induced by low oxygen levels in this cancer type [119].

In **breast cancer (BC)**, TRAF2 upregulation increased the migration of tumor cells and supported osteolytic metastasis by enhancing osteoclastogenesis. The authors suggested that the aggressive behavior and bone tropism of BC cells are, at least in part, dependent on the TRAF2/NF- κ B axis [120]. Moreover, TRAF2 seems to promote BC cells' resistance to cell-detachment-induced apoptosis (anoikis) [121]. Given the importance of Th17 cells in BC [122], TRAF2 may enhance BC aggressiveness by promoting Th17 cell differentiation. In **prostate cancer (PCa)** cell lines, it has been shown that TRAF2 participates in the PI3K/Akt pathway activation, inhibiting apoptosis and promoting cell proliferation, invasion, and migration [123]. In **melanoma** cells, findings suggest that TRAF2 sustains the downstream signaling of

Table 1. TRAF2 functions in the innate and adaptive immune systems.

Target cell type	TRAF2 functions
Innate immunity	
Macrophages	<ul style="list-style-type: none"> • Hinders the differentiation of monocytes into fully active macrophages [62] • Promotes inflammatory activities and controls macrophage activation, survival and death [71] • Induces type I interferon and immune responses against infections [63]
DC	<ul style="list-style-type: none"> • Regulates DC functions [72] • Sustains type I IFN induction and immune responses against infections [63] • Sustains the activation of NF-κB and the expression of IL-12 and anti-apoptotic genes [70]
MDSCs	<ul style="list-style-type: none"> • Enhances the immune suppressive properties [73]
NK cells	<ul style="list-style-type: none"> • Enhances NF-κB activation, which increases the expression of Fas, thus promoting cytotoxic activity [64]
Adaptive immunity	
CD8 + T cells	<ul style="list-style-type: none"> • It is essential for the activation of TNFR1 pro-survival signaling in activated CD8 + T cells [74]
Memory T cells	<ul style="list-style-type: none"> • Activation and survival [75]
Th17	<ul style="list-style-type: none"> • Regulates the differentiation [65, 66]
Tregs	<ul style="list-style-type: none"> • Promotes the differentiation [65, 66] • Sustains the phenotypic stability, proliferation, activation and suppressive activity [66]
B cells	<ul style="list-style-type: none"> • Negatively regulates the survival of B cells [32] • Sustains B-cell activation [69] • Regulates B-cell CD40 function in T-dependent antibody responses [72]
Bregs	<ul style="list-style-type: none"> • Modulates the secretion of inflammatory cytokines [68]
Stem cells with immunomodulatory effects	
MSCs	<ul style="list-style-type: none"> • Enhances immunosuppression by repressing the proliferation and functions of Tregs and Bregs and stimulating the activities of immune suppressive cells [67]

IL-17, increasing aggressiveness [124]. Xu et al. demonstrated that, by inhibiting autophagy, TRAF2 promotes the macrophage polarization towards the M2 pro-tumoral phenotype and their infiltration into the tumor, alongside angiogenesis and cancer progression in **clear cell renal carcinoma** [83]. In **B-cell lymphoma**, the potential role of inhibiting TRAF2 to increase the response toward chemotherapeutics has been suggested [125]. A recent study also suggested the role of the TNFR1/2 complex in promoting **leukemia** progression [126].

TRAF2 seems to be required for tumor growth promotion by inhibiting apoptosis, promoting a malignant phenotype through EMT, regulating the sensitivity of certain cancer cells to chemotherapy and radiotherapy, and inducing immune suppression. Although evidence indicates that TRAF2, by promoting the activation of NF- κ B, enhances the CD8⁺-related anti-tumor immune response [127], hints to double-edged sword effects of TRAF2 hyperactivation are rare, indicating it as mostly pro-cancerogenic.

