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TNF and cancer: the two sides of the coin

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1. ABSTRACT

Despite its name, discovery history and approval as anticancer agent, tumor necrosis factor (TNF) has been implicated in both cancer development and progression in some preclinical models. In particular, as a central mediator of inflammation, TNF might represent one of the molecular links between chronic inflammation and the subsequent development of malignant disease. Furthermore, deregulated TNF expression within the tumor microenvironment appears to favor malignant cell tissue invasion, migration and ultimately metastasis formation. On the other side, TNF clearly possesses antitumor effects not only in preclinical models but also in the clinical setting. In order to reconcile these conflicting findings, we provide readers with an overview on the most relevant available evidence supporting anticancer as well as cancer-promoting TNF effects; on the basis of these data, we propose a model to explain the coexistence of these apparently paradoxical TNF activities.

2. INTRODUCTION

Tumor necrosis factor (TNF) is a vital cytokine involved in inflammation, immunity, and cellular organization (1). This biological response modifier was shown to replicate the ability of endotoxin to induce hemorrhagic necrosis of solid tumors in animal models (2), which provided an explanation for the anticancer effect of the so called "Coley's toxin". This filtrate from cultures of *Streptococcus pyogenes* and *Serratia marcescens* was developed at the turn of the 20th century (3) and was associated with high fever and tumor necrosis in responding patients (particularly those with sarcoma, but also patients with carcinoma and lymphoma) (3). The phenomenon of tumor necrosis is now attributed, at least in part, to a vascular thrombotic mechanism mediated by TNF released by macrophages activated by the endotoxin contained within the Coley's toxin (Figure 1). In the light of these potential TNF therapeutic properties, after the TNF

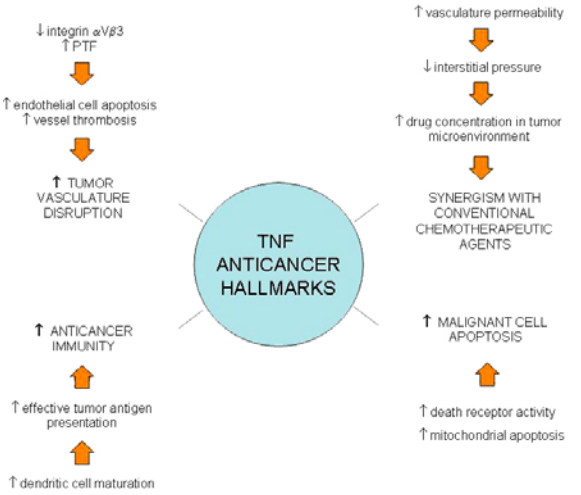

Figure 1. The four hallmarks of TNF anticancer activity. Although in preclinical models TNF exerts both direct cytotoxicity against malignant cells and stimulates anticancer immunity, the antitumor activity observed in humans appear to depend mainly on the cytokine ability to act as vascular disrupting agent and to increase the therapeutic effect of conventional antineoplastic drugs (see text for more details).

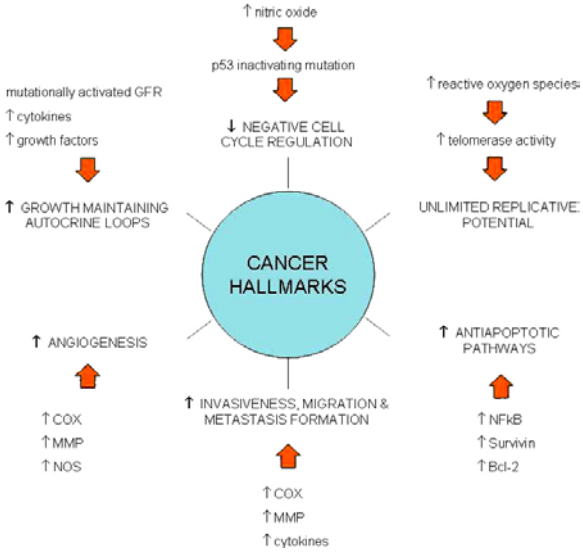

Figure 2. The six hallmarks of cancer. According to Hanahan and Weinberg (92), six cellular alterations collectively drive a population of normal cells to become a cancer. These cancer hallmarks are: 1) self-sufficiency in growth signals, 2) insensitivity to antigrowth signals, 3) evasion of apoptosis, 4) limitless replicative potential, 5) sustained angiogenesis, and 6) tissue invasion and metastasis. Some preclinical evidences suggest that TNF overproduction during chronic inflammation (by immune cells) and within the tumor microenvironment (by malignant cells and/or tumor infiltrating macrophages and lymphocytes) might promote tumor development and progression by influencing the six hallmarks of cancer (13) (see text for more details).

