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TNF in the era of immune checkpoint inhibitors: friend or foe?

Allen Y. Chen[1,3,4], **Jedd D. Wolchok**[2,4], **Anne R. Bass**[1,4,†]

[1]Division of Rheumatology, Hospital for Special Surgery, New York, NY, USA.

[2]Human Oncology and Pathogenesis Program, Immuno-Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA.

[3]New York Presbyterian Hospital, Weill Cornell Medicine, New York, NY, USA.

[4]Department of Medicine, Weill Cornell Medicine, New York, NY, USA.

Abstract

Immune checkpoint inhibitors (ICIs) are effective in the treatment of patients with advanced cancer and have emerged as a pillar of standard cancer care. However, their use is complicated by adverse effects known as immune-related adverse events (irAEs), including ICI-induced inflammatory arthritis. ICI-induced inflammatory arthritis is distinguished from other irAEs by its persistence and requirement for long-term treatment. TNF inhibitors are commonly used to treat inflammatory diseases such as rheumatoid arthritis, spondyloarthopathies and inflammatory bowel disease, and have also been adopted as second-line agents to treat irAEs refractory to glucocorticoid treatment. Experiencing an irAE is associated with a better anti-tumour response after ICI treatment. However, whether TNF inhibition can be safely used to treat irAEs without promoting cancer progression, either by compromising ICI therapy efficacy or via another route, remains an open question. In this Review, we discuss clinical and preclinical studies that address the relationship between TNF, TNF inhibition and cancer. The bulk of the evidence suggests that at least short courses of TNF inhibitors is safe in the treatment of irAEs in patients with cancer undergoing ICI therapy. Data from preclinical studies hint that TNF inhibition might augment the anti-tumour effect of ICI therapy while simultaneously ameliorating irAEs.

ToC blurb

TNF inhibitors are used to treat various immune-related adverse events caused by immune checkpoint inhibitors (ICIs). However, whether TNF inhibition compromises the efficacy of ICI therapy is unknown. This Review discusses the relationship between TNF, TNF inhibition and cancer.

† bassa@hss.edu .

Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

A.Y. Chen declares no competing interests. J.D. Wolchok is a consultant for Adaptive Biotech, Amgen, Apricity, Arsenal, Ascentage Pharma, Astellas, AstraZeneca, Bayer, Boehriner Ingelheim, Bristol Myers Squibb, Eli Lilly, F Star, Imvaq, Kyowa Hakko Kirin, Merck, Neon Therapuetics, Psioxus, Recepta, Sellas, Serametrix, Surface Oncology, Syndax and Syntalogic, Takara Bio, Trieza and Truvax; receives research support from AstraZeneca, Bristol Myers Squibb and Sephora; and has equity in Adaptive Biotechnologies, Apricity, Arsenal, Beigene, Imvaq, Linneaus, Tizona Pharmaceuticals. A.R. Bass declares no competing interests.

Introduction

Immunotherapy is now a standard approach to cancer treatment alongside surgery, radiation, chemotherapy and targeted therapies. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that augment the pre-existing host anti-tumour response by blocking down-regulators of the immune system including cytotoxic T lymphocyte antigen 4 (CTLA4), programmed cell death 1 (PD1) and programmed cell death ligand 1 (PDL1). However, in augmenting host immune responses, ICIs cause autoimmune adverse effects, termed immune-related adverse events (irAEs), in >80% of treated patients, including high grade irAEs in ~60% of patients being treated with a combination of ICIs, ~30% of patients being treated with a CTLA4 inhibitor and ~20% of patients being treated with an inhibitor of the PD1 pathway[1–4]. Almost any organ of the body can be affected by irAEs, but different ICIs tend to target different organs. For example, rash and colitis are common with anti-CTLA4, whereas arthritis and pneumonitis are more characteristic of anti-PDL1 and anti-PD1 therapy[1].

Approximately 4% of patients with cancer undergoing ICI therapy develop inflammatory arthritis[5], the majority of whom present with either a rheumatoid arthritis (RA) or a polymyalgia rheumatica phenotype[5–7]. Rheumatoid factor and anti-cyclic citrullinated peptide antibodies can be present in such patients but are less common than in patients with RA[6,7]. Guidelines for the management of ICI-induced inflammatory arthritis are based on expert consensus and borrow heavily from treatments that were developed for RA[8]. Most patients are initiated treated with corticosteroids at doses determined by the severity of arthritis, and steroid-sparing agents including hydroxychloroquine, sulfasalazine and methotrexate. TNF inhibitors and occasionally IL-6R blockers are used in patients with steroid-refractory or persistently steroid-dependent arthritis[9–12].

Data from various studies show that patients undergoing ICI therapy who develop irAEs have improved progression-free survival and overall survival[13–15], suggesting that ICIs augment shared immune pathways that promote both irAEs and anti-tumour activity. This finding raises the logical question as to whether immunosuppressive agents used to treat irAEs also promote cancer progression, whether by interfering with the anti-tumour activity of ICIs or via another route. Although studies have documented the oncologic safety of using corticosteroids to control irAEs[16], treatment of irAEs with high-dose corticosteroids, although life-saving for patients with severe irAEs such as myocarditis or colitis[17,18], was noted to reduce overall survival of patients with hypophysitis[19]. Survival was also reduced in those patients who were receiving corticosteroid treatment at the time of initiation of ICI therapy[20]. This finding implies a need to identify targeted therapies that block pathways that contribute to irAE pathogenesis but that spare those pathways that contribute to cancer survival.

