Tumor Necrosis Factor on Cellular and Humoral Immunity among End Stage Kidney Disease Patients

Mahmoud Mohammed Khaled [1], Mohamed Ali Fahmi Zanaty[1], Niveen S. S. Sakla [1], Ali Moustafa Shendi [1], Mustafa N.M. [2]

[1]Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt.

[2]Clinical Pathology Department, Faculty of Medicine, Zagazig University, Egypt.

Corresponding author: Mahmoud M. Khaled, Email: mahmoudkhalid282@gmail.com

Abstract

The burden of end-stage kidney disease (ESKD) on the world's health system is rising quickly. Low- and middle-income nations are disproportionately affected by the inability to provide care for many individuals who are at risk of and in need of treatment for ESKD. Similar to individuals with other types of acquired immune deficiencies or those undergoing immunosuppressive therapy, patients with chronic renal failure are at significant risk for developing infectious problems. Multiple factors, including uraemic intoxication, altered renal protein metabolism, and particular side effects of renal replacement treatment, all contribute to secondary immune failure in uraemia. Infections still rank as the second most common cause of death, and they are frequently detected in uraemic patients. The tumor necrosis factor (TNF) and its corresponding receptor superfamily (TNFRSF) mediate developmental, homeostatic, and stimulus-responsive processes in many organ systems. The ligands and receptors in TNF superfamilies form communication pathways between many different cell types.The aim of the present study was to review TNF on cellular and humoral immunity among end stage kidney disease patients.

Keywords: Tumor Necrosis Factor; End Stage Kidney Disease; Humoral Immunity

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INTRODUCTION

Loss of renal function is closely associated with an environment that is pro-inflammatory and has a correspondingly compromised immune system **(1)**. The immune system is classically divided into innate and adaptive compartments although multiple interactions between these compartments exist. The innate immune system offers a direct and nonspecific response to infection and tissue injury **(2)**.

Patients with end-stage renal disease (ESRD) are affected clinically in a wide range of ways, both in terms of morbidity and death, by the immune system deficiency caused by uraemia. These patients have a higher risk of developing tumors linked to viruses, are more sensitive to

infections, and do not respond well to routine vaccinations. Proinflammatory cytokines may cause oxidative stress, whereas oxidative stress may cause an inflammatory immune response in patients with ESRD (2,3). Increased oxidative stress and immune cell activation are related phenomena that are most likely to cause the proinflammatory milieu in these patients (4).

ESRD has a detrimental effect on both the innate and adaptive cellular immune systems. However, each cell type is affected to a different extent with regard to their numbers and function. Signs of activation, loss of function or a combination of both might be found (2).

In patients with ESRD, inflammation is strongly associated with an increased risk of atherosclerotic disease (5). As activated T cells, monocytes and macrophages have critical roles in the formation of atherosclerotic plaques, the two major causes of death in patients with ESRD are cardiovascular disease and