gene cloning in 1984 (4), investigators tested the anticancer activity of this cytokine in the clinical setting either alone, or in combination with conventional chemotherapeutic agents or as part of anticancer vaccination regimens (5-7). However, systemic TNF therapy proved ineffective with a lack of objective tumor response and serious side-effects (septic shock-like syndrome), which redirected researchers towards alternative forms of local delivery such as isolated limb perfusion (for the treatment of limb-threatening melanoma (8, 9) and soft tissue sarcomas (10, 11)) and isolated hepatic perfusion (for the treatment of unresectable liver tumors (12)), as described in detail in other articles of this Frontiers in Bioscience issue.

A decade of clinical experimentation ultimately led to a license from the European Medicine Evaluation Agency (EMEA) for the use of TNF (in combination with melphalan) as a loco-regional treatment for inoperable soft tissue sarcomas. Despite its approval for human use as anticancer agent in Europe, TNF is not approved in the USA and its role in cancer therapy is still debated (13-16), as its activity in advanced melanoma has been recently questioned (17) and no survival advantage has ever been demonstrated with its loco-regional administration (5, 10, 18).

In parallel with the growing availability of clinical data for TNF therapy in malignant disease, increasing evidence attributed a role for TNF in rheumatoid arthritis, inflammatory bowel disease, diabetes, sepsis, and several infections, including HIV (1). Furthermore, several studies have implicated endogenous TNF in tumor-cell growth and stromal interactions that facilitate tumor development and progression (13). Although TNF is capable of initiating tumor apoptosis (directly or indirectly, as below described in detail), evidence is accumulating that these pathways are frequently deactivated within tumor cells. Moreover, under some circumstances TNF can provide a survival signal for the cancer cell and hence it has been referred to as a "tumor promoting factor" (19).

On top of these considerations, the concept of cancer as a purely genetic disease has been re-evaluated and the importance of the tumor microenvironment and inflammation in cancer progression has been emphasized (20-22). In particular, as a central mediator of inflammation, TNF provides a molecular link between chronic inflammatory stimuli and the subsequent development of malignant disease (23) (Figure 2). Overall, its potential role in cancer progression has stimulated interest in the use of TNF antagonists for the prevention and treatment of cancer (24, 25).

In order to shed some light on this paradoxical situation, we provide readers with an overview on the most relevant available evidence supporting anticancer as well as cancer-promoting TNF effects; on the basis of these data, we propose a model to explain the coexistence of these apparently opposite TNF activities.

3. TNF ANTICANCER ACTIVITIES

3.1. TNF direct cytotoxicity

Direct cytotoxicity was among the first *in vitro* activities attributed to TNF (26). TNF receptor-1 (TNFR1),

which is expressed on virtually any cell type, has been demonstrated to exert cytostatic/cytotoxic effects on some animal and human tumor cell lines. Intriguingly, the genomic derangement proper of cancer development can itself sensitize malignant cells to TNF-driven cell death by leading to the over-expression of cathepsin-B (27), which might partly explain the selective cytotoxicity of TNF towards cancer as compared to normal tissues. However, several malignant cell lines and most normal cells (including endothelial cells) are resistant to TNF. In line with the fact that apoptosis can follow direct initiation of the caspase cascade by TNFR1 engagement while pro-survival effects require de novo expression of anti-apoptotic proteins, inhibition of protein synthesis (e.g. by cycloheximide) significantly increases TNF-mediated apoptotic rates both in normal and malignant cells (28), and is widely used for *in vitro* experiments dealing with TNF-induced apoptosis. A growing list of potential mechanisms underlying this variability in cell sensitivity to TNF-driven cytotoxicity is fostering the search for novel methods to boost TNF anticancer properties, as presented in detail in a dedicated article of this Frontiers in Bioscience issue.

3.2. TNF as a tumor vasculature disrupting agent

Physiologically, blood vessels are among the primary targets of the cytokine during inflammation, where the major effect of TNF on endothelium is endothelial cell activation, including upregulation of cell surface receptors (e.g. leukocyte adhesion molecules) and loss of intercellular adhesion (29). These events enhance leukocyte adhesion and lead to their migration into local areas of inflammation, thus favoring the clearance of the noxious agent. Under pathological circumstances, TNF overexpression sustains inflammatory phenomena (e.g. capillary leakage, congestion and leukocyte adhesion to the vessel wall, leukocyte diapedesis through the endothelium, tissue damage by infiltrating leukocytes) characteristic of some disorders, such as septic shock and autoimmunity.

