TNFR2: A Novel Target for Cancer Immunotherapy

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Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy but exhibit variable efficacy and relapse and can induce autoimmunity. Tumor necrosis factor (TNF) receptor 2 (TNFR2) is a signaling molecule found on the surface of a subset of potent regulatory T cells (T\textsubscript{reg}s) that can activate the proliferation of these cells through nuclear factor kappa B (NF-κB). TNFR2 is also abundantly expressed on the surface of many human tumors. We propose that blocking TNFR2 might target abundant TNFR2\textsuperscript{+} tumor-infiltrating T\textsubscript{reg}s and directly kill TNFR2-expressing tumors. We also posit that TNFR2 inhibitors might potentially constitute safer and more targeted alternatives to ICI cancer treatment because the expression of TNFR2 on immune cells, concentrated in the tumor microenvironment of various cancers, appears to be more selective than that of checkpoint molecules.

Basics of Immunotherapy

Monoclonal antibodies (mAbs) (see Glossary) are precision tools that allow the targeting of tumor antigens with greater selectivity. Rituximab was the first antibody-based cancer therapy; it targets the CD20 antigen expressed in non-Hodgkin’s lymphoma and B cell chronic lymphocytic leukemia [1]. Since its approval in 1997, more than 20 other antibody therapies have been brought to the market to treat different forms of cancer [2]. Antibody-based cancer treatment strategies can be grouped into four different categories: (i) direct tumor cell killing by agonism, antagonism, or the delivery of a toxin, cytokine, or radioactive isotope in the form of an antibody-drug conjugate (ADC); (ii) vascular and stromal cell ablation to cut off the supply of nutrients to tumor cells; (iii) blocking T\textsubscript{reg}s that are immunosuppressive and thereby promote the survival of tumor cells; and (iv) other immune-mediated approaches that include complement activation, T cell activation, and antibody-dependent cellular cytotoxicity (ADCC).

T cells have been an important focus of cancer immunotherapy due to their capacity to directly kill tumor cells if they are CD8\textsuperscript{+} cytotoxic T lymphocytes (CTLs), also known as CD8\textsuperscript{+} effector T cells (T\textsubscript{eff}). However, T\textsubscript{reg}s can suppress T\textsubscript{eff} and thereby deter the proper host immune response to eliminate a tumor [3,4]. Consequently, an ideal treatment approach might include inhibition of suppressive T\textsubscript{reg}s and the simultaneous activation of cytotoxic CD8\textsuperscript{+} T\textsubscript{eff}s.

TNFR2 is a cell-surface receptor that regulates cell survival and proliferation [5] and targeting this receptor has recently emerged as a potential next-generation cancer therapeutic approach [6]. Certain human tumor cells can aberrantly express TNFR2 and tumor infiltrates are dominated by highly suppressive TNFR2\textsuperscript{+} T\textsubscript{reg}s [7,8]. We postulate that targeting TNFR2 on the surface of tumor cells and on tumor-infiltrating T\textsubscript{reg}s may have the potential to combine direct tumor cell killing with the inhibition of immunosuppressive T\textsubscript{reg}s. Here we introduce TNFR2, discuss its role in T\textsubscript{reg} expansion and contraction, and summarize emerging approaches to putatively target TNFR2 in certain cancers.
Novel Cancer Treatment Strategies Can Include Elimination of Suppressive TregS

Cancer cells can escape cell death and proliferate by inducing the proliferation of immunosuppressive tumor-infiltrating TregS. TregS, in turn, can allow cancer cells to survive by suppressing subsets of CD8+ T effS [9]. Several promising cancer therapies have aimed to block Treg expansion in many cancer settings [4]. However, finding a targeted approach to remove or inactivate host TregS, especially TregS in the tumor microenvironment only, has remained particularly challenging [7,10,11]. The tumor microenvironment constitutes the tumor, surrounding vessels, stroma, and non-cancerous cells in addition to associated immune cells, including T and B cell infiltrates. Countertuitively, certain immune cell populations (e.g., TregS) can play a dual role: they might contribute to protecting a tumor, preventing the host’s immune system from killing undesired tumor cells [12]. New approaches that block TregS have also been hampered by the fact that many surface receptors of TregS (Figure 1), such as immune checkpoint molecules [e.g., programmed cell death protein 1 (PD-1), CTL-associated protein 4 (CTLA-4)], are diffusely expressed in cells of the human immune system. Thus, attempts to target such Treg receptors in humans have encountered systemic toxicity and lethal autoimmunity [13].

