ELSEVIER

Tumor necrosis factor-α in the pathogenesis and treatment of cancer

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The critical pathogenic role of tumor necrosis factor (TNF)α in inflammatory disorders such as rheumatoid arthritis and inflammatory bowel disease is well established. The role played by TNFα in both the treatment and pathogenesis of cancer remains less understood. Recent advances help to create a framework for understanding seemingly paradoxical effects of TNFα as both an anti-tumour agent and a mediator of tumour growth. High pharmacological doses of TNFα combined with chemotherapy can regress otherwise intractable tumours, and efforts continue to optimize delivery to avoid severe toxicities. Mounting evidence demonstrates that pathophysiological concentrations of endogenous TNFα act to promote tumour genesis and growth. The cellular and molecular pathways mediating these phenomena are starting to be clarified. Current data support the continued development of both TNFα and anti-TNFα therapy for clinical treatment of cancers in distinct settings.

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Current Opinion in Pharmacology 2004, **4**:314–320

This review comes from a themed issue on
Cancer
Edited by Aristides Eliopoulos and Lawrence Young

Available online 17th June 2004

1471-4892/$ – see front matter

DOI 10.1016/j.coph.2004.04.004

Abbreviations

CLL	chronic lymphocytic leukemia
GVHD	graft versus host disease
IL	interleukin
MDS	myelodysplastic syndrome
MMP	matrix metalloproteinase
NF-κB	nuclear factor-κB
TNF	tumor necrosis factor
TNFR	TNF receptor

Introduction

Tumor necrosis factor (TNF)α is a potent pleiotropic proinflammatory cytokine produced by macrophages, neutrophils, fibroblasts, keratinocytes, NK cells, T and B cells, and tumour cells. TNFα mediates host responses in acute and chronic inflammatory conditions, and is a mediator of protection from infection and malignancy. The biology of the TNF/TNF receptor (TNFR) system has previously been reviewed [1•,2••,3]. TNFα mediates tumour regression, and recombinant TNFα is approved in Europe to be administered locoregionally at supra-physiological levels as a therapy for sarcoma [4]. The concept that the major effects of endogenous TNFα in cancer are opposite to the effects observed with high dose TNFα therapy has gained momentum recently [5••]. Instead of causing tumour regression, cancer-derived TNFα can mediate tumour progression by causing the proliferation, invasion and metastasis of tumour cells (see also Update). The paradox that this cytokine is both a 'tumour necrosis factor' and a 'tumour-promoting factor' is lucidly explored by Balkwill [6••]. This paradox can be explained partly by the differences in levels of TNFα in distinct settings. When TNFα is administered therapeutically in extremely high doses, it acts as a vasculotoxic tumour-regressing agent. However, when TNFα is produced by tumours and tumour-associated macrophages or stromal cells at physiological levels, it promotes tumour growth and additional macrophage recruitment, stimulating the elaboration of angiogenic and growth factors from infiltrating cells.

TNFα-mediated cellular signaling

The signaling pathways that determine whether a cell will respond to endogenous TNF by proliferating or by undergoing apoptosis continue to be elucidated. Micheau and Tschopp [7••] reported a new model with evidence for the production of two distinct intracellular complexes after TNFα binds to TNFR1 in HT1080 fibrosarcoma cells. The first complex promotes cell survival by induction of nuclear factor-κB (NF-κB). The second complex, formed substantially later after receptor ligation, is cytoplasmic and spatially removed from the initial receptor complex. The second complex is pro-apoptotic but can be inhibited by anti-apoptotic gene products previously induced via the NF-κB pathway. This system represents a switch that can determine the fate of a given cell receiving a TNFα signal. That fate clearly will vary depending upon the presence or absence of key signaling factors resulting from cell-specific gene expression or the mutational status of the cell.