Vascular effects are currently believed to be critical also for TNF antitumor activity (7, 15). Since the identification of TNF as the major mediator of endotoxin necrotizing effects in mouse tumor models, the attention has been drawn on the tumor vascular damage caused by TNF. The most striking evidence in favor of this hypothesis comes from animal experiments. In the syngeneic model of methylcholanthrene-induced murine fibrosarcoma, tumor cells are resistant to the cytotoxic effect of TNF *in vitro*, whereas *in vivo* systemic administration of TNF consistently causes hemorrhagic necrosis of subcutaneous (vascular) but not intraperitoneal (avascular, ascitic) tumors (30). Intratumoral TNF injection also causes hemorrhagic necrosis of human tumors transplanted into nude mice, while TNF intraperitoneal and systemic administration does not (31).

These findings can be explained by considering that, although low-dose TNF has a favorable effect on angiogenesis, higher doses cause destruction of newly formed blood vessels (32). Concordantly, TNF induces a dose-dependent reduction of tumor blood flow (33), and the degree of tumor vascularization directly correlates with tumor response to TNF-based treatment both in animal and human models (34).

The cascade of cellular/molecular events leading to the TNF-mediated ischemic insult of tumor tissue is still unraveled. In the 1980s, it was hypothesized that TNF-induced coagulation in the tumor vasculature might be one potential mechanism of tumor necrosis. This is supported by the observation that tumor necrosis can be achieved through selective induction of thrombosis within cancer-associated endothelium by targeting the pro-coagulant tissue factor (PTF) (35), which is known to be induced by TNF *in vivo*. Moreover, if PTF expression is inhibited, TNF-mediated fibrin deposition is decreased and blood flow restored (36). Besides direct endothelial cell stimulation by endotoxin and TNF, adhesion of leukocytes to endothelium and co-culture of monocytes with endothelial cells can also induce PTF expression by endothelial cells (37).

These findings do not allow to define whether leukocytes and/or endothelial cells initiate tumor necrosis. However, some authors have recently shown that TNFR1 expressed on the surface of tumor endothelial cells is likely to be the most important target of TNF antitumor activity (38). Using TNFR1 and TNF receptor-2 (TNFR2) deficient mice, they observed that TNF administration results in tumor necrosis only in wild-type and TNFR2-/- but not TNFR1-/- animals. Moreover, after implanting wild-type and TNFR1-/- tumor in wild-type mice, tumor necrosis occurs independently of TNFR1 expression by tumor cells and leukocytes. As TNF administration results in both activation and focal disruption of TNFR1-expressing tumor endothelial cells, these cells are indicated as the key target of the cytokine.

Nevertheless, it remains unclear whether coagulation following induction of PTF expression is the cause or rather the consequence of tumor vasculature disruption. Moreover, the reason for TNF selective cytotoxicity towards tumor tissue as compared to normal tissues remains incompletely elucidated. Some investigators have demonstrated that TNF causes a reduced activation of integrin-alpha-V-beta-3, which is selectively expressed by proliferating endothelium, such as that of growing tumor masses (39). The antagonization of this cell surface molecule is known to induce apoptosis of angiogenic blood vessels and might be responsible for the tumor-selective activity of TNF.

Alternatively, other investigators have hypothesized that higher levels of endothelial nitric oxide synthase in tumor vessels (rather than in normal surrounding tissues) might condition sensitivity to TNF, as nitric oxide neutralization significantly reduces endothelial cell sensitivity to TNF *in vitro* (40).

3.3. TNF synergism with chemotherapeutic drugs

Despite the antitumor effects illustrated above, TNF alone is only marginally active in inducing tumor regression in some *in vivo* animal models (using both autologous and xenogeneic/human tumors) and most

importantly in humans, even when high doses are given through locoregional drug-delivery systems (26, 41-43). Conversely, in several animal and human models of systemic and/or locoregional cancer treatment the combination of TNF with conventional antineoplastic agents (e.g. melphalan, doxorubicin, paclitaxel, actinomycin-D, cisplatin) strikingly increases the tumor response rates (5, 7).

