TNFα

Subjects: Biochemistry & Molecular Biology
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About 60 years ago, it was reported that bacterial endotoxin administration to mice resulted in the release of a serological protein with necrotic anti-tumor activity at high concentrations. Due to the latter characteristic, this protein was termed tumor necrosis factor (TNF) and considered a breakthrough for cancer therapy. Today, the TNF superfamily consists of 19 members and 29 TNF receptors .Within this family, functional TNFα is represented by a trimer of 17.35 kDa monomers, folded into a rigid bell-shaped “jelly roll” composed of antiparallel filaments. It exists in two forms: a transmembrane form (tmTNFα) next to a soluble (sTNFα) form. The latter one is cleaved from tmTNFα by the metalloproteinase TNF-alpha-converting enzyme (TACE).

Keywords: TNFα ; TNFR1 ; TNFR2 ; lung cancer ; immunotherapy ; immune checkpoint inhibition (Min. 5–Max. 8)

1. The Pleiotropic Immunological Biology of TNFα

Soluble TNFα is mainly secreted by activated macrophages [1] and to a lesser extent, by T lymphocytes, natural killer (NK) cells, neutrophils, endothelial and cardiac muscle cells, fibroblasts, and osteoclasts [2][3]. By comparison, tmTNFα is expressed constitutively on the surface of a broad range of immune cells such as alveolar and non-alveolar macrophages [4], monocytes [5], lymphocytes [6], dendritic cells (DCs), and NK cells [7]. In addition, its expression has been reported on non-immune cells such as adipocytes [8] and tumor cells [9].

In general, sTNFα is rapidly released upon trauma or infection, as it is bestowed with a determining role in immunoregulatory processes such as immune ontogeny, inflammation, and apoptosis [2]. As a soluble pro-inflammatory cytokine, it primarily acts at sites remote from the TNFα-producing cells to support the production of downstream pro-inflammatory cytokines along with the recruitment, activation, and regulation of inflammatory cells such as macrophages. To illustrate, when macrophages are activated by Toll-like receptors, they secrete sTNFα, which subsequently regulates macrophage differentiation in an autocrine fashion [10]. Hence, TNFα neutralizing antibodies have been shown to reduce the production of several pro-inflammatory cytokines and growth factors such as interleukin-1 (IL-1) and granulocyte-macrophage colony-stimulating factor (GM-CSF) [11]. Of note, sTNFα has an intrinsic pleiotropic activity as it is also involved in anti-inflammatory responses that aim to restore homeostasis [12].

TNFR1, also known as tumor necrosis factor receptor superfamily, member 1A (TNFRSF1A) or CD120a, is expressed on almost all host cells including various tumor cell types [13][14][15][16] and tumor-associated endothelial cells [17]. In contrast, TNFR2 (TNFRSF1B or CD120b) is predominantly located on the surface of immune cells, such as NK cells, macrophages [18], regulatory T cells (Tregs), suppressive myeloid cells [19], and endothelial cells [20].

2. TNFα Plays Opposing Roles in Cancer

Despite TNFα’s denomination, in vitro reported tumor necrosis after high TNFα concentrations appeared a phenomenon that is not so straightforwardly translated to successful cancer treatments in vivo. The latter is partly explained by TNFα’s multifunctionality as a cytotoxic but also immune modulating cytokine. As the immune system plays a complex role on the tumor microenvironmental (TME) battlefield, TNFα is used as a weapon to modulate and/or kill tumor cells, immune cells, and/or endothelial cells [21].

While a high concentration of TNFα has been linked to hemorrhagic necrosis, it is now widely accepted that chronic exposure to TNFα is more likely to promote tumor progression. First, it has been demonstrated repeatedly that chronic inflammation, in which the innate immune system plays a leading role, can promote cancer onset as well as progression and metastasis, typifying the “never-healing-wound” character of solid cancers [22][23]. Indeed, chronic exposure to TNFα can promote cellular transformation via the induction of direct mutations and DNA damage [24] as well as via profound epigenetic changes that modulate the expression level of oncogenes and tumor suppressor genes [25]. In addition, inflammation influences epithelial-to-mesenchymal cell transition (EMT) and subsequent cancer cell invasion. Further,

TNFα has been shown to affect expression of EMT-inducing transcription factors, particularly in synergy with TGFβ [26]. Moreover, TNFα associated with chronic inflammation can be held responsible for the observed phenomenon of cancer cell specific resistance to TNFα-induced cell death [27]. Specifically, chronic TNFα/TNFR1 binding increases the expression of anti-apoptotic, angiogenic, and invasive proteins via the TAK-1, MAPKs, Akt, IKK, AP-1, and NF-κB signaling pathways [18][28][29]. Notably, also the ligands and receptors of the LTα family with, among others, affinity for TNFR1 and 2, have been linked to increased carcinogenesis, as extensively reviewed elsewhere [30][31].