TNFα as a therapy for cancer

Systemically administered TNF-α was evaluated in the clinic in the 1980s as a therapy for solid tumours, and was found to have severe toxicities, most notably hypotension and organ failure [8]. Studies revealed that the maximally tolerated dose of TNFα was significantly lower than that required to cause anti-tumour effects. The delivery of

is now accomplished by isolated limb perfusion in which the circulation of the limb is connected surgically to a bypass circuit into which drugs are administered [9•]. Isolated limb perfusion with TNFα in combination with chemotherapy is approved in Europe for the treatment of locally advanced unresectable soft-tissue sarcomas (for a summary of the clinical studies of isolated limb perfusion with TNFα, see [9•]). Positive clinical data have been reported with this TNFα therapy for in-transit melanoma and drug-resistant bony sarcomas [9•]. Although effective, this procedure is highly specialized and not widely used. The mechanism of action is believed to involve direct toxic effects on the tumour, without affecting normal vasculature. TNFα causes vessel regression, as well as hemorrhagic necrosis, because it induces endothelial cell apoptosis, resulting in a procoagulant endothelium. TNFα enhances vascular permeability, facilitating the uptake and accumulation of chemotherapeutic drugs such as melphalan and doxorubicin [9•], as well as antibodies [10]. TNFα alone is not effective when administered via isolated limb perfusion, suggesting that chemotherapy accumulation is a major mechanism of action. The specific effect of TNFα on angiogenic, but not normal, vasculature might be attributable to the deactivation of the angiogenesis-associated integrin αvβ3. TNFα in combination with interferon-γ leads to endothelial apoptosis [11].

Many approaches are being used to target therapeutic TNFα directly to tumours, without causing systemic toxicity. These include gene therapy (TNFerade) [12] and TNFα conjugated to targeting peptides or single chain antibody fragments (see also Update) [13–15].

Role of TNFα in the pathogenesis of cancer

In contrast to the use of pharmacologic doses of TNFα as an anti-cancer therapeutic, mounting evidence suggests that TNFα acts to promote tumour growth and progression at physiologically relevant concentrations [16]. Some of the most detailed work regarding the role of TNFα as a tumour promoter was published in a series of papers from the laboratory of Fran Balkwill [16,17•,18]. The authors used the induction of skin tumours in mice as a model system to understand the growth-promoting actions of TNFα and its signaling pathway. In this system, 9,10-dimethyl-1,2-benzanthracene (DMBA) is used as a topical DNA-damaging tumour inducer; 12-O-tetradecanoylphorbol-13-acetate (TPA) is then applied as a tumour promoter. TNFα was first implicated in tumour growth in this model by the observation that TNFα knockout mice are highly resistant to the generation of skin tumours by this method. The presence of functional TNFα has no effect on DNA mutation rates or tumour initiation, but instead profoundly influences tumour promotion. TPA was shown to induce TNFα in skin keratinocytes of wild-type mice. The production of [redacted] scription pathway, such as granulocyte-macrophage colony-stimulating factor, matrix metalloproteinase (MMP)-3 and MMP-9, is important for the tumour-promoting effect. Anti-tumour effects were also observed following pharmacologic intervention with a neutralizing anti-mouse TNFα antibody. The potential role of TNFα in the growth of human skin cancers, initiated largely by UV radiation, is an important area for future investigation.

Clinical observations supporting a role for TNFα in tumor growth

TNFα plasma levels in cancer patients

Several reports have associated detection of abnormally high levels of TNFα protein in the blood of cancer patients with a wide range of tumour types [19], including pancreatic [20], kidney [21], breast [22], asbestosis induced lung [23] and prostate cancer [24]. Within groups of patients with the same tumour type, higher levels of TNFα have been correlated with advanced tumour stage, greater paraneoplastic complications and shorter survival time. However, circulating TNFα is not always detectable in cancer patients and can vary within individual patients over time and course of disease [25]. Regulation of TNFRs is critical to tumour cell responsiveness to TNFα, and tumour tissue levels of TNFα might be more relevant than blood levels in explaining pro-tumourigenic associations.