The mechanism of this anticancer synergism has been the object of some hypotheses. The ischemic insult to tumor masses following TNF-driven disruption of tumor vessels might be insufficient to cause cancer regression and might be effectively complemented by the direct cytotoxicity of antineoplastic drugs on malignant cells. Moreover, TNF improves the pharmacokinetic profile of co-administered drugs by increasing the permeability of tumor vessels and lowering interstitial pressure within the diseased tissue (44), which in turn augments drug concentration within the tumor microenvironment.

3.4. TNF and antitumor immunity

Some investigators describe a significant reduction in tumor response rates when immunodeficient mice are treated with TNF, suggesting that TNF antitumor activity is at least in part mediated by the immune system (45, 46). It is well known that TNF stimulates innate immunity both *in vitro* and in animal models (1). TNF induces the production of other cytokines (e.g. interleukin-1 [IL-1], IL-6 and IL-8) and cytotoxic factors (e.g. nitric oxide (NO), reactive oxygen species [ROS]) by macrophages, which can mediate tumor suppression in mice (47). In humans, antitumor cytolytic activity and production of cytotoxicity-related proteins (e.g. interferon-gamma [IFN-gamma]), TIA-1) by natural killer (NK) cells are enhanced by TNF *in vitro* (47, 48).

Adaptive immunity also appears to be involved in TNF mediated tumor regression, as suggested by the observation that the ability of T-lymphocytes to reject established tumors is severely compromised in TNF-knockout animals (49, 50) as well as in animals treated with neutralizing anti-TNF antibodies (51). As it effectively promotes the maturation of CD34+ myeloid cells into dendritic cells, which are the most powerful antigen-presenting cells, TNF has been included in most protocols of dendritic cell-based cancer vaccines (52). However, in this case, TNF is not used as a direct anticancer agent but rather as an immunological adjuvant aimed at reversing the state of tolerance of immune cells towards malignant cells.

4. TUMOR PROMOTING EFFECTS OF TNF

While physiologically TNF plays a major role in growth regulation, cell differentiation, response to viral, bacterial, fungal, and parasitic infections, its inappropriate overexpression has been implicated in the pathogenesis of a wide spectrum of human disorders, such as autoimmunity (e.g. multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease), allergy, septic shock, allograft rejection and insulin resistance (1).

Despite the above-discussed evidence of its antitumor activity, TNF may also exert tumor-promoting effects (19) (Figure 1). Within the tumor microenvironment, TNF can be produced by both tumor-infiltrating macrophages and by several types of animal and human malignant cells (e.g. ovarian, colorectal, esophageal, prostate, bladder and renal-cell carcinomas; melanoma, and hematological malignancies). The role played by TNF in tumor promotion has been extensively analyzed, as below summarized.

4.1. TNF and cancer development

In vitro, low-dose TNF can promote the proliferation of some malignant cell lines (53, 54). This finding is supported by the recent observation that the cytokine upregulates the expression of positive cell-cycle regulators (Ras, c-Myc) and decreases the levels of cyclin-dependent kinase (Cdk) inhibitors, a phenomenon that has been linked to the progression Barrett's disease > mucosal dysplasia > esophageal adenocarcinoma in humans (55).

TNF may act as an autocrine tumor growth factor also by promoting cell survival through the activation of the anti-apoptotic/ survival/proliferation pathways hinging upon the activity of nuclear factor kappa B (NFkB), protein kinase B (PKB)/Atk and mitogen activated protein kinase (MAPK) family members. Although TNF shows a protective effect on radiation-induced lymphoma (56), other *in vitro* and *in vivo* animal models of chemical carcinogenesis suggest that TNF can favor cancer development (57, 58): in particular, knockout experiments have shown a higher incidence of cancer in animals TNF+/+ rather than in those TNF-/-.

The molecular details of such tumor promoting activity are unknown, but it has been hypothesized that TNF might cause DNA damage and inhibit DNA repair by enhancing the production of genotoxic molecules (e.g. nitric oxide, ROS) by cancer cells themselves or bystander cells, such as tumor-infiltrating macrophages (59). Moreover, the resistance of TNF-/- mice to chemical carcinogenesis might be related to a temporal delay in the activation of protein kinase C (PKC) and AP-1 (60). This delay appears to affect the expression of genes known to be involved in tumor development, such as granulocyte macrophage colony stimulating factor (GM-CSF) and matrix metalloproteinases (MMP)-3 and -9, which are suppressed in the TNF-/- mice but not in wild-type mice treated with carcinogens.