The question of whether a treatment for irAEs promotes cancer progression is particularly relevant to rheumatologists because ICI-induced inflammatory arthritis often persists and can require long-term treatment with DMARDs such as TNF inhibitors[10]. In this Review, we address this question for TNF inhibitors by drawing from literature on the link between TNF

and cancer, the link between TNF inhibitors and cancer both within and outside the context of ICIs, and the role of TNF in the tumour microenvironment.

The multifaceted effects of

When TNF was first isolated in 1975 by Carswell, Old and colleagues, it was identified as the factor responsible for endotoxin-induced haemorrhagic necrosis of experimental tumours[21]. The line of research leading to the isolation of TNF can be traced back to William Coley's use of bacterial extracts to treat patients with cancer starting in 1896[22]. Although the validity of the clinical case series reported by Coley was controversial, his work motivated subsequent pre-clinical studies in animal models. Further research in 1944 showed that lipopolysaccharide (LPS) endotoxin was the active agent in bacterial extracts that induced haemorrhagic tumour necrosis in a mouse model of benzopyrene-induced skin tumours[23]. In 1962, researchers found that serum from endotoxin-treated animals also induced tumour necrosis, implying that bacterial endotoxin acts indirectly, inducing an intermediary 'tumour necrosing factor' that acted on tumours[24]. It was this factor that was isolated by Carswell et al in 1975[21]. The gene encoding human TNF was cloned in 1984[25] and the gene encoding mouse TNF was cloned in 1985[26]. Ascertaining the sequence of TNF led to the discovery that this protein is the same protein molecule as cachectin[27], a factor found to mediate acute shock and chronic cachexia during infection. Development of anti-TNF antibodies led to the discovery that TNF has an important role in RA synovial inflammation[28]. The delineation of multiple physiologic roles for TNF led to further studies of TNF in the context of cancer, sepsis and inflammatory disease

In this Review, we discuss the role of TNF in cancer as is relevant to the safety of TNF inhibitors in the treatment of irAEs. We also discuss the role of TNF in inflammatory disease as is relevant to the efficacy of TNF inhibitors in the treatment of irAEs, with the caveat that irAEs are iatrogenic disease entities whose aetiology is not well-understood and might be different from that of spontaneous inflammatory diseases. Although irAEs are known to be caused by ICIs, it is not yet known which of cell types that are modulated by ICIs mediate these autoimmune toxicities, or why TNF inhibition is an effective treatment, although previous work on the mechanism of action of TNF inhibitors will be a valuable guide. The roles of TNF in cancer and inflammatory diseases are summarized in Box 1.

Role of TNF in cancer

Early optimism that TNF would be a useful anti-cancer therapy was tempered by the realization that it has a narrow therapeutic window. In clinical trials, systemically administered TNF caused acute shock but without the anti-tumour responses originally reported by Coley[29]. The physiologic serum concentration of TNF in humans is on the order of 10 pg/mL[30], whereas the doses of TNF used in these clinical trials corresponded to TNF serum concentrations on the order of 10 ng/mL[29]. It is now thought that haemorrhagic tumour necrosis induced by high-dose TNF is largely mediated by the pro-coagulant effects of TNF that lead to thrombosis within the tumour vasculature[31]. TNF has been shown to induce endothelial cell apoptosis in vitro[32]. If this process occurs in vivo it could be another mechanism by which high-dose TNF induces haemorrhagic tumour necrosis. The

current consensus is that soluble TNF alone, at levels tolerated by patients, is not directly cytotoxic to cancer cells[33]. However, non-soluble TNF or TNF in conjunction with a second effector molecule can be directly cytotoxic. TNF does have direct cytotoxic effects on cancer cells when used together with small molecules that oppose inhibitor of apoptosis proteins (IAPs)[34]. In addition, membrane-bound TNF (which serves as a ligand to TNF receptors on adjacent cells) has been shown, in vitro, to have direct cytotoxic effect on target cells, including the KYM-1D4 cancer cell line[35,36].

In parallel with studies of TNF as a potential anti-tumour therapy, evidence began to emerge in the late 1980s that TNF could in fact be a tumour promoting factor. Patient-derived juvenile chronic myelogenous leukemia cells were found to produce TNF and use it as an autocrine growth factor[37]. Another study, in a rabbit cornea model, showed that low-dose TNF induces angiogenesis, an unexpected finding given that high-dose TNF causes destruction of tumour vascular beds[38]. This finding prompted studies that found that TNF stimulated tumour growth and does so in part by mediating angiogenesis[39].

Work since the late 1990s has shown that TNF at physiologic levels (as opposed to the supraphysiologic levels of TNF used in anti-tumour therapy) has a major role in tumorigenesis. In the 1990s, methods to generate gene knockout mice provided powerful tools to elucidate the role of specific genes in mammalian biology. The development of TNF knockout mice led to the discovery that lack of TNF had a protective effect against skin tumours induced by the carcinogen DMBA[40]. Similarly, TNF receptor knockout mice were also protected from UVB-induced skin tumours[41]. Administration of TNF inhibitors to mice had a protective effect in urethane-induced pulmonary tumours and colonic tumours associated with chemically induced colitis[42,43].

Additional evidence for a pro-tumorigenic role for TNF came from studies of gastric cancer associated with *Helicobacter pylori* infection. Gastric mucosal tissue samples from patients with chronic gastritis, gastric intestinal metaplasia, gastric dysplasia or gastric adenocarcinoma showed higher expression levels of TNF than samples from healthy individuals. Moreover, in the same individuals, a higher expression of TNF was associated with positivity for *H. pylori*, suggesting that the association of gastric cancer with *H. pylori* infection might in part be mediated by the induction of host TNF production by *H. pylori*[44]. Indeed, *H. pylori* can produce Tip-α, a protein that induces host TNF production and functions as a pro-tumorigenic factor in a manner possibly mediated by TNF signalling[45].