Endometriosis and ovarian cancer develop along a continuum of malignant transformation and promotion. Serum TNFα has been associated significantly with endometriomas and malignant, cystic and ovarian cancers, but not with benign tumours [26]. Inflammatory conditions associated with endometriosis and ovarian cancer include exposure to exogenous irritants and ovulation, accompanied by cell proliferation, oxidative stress, vascular permeability, and overproduction of prostaglandins, leukotrienes, TNFα, interleukin (IL)-6 and IL-1 [27••]. mRNA for these cytokines is found in epithelial ovarian tumours and in related ascites. TNFα is prevalent in peritoneal fluid around endometrial foci. Attracted platelets and macrophages secrete vascular endothelial growth factor, MMP-9 and transforming growth factor-β, and promote infiltration of ectopic endometrium and/or invasion and metastasis. The invasive tissue of endometriosis is surrounded by an ineffective immune response, just as ovarian tumours are surrounded by inflammatory cells impotent against the neoplasia. Chronic inflammation might invoke a switch from Th1-dominant to a Th2-dominant microenvironment linked to mutagenesis. Progression can be modified by immunosuppression, suggesting a therapeutic role for anti-inflammatory agents.

Esophageal metaplasia (Barrett's oesophagus), in the setting of chronic inflammation can progress to adenocarcinoma (Barrett's adenocarcinoma). Tselepsis *et al.* [28••] [redacted]

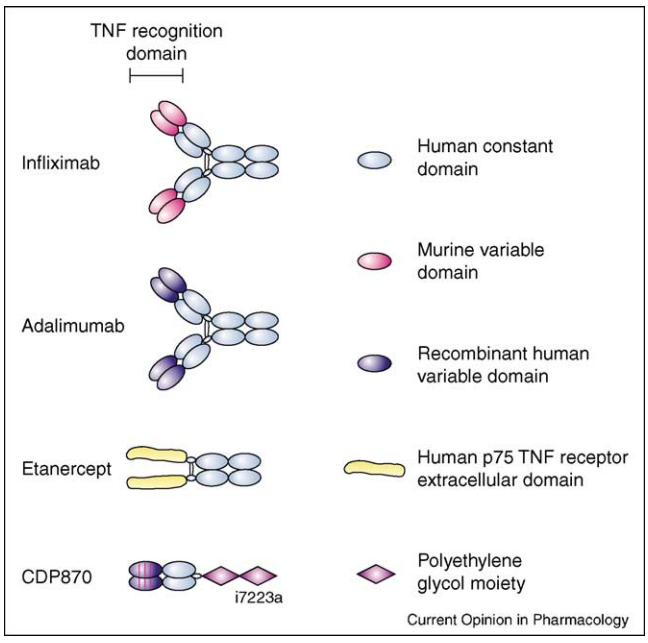
absent in normal gastric and esophageal squamous mucosae, but increased in sections from metaplasia through dysplasia to carcinoma. Elevated TNFα immunoreactivity in non-dysplastic Barrett's oesophagus is localized to mucosal regions of prominent lymphoid infiltrate where metaplastic stem cells are located. Within individual glands, the most dysplastic cells express TNFα, and TNFR1 levels are increased during disease progression, potentially amplifying the TNFα signal. This study demonstrated a novel signaling pathway for oncogene activation by an inflammatory cytokine.

In chronic lymphocytic leukemia (CLL), neoplastic lymphocytes release TNFα spontaneously *in vitro*, and leukaemic lymphocytes are more proliferative and viable when exposed to TNFα. TNFα in CLL patients correlated with extent of disease, serum β_2-microglobulin, low hemoglobin and low platelets, as well as with karyotype. TNFα levels were predictive of survival, independent of staging, β_2-microglobulin, hemoglobin, and white blood cell and platelet counts [29••].