Finally, the fatal lymphoproliferative disorder that develops in FAS ligand (CD95L) deficient mice is attenuated by crossing these animals with TNF-/- mice (61). Analogous findings have been reported using TNFR knockout animals. In a model of skin carcinogenesis, both TNFR1 and TNFR2 are required for tumor development (62). By contrast, in a liver tumor model, carcinogenesis only depends upon TNFR1 expression (63).

4.2. TNF and cancer progression

In preclinical models exogenous TNF can promote the process of tumor metastatization (13). For instance, antibody-based neutralization of TNF

endogenously produced by malignant cells is sufficient to reduce the metastatization rate in a murine model of methylcholanthrene-induced sarcoma (64). More recently, TNF auto-vaccination has been successfully tested in the murine B16F10 melanoma model to inhibit the metastatization process *in vivo* (65). Other investigators used TNFR1-/- mice to show that endogenous TNF is essential for promoting liver metastasis after intrasplenic administration of a colonic adenocarcinoma cell line (66).

While studying the role of TNF in tumor progression, transgenic mice overexpressing TNF are unsuitable as they become rapidly ill owing to the early onset of severe inflammatory diseases. Nevertheless, some authors observed that TNF-secreting cancer cells show an enhanced rate of metastasis formation, a phenomenon that can be reversed by TNF-neutralizing antibodies (13, 64). Despite these findings, this effect is not universal as TNF-transfected tumors could either be rejected or cause decreased survival according to the tumor cell line utilized (67).

Given its pleiotropic functions, TNF may favor tumor progression in different ways. Expression of matrix metalloproteinases (MMP) by malignant cells is enhanced by TNF (68). Moreover, although high-dose TNF induces collapse of tumor vasculature, low chronic doses of the cytokine are believed to promote angiogenesis (69). The TNF-driven overexpression of various factors (e.g. vascular endothelial growth factor [VEGF], VEGF receptors, basic fibroblast groth factor [b-FGF], IL-8, ephrin-A, nitric oxide synthase, E-selectin, intercellular adhesion molecule-1 [ICAM-1]) has been postulated to mediate this pro-angiogenic effect (13, 70, 71).

Finally, it has been recently hypothesized that TNF might promote tumor invasiveness by interfering with the activation of the oncogene c-Src, which is correlated with progression of colorectal cancer *in vivo*: as a matter of fact, in an *in vitro* model TNF causes c-Src activation through the production of ROS, which ultimately lead to reduced E-cadherin levels and enhances the invasive potential of c-Src transfectants cultured in soft agar (72).

4.3. TNF gene polymorphisms

To demonstrate the TNF role in human cancer biology *in vivo* is a highly challenging issue. An approach to test the hypothesis that endogenously produced TNF can affect human tumor biology *in vivo* is to study the epidemiological correlation between TNF gene polymorphisms and cancer incidence.

Many studies report an association between single nucleotide polymorphisms of the TNF gene and the risk of developing various types of cancers. For instance, a significant link between TNF polymorphisms +488A and -859T and risk of bladder cancer has been detected in a study considering 196 patients and 208 controls (73). The relative risk of renal cell carcinoma is 6.5-fold higher in patients with the GA genotype at locus -238 and 2.9-fold higher in those with the GA genotype at locus +488 when comparing normal tissue from renal cell carcinoma patients (n=81) with that from healthy controls (74). Yet, considering 73 patients with prostate carcinoma, the relative incidence for cancer is 17-fold higher in subjects with genotype GA at +488 region of TNF gene (75). Associations between TNF microsatellite polymorphisms and basal cell skin carcinoma have been also reported (76).

Most interesting are the observations made on the polymorphisms of the promoter region believed to be responsible for an increased transcription of TNF. One such polymorphism at position -308 is associated with greater susceptibility to various carcinomas (e.g. hepatocellular (77), gastric (78), and breast carcinoma (79)). Similar findings have been reported on the relationship between the frequency of the TNF 857T allele, known to be associated with high transcriptional levels of TNF, and the incidence of adult T-cell leukemia/lymphoma among individuals with HTLV-1 infection (n=151) (80).

Polymorphisms leading to a high production of TNF are also linked to an increased risk of developing multiple myeloma (81) and, in patients with hematological malignancies, to treatment failure, shorter progression-free survival and poorer overall survival (82).