Even if chronic inflammation is not involved in the onset of tumor cell transformation, the immune system often becomes a co-worker during cancer progression. Today it is generally accepted that the immune system can identify and control nascent malignancies in a process called cancer immunosurveillance. In contrast, the latter can also promote tumor progression through the selection of poorly immunogenic variants and suppression of anti-tumor immunity. Together, the dual host-protective and tumor-promoting actions of immunity are referred to as cancer immunoediting and comprise three distinct phases: the elimination, equilibrium, and escape phase [32][33][34].

During the equilibrium phase, anti- and pro-tumor immunity are in balance and/or immune-mediated tumor dormancy is installed [34]. It was reported that the absence of TNFR or IFN-γ promoted angiogenesis and multistage carcinogenesis in an experimentally induced pancreatic murine tumor model, suggesting that a coordinated interaction between IFN-γ and TNFα was responsible for the activation of TAA-specific cytotoxic T cells [35]. Moreover, the combination of IFN-γ and TNFα drove pancreatic tumor cells into STAT-1 and TNFR1-mediated senescence [36]. Because IFN-γ and TNFα induce senescence in numerous murine and human cancers, this may be a general mechanism for arresting cancer progression.

3. Linking TNFα to Antitumor Immunotherapy in Lung Cancer

The goal of antitumor immunotherapy is to completely and specifically eradicate both primary and metastatic tumor lesions by mobilized cytotoxic effector cells. Hence, immunotherapy can achieve actual cures of advanced lung cancer patients, representing an unprecedented reality [37][38]. Therefore, the first FDA approval of an immunotherapeutic treatment for squamous cell NSCLC benchmarked a revolutionary era for lung cancer patients. This treatment is based on blocking the immune checkpoint programmed death-1 (PD-1) pathway. Under healthy conditions this pathway is used to put an adequate brake on T cell stimulation and return to homeostatic conditions. As tumor cells can express the PD-1 ligand (PD-L1) themselves, they can corrupt this pathway to hinder their execution by PD-1 + TAA-specific cytotoxic effector cells [39][40]. Since 2016, five PD-(L)1 inhibitors (nivolumab, pembrolizumab, atezolizumab, durvalumab, and cemiplimab) have been approved by the FDA as second- and/or first-line treatment options for advanced NSCLC [41]. Notably, for the treatment of SCLC, both nivolumab and pembrolizumab were originally approved [42] yet have been withdrawn from the US market since confirmatory trials failed to evidence improved survival outcomes. Additionally, only ~20% of unselected NSCLC patients benefit from blocking immune checkpoints, and many of the initial responders eventually develop resistance to therapy. Moreover, the growing trend to combine several immune checkpoint inhibitors (ICIs) coincides with a growing occurrence of severe to fatal immune-related adverse effects (irAEs), often related to a local increase in TNFα [43]. Together with the emerging concept of hyperprogression upon ICI [44], these phenomena cast light on the current knowledge gap of immunotherapy hampering mechanisms.

In search for clues, the relationship between TNFα and immune checkpoint signaling in the TME is being explored, hinting towards a lead role for TAMs. While IFN-γ is the main regulator of PD-L1 expression in tumor cells, PD-L1 expression in TAMs seems to be regulated via TNFα [45]. In 2017, Hartley et al. demonstrated that TNFα increases the expression of PD-L1 on bone marrow-derived monocytes and macrophages. They found that this was maintained through the secretion of versican by tumor cells, which stimulated the production of TNFα by monocytes themselves in a TLR2-dependent manner [46]. One year later, the same group provided more evidence on the interactions between the TNFα and PD-L1 pathways, as they demonstrated that PD-L1 blockade increased spontaneous macrophage proliferation, survival, and activation in vitro. Via RNAseq and IPA software analysis of these anti-PD-L1 treated macrophages, they further revealed an activated TNFR2 signaling profile [45]. Furthermore, it was recently shown in NSCLC patients that TNFα-secreting TAMs can enhance hypoxia and aerobic glycolysis and that TAMs dampen PD-L1 expression on murine lung tumor cells specifically [47][48]. The latter does contradict the observation that TAM-secreted TNFα could stabilize PD-L1 expression on 4T1 mammary cancer cells, triggering immunosuppression in vivo [49].