Another line of evidence indicating that TNF is pro-tumorigenic comes from genetic studies of human populations. The -308G/A polymorphism in the promoter of *TNF* regulates *TNF* transcription; the less common A variant promotes transcription of the gene. As a result, individuals with the heterozygous G/A genotype have a two-fold increase in TNF production over individuals with the G/G genotype (as shown in a whole blood LPS stimulation assay[46]). Evidence from a number of case-control studies show that individuals with this promoter polymorphism have an increased risk of cancer risk. A study of 9,986 patients with gastrointestinal cancer (colorectal, oesophageal, gastric, hepatocellular or pancreatic cancer) and 15,511 healthy individuals showed that the A/A and G/A genotypes taken together confer 1.2-fold odds of gastrointestinal cancer compared with the G/G genotype

(95% CI 1.1–1.4)[47]. Another study of 5,757 patients with prostate cancer and 6,137 healthy individuals showed that the A/A and G/A genotypes taken together confer 1.5-fold odds of prostate cancer compared with the G/G genotype (95% CI 1.1–2.1)[48].

Role of TNF in inflammatory disease

The first randomized double-blind trial of a TNF inhibitor for the treatment of inflammatory disease was a study in RA in which TNF inhibition showed considerable efficacy[49]. This study demonstrated the therapeutic potential of TNF inhibitors for inflammatory disease and spurred further studies that expanded clinical indications to psoriatic arthritis, psoriasis, ankylosing spondylitis, juvenile RA. Crohn's disease and ulcerative colitis[50].

The clinical promise of TNF inhibitors also motivated studies into its mechanism of action and the role of TNF in inflammatory disease. TNF has a gatekeeping role in local tissue inflammation through its effects on vascular endothelial cells; it upregulates endothelial cell expression of surface adhesion molecules that recruit circulating leukocytes into the local tissue[51]. TNF also induces endothelial cell expression of cyclooxygenase 2 and subsequent prostaglandin release, resulting in vasodilation[51].

TNF both promotes and restrains inflammatory processes through opposing functional consequences of signalling through its two surface receptors: TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2). TNFR1 is expressed on all cells, whereas TNFR2 is expressed on a restricted subset of cell types including immune cells, endothelial cells and neurons. In general, TNF activates innate immune responses via TNFR1 signalling, while suppressing adaptive immune responses via TNFR2 signalling[52]. TNFR1 signalling in mesenchymal cells activate an innate immune response that promotes disease in RA, spondyloarthropathies (SpA) and inflammatory bowel disease (IBD)[53]. By contrast, TNFR2 signalling seems sufficient to ameliorate T cell-driven experimental autoimmune encephalomyelitis[53], although the T cell subsets that mediate this effect is unknown. The suppressive effect of TNFR2 signalling on the adaptive immune response is thought to explain the unexpected aggravation of disease by TNF inhibition in a trial in patients with multiple sclerosis, as well as the sporadic occurrence of demyelinating disease in patients receiving a TNF inhibitor for other diseases[52].

The duration, or chronicity, of TNF signalling helps to determine its effect on inflammatory pathology. Administration of TNF three times a week in NZB/W F1 lupus-prone mice delayed the onset of renal disease and led to improved survival at 3 months[54]. Similarly, TNF administered recurrently over 3 months protected non-obese diabetic mice against the development of diabetes[55]. In transgenic mice with T cells expressing a T cell receptor (TCR) specific for the influenza hemagglutinin antigen, repeated administration of TNF over 3 weeks yielded $CD4^+$ T cells that had attenuated responses to TCR stimulation. Such T cells had a reduced capacity to proliferate and produce cytokines after TCR stimulation with the specific antigen[56]. Data from in vitro assays also showed that $CD4^+$ T cells persistently exposed to TNF have attenuated TCR signalling. Thus, chronic TNF signalling might ameliorate autoimmune inflammation in part by reducing $CD4^+$ T cell responsiveness to antigen stimulation.

How TNF modulates cells in inflammatory disease tissue has been most closely studied for RA and IBD. Synovial samples from patients with RA show robust immunohistochemistry staining for TNF[57] and synovial fibroblasts and macrophages from patients with RA express TNF receptors[58]. TNF signals through TNFR1 on synovial fibroblasts to induce the production of IL-6, IL-8 and prostaglandin E2[59], all of which have pro-inflammatory properties. TNF has also been shown to signal through TNFR1 on $CD4^+$ T cells to inhibit T_H1 and T_H17 cell differentiation and expansion in a mouse model of collagen-induced arthritis. In that model, TNF inhibitor treatment increased the numbers of T_H1 and T_H17 cells, which are considered pathogenic, but treatment also inhibited the accumulation of these cells in the joint[60]. This finding concurs with the observation in patients with RA that TNF inhibition can increase numbers of pathogenic T cells while ameliorating arthritis[60]. In studies of IBD, TNF inhibition induced macrophage differentiation to a regulatory phenotype that ameliorates intestinal inflammation[61]. TNF signalling through TNFR2 in various T cell subsets have different effects on experimental colitis. For example, TNFR2 signalling in regulatory T (T_{reg}) cells and $CD8^+$ T cells ameliorates colitis[62,63], whereas in $CD4^+$ effector T cells this signalling exacerbates colitis[64].