Anti-TNFα therapy in cancer

Tsimberidou and Giles [30] review potential clinical indications for agents that block or inactivate TNFα (Figure 1), specifically the soluble TNFα receptor fusion protein etanercept and the anti-TNFα antibody infliximab, in multiple myeloma, myelodysplastic syndrome (MDS), acute myelogenous leukemia and myelofibrosis [30]. The limited efficacy of monotherapy points to the need to optimize dose and schedule, to combine anti-TNFα agents with active biological or cytotoxic agents, and to understand individual patient proteomic patterns of disease and gene polymorphisms that could predict response.

Figure 1



Multiple anti-TNF agents are currently marketed or in clinical development. Several anti-TNF biologics are illustrated above, including antibodies (infliximab and adalimumab), the modified antibody fragment CDP870, and the soluble receptor etanercept. The various domains present in the structures are illustrated for

Investigative and clinical uses of TNFα blockade in graft versus host disease (GVHD) are founded on the established role of upregulated TNFα as a consequence of conditioning regimens and as an effector molecule in multi-organ reactivity to allogeneic graft cells [31,32•]. Infliximab has shown activity in refractory acute and chronic GVHD [33]. With added immunosuppression and risk of serious infections, vigilance is required when using anti-TNF agents in patients with GVHD [34]. No studies yet have elucidated the kinetics, optimal dose and schedule of anti-TNF agents in GVHD [35].

Anti-TNFα agents can inhibit the excessive apoptosis in haematopoietic cells, which is suspected as the cause of cytopenias in MDS. The hyperproliferative marrow of MDS, with excessive apoptosis and overexpression of TNFα, compels intervention to modulate the dysregulated cytokine milieu in haematopoietic tissues. Therapeutic activity of infliximab suggests that the microenvironment of the marrow is more directly affected than are the dysplastic haematopoietic cells [36,37]. A logical next step would be to use a specific anti-TNF agent to modulate cell–cell signaling and stromal interactions in the marrow, combined with a cytotoxic agent known to be active against the myelodysplastic clone. Etanercept was tested in a Phase I clinical study in combination with IL-2 to determine if it could modulate the biological effects, and reduce toxicity, of high-dose IL-2 administration. TNFα bioactivity was inhibited, and the polymorphonuclear leukocyte chemotactic defect normally seen with IL-2 was not observed. Increases in levels of C-reactive protein, IL-6, IL-8 and IL-1 receptor antagonist were partially suppressed relative to historical controls [38].

A pilot study of etanercept in patients with refractory multiple myeloma reported tolerability but no objective responses, and some evidence of acceleration of disease soon after starting therapy [39]. TNFα was increased during treatment compared with pretreatment values; this is probable evidence of accumulation of the bound cytokine. More research on mRNA expression in the myeloma and stromal cells might determine if the bioactivity of increased TNFα was attenuated fully. Infliximab and etanercept differ in function: etanercept binds and blocks both TNFα and lymphotoxin (TNFβ), whereas infliximab binds only to TNFα. Infliximab, but not etanercept, binds to soluble TNFα bound to cell-surface

infliximab; TNFα dissociates more rapidly from etanercept, releasing bioactive TNFα [40]. Given these differences and the expectation that blocking TNFα should show anti-myeloma activity [41], it could be worthwhile to investigate infliximab in this disease.

Potential risks of anti-TNF-α therapy

Because of the adaptive protective purpose of inflammation, pharmacological inhibition of this proinflammatory cytokine could have adverse effects in the host, unrelated to the target disease of the anti-TNFα therapy. The risk of reactivation of latent tuberculosis is addressed in the prescribing information for infliximab (REMICADE®; Centocor Inc, Malvern, PA). Preemptive systemic antifungal therapy is recommended for patients receiving infliximab for treatment of GVHD [34]. Smith and Skelton [42] reported cases of squamous cell carcinoma that became evident and grew rapidly during an initial period of etanercept therapy for rheumatoid arthritis. The tumours might have been present, but occult before disruption of immunological control. Etanercept could disable innate anti-tumour surveillance by blockade of both lymphotoxin α and the cytotoxic effects of TNFα. Additional proposed mechanisms include the inhibition of the Th1 cytokine pattern and impairment of cytotoxic T cells. All cases were in chronically UV-damaged actinic skin predisposed to tumourigenesis by long-term, low-level production of TNFα. No new squamous cell carcinomas developed in patients who continued treatment for more than one year, suggesting prolonged anti-TNFα therapy could be preventive of cutaneous malignancies.