Figure 5 schematically represents the TRAF2-mediated pathways involved in the proliferation and aggressiveness of cancer cells, and Table 2 describes the role of TRAF2 in the different types of cancer [53, 76, 79, 80, 82, 83, 92, 93, 103, 105, 107, 109–113, 115–121, 123–126].

THERAPEUTIC STRATEGIES TARGETING TRAF2 OR TRAF2-INTERACTING MOLECULES

Modulating TRAF2 expression or activity can influence downstream TNFR signaling and is emerging as a promising cancer therapy target due to its pro-tumoral role. However, effective TRAF2 inhibition is challenging, as it interacts with multiple binding partners and pathways. Researchers are investigating natural and synthetic molecules that directly target TRAF2 or its interacting partners as potential anti-cancer strategies.

In IFN γ -resistant melanoma cells, TRAF2 and cIAP1 were identified as key factors increasing sensitivity to CD8 + T-cell mediated killing by lowering the TNF cytotoxicity threshold and, therefore, increasing immunotherapy efficacy. This study showed that TRAF2 loss enhanced the efficacy of cIAP1/2 inhibition by the

Smac/DIABLO mimetic birinapant. Combined TRAF2 and cIAP1/2 inhibition improved immune checkpoint blockade (ICB) efficacy in mouse cancer models [128]. Antagonists of cIAPs, which also inhibit TRAF2, are being evaluated as anti-cancer agents in clinical trials but have shown limited efficacy [129]. Since TNFRs can deplete cytosolic TRAF2 [34], their modulation could act as selective inhibitors of the cytosolic functions of TRAF2. Strategies that target TNFR2 seem to be of particular interest due to its expression being much higher in cancer cells and other TME cellular components [81]. There is an ongoing phase I/II clinical trial utilizing BI-1808, an anti-TNFR2 fully human antibody, as a single agent or in combination with immunotherapies in subjects with advanced cancers. BI-1808 was able to deplete the TME of Tregs, modulate MDSCs and promote CD8 + T-cell expansion [130]. According to these results, another anti-TNFR2 antibody, APX601, was also able to reverse the immune suppressive characteristics of the TME [131]. Eriodictyol, which is a flavonoid belonging to the subclass of flavanones, was able to induce apoptosis of tumor cells by enhancing TNFR1 expression and was able to reduce experimentally induced lung metastasis in vivo [132].

Besides this, TRAF2 also displays functions that are independent of TNFRs and cIAPs, suggesting that direct TRAF2 inhibitors might offer additional therapeutic benefits, especially in combination with ICB. TRAF2 silencing, through small interfering RNA, partially reversed radioresistance and significantly suppressed glioblastoma cell growth [116]. TRAF2-silencing also attenuated in vitro the migration and invasion capacities of gastric cancer cells [133]. TRAF2 ablation, besides boosting the classical NF- κ B pathway downstream of TNFRs and redirecting TNF signaling favoring apoptosis, has also been suggested as a tool to increase the susceptibility of tumors to immunotherapy by counteracting ICB [3]. A meta-analysis of over 1000 ICB-treated patients found that TRAF2 loss correlated with a positive clinical response, suggesting that targeting TRAF2 could enhance ICB efficacy [134]. Liquidambaric acid (LDA), a pentacyclic triterpenoid, is a TRAF2-interacting molecule with potential anti-tumoral effects, shown to inhibit colon cancer growth. LDA selectively blocks β -catenin–TRAF2 interaction without affecting others, highlighting its potential for

Table 2. The role of TRAF2 as tumor promoter or tumor suppressor in different types of cancer.