ICI-induced inflammatory arthritis and ICI-induced colitis share molecular features with RA and IBD, respectively. Synovial biopsy samples from patients with ICI-induced inflammatory arthritis showed robust staining for TNF[65], similar to synovial samples from patients with RA[57]. Similarly, colonic biopsy samples from patients with ICI-induced colitis showed evidence of increased TNF signalling in myeloid cells as compared with cells from healthy individuals[66], which is in line with the finding that TNF signalling in macrophages helps to mediate IBD[61]. These shared molecular features provide support for borrowing TNF inhibition from the RA and IBD armamentarium to treat ICI-induced inflammatory arthritis and ICI-induced colitis.

TNF inhibitor use and cancer risk

In this section, we review data from clinical studies investigating the link between TNF inhibitor use and the risk of cancer and use this information to make inferences regarding the safety of TNF inhibitors during irAE treatment. Currently, limited data are available regarding the effect of TNF inhibitor treatment on the efficacy of ICI therapy (that is, the effect on cancer survival), but we can also draw from a large body of data on the link between TNF inhibition and cancer risk accumulated over many patient-years of experience using a TNF inhibitor for a wide range of indications.

Effects on ICI efficacy

In a study of 27 ICI-treated patients with melanoma who developed colitis and underwent TNF inhibitor treatment, the patients had a median progression free survival of 3 months, which is comparable to that reported in previous studies of ICI-treated patients with melanoma who did not undergo TNF inhibitor treatment[67]. Similarly, a retrospective study of patients with ICI-induced colitis found no difference in overall survival in those patients treated with corticosteroids alone (n=38) compared with those patients treated with corticosteroids plus a TNF inhibitor (n=23) (p=0.263)[68]. By contrast, in a study published

in 2020, Verheijden and colleagues[69] examined patients with grade ≥ 3 irAEs of various types (65 of whom received a TNF inhibitor and 157 of whom received corticosteroids only), the median overall survival was lower in the TNF inhibitor-treated group than in the corticosteroid-only group (17 versus 27 months; adjusted HR 1.61; 95% CI 1.03–2.51). However, the use of overall survival as the endpoint might have introduced confounders as some high-grade irAEs (such as colitis) have a higher mortality than others (such as high-grade endocrine toxicity, which can be treated with hormone replacement). In the Verheijden study, 61 of the 65 patients in the TNF inhibitor group had ICI-induce colitis, whereas the breakdown of irAE subtypes was not reported for the corticosteroid-only group. This study also failed to account for the time to irAE onset which, as a rule, is shorter for colitis than for endocrinopathies[70,71] and is shorter for more severe than for less severe irAEs[70–72]. This difference could have biased the results due to different follow-up times and treatment exposures between patients who did versus patients who did not require a TNF inhibitor[73]. For example, patients who did not require a TNF inhibitor might also be ones who developed later-onset irAEs; to be included in this group, patients had to have first survived long enough to acquire a later-onset irAE.

Empirically, it is notable that despite extensive efforts to identify tumour biomarkers that predict clinical response to ICI therapy, TNF has not emerged as one such biomarker[74–76]. This finding suggests that TNF signalling in the tumour microenvironment has a neutral net effect on pathways that promote or inhibit the anti-tumour activity of ICI therapy, implying that TNF inhibition does not diminish this activity.

Effects on risk of cancer

Post-marketing surveillance of TNF inhibitor treatment in patients with RA, SpA, IBD and psoriasis provides data on the effects of decreasing levels of TNF on cancer risk. However, these studies might be biased by the fact that patients with autoimmune disease have a higher baseline risk of cancer than the general population, including a higher risk of lymphoma and lung cancer for patients with RA and a higher risk of non-melanoma skin cancer for patients with psoriasis[77–79]. This elevated risk is thought to be caused by the presence of chronic inflammation, but shared genetic and environmental risk factors might also have a role[77]. Thus, disease severity (which is associated with the degree of inflammation) could confound the analysis of TNF inhibitor-associated cancer risk, at least in observational studies, if TNF inhibitor treatment is given preferentially to patients with more active disease. Risk assessment is also confounded by concomitant medications taken by patients on a TNF inhibitor, as some conventional DMARDS are also associated with risk of cancer. Examples include an elevated risk of hepatosplenic T cell lymphoma in TNF inhibitor-treated patients with IBD taking concomitant thiopurines (for example, azathioprine or 6-mercaptopurine)[80] and an increased incidence of non-melanoma skin cancer in patients taking methotrexate[81]. Other factors that bias some studies of cancer risk in TNF inhibitor-treated patients include the use of self-reported cancer diagnoses, a lack of an active comparator group (for example, patients being treated with other DMARDs), a lack of adjustment for other treatments and comorbidities and inconsistent definitions of the time of TNF inhibitor exposure[82].

Solid tumour malignancies—The above methodological limitations could, if anything, introduce spurious associations between TNF inhibition and cancer where there is none. It is therefore reassuring that most observational studies of patients with RA, SpA, IBD and psoriasis have failed to show any increased risk of cancer in patients being treated with a TNF inhibitor[83–86]. For example, a systematic literature review and meta-analysis of 9 large RA registries (87,018 patient years in the TNF inhibitor treatment group and 50,734 patient years in the untreated control group) found no increased risk of solid tumours in the TNF inhibitor-treated patients (risk ratio 0.84; 95% CI 0.60–1.18)[86]. An early meta-analysis of clinical trials did show an elevated risk of cancer risk TNF inhibitor-treated patients (odds ratio 3.3; 95% CI, 1.2–9.1)[87], but was criticized for not using individual level data and for using an average follow-up period, even though TNF inhibitor-treated patients had a longer follow-up period[82,88]. Subsequent meta-analyses of clinical trials have failed to show an increased cancer risk in patients being treated with a TNF inhibitor[89–92], and studies using large administrative datasets have been similarly negative[93,94]. One exception is the Wegener's Granulomatosus Etanercept Trial (WGET), which compared cyclophosphamide alone to cyclophosphamide plus a TNF inhibitor (etanercept) for the treatment of granulomatosis with polyangiitis, and found a higher incidence of solid tumours in patients who received combination therapy[95]. This finding suggests that there might be synergistic toxicity when TNF inhibitors are used together with cytotoxic agents, similar to that observed when TNF inhibitors are combined with thiopurines[80]. Such synergistic effects might have relevance for patients with cancer receiving ICI therapy in combination with chemotherapy who require irAE management.