Pharmacovigilance data on etanercept, infliximab and adalimumab were reviewed by the FDA in 2003, with a focus on lymphoproliferative disease in patients treated with these anti-TNFα agents, relative to the rate expected in populations with immune-mediated diseases [43]. The potential role of TNFα-blocking therapy in the development of malignancies is not known. A prospective study of 18 572 patients with rheumatoid arthritis treated with anti-TNFα therapy plus methotrexate reported an increased standard incidence ratio compared with patients not receiving methotrexate or biologics, but confidence intervals overlapped for all treatments [44]. Patients with highly active disease and/or chronic exposure to immunosuppressant therapies could have several-fold higher risk for development of lymphoma, thus caution should be exercised when considering anti-TNFα agents in patients either with a history of malignancy or who develop malignancy during treatment.

The FDA also reported on the risk of histoplasmosis [45], lymphoma [46] and/or listeriosis [47]. The Mayo clinic reviewed the safety of infliximab in 500 patients with Crohn's disease treated with infliximab [48]. The biological basis of cancer warrants heightened vigilance and consideration of the benefit to risk ratio when prescribing anti-TNF therapies.

Anti-TNFα therapy in cancer supportive care

In addition to direct anti-tumour effects, anti-TNFα therapies are being tested for supportive care indications. These include cancer-related cachexia, fatigue, depression, amelioration of chemotherapy-induced toxicities and metastatic bone pain [49,50]. TNFα has long been associated with cachexia, and trials are underway testing anti-TNFα agents in this condition [51,52]. Ramesh and Reeves [53] recently demonstrated a role for TNFα in a mouse model of cisplatin-mediated renal injury. Treatment of animals with TNFα synthesis inhibitors or anti-TNFα antibodies prevented kidney damage in the model.

TNFα appears to play a complex role in side effects of radiotherapy, and anti-TNFα treatments could be useful in their management [54,55]. TNFα is also a known activator of osteoclasts [56] and mediator of neuropathic pain [57]. An intriguing pair of clinical cases, in which etanercept was used to treat refractory metastatic bone pain, suggest that anti-TNFα agents may ultimately play a role in controlling cancer pain [58•]. The potential value of anti-TNFα agents in these debilitating conditions presents broad opportunities to improve cancer care.

Conclusions

It is likely that there is no 'right' or 'wrong' answer to the question of whether TNFα is good or bad for the tumour. Research should continue to optimize the use of pharmacological TNFα to treat cancer, as well as the use of neutralizing therapies to inhibit the effects of pathophysiologically derived TNFα. As we increase our understanding of the complex biology of TNFα in differing contexts within oncology and hematology, these opposing approaches should prove more effective against cancer.

Update

Recent results further support the anti-tumor effectiveness of TNFα when delivered by gene therapy approaches. Hecht *et al.* [59] reported preliminary evidence for dose-dependent improvement in progression-free survival in a phase I/II trial of TNFerade in combination with radiation and 5-flourouracil in pancreatic cancer patients. Zarovni *et al.* [60] demonstrated substantially improved anti-tumor efficacy in animal models with tumor vessel-targeted peptide–TNFα fusion proteins. The molecules were delivered by intramuscular injection of cDNA expression vectors.

Additional evidence demonstrating the pro-metastatic effects of TNFα has been published recently. Mochizuki *et al.* [61] reported that TNFα promoted metastasis of

wall in a mouse model. Hagemann *et al*. [62] showed that macrophage-induced invasion by human breast cancer cells was mediated by MMPs and was dependent upon TNFR activity.

Acknowledgements

The authors would like to thank Patti Sassoli for her able and patient assistance in creating this review.

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