Again, available evidence is far from univocal. In contrast with the above studies, some authors have reported opposite findings. For instance, there is no statistically significant association between TNF haplotype and clinical outcome of children with lymphoblastic leukemia (n=214) (83). In a series including 96 patients with prostate carcinoma, the polymorphism of the TNF gene promoter at position -308 does not correlate with cancer incidence (84); similarly, in a North European study (cases, n=709; controls, n=498), no association exists between the -308 polymorphism and susceptibility to breast cancer (85). In another recent study (n=80), the survival of patients with osteosarcoma is not affected by the same polymorphism (86).

Intriguingly, other authors not only report a lack of correlation between the -308 TNF polymorphism and cancer risk, but also describe a protective role of polymorphisms -238A and +857T in the incidence of different tumor types (87, 88).

5. PERSPECTIVE

The role played by TNF in cancer development/progression might appear to shadow the anticancer potential of this cytokine. Although further elucidation of TNF biology is warranted to explain some apparent inconsistencies and define the actual role of TNF in cancer therapy, the above reported data support the following clear-cut distinction regarding TNF dosage/expression levels and timing of expression/administration: high-dose single-shot TNF-based regimens can induce tumor regression in *in vivo* animal and human models, whereas endogenous low-dose TNF chronically produced within the tumor microenvironment is associated with cancer development/progression in some preclinical models.

Despite this distinction, some preclinical findings remain conflicting and the scientific community awaits for an improvement in the cytokine therapeutic index to consecrate TNF as an antineoplastic agent for routine use.

Defining the role of TNF in cancer therapy is a challenging task. The pleiotropic nature of the cytokine, which can stimulate multiple, complexly interconnected pathways often involved in opposing phenomena, makes it difficult to discern the ultimate effect of TNF based on *in vitro* data. On the other side, the outcome of *in vivo* animal studies can be affected by a number of biological variables. For instance, different type/degree of derangement of the apoptotic/survival machinery of cancer cells might account for the wide range of TNF sensitivity observed in different tumor models. Besides intrinsic features of malignant cells, tumor microenvironment can also have a profound influence on the relationship between TNF and malignancy. For instance, in a model of TNF-transfected murine carcinoma, tumor growth is inhibited in the lungs but not in the skin because of the different expression of TACE (TNF alpha converting enzyme, a member of the matrix metalloproteinase family that cleaves soluble TNF from membrane-bound pro-TNF (89)) by normal tissues (90). To take another example, the degree of tumor vascularization as well as the levels of nitric oxide produced by tumor endothelial cells may also condition the sensitivity of malignant cells to TNF therapy (40), which ultimately might explain different tumor responses observed in the clinical setting.

In humans, although TNF antitumor activity appears quite evident in some non-comparative studies (15), the lack of synergistic effect shown in a recent phase III randomized controlled trial (17) (comparing melphalan alone to melphalan plus TNF) coupled with the fact that no TNF-based treatment has thus far proved to affect patient survival does not allow oncologists to use TNF as a routine antineoplastic agent. Moreover, due to systemic toxicity, TNF administration through sophisticated locoregional drug-delivery systems (such as isolated limb perfusion or isolated liver perfusion) is currently mandatory.

The impossibility to administer TNF through the systemic route likely prevents clinicians from assessing the effectiveness of this cytokine in terms of patient overall survival, which mainly depends upon the metastatic spread throughout the body and thus is not affected by locoregional treatments. In this respect, the development of novel tumor-specific drug-delivery systems and/or TNF sensitizers might not only increase the antineoplastic activity of TNF but also allow oncologists to administer the cytokine systemically. Hopefully, the clinical implementation of TNF sensitizers, that is molecules able to augment TNF cytotoxicity selectively against malignant cells (91), will allow to increase the therapeutic index of TNF to the extent necessary to make its systemic administration feasible and effective, as discussed in detail in a dedicated article in this issue of Frontiers in Bioscience.

6. ACKNOWLEDGEMENTS

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Abbreviations: TNF: tumor necrosis factor; NK: natural killer; TNFR: TNF receptor; PTF: pro-coagulant tissue factor; nitric oxide (NO); reactive oxygen species (ROS); IFN: interferon; IL-1: interleukin-1; nuclear factor kappa B (NFkB); PKB: protein kinase B; MAPK: mitogen activated protein kinase; GM-CSF: granulocyte macrophage colony stimulating factor; MMP: matrix metalloproteinases; VEGF: vascular endothelial growth factor; b-FGF: basic fibroblast groth factor; ICAM-1: intercellular adhesion molecule-1; TACE: TNF alpha converting enzyme

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