Lymphoma—A small number of studies have suggested patients being treated with a TNF inhibitor have an increased risk of developing a lymphoma. One published series described 48 cases of malignancy reported to the FDA in children on a TNF inhibitor, half of which were lymphomas[96]. Even though this case series did not control for confounding factors such as the risk of cancer associated with the underlying condition or concomitant medications, the FDA issued a black box warning of cancer risk in children being treated with a TNF inhibitor and later warned of an excess risk of developing especially rare hepatosplenic T cell lymphomas for children with IBD being treated with a combination of a TNF inhibitor and thiopurine[97]. An analysis of TNF inhibitor-treated patients with IBD in the French National Health insurance database also showed a higher rate of lymphoma (HR 2.41, 95% CI 1.60–3.64)[98] compared with patients IBD who had no TNF inhibitor exposure; furthermore, a study of patients with juvenile idiopathic arthritis, IBD or psoriasis that used a Medicaid database hinted at a similar, albeit non-significant, increase in risk of lymphoma (adjusted HR 2.64, 95% CI 0.93–7.51)[93]. However, administrative datasets lack important information about confounders such as disease phenotype and severity, and many other prospective rheumatic disease registries have failed to show any increased risk of lymphoma in TNF inhibitor-treated patients[83,99–102].

Skin cancer—One study of a Swedish RA registry found an increased risk of melanoma in TNF inhibitor-treated patients with RA[103]. By contrast, no increased risk was found in a larger study that combined 11 European RA registries[104], in a Scandinavian SpA registry study[105] or in a large meta-analysis of RA clinical trials[106]. However, patients with psoriasis

or RA undergoing TNF inhibitor treatment might have an increased risk of non-melanoma skin cancer[107,108]. With the possible exception of non-melanoma skin cancer[109], studies have also failed to show an increased risk of cancer recurrence in patients with cancer being treated with a TNF inhibitor[110,111].

In summary, although the assessment of TNF inhibitor-associated cancer risk is confounded by the excess background risk in patients with rheumatic diseases, available evidence suggests that these inhibitors do not increase the risk of solid tumours. The risk might be increased for lymphoma, particularly in patients with IBD being treated with a TNF inhibitor plus thiopurines, or for non-melanoma skin cancer in patients with psoriasis being treated with a TNF inhibitor. These data provide reassurance about the safety of TNF inhibition for the treatment of irAEs in the setting of ICI use, except perhaps in patients being treated for lymphoma.

irAE therapy: is TNF inhibition safe?

In this section, we review preclinical studies of the effects of TNF and TNF inhibition in the tumour microenvironment, and synthesize this information to make supporting inferences regarding the safety of TNF inhibitors in the treatment of irAEs. We summarize the immune and non-immune cell types present in the tumour microenvironment (Table 1), and discuss studies that address the effect of TNF, TNF inhibitors or ICIs on relevant cell types. We synthesize information from these studies into a model of interactions between cell types that also incorporates TNF inhibition and ICI therapy (Figure 1). This model enables us to systematically analyze the different paths by which TNF inhibitors and ICIs regulate cancer cell proliferation, and to make a prediction regarding the net effect of TNF inhibitors on tumour growth. We also discuss two preclinical studies that test this prediction.

The general pattern that emerges from this model is that TNF inhibition promotes the activity of anti-tumour immune cell types (such as $CD8^+$ cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells) while restraining the activity of immunosuppressive cell types (such as T_{reg} cells, myeloid-derived suppressor cells (MDSCs) and mesenchymal stromal cells (MSCs), with an expected net anti-tumour effect that augments the benefits of ICIs. The effect of TNF inhibition on dendritic cells and naïve $CD8^+$ T cells is an exception that might be pertinent in the setting of prolonged TNF inhibitor use. A further caveat is that although two preclinical studies have tested the net effect of TNF inhibition on tumour growth, studies in patients will be needed to validate this model in the clinical setting.

ICIs, TNF inhibitors and tumorigenesis

ICIs that target CTLA4, PD1, or PDL1 inhibit signalling through co-inhibitory[112] pathways in tumour-infiltrating T cells[113]. Both inhibition of CTLA4 signalling and inhibition of PD1 signalling promote proliferation of exhausted PD1-positive CTLs, which subsequently become ‘reinvigorated’ to take on an effector-like phenotype associated with anti-tumour activity[114]. These CTLs continue to express PD1 but proliferate and express the activation surface markers HLA-DR and CD38[115]. ICIs have differing effects on different subtypes of T helper (T_H) cells[114,116], but overall promote the function of tumour-infiltrating T cells with a net anti-tumour effect. PD1 signalling in myeloid precursor cells promotes

the development of MDSCs, which are pro-tumorigenic; thus, ICI might also exert their anti-tumour effect in part by inhibiting MDSC development[117]. The interactions between ICIs and tumour microenvironment immune cells including T_{reg} cells, tumour-associated macrophages and MDSCs, have been comprehensively reviewed elsewhere[74].

