TNF: A signaling pathway related to the activation of NF-κB

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1 Introduction

1.1 Tumor necrosis factor biology

TNF is essential for the development of lymphoid tissue and has a homeostatic role against some bacterial infections. TNF also has known as a sentinel cytokine or “the body's fire alarm” by initiating defense mechanism to local injury. At low concentrations in tissues, it acts as an amplifier adjacent to infections. At high concentrations, inflammation and organ injuries are proceeding, causing systemic clinical pathologic abnormalities. During sepsis condition by lipopolysaccharide (LPS) of gram negative bacteria, acute release of very large amounts of TNF may lead to septic shock. While at illness state, TNF along with other cytokines such as interleukins: IL-1 and IL-6 are predominating as pro-inflammatory cytokine. It has also been suggested to be an immunoregulatory agent that can adjust the balance of T regulatory cells.

In response to TNF, endothelial cells initiate inflammation by acting together with different factors of adhesion molecules for leukocytes, including E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). Collaboration with other chemokines (including IL-8, monocyte chemotactic protein-1: MCP-1 and interferon-inducible protein 10: IP-10), leading to recruitment of different populations of leukocytes regardless antigen recognition. In addition, TNF has a role in vasodilation by promoting expression of cyclo-oxygenase 2; other role in intravascular thrombosis by down-regulation the expression of anticoagulant protein, such as thrombomodulin.

Many different immune and nonimmune cell types can produce TNF, including macrophages, T cells, mast cells, granulocytes, natural killer (NK) cells, fibroblasts, neurons, keratinocytes and smooth muscle cells. Within 30 minutes, TNF can be stimulated in macrophages as TNF mRNA by bacteria, viruses, immune complexes, other cytokines (e.g., interferon (IFN-γ)), granulocyte macrophage colony-stimulating factor (GM-CSF), IL-1, IL-17), complement factors, tumor cells, irradiation, ischemia/hypoxia and trauma. TNF production is regulated by positive and negative feedback mechanisms. So, TNF induces the production of other cytokines, such as IL-1, IL-2 and IFN-γ which in turn can induce TNF production. TNF activates other negative-feedback regulators, such as IL-10, prostaglandins and corticosteroids, which inhibit transcription of TNF mRNA.

TNF is released from cells as a soluble cytokine (sTNF) after being enzymatically cleaved from its cell-surface-bound precursor (tmTNF) by TNF-alpha-converting enzyme (TACE). TACE, also known as ADAM-17; is associated in processing many proteins within the cell membrane, including TNF receptors, which are released by its action to generate soluble form which will neutralize the actions of TNF.

TACE may hence be both pro- or anti-inflammatory, according it acts on an effector (e.g. macrophage) or on a target (e.g. endothelial cell, releasing ligand or receptor, respectively.)
Both homotrimer, sTNF and tmTNF ligands are biologically active and react with the 2 receptors of TNF. TNFR-1 is expressed on almost all cell types except erythrocytes, where TNFR-2 is usually stimulated and expressed on endothelial and hematopoietic cells. Certain pairings are more preferential over others; sTNF binding to TNFR-1 and tmTNF binding to TNFR-2. However, receptor-mediated effects of sTNF and tmTNF can lead alternatively to the activation of NF-κB; a family of transcription factors that control a large number of inflammatory genes and a distinct signaling pathway leads to caspase-8 and caspase-3 dependent apoptosis.

Related to the work with receptor knockout mice and cell culture; both the pro-inflammatory and the apoptosis pathways that are activated by TNF and linked to tissue injury, are usually dependent on TNFR-1. The significance of TNF-2 signaling has been shown to mediate tissue repair and angiogenesis. The utilization of different signaling mechanisms by TNFR-1 and TNFR-2 is consistent with the ability of each receptor to signal distinct biological responses in cultured cells. Under certain circumstances, TNFR-2 may contribute to TNFR-1 responses, particularly at low concentrations of TNF. Structure, expression and function of TNFR-1 and TNFR-2 are summarized in (table 1).

1.2 Contribution of TNF and NF-κB in autoimmune diseases

Autoimmune disease is a disorder in which impaired function and destruction of tissue are caused by an immune reaction in which abnormal antibodies are created and attack the body’s own proteins, cells and tissues. This can lead to the expansion of certain pathological actions as in rheumatoid arthritis, Crohn’s disease, multiple sclerosis, systemic lupus erythematosus, diabetes mellitus type 1 and Sjogren’s syndrome. They may be associated with excessive levels of TNF, so they have the advantages of anti-TNF therapies when administered besides other immunosuppressive treatments. The approved therapies (infliximab, adalimumab and etanercept) are monoclonal antibodies or inhibitory molecules that block TNF activity. Although, anti-TNF treatments decrease the disease-associated inflammation, they do not reverse the corresponding mechanisms of autoimmunity and occasionally lead to unfavorable conditions especially when presence of pathogenic infections.

Rheumatoid arthritis which considered as a common example of autoimmune diseases, is a chronic inflammatory disorder, recognized by inflammation of synovial tissue, leading to progressive damage, causing a painful swelling that can eventually result in bone erosion and joint deformity. This damage is linked to accumulation of inflammatory cells, primarily T cells and macrophages, but also B cells, plasma cells and dendritic cells may be involved. Many proinflammatory cytokines, including IL-1, IL-6, TNF and GM-CSF, are predominated within the damaged joint.

<table>
<thead>
<tr>
<th>Table 1: Comparison between TNFR1 and TNFR2</th>
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<tr>
<td><strong>Structure</strong></td>
</tr>
<tr>
<td>TNFR1</td>
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<tr>
<td>- Extracellular domain:</td>
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<tr>
<td>cysteine-rich and analogous to TNFR1</td>
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<tr>
<td>- Intracellular domain:</td>
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<td>apoptosis domain; not analogous to TNFR1</td>
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<tr>
<td>TNFR2</td>
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<tr>
<td>- Extracellular domain:</td>
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<tr>
<td>cysteine-rich and analogous to TNFR1</td>
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<tr>
<td>- Intracellular domain:</td>
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<tr>
<td>no apoptosis domain; not analogous to TNFR1</td>
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Indeed, TNF, IL-1 and LPS can activate transcription factor NF-κB. Activated NF-κB, has been concerned with the regulation of genes associating with cytokine production, expression of cell surface adhesion epitopes, lymphocyte maturation, MHC class I antigen processing and presentation, and defense against apoptosis, via promotes the transcription of antiapoptotic agents, after exposure to TNF. The selective susceptibility of autoreactive T cells to TNF induced apoptosis appears to form a range of errors in activating (NF-κB)

In normal T cells, activation of NF-κB occurs in the cytoplasm and requires intact proteasomes to cleave the active form of NF-κB from the inhibitory protein IκB-α (after phosphorylation and ubiquination). Once released, the active form of NF-κB is liberated to enter the nucleus and to express target genes that prevent cell death in response to TNF exposure. Autoimmune diseases have defective proteasomes that are unable to activate NF-κB from IκB-α, by masking the nuclear localization signals (NLS) of NF-κB proteins and keeping them sequestered in an inactive state in the cytoplasm, and
blocks the capacity of NF-κB transcription factors to bind to DNA; then NF-κB can not enter the nucleus and the apoptosis mechanism is activated after exposure to TNF-α.

1.3 Contribution of TNF and NF-κB in cancer

Also, TNF is well-known in cancer treatment strategies as in soft-tissue sarcoma (STS), unresectable tumors of various histological types, and melanoma in transit metastases restricted to the limb. When TNF-bound TNFR-2 interacts with TNFR-associated factor 2 (TRAF-2); then the expression of survival/antiapoptotic genes is upregulated. The activation of NF-κB transcription factor by TRAF2 signalling pathway has been recognized via NF-κB–inducing kinase (NIK) and the inhibitor of κB kinase (IKK) complex. NIK is a key enzyme for the alternative activation pathway of the NF-κB [27], where; IKK which consists of 2 subunits (catalytic: IKK-α, IKK-β and regulatory: IKK-γ), starts phosphorylate the inhibitory IκBα protein. This phosphorylation leads to the dissociation of IκBα from NF-κB. NF-κB, which is now free to migrate into the nucleus and activates the expression of at least 150 genes; some of which are anti-apoptotic (Figure 1).

Since NF-κB is the major survival factor in preventing TNF induced apoptosis, thus the inhibition of this transcription factor may develop the efficiency of apoptosis-inducing cancer therapies. NF-κB activation in many human cancer cells is aberrant or constitutive, and its role in the regulation of the apoptosis–proliferation balance in malignancies specify its task in oncogenesis. In apoptosis TRAF-1 is predominated, where IKK does not show phosphorylation, thus dissociation of NF-κB/IκB-α is unreachable and entry the nucleus is forbidden. Upon TNF treatment of cancer cells, the healthy endothelium stays intact as it is insensitive towards TNF by its lack of TNFR-1 expression on the membrane. While, tumor endothelium binds TNF by TNFR-1, and the selectively targeted tumor vessels are gradually not efficient and regress.

2 Conflict of interest

Author has no conflict of interest.

3 References

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Fig. 1 TNF survival pathway


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