Only a subpopulation of TregS express TNFR2: TNFR2-expressing TregS in humans and rodents represent the most suppressive subset of TregS [4,14–18]. These TregS are unusually abundant in tumors of diverse types including ovarian, metastatic melanoma, and colon [19,20]. Furthermore, unlike most cell-surface markers, TNFR2 signaling is a potent activator of Treg expansion or contraction [17]. In adult human CD4+ T cells, TNFR2 has been reported to act as a bidirectional signaling ‘switch’ able to modulate Treg fate depending on whether it is triggered by an agonist or an antagonist: agonism has been found to expand TregS while antagonism has led to Treg contraction in vitro [17]. Mechanistically, TNFR2 activation has been shown in human CD4+ and CD8+ T cells to result in constitutive downstream agonism and heightened cell proliferation through NF-κB signaling [17,21,22] that includes PI3K and AKT activation [23,24].

Aberrant expression of TNFR2 on tumor cells has been shown in human renal cell carcinoma, colon cancer, Hodgkin’s lymphoma, multiple myeloma, cutaneous non-Hodgkin’s lymphoma,

Figure 1. Immunoregulatory Receptors Expressed on Regulatory T Cells (TregS). Immunomodulatory receptors expressed on TregS can be targeted by immunotherapies. Examples include programmed cell death protein 1 (PD-1), cytotoxic T lymphocyte antigen 4 (CTLA-4), tumor necrosis factor (TNF) receptor 2 (TNFR2) [TNFR superfamily 1b (TNFRSF1b)], TNFRSF25, 4-1BB (TNFRSF4), glucocorticoid-induced TNF-related protein (GITR) (TNFRSF18), OX40 (TNFRSF5), CD27 (TNFRSF7), Neuropilin, vascular endothelial growth factor receptor (VEGFR), lymphocyte activation gene protein 3 (LAG3), inducible T cell costimulator (ICOS), and IL-2 receptor α or CD25.
and ovarian cancer [8,18,25–28]. Presumably, the overexpression of TNFR2 on tumors exploits this growth receptor for enhanced proliferation. Similarly, novel TNFR2 mutations in cancer have been associated with gene duplications and constitutive agonism [8]. Moreover, TNFR2 is also expressed on murine CD11b⁺GR-1⁺ myeloid-derived suppressor cells (MDSCs) and its inhibition can control metastasis in a murine liver cancer model [29]. This suggests that the use of TNFR2 inhibitors might potentially prevent metastatic progression in liver, colon, lung, and, possibly, other types of cancer, although this has not been extensively tested [29]. We hypothesize that the abnormal expression of TNFR2 on tumor-infiltrating TregS, MDSCs, and tumor cells themselves represents multiple ways for tumor cells to expand utilizing TNFR2 signaling. Thus, it is possible that TNFR2 blockade in addition to inhibition of Treg expansion might also directly inhibit tumor growth and metastasis in certain cancers, although this remains largely speculative since human trials have not yet begun. We also hypothesize that TNFR2 blockade on TregS might ideally enable TeffS to proliferate. Below, we review the rationale for such an approach.

**TNFR2 as a Putative Target for Cancer Therapy**

TNFR2 is a member of the TNFR superfamily (TNFRSF) and is activated by TNF [30]. The signaling circuitry of TNFR2 differs from that of the other TNFR. TNFR1: TNFR1 contains an intracellular death domain and can activate either apoptotic or inflammatory pathways, while TNFR2 binds TNF receptor-associated factors (TRAFs) and can activate both the canonical and the noncanonical NF-κB pathway to control cell survival and proliferation in both humans and mice [31]. TNFR1 is expressed on all lymphoid cells and is commonly expressed on parenchymal cells in mammals [32,33]. By contrast, TNFR2 has limited expression: its expression is restricted to minor subpopulations of the lymphoid system, such as highly suppressive TregS, MDSCs, endothelial cells, and select neurons during growth, in normal mammals, but in the tumor microenvironment its expression is enriched [34,35]. Studies in baboons have shown that the known toxicity of high-dose TNF is mediated solely by TNFR1 and not by TNFR2; this was determined by using mutants of TNF that were selective for either TNFR1 or TNFR2 [36,37]. Moreover, TNFR2 is present at a tenfold higher density than TNFR1 in naturally occurring TregS in human blood [34].