Cancer type	TRAF2 activity/role
Gastric cancer	<ul style="list-style-type: none"> Increases proliferation, migration and invasion [121] Has a potential role in promoting EMT by downregulating E-cadherin
Hepatocellular carcinoma	<ul style="list-style-type: none"> Promotes the Wnt-β-catenin signaling, which activates the PI3K/Akt and NF-κB signaling pathways promoting cell proliferation and metastasis [107, 108] Supports the canonical NF-κB pathway, enhancing resistance to apoptosis [113] It might play an important role in the resistance to immunotherapy by increasing PD-L1 expression Prevents ROS production and mitochondrial dysfunction, protecting against cell cycle arrest and senescence [109] By impairing NIK function, the complex cIAP-TRAF2 activates the noncanonical NF-κB pathway and supports cell proliferation [110, 112], resistance to apoptosis in both hepatitis B virus-derived HCC and spontaneous HCC [113] and macrophage polarization toward a pro-tumoral M2 phenotype thus contributing to cancer progression [114] Activates mTOR, suppresses autophagy and promotes cell survival and proliferation by [110] Contributes to drug resistance supporting ER stress response [111]
Non-small-cell lung cancer	<ul style="list-style-type: none"> Enhances NF-κB activation, conferring resistance to TNF-mediated apoptosis [76, 82, 121] Promotes cancer cell proliferation and potentially serves as a target to sensitize cells to argon-helium cryoablation [115] and radiotherapy [116]
Ovarian Cancer	<ul style="list-style-type: none"> Enhances NF-κB activation, leading to tumorigenesis [117]
Nasopharyngeal carcinoma	<ul style="list-style-type: none"> Induces resistance to radiotherapy [118]
Colon Cancer	<ul style="list-style-type: none"> Stabilizes the β-catenin-TNFK-TCF4 complex, activating the expression of Wnt target genes, which drive tumor development [53] Leads to JNK activation, which promotes EMT, especially under low oxygen conditions [119]
Breast cancer	<ul style="list-style-type: none"> Increases tumor cell migration and promotes bone metastasis via osteoclastogenesis through NF-κB activation [120] By interacting with focal adhesion kinase (FAK), TRAF2 seems to promote BC cell resistance to cell-detachment-induced apoptosis (anoikis) TRAF2 may contribute to Th17 cell differentiation and cancer progression
Prostate cancer	<ul style="list-style-type: none"> Activates PI3K/Akt, inhibiting apoptosis and promoting proliferation, migration and invasion [123]
Melanoma	<ul style="list-style-type: none"> Sustains the downstream signaling of IL-17, resulting in the induction of proliferation and invasion [124]
Clear cell renal cell carcinoma	<ul style="list-style-type: none"> Promotes M2 macrophage polarization and infiltration into tumors, aiding cancer progression and angiogenesis [83]
B-cell lymphoma	<ul style="list-style-type: none"> Increases resistance to chemotherapeutics [125]
Leukemia	<ul style="list-style-type: none"> The TNIK/TRAF2 complex activates Wnt signaling downstream of CD27, promoting tumor progression [126]
Mantle cell lymphoma Diffuse large B-cell lymphoma Multiple myeloma	<ul style="list-style-type: none"> TRAF2 acts as a tumor suppressor [79, 80]

targeted TRAF2 inhibition [53]. An LDA analog selectively targeted TRAF2 with higher binding affinity than LDA, inhibiting Wnt and TNF signaling and hindering the growth of colon cancer cells in xenograft mice [106]. Peptidomimetics targeting the TRADD-TRAF2 interaction have been identified [135], but their usefulness to inhibit TRAF2 functions requires further investigation.

Additionally, TNF-like weak inducer of apoptosis (TWEAK), a ligand of Fn14, also makes cancer cells more vulnerable to TNF-mediated killing, supporting Fn14's role in depleting cytosolic TRAF2-cIAP1/2 complexes [128]. Vince et al. [136] found that TWEAK-FN14 signaling leads to the lysosomal degradation of the cIAP1-TRAF2 complex, sensitizing tumor cells to TNF- α . Michaelson et al. [137] developed an Fn14 agonistic antibody that inhibited growth in approximately 50% of a tested panel of 38 human tumor cell lines.