Effect of TNF on CTLs and NKs—TNF signals through TNFR2 on CTLs to promote activation-induced cell death[118,119], thereby depleting the pool of anti-tumorigenic CTLs. TNF also signals through TNFR1 on CTLs to inhibit CTL infiltration into mouse B16K1 melanoma tumours, whereas TNF inhibition promotes CTL infiltration into tumours[120]. Moreover, TNF signalling in NK cells induces the expression of the co-inhibitory receptor TIM-3[121] and decreases the expression of the activating cytotoxicity receptor NKp46[122], thereby impairing NK cell anti-tumour activity. As TNF signalling restrains the function of these two anti-tumour immune cell types, it can be inferred that TNF inhibition could promote their function.

Effect of TNF on T cells—TNF signals through TNFR2 on T_{reg} cells to promote T_{reg} cell proliferation[123] and thereby increases their suppressive function as a population[123]. TNF might also inhibit the suppressive function of T_{reg} cells in vitro[124,125], but this effect seems to be outweighed in vivo by the effect of TNF on T_{reg} cell population expansion[123,126]. TNFR2-positive T_{reg} cells (defined as $CD4^+$ $CD25^+$ $TNFR2^+$ cells) suppress the proliferation of non-T_{reg} cells (defined as $CD4^+$ $CD25^-$ cells)[127] to a greater extent than TNFR2-negative T_{reg} cells, and are found at high density in Lewis lung carcinoma tumours[127], as well as in human ovarian cancer ascites[128]. In a B16F10 mouse model of melanoma lung metastasis, administering TNF promotes pulmonary T_{reg} cell proliferation and increases metastatic tumour growth[129]. A TNFR2 blocking antibody inhibits proliferation of T_{reg} cells isolated from human peripheral blood, and kills T_{reg} cells isolated from ascites of patients with ovarian cancer[130], as well as from the blood of patients with cutaneous T cell lymphoma[131]. It can be inferred that TNF inhibition, by exerting the opposite effect as TNF, would restrain the function of immunosuppressive T_{reg} cells.

TNF signals through TNFR2 on T_H cells to promote T_H cell proliferation and T_H1 pro-inflammatory cytokine production[64], and to promote their resistance to suppression by T_{reg} cell[132]. The effect of TNF inhibitors on T_H1 cells might then be an exception to the general pattern seen for other immune cell types, in that TNF inhibition would restrain the function of these anti-tumour immune cells. Nevertheless, as TNF inhibitors restrains T_{reg} cells, which suppress T_H1 cells, TNF inhibitors might indirectly promote T_H1 cell function. TNF also signals through TNFR1 on T_H cells to increase the relative number of T_H17 cells and T_H17 cytokine production[133]. Evidence suggests that T_H17 cells can have both pro-tumour and anti-tumour effects: for example, T_H17 cells recruit pro-tumour myeloid cells[133], recruit anti-tumour T_H1 cells[134] and promote activation of anti-tumour CTLs[135].

Effect of TNF on MDSCs and MSCs—TNF signals through TNFR2 on MDSCs to promote MDSC survival[136] and their suppressive activity[137]. TNF inhibition impairs the growth of mouse FB61 fibrosarcoma tumours and simultaneously impairs peripheral accumulation of MDSCs, suggesting a correlation between an increased number of MDSCs and tumour growth in this model[136]. TNF also induces lymphoma-associated MSCs

to express high levels of chemokine ligands for the chemokine receptor CCR2. These chemokines recruit CCR2-expressing tumour-associated macrophages into the tumour with overall pro-tumorigenic effect[138]. It can be inferred that TNF inhibition would then restrain the function of immunosuppressive MDSCs and MSCs.

Effect of TNF on cancer cells—Finally, TNF signalling in cancer cells helps them evade immune surveillance while promoting their survival and proliferation[130], with overall pro-tumorigenic effect. In several cancer cell lines, TNF signalling increases the surface expression of PDL1, an immune checkpoint ligand that helps cancer cells evade T cell immune surveillance[139]. In human melanoma lesions, PDL1 gene expression positively correlates with TNF gene expression[140]. TNF signalling also promotes de-differentiation of melanoma cells accompanied by loss of immunogenicity, which helps cancer cells to evade T cell immune surveillance[141]. Hence, TNF inhibition might exert a direct inhibitory effect on cancer cells

Overall, the model of interactions depicted in Figure 1 predicts that TNF inhibitors augments ICI anti-tumour activity by promoting CTL activity, and that TNF inhibitors promote additional anti-tumour activity through ICI-independent pathways.

Prolonged use of TNF inhibitors

In contrast to the short-term effects of TNF inhibition on tumorigenesis, prolonged use of a TNF inhibitor might deplete the anti-tumour CTL pool via inhibition of naïve $CD8^+$ T cell differentiation into CTLs, leading to decreased numbers of tumour antigen-specific CTLs relative to that of tumour antigen-specific naïve $CD8^+$ T cells. This depletion might occur because TNF signals through TNFR2 on naïve $CD8^+$ T cells to provide a co-stimulatory signal that promotes TCR-mediated proliferation, activation and differentiation into CTLs[142,143]. Moreover, TNF signalling supports the dendritic cells that promote naïve $CD8^+$ T cell differentiation. TNF signalling through TNFR1 in immature dendritic cells induces their maturation, whereas TNF signalling through both TNFR1 and TNFR2 in dendritic cells promote their survival[144].

Although a CTL depletion effect has not been investigated in preclinical models or in patients, this effect is of particular concern with regard to chronic use of TNF inhibitors and has relevance to the management of ICI-induced inflammatory arthritis, which is often persistent. It would be worthwhile to study whether CTL depletion occurs in patients receiving ICI therapy plus prolonged TNF inhibitor therapy compared with patients receiving ICI therapy alone or ICI therapy plus prolonged therapy with corticosteroids. If CTL depletion is observed, another important question would be whether this effect correlates with clinical outcomes such as progression-free survival.