TNFR2 is an attractive candidate in cancer therapy for several reasons. In various human and murine cancers, abundant TNFR2-expressing TregS are found within the tumor microenvironment, and emerging data indicates that following ICI therapy tumor escape may be driven by TNFR2 upregulation on infiltrating TregS [16,38,39]. Furthermore, gene duplications and activating mutations in TNFR2 have been found in cutaneous T cell lymphomas, endowing the tumor cells with a mechanism for selective and preferential expansion [8]. Also, mice lacking the Tnfr2 gene have shown improved immune responses to tumors due to the lack of TNFR2-expressing TregS or have failed to develop systemic autoimmunity [29,40–42]. The lack of autoimmunity in the Tnfr2⁻/⁻ mice could be due to the restricted distribution of TNFR2. Because loss of TNFR2 function appears to affect only a subset of TregS, we speculate that, potentially, other fully functional TregS that express other surface markers might still be able to maintain systemic immune balance.

**Dominant TNFR2 Antagonistic Antibodies Can Inhibit the Proliferation of Human Ovarian Cancer Cells and Tumor-Associated TregS**

A recent study identified several antagonist antibodies to TNFR2 [43]. They were classified as dominant or recessive antagonists based on their effect on Treg induction and tumor cell suppression in fresh human tumors or fresh human tumor-derived TregS isolated from the tumor microenvironment. In culture the dominant antagonists suppressed Treg proliferation, which in turn enabled expansion of TeffS. The dominant antagonistic antibodies directed against TNFR2...
also killed human ovarian tumor cells by blocking the binding of TNFR2 to its cognate ligand TNF; these effects were achieved even under increasing concentrations of TNF – a TNFR2 agonist found in high concentrations in the tumor microenvironment. Consequently, these antibodies were referred to as dominant antagonists. By contrast, the recessive antagonist antibodies acted as weak antagonists and were unable to compete against higher concentrations of TNF in binding assays [43]. The dominant antagonists bound to a site on TNFR2 that differed from the binding site of the recessive antagonists on human T cells [43]. Moreover, the dominant antagonist antibodies exhibited a smaller effect on circulating TregS from healthy donors when compared with tumor-associated TregS. This suggested that dominant antagonist antibodies might harbor specificity for the tumor microenvironment and could potentially provide a more targeted therapy against tumors than other forms of immunotherapy; however, this has not yet been tested [43]. Further characterization of TNFR2 dominant antagonist antibodies revealed that they required the full F(\text{ab})\text{\textsubscript{2}} to be functional; a single Fab domain was incapable of competing with TNF to inhibit its binding and subsequent TNFR2 activation [43].

This study illustrates that there can be significant differences between antibodies designed for the same purpose, and without careful side-by-side analysis of their binding mode and mechanism of action their functional comparison can prove difficult. Although antibodies to common checkpoint inhibitor targets such as PD-1, PDL-1, or CTLA-4 can be designed by blocking ligand and receptor interactions, agonist or antagonist antibodies to TNF superfamily (TNFSF) members have been more challenging to generate [43,44]. We speculate that this may be due to the high-avidity binding between the trimeric natural TNFSF ligands and the three receptors binding to them and the additional need for the receptors to form cell-surface crosslinking networks that are neither easy to disrupt for negative signaling [43] nor easy to stabilize for positive signaling [44].