CXC195 is a tetramethylpyrazine analog that induced apoptosis of a bladder cancer cell line by inducing mitochondrial dysfunction and ER stress-induced activation of JNK through the formation of an IRE1-TRAF2-ASK1 complex [138]. Verproside, a compound extracted from *Veronica* species, exhibits cytostatic activity by blocking the TNF/NF- κ B signaling in rhabdomyosarcoma cell lines,

and it seems that this action is due to its interaction with the TRAF2-TRADD complex [139]. TNIK inhibitors seem to be promising anticancer agents since they interfere with the TRAF2 activity of promoting the Wnt- β -catenin signaling. A TNIK inhibitor, NCB-0846, due to its ability to block the EMT process in lung cancer cells, represents a potentially promising approach for the prevention of metastasis [140]. NCB-0846 was also able to sensitize TNIK-overexpressing lung squamous cell carcinoma to radiotherapy in *in vitro* and *in vivo* models [141] and to hinder papillary thyroid carcinoma progression by inhibiting cytoskeletal remodeling [142]. A recent study showed that OBD9, an oxetane derivative of the benzimidazole mebendazole with TNIK inhibitory activity, exhibits strong anticancer activity in various cancer cells, particularly colorectal cancer, by inducing TNIK autophagic degradation and blocking TCF4/ β -catenin-mediated gene expression [143]. It has been shown that wogonoside, a flavonoid compound, inactivated NF- κ B signaling by decreasing TRAF2/4 expression. Consequently, Wogonoside inhibited Twist, a transcription factor driving EMT, thereby downregulating MMP-9, MMP-2, vimentin, and CD44v6 expression in TNF- α -induced triple-negative breast cancer (TNBC) cells [144]. This article suggests wogonoside as a potential TNBC

Table 3. Anti-cancer therapeutic strategies targeting TRAF2 or TRAF2 interactors.

Therapeutic strategy	Effects on cancer cells and TME
TRAF2 silencing	<ul style="list-style-type: none"> • Induce growth arrest and reverse the radioresistant phenotype of glioblastoma cells [110] • Inhibits the migration and invasion of gastric cancer cells in vitro [121]
Copine 1 silencing (TRAF2 interactor)	<ul style="list-style-type: none"> • Induces cell cycle arrest in prostate cancer cells [142]
Anti-TNFR2 antibody BI-1808	<ul style="list-style-type: none"> • Depletes the TME of Tregs, modulates MDSCs and promotes the expansion of CD8 + T cells [128]
Anti-TNFR2 antibody APX602	<ul style="list-style-type: none"> • Reverses the immune suppressive characteristics of the TME [129]
Anti-Fn14 agonistic antibody	<ul style="list-style-type: none"> • Inhibits the growth of several cancer cell lines potentially through the depletion of TRAF2-cIAP1/2 [132]
Tetramethylpyrazine analog CXC195	<ul style="list-style-type: none"> • Induces apoptosis of bladder cancer cells [133]
Verproside	<ul style="list-style-type: none"> • Probably interacts with TRAF2/TRADD, inhibiting the activation of NF-κB in rhabdomyosarcoma cell lines [134]
TNIK inhibitor NCB-0846	<ul style="list-style-type: none"> • Inhibits TNIK and the EMT process in lung cancer and sensitizes TNIK-overexpressing lung squamous cell carcinoma to radiotherapy [136] • Hinders papillary thyroid carcinoma progression by hampering migration as a consequence of the inhibition of cytoskeletal remodeling [137]
TNIK inhibitor OBD9	<ul style="list-style-type: none"> • Induces autophagic degradation of TNIK and, subsequently, blocks the TCF4/β-catenin [139]
Wogonoside	<ul style="list-style-type: none"> • Downregulates TRAF2 and TRAF4 and, consequently, inactivates NF-κB and inhibits Twist expression and EMT [138]
Suramin analog NF023	<ul style="list-style-type: none"> • Disrupts the interaction between cIAP and TRAF2 and, consequently, inhibits NF-κB [14]
Liquidambaric acid (LDA)	<ul style="list-style-type: none"> • Targets TRAF2 and inhibits Wnt-β-catenin in colon cancer [40]
LDA analog	<ul style="list-style-type: none"> • Inhibits Wnt and TNF signaling and inhibits colon cancer cell growth in a mouse model [122]
Smac/DIABLO mimetic (cIAP1 and 2 inhibitors)	<ul style="list-style-type: none"> • Increases the efficacy of ICB in TRAF2-depleted cancer cells [125]
Xinfeng	<ul style="list-style-type: none"> • Downregulates TRAF2 and hampers NF-κB activation [140]
Putative NF- κ B inhibitor P3-25	<ul style="list-style-type: none"> • Inhibits the TRAF2-mediated activation of NF-κB and AP-1 [141]
Tannic acid	<ul style="list-style-type: none"> • Downregulates several genes, including TRAF2, and upregulates various pro-apoptotic genes, inhibiting prostate cancer cell growth [143].
Sangganon C	<ul style="list-style-type: none"> • Increases TRAF2 expression and NF-κB activation [74] • It might be useful for mantle cell lymphoma, diffuse large B-cell lymphoma, multiple myeloma, some types of sarcomas and HCC associated with metabolic-associated fatty liver disease
Peptidomimetics with the potential to inhibit the TRADD-TRAF2 interaction	<ul style="list-style-type: none"> • It might be useful in cancer treatment, but further studies are needed