Data from preclinical models

The predictions outlined in our model (Figure 1) have been tested in a mouse model of engrafted B16K1 melanoma in which the tumours are being treated with an anti-PD1 therapy[140]. In this model, treatment with a TNF inhibitor augmented the anti-tumour activity of ICI therapy, as assessed by the proportion of tumours that completely regress and by

overall survival. Moreover, this improved ICI efficacy was associated with an increased proportion of CTLs out of the total number of cells in the tumours, and a decreased amount of cell death of these CTLs, suggesting that the improved ICI efficacy was attributable to a TNF inhibitor-mediated increase in CTL activity. The researchers also found that TNF inhibitor treatment alone did not have anti-tumour activity in this tumour model, contradicting our prediction that TNF inhibitors have ICI-independent anti-tumour activity. However, additional factors might be present that contribute to the tumour response to TNF inhibition that are not accounted for in our model.

In another preclinical study, researchers created a mouse model of ICI-induced colitis, in which the mice were given a combination of anti-CTLA4 and anti-PD1 therapy to treat engrafted MC38 tumours[145] and were concomitantly given dextran sulfate sodium to induce colitis, which is exacerbated by the combination ICI treatment. In this model, TNF inhibitor treatment both ameliorated colitis and augmented ICI anti-tumour activity. The improved ICI efficacy was associated with an increase in tumour antigen-specific CTLs in the tumours, and decreased cell death of these CTLs. A limitation of both of the studies described in this section is that the duration of TNF inhibitor treatment was at most 10 days, so the studies did not address the question of what the effect of chronic TNF inhibitor treatment is on CTL activity or ICI efficacy. Preclinical and clinical studies that look at an extended duration of TNF inhibitor treatment would be valuable.

Conclusion

TNF is a pleiotropic cytokine with pro-inflammatory and immunosuppressive effects in inflammatory disease and cancer. TNF inhibitors are effective treatment for a number of inflammatory diseases including RA, IBD and ICI-induced inflammatory arthritis. Multiple clinical studies of TNF inhibitors in patients with inflammatory disease support the hypothesis that TNF inhibitor poses a relatively low risk of cancer, but limited clinical data is available regarding its risk profile in patients with cancer undergoing ICI therapy. TNF can promote or inhibit the activities of the immune cells and cancer cells within tumours. The net effect of TNF inhibition on tumorigenesis might be positive or negative depending on qualitative (that is, the presence of specific cell types) and quantitative (that is, the local concentration of TNF) factors. Moreover, acute versus chronic TNF inhibition might have opposing effects on tumour growth. Preclinical models can be extrapolated to the clinic only to the extent that the qualitative and quantitative details of the experimental model match those found in patients. Despite these caveats, the bulk of current data supports two conclusions: TNF inhibitor treatment of rheumatic diseases does not seem to increase the risk of cancer, except for non-melanoma skin cancer and possibly lymphoma, and preclinical data suggest that short-term TNF inhibitor treatment of irAEs should not diminish the anti-cancer efficacy of ICI therapy. Thus, short courses of TNF inhibitors might be safe to use in treatment of ICI-associated irAEs. Further studies in preclinical models are required to directly assess the safety of long-term TNF inhibitor use in the context of ICI cancer treatment. Clinical studies that directly assess the effect of TNF inhibitor treatment on ICI efficacy are required to draw conclusions regarding the short-term and long-term safety of TNF inhibitor treatment for irAEs. Preclinical studies provide evidence that TNF inhibitors, despite their efficacy in ameliorating irAEs, do not also restrain anti-cancer immune activity.

The data from these studies suggests that different arms of the immune response are important for anti-self versus anti-cancer activities, with TNF inhibition restraining some arms of the immune response while promoting or having a neutral effect on others. The cellular and molecular details of how the pleiotropic effects of TNF signalling interact with different arms of the immune response remain to be fully delineated. A more complete map of these interactions might reveal novel drug targets for the treatment of inflammatory disease and cancer.

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Key points

Roles of TNF in cancer and inflammatory disease.

Pro-cancer effects

- Induces tumour angiogenesis[39]
- Promotes cancer cell survival and proliferation[130]
- Helps cancer cells evade immune surveillance[139,141]

Anti-cancer effects

- Induces haemorrhagic tumour necrosis via pro-coagulant effect[31], by inducing endothelial cell death[32]
- Membrane TNF has direct cytotoxic activity against cancer cells[36]

Pro-inflammatory effects

- Upregulates endothelial cell expression of leukocyte adhesion molecules[51]
- Induces synovial fibroblast production of IL-6, IL-8, and prostaglandin[59]
- Induces macrophage pro-inflammatory phenotype[61]

Anti-inflammatory effects

- Ameliorates T cell driven experimental autoimmune encephalomyelitis[53]
- Promotes regulatory T cell suppressive function[62]
- Chronic TNF attenuates T cell response to antigen stimulation[56]