Another study performed targeted phage-display screening on human TregS to identify antibody-mimetic designed ankyrin repeat proteins (DARPins) with preferential binding to TregS over T effS [38]. The most selective DARPins were all found to bind TNFR2, demonstrating that TNFR2 was highly and preferentially expressed on human TregS over T effS in vitro [38]. This is important because it may indicate that anti-TNFR2 antibodies could be used to preferentially target TNFR2 on TregS.

**FcY Receptor Binding and Nonspecific Immune Activation via Immunotherapy**

The Fc portion of therapeutic IgG antibodies binds FcY receptors expressed on cells of the immune system, such as B lymphocytes, macrophages, dendritic cells, granulocytes, natural killer cells, platelets, and mast cells. The effect of binding depends on the receptor subtype and can be either activating or inhibitory. ADCC can be important for the therapeutic effect of antibodies; however, antibodies that depend on their Fc regions for activity may be more restricted in their clinical utility, presumably because natural killer cells and monocytes bearing FcY receptors would need to be near a therapeutic antibody at a tumor site. Another clinical limitation of Fc-mediated antibody binding stems from the existence of polymorphisms in FcY receptor genotypes; human cancer treatments with diverse therapeutic antibody isotypes might then need to be tailored to human FcY receptor variants to facilitate binding. In addition, binding of antibody Fc receptors to associated lymphocytes can also cause secretion of undesired cytokines. Remarkably, dominant antagonist TNFR2 antibodies have not been found to require Fc-mediated antibody binding to suppress the proliferation of TregS or tumor cells [43]. This clue prompted a more thorough investigation on whether these antibodies might function through a different mechanism than Fc binding [43]. For instance, an anti-DR5 (anti-TNFRSF10B) antibody was found to function without the need for Fc-mediated crosslinking [44]. This suggested that, at least for some antibodies against TNFRSF members (both agonists and antagonists), Fc-mediated ADCC may not be required for their function [44].
Natural Expression of TNFR2 on CD4+ T_{reg}s versus CD8+T_{eff}s: Lessons from Cancer and Autoimmunity

In autoimmunity an underlying NF-κB signaling defect results in an immune imbalance, yielding more autoreactive cytotoxic CD8+ T_{eff}s than immunosuppressive CD4+ T_{reg}s [45,46]. An excess of T_{eff}s can contribute to the destruction of normal tissues (Figure 2A) [47]. In humans with autoimmune disease and in animal models of autoimmunity, TNFR2 agonism has been found to restore this immune cell balance by selectively killing autoreactive T cells and expanding suppressive T_{reg}s [17,45,46,48–50]. Data supporting this conclusion came from animal models using Tnfr2^{−/−} mice and the development of TNFR2 agonistic and antagonistic antibodies to the human TNFR2 receptor for in vitro studies [43].

(A) The autoimmune microenvironment

(B) The tumor microenvironment

Figure 2. Impact of Tumor Necrosis Factor (TNF) Receptor 2 (TNFR2) Agonism and Antagonism in the Autoimmune and Tumor Microenvironments. (A) In the autoimmune microenvironment, autoreactive CD8+ effector T cells (T_{eff}) are more abundant than the immunosuppressive CD4+ regulatory T cells (T_{reg}), resulting in tissue destruction. TNFR2 agonism restores the immune cell balance by expanding T_{reg}s and selectively eliminating autoreactive T_{eff}s. (B) In the tumor microenvironment, tumor cells are infiltrated by immunosuppressive T_{reg}s that suppress T_{eff}s and allow tumor growth. TNFR2 antagonism restores the T cell balance by eliminating T_{reg}s and activating T_{eff}s, resulting in tumor cell death.
The opposite appears to be true in the cancer microenvironment (Figure 2B). In most human cancers, often referred to as ‘hot tumors’, the tumor might be infiltrated with highly suppressive T_{reg}S and T_{eff}S might not be sufficiently effective to overcome the tumor burden. TNFR2 antagonism on lymphocytes from the tumor microenvironment can rapidly induce T_{reg} death, leading to rapid expansion and activation of T_{eff}S to lyse tumor cells [43]. In addition, in cases such as ovarian cancer, where tumors express TNFR2, TNFR2 antagonism might provide additional therapeutic benefits by direct tumor killing as well. Therefore, TNFR2 antagonist antibodies specific for T_{reg}S in the tumor microenvironment might exhibit tumor T_{reg}-preferential killing and, possibly, direct tumor cell killing, rendering TNFR2 targeting a potential new dual-purpose cancer therapeutic, but this remains to be tested (Box 1).