therapy and supports TRAF2's role in EMT, highlighting its potential as a therapeutic target in epithelial cancers. Structure-based computational screening identified NF023, a suramin analog, as a candidate for modulating NF- κ B by disrupting the cIAP2-TRAF2 interaction, potentially affecting cancer cell survival [23].

Fang et al. showed that Xinfeng Capsule is able to inhibit NF- κ B activation by downregulating TRAF2 [145]. Therefore, it is possible to speculate the use of this medicinal plant blend also in a cancer context. The compound P3-25 was shown to be promising since able to inhibit the TRAF2-mediated NF- κ B and AP-1 pathway activation [146]. Also, the silencing of copine 1 (CPNE1), a TRAF2 interactor, induced cell cycle arrest in PCa cells and this anti-tumor effect was reversed by overexpressing TRAF2 [147]. Tannic acid was able to downregulate several genes, including TRAF2, and to upregulate various pro-apoptotic genes, inhibiting PCa cell growth [148]. In rare cases, TRAF2 might be beneficial for cancers since it displays an anti-tumoral activity. A study showed that Sanggenon inhibits porcine reproductive and respiratory syndrome replication by suppressing NF- κ B activation through increased TRAF2 expression [74]. Thereby, Sanggenon might be useful for mantle cell lymphoma, diffuse large B-cell lymphoma, multiple myeloma, some types of sarcomas and HCC associated with metabolic-associated fatty liver disease.

The anti-cancer therapeutic strategies targeting TRAF2, which either inhibit or activate its expression or target TRAF2 interactors, are outlined in Table 3.

FUTURE DRUG DESIGN

TRAF2 inhibition holds promise for reducing cancer aggressiveness, overcoming immune escape, and addressing resistance to conventional therapies, especially in combination with chemotherapy, radiotherapy, or immunotherapy. However, its biochemical and pharmacological properties remain poorly understood. Future drug design may benefit from exploring its structural and dynamic features. Comparative studies between TRAF1 and TRAF2 have revealed distinct affinities for proteins, such as TRADD, TANK and caspase 2, attributed to specific amino acids in their C-terminal domains. TRAF2's uneven globular surface facilitates interactions with membrane receptors (e.g., TNFRs) and adaptor proteins (e.g., TRADD). Its rough outer surface offers anchoring points for medium-sized molecules, potentially enabling inhibition of its protein interactions (Fig. 6). Recent in silico studies have identified peptides capable of disrupting the TRAF2-TRADD interaction. Additionally, the dissociation of TRAF2's trimeric structure into monomers under acidic conditions, such as