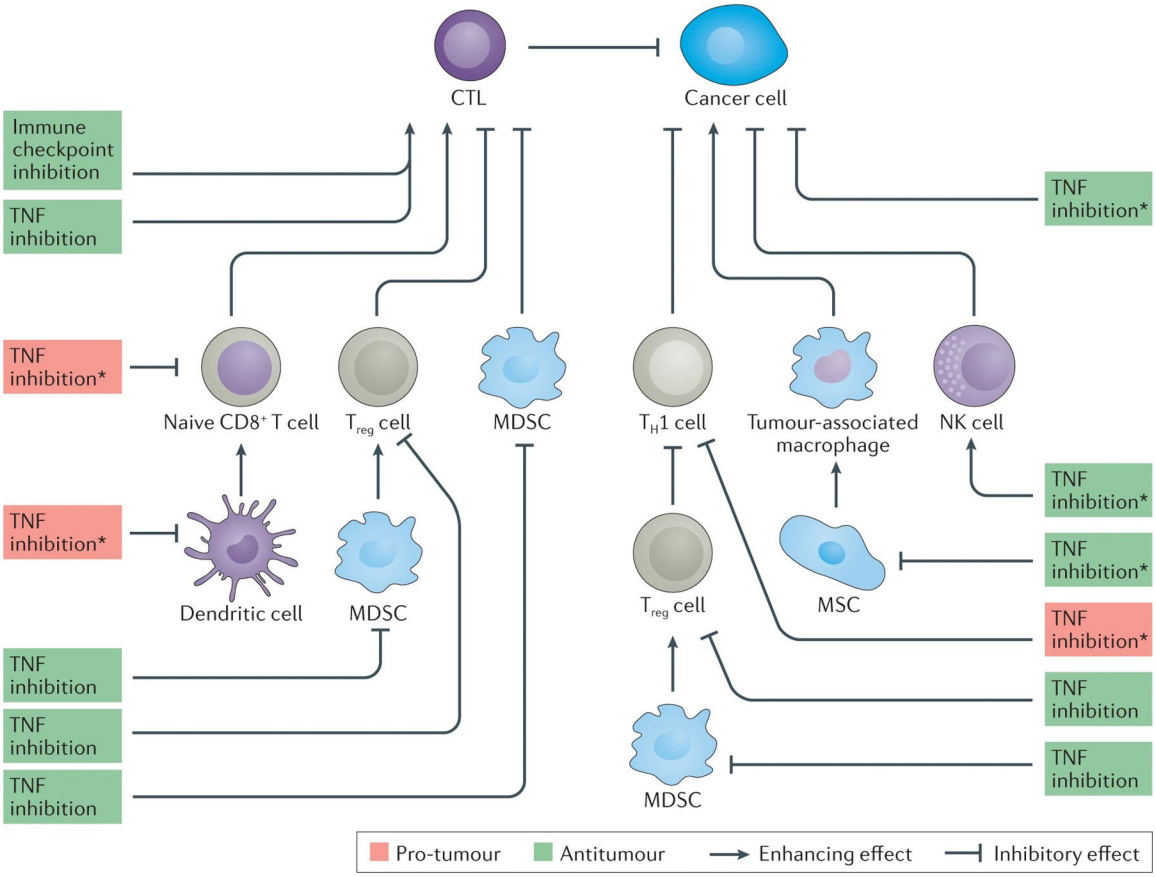

Figure 1: Pro-tumour and anti-tumour effects of TNF inhibition and ICI therapy.

A model of immune interactions in the tumour microenvironment. CTLs have direct cytotoxic effects on cancer cells, and moreover serve as a hub to integrate the indirect effects of other immune cell types, TNF inhibition and ICI therapy. Naïve $CD8^+$ T cell differentiation replenishes the CTL pool. NK cells, T_H1 cells, and tumour-associated macrophages have direct effects on cancer cell proliferation, and integrate the indirect effects of other immune cell types and TNF inhibition. TNF inhibition has a direct inhibitory effect on cancer cell proliferation. This model maps the different paths by which TNF inhibition exerts pro-tumour or anti-tumour effects. Each path starts with TNF inhibition exerting a direct effect on a cell type; *denotes that the effect of TNF inhibition is inferred from experimental data on TNF

Table 1:

Activities of various cell types in tumours and their effects on tumours.

Effect on tumour	Cell type	Mechanism	Refs
Anti-tumour effects	CTLs	Kill cancer cells that display THE tumour-associated antigen and produce IFNγ, which has anti-tumour effects	146, 147
	NK cells	Kill cancer cells that over-express ligands recognized by NK cell receptors	148
	T_H cells	Maintain adequate numbers of CTLs and promote CTL tumour infiltration	149
	T_H1 cells	Produce IFNγ, which has anti-tumour effects, and promote the development of tumour antigen-specific CTLs	147,150
	Dendritic cells	Present tumour antigens to naïve antigen-specific T cells to induce their effector differentiation, including into T_H1 cells and CTLs	150
Mixed effects	T_H2 cells	Can be pro-tumorigenic or anti-tumorigenic depending on context	151
	T_H17 cells	Can be pro-tumorigenic or anti-tumorigenic depending on context	133–135,151
	Endothelial cells	Regulate immune cell infiltration into tumours via adhesion molecules	152
	MSCs	Regulate immune cell infiltration into tumours via chemokines	138
Pro-tumour effects	T_H cells (non-canonical)	Follicular helper-like $CD4PD1^{hi}$ T cells are pro-tumorigenic	116
	T_{reg} cells	Inhibit T_H cell proliferation, differentiation of naïve $CD4^+$ T cells into T_H1 and T_H2 cells, and CTL cytotoxicity	153, 153, 154
	MDSCs	Decrease the numbers of CTLs, T_H cells and NK cells, increase the numbers of T_{reg} cells and inhibit the activity of CTLs by inactivating TCRs	146,155
	Tumour-associated macrophages	Produce CCL22, which recruits T_{reg} cells, and IL-10 and TGFβ, which are immunosuppressive cytokines	156

CTLs: $CD8^+$ cytotoxic T lymphocytes. NK cells: natural killer cells. T_H cells: $CD4^+$ T helper cells. T_{reg} cells: $CD4^+$ regulatory T cells. MDSCs: myeloid-derived suppressor cells. MSCs: mesenchymal stromal cells.