We propose that TNFR2 might modulate immune responses in both autoimmune and tumor microenvironments via opposing effects on CD4\(^+\) T_{reg}S and CD8\(^+\) T_{eff}S, although the exact mechanisms remain to be determined. On the one hand, TNFR2 agonism to promote T_{reg} expansion and elimination of cytotoxic CD8\(^+\) T_{eff}S might provide a therapeutic opportunity in autoimmunity. On the other hand, TNFR2 antagonism could be exploited in cancer to eliminate tumor-infiltrating immunosuppressive T_{reg}S, allowing cytotoxic CD8\(^+\) T_{eff}S to proliferate. Although the applicability of TNFR2 antagonism in cancer remains to be tested, the utility of TNFR2 agonism, through indirect stimulation of TNFR2 T_{reg}S, is currently being evaluated in trials and has already had positive outcomes in rheumatoid arthritis and other autoimmune diseases [48].

**Soluble TNFR2, A Putative Marker of T_{reg} Expansion in Cancer, Can Be Inhibited with TNFR2 Antagonism**

Soluble TNFR2, whether in the serum of cancer subjects or in culture media taken from TNF-stimulated or potent TNFR2 agonist-induced CD4\(^+\) T cells, is a good indicator of TNFR2 activity. This is because soluble TNFR2 forms only when TNFR2 trimerizes with TNF and this tightly clustered complex becomes susceptible to membrane cleavage by TACE enzymes [51].

Measuring the amount of sTNFR2 in culture supernatants after treatment with IL-2, TNF, TNFR2 agonistic antibodies, or TNFR2 antagonistic antibodies in patients may provide information on TNFR2 surface expression, downstream NF-κB activation, and serum sTNFR2 levels. Specifically, in vitro treatment of CD4\(^+\) T cells with IL-2, TNF, or TNFR2 agonism can exponentially and rapidly induce sTNFR2 shedding [52]. In marked contrast, inhibition of TNFR2 signaling with TNFR2 antagonistic antibodies can reduce sTNFR2 culture levels [43]. This is because, in addition to blocking TNF binding and signaling, TNFR2 antagonist antibodies can also inhibit the cleavage of the receptor from the cell surface, thereby reducing sTNFR2 levels [43].

These findings might support the concept that T_{reg} expansion through TNFR2 activation might be monitored by measuring sTNFR2 in serum. The data also suggest that patients with tumors

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**Box 1. T_{reg}S in Immune Homeostasis and Cancer Therapy**

T_{reg}S can be subdivided into ‘natural’ T_{reg}S (nT_{reg}S), which develop in the thymus, and ‘induced’ T_{reg}S (iT_{reg}S), which develop from conventional CD4\(^+\) T cells in the periphery [78]. iT_{reg}S accumulate in many tumors and are thought to represent a major immune resistance mechanism. For this reason they are important cellular targets for cancer therapy. T_{reg}S are distinguished from other T cells by the expression of the forkhead transcription factor FOXP3 [79]. T_{reg}S produce inhibitory cytokines such as transforming growth factor beta (TGF\(\beta\)), IL-10, and IL-35 and are viewed as important cellular targets for therapy. T_{reg}S do not express unique cell-surface receptors but they do express abundant levels of multiple immune-checkpoint receptors such as CTLA-4, PD-1, T cell membrane protein 3 (TIM3), the adenosine A2a receptor (A2aR), and lymphocyte activation gene 3 (LAG3). They also express costimulatory receptors of the TNFSF such as TNFR2 (TNFRSF1b), TNFRSF25, 4-1BB (TNFRSF9), glucocorticoid-induced TNF-related protein (GITR) (TNFRSF18), OX40 (TNFRSF5), and CD27 (TNFRSF7) [80] (Figure 1).
with a poor prognosis and associated high serum sTNFR2 levels might possibly benefit from TNFR2 antagonistic antibody therapy [43]. However, robust experimental testing is warranted to provide further mechanistic insight and to validate this hypothesis.