As melanoma remains the textbook example for immunotherapy responsiveness, TNFα targeting studies are most numerous for this cancer type. Overall, preclinical TNFα blockade has been shown to reduce the induction of irAEs upon ICI combinations and even improve therapeutic effectiveness of ICIs [43][50]. Upon adoptive CD8 + T cell transfer, TNFα appeared to be a crucial factor in the incitement of melanoma dedifferentiation, which resulted in immune escape and melanoma relapse [51]. Bertrand et al. partly explained these effects by the observation that TNFα/TNFR1 signaling triggers AICD of tumor-infiltrating CD8 + T cells in melanoma, with subsequent lack of response to anti-PD-1 therapy [52].

Hence, via systemic administration of etanercept, melanoma growth was inhibited in immunocompetent animals specifically. Notably, similar effects were seen in TNFR1-ko, but not TNFR2-ko, mice, suggestive for the decisive role of TNFR1 in this AICD of CD8 + T cells [53]. A few years later, Bertrand et al. further validated these findings by showing that anti-PD-1 therapy can stimulate T-cell expression of the alternative checkpoint T-cell immunoglobulin and mucin domain 3 (TIM-3) via TNFα. Moreover, they could demonstrate that co-blockade of PD-1 and TNFα overcomes resistance to anti-PD-1 monotherapy [50]. Hence, we eagerly await the results from the first Phase Ib, open-label trial [54] that is evaluating the administration of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) in combination with the anti-TNFα drug infliximab or certolizumab in patients with advanced melanoma.

4. Conclusions and Future Perspectives on TNFα Modulation for Lung Cancer Treatment

The multitude of contradictory findings currently poses a stalemate for TNFα pathway-affecting strategies in combination with immunotherapy to treat lung cancer and suggests the need for additional research into biomarkers to guide rationalized therapy combinations. This conundrum is reflected by the range of preclinical studies that report on the therapeutic efficacy of TNFα upon its administration as well as its inhibition [55]. To illustrate, when a TNF-based Activity-on-Target cytokine (AcTakine) was specifically targeted to the CD13 + neovasculature in vivo, the rapid destruction of the tumor neovasculature and complete regression of large, established tumors was demonstrated. In contrast, selective blockage of sTNFα via INB03 led to a reduced carcinogen-induced tumor incidence and growth rate [56]. Moreover, a detrimental role has been attributed to sTNFα and TNFR1 for melanoma-infiltrated functional CD8 + T cells as well as the onset of irAEs, rationalizing combined TNFα-blockade with immunotherapy to treat melanoma.

By mining existing next-generation sequencing data from LUAD patients, the latter were shown to contain less TNF , and because of the significant reduction in TACE , sTNFα protein is likely to be most decreased. Together with the notion that tmTNFα, and not sTNFα, has been shown to play a key role in Th1-polarized antitumor immunity and improved lung cancer patient survival [57][58], this argues against a tumor promoting role for TNFα in lung cancer, discouraging TNFα-blockage for lung cancer treatment today. Additionally, the role of TNFR2 in lung cancer progression remains undetermined and requires more research. High amounts of TNFR2 + Tregs have been found in the TME of human advanced lung cancers, and TNFR2 has recently been identified as a tumor-promoting oncogene with new biomarker potential for cancer [59][60]. However, upon mining the currently available transcriptomic dataset from a TCGA LUAD patient cohort, we demonstrated that the expression of TNFR2 is markedly decreased in the lung TME. Moreover, pre-clinically, TNFR2 agonists as well as antagonists have been linked to antitumoral effects, arguing against the effectiveness of TNFR2 modulation for lung cancer therapy [61][62][63][64].

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