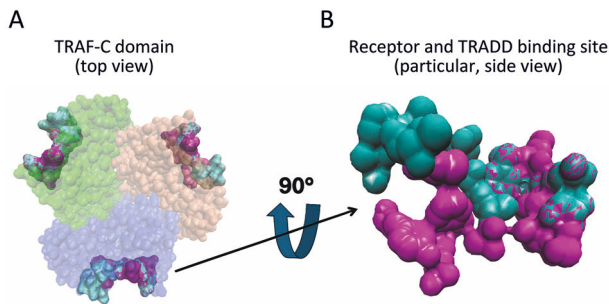


Fig. 6 TRAF2-C surface structural features. **A** Schematic representation of trimeric TRAF2-C (top view) cartoon (PDB file 1ca4) with the three subunits in different colors (blue, green and orange). The surface residues involved in the interaction with TRADD or with CD40 receptor peptide are shown in cyan and in purple, respectively (obtained from PDB files 1f3v and 1qsc). **B** Details of the TRADD and/or CD40 binding residual surface (side view) obtained from panel (A) upon a rotation of 90°.

binding to ganglioside-containing membranes (GM1) [145], is a process that is known to induce vesiculation [12, 13, 145]. This monomer-trimer equilibrium could serve as a therapeutic target, offering opportunities to modulate TRAF2 activity *in vivo*. These findings highlight TRAF2 as a promising yet underexplored target for future cancer therapy strategies.

CONCLUSIONS

TRAF2 is a critical signaling hub involved in modulating pathways downstream of TNFR1 and TNFR2, influencing cell survival, apoptosis, inflammation, immune regulation, and cancer progression. TRAF2 supports macrophage activation, survival of DC, Treg and B cells, NK cell cytotoxicity, Th17 differentiation, and T-cell memory. Additionally, TRAF2 enhances the immunosuppressive functions of MDSCs in tumors, establishing its position as a key mediator of immune homeostasis and cancer immune evasion. In cancer, TRAF2 activates NF- κ B to drive inflammation, angiogenesis, and immunosuppressive TME. It also supports tumor progression by promoting EMT and ER stress responses, enhancing resistance to apoptosis and anti-cancer therapies. Studying TRAF2 is crucial for understanding tumor signaling and interactions within the TME, including its role in immune dynamics, chemoresistance, and metastasis. Targeting TRAF2 remains challenging, but inhibitors, neutralizing antibodies, and peptides disrupting its interactions with TRADD or cIAPs show promise. Combining TRAF2 inhibition with chemotherapy or targeted therapies (VEGF, mTOR, or PD-L1 inhibitors) may enhance efficacy. These strategies offer the potential for tailored anti-cancer treatments that disrupt oncogenic pathways while preserving immune function. Further structural studies are needed to explore rare cases where TRAF2 may support anti-tumor immunity and to refine therapeutic approaches.

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ACKNOWLEDGEMENTS

The work of DN, LDP and GM on TRAF2 was supported by PRIN 2022, grant 2022PJKF88, to GM. The studies of GC were sustained through the “Umberto Veronesi” Foundation project: “Massive CDH1 genetic screening in the so-called hereditary breast-gastric cancer syndrome”. The work was also supported by the Italian Ministry of Health Ricerca Corrente to IRCCS IEO, European Institute of Oncology, and IRCCS MultiMedica, Italy. We acknowledge Lara Vecchi, Valentina Attanasio, and Aashni Shah (Polistudium Srl, Milan Italy) for editorial assistance and Massimiliano Pianta (Polistudium, Srl, Milan Italy) for graphic support.

AUTHOR CONTRIBUTIONS

Manuscript drafting: AA, DN; manuscript editing and illustration: AA, DN, LDP, GM; research and editing: DN, DB, AA, LDP, GM, DB, NF, DN, GC; revision and approval of the final version of the manuscript: all.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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