**Checkpoint Inhibitors, Failed Chemotherapy, and TNFR2-Driven Resistance**

The surge of therapeutic antibodies against immune checkpoints has resulted in a new era in cancer care. Anti-PD-1/PDL-1 and anti-CTLA-4 antibody immunotherapies have increased the survival rate for patients with melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, Hodgkin’s lymphoma, and urothelial carcinoma [53–55]. In addition, hundreds of clinical trials are now in development to utilize these therapies alone or in combination with other therapies to treat difficult malignancies [56]. Nevertheless, these drugs present new challenges. Checkpoint blockade therapy (ICI) can be associated with primary and secondary resistance of unknown origin. That is, for each cancer type there are subpopulations of cancer patients who are not responsive or in whom the treatment fails after initial dramatic positive outcomes. In addition, ICI in humans has also led to systemic autoimmunity including lethal myocarditis, colitis, pan-hypopituitarism, type 1 diabetes, dermatitis, autoimmune hepatitis, autoimmune myocarditis, autoimmune hypophysitis, autoimmune bullous skin disorders, and others [57–69]. These adverse events are unsurprising in light of preclinical data showing that mice lacking checkpoint proteins manifest various types of systemic autoimmunity [69,70].

We propose that such autoimmune effects might occur because the subset of TregS expressing CTLA-4 or PD-1 play a critical role in immune regulation [71,72] and when targeted by anti-CTLA-4 or anti-PD-1 antibodies might lead to immune deregulation and severe autoimmune side effects. By contrast, TNFR2 antagonism is likely to be safer than ICIs because TNFR2 expression is restricted to a minor subpopulation (10–12%) of potent TregS that appears to be highly concentrated in the tumor microenvironment and several other immune and epithelial cells [33]. The more limited expression of TNFR2 might potentially help to explain the lack of serious autoimmune side effects observed in Tnfr2−/− mice [73] and suggests that TNFR2 merits further investigation as an attractive next-generation candidate cancer target.

In addition to reports of TNFR2 being dominant in the tumor microenvironment, large-scale human tumor profiling has begun to demonstrate the existence of TNFR2-expressing TregS at tumor sites. For instance, a recent study in which thousands of diverse human subjects with >22 different forms of human cancer were sampled demonstrated that as the immunosuppressive infiltrates increased, increased TNFR2 expression was observed on tumor-specific T cell infiltrates [38]. This observation was replicated on examination of the tumor microenvironment transcriptome in metastatic melanoma: the data revealed that TNFR2 and FOXP3 mRNAs were upregulated following failed checkpoint inhibitory therapy [39]. Because TNFR2 and FOXP3 have been implicated in promoting the survival of human tumor cells [74], their upregulated expression could potentially contribute to tumor escape mechanisms leading to drug resistance. These data suggest that TNFR2 expression on select tumors as well as on abundant immunosuppressive TregS could potentially set the stage for tumor immune escape during ICI and drug resistance. We speculate that this might be overcome by treatment with TNFR2 antagonistic antibodies, although this remains to be tested in a clinical setting. In breast cancer TNFR2 drives adriamycin resistance by repairing chemotherapy-induced DNA damage in cancer cells in culture [75]. In colon cancer resistance is also driven by direct TNFR2 oncogene expression and downstream activation of P13K–AKT signaling, thereby promoting select tumor growth in vitro [76]. In yet another example, TregS were found to express high levels of TNFR2 and ICOS in a mouse model of mesothelioma and the success of chemotherapy depended on the concurrent depletion of these suppressive TregS [77]. Further studies will involve extensive and robust preclinical testing of diverse tumor types examining the potential of
Box 2. Clinician’s Corner

- The healthy immune system displays a balance of T\textsubscript{reg} and T\textsubscript{eff}. In cancer the balance is disrupted, with too many suppressing T\textsubscript{reg} and too few or inactive cytotoxic T\textsubscript{eff}. In autoimmunity the opposite holds: there may be too few suppressing T\textsubscript{reg} and too many self-reactive T\textsubscript{eff} (Figure 2).
- The tumor microenvironment of most advanced human cancers, often referred to as ‘hot tumors’, is dominated by T\textsubscript{reg} that prevent tumor rejection. Furthermore, T\textsubscript{reg}'s role in the tumor microenvironment expresses TNFR2, a cell-surface marker on one of the most suppressive T\textsubscript{reg} subtypes.
- It has gradually been possible to design and characterize TNFR2 antagonistic antibodies with two desirable features. TNFR2 antagonistic antibodies can kill, rapidly and with high potency, tumor-residing TNFR2-expressing T\textsubscript{reg}. T\textsubscript{reg} elimination, in turn, unleashes rapid T\textsubscript{eff} expansion. The elimination of a subset of T\textsubscript{reg} and expansion of T\textsubscript{eff} may be a highly attractive combination therapy that merits further investigation.
- TNFR2 is more than a receptor on suppressor T\textsubscript{reg}. TNFR2 activates signaling by NF-\kappa B, a transcription factor that mediates cell proliferation and growth. It is therefore unsurprising that, in some cases, tumor cells that aberrantly express TNFR2 may rely on TNFR2 as an oncoprotein for cellular expansion. Thus, TNFR2 antagonistic antibodies might also directly kill TNFR2-expressing tumor cells, as confirmed in ovarian cancer but with further human tumor susceptibility to be determined.

these antibodies to modulate antitumor immunity, T\textsubscript{reg} suppression, and T\textsubscript{eff} proliferation as well as the mechanistic underpinnings that might regulate these effects.

Concluding Remarks

Antibody therapies, and particularly, checkpoint blockade via anti-PD-1 and anti-CTLA-4 antibodies, have shown remarkable success in cancer immunotherapy over the past 5 years, extending the lives of patients with certain malignancies. However, not all patients have responded to these therapies; patients can relapse and serious autoimmune side effects can ensue. We propose that TNFR2 antagonism might represent a powerful new strategy in cancer immunotherapy for at least some types of tumor. According to ovarian, lung, and cutaneous T cell lymphoma human data, TNFR2 antagonism can not only block tumor-infiltrating T\textsubscript{reg} expansion but also eliminate tumor cells. These dual benefits suggest that TNFR2 targeting might prove to be a promising tool for cancer therapy, particularly for a number of cancers where TNFR2 has been identified as an oncogene. For all novel molecular targets of cancer immunotherapy, the ultimate test will be to perform human clinical trials. Although many unanswered questions remain (see Outstanding Questions and Box 2), and extensive preclinical validation is warranted, we propose that TNFR2 antagonism in cancer therapy should emerge as a promising new line of oncolgical research.

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Outstanding Questions

TNFR2 polymorphisms may affect therapeutic response rates. It will be important to test whether TNFR2 antagonism can block all oncogenic versions of TNFR2 expressed on cancer cells. To date no variability has been seen in response to antagonistic treatment of TNFR2. T\textsubscript{reg}'s in human ascites from ovarian cancer patients, but other tumor types will need to be studied.

TNFR2 is also expressed on T\textsubscript{eff}. While tumor-infiltrating T\textsubscript{reg}'s are known to express much higher levels of TNFR2 than circulating T\textsubscript{eff}, future experiments will need to carefully test the effect of TNFR2 antagonism on the expression and activation of T\textsubscript{eff}.

Other members of the TNFSF such as OX40, 4-1BB, and DR3 are also highly expressed on T\textsubscript{reg} and have a costimulatory role similar to that of TNFR2. Their antagonistic targeting in cancer should also be considered, although these cell-surface proteins have broader lymphoid and parenchymal expression and recent profiling data suggest that their expression is less dominant in the tumor microenvironment or after ICI therapy failure.

TNFR2 overexpression in certain tumor cells is currently being identified as a possible escape mechanism following anti-PD-1/PDL-1 and anti-CTLA-4 ICIs therapies. Experiments need to be conducted to determine whether anti-TNFR2 therapy might be more beneficial if administered a priori, in combination with ICIs, or as a follow-up therapy following ICI failure, for optimal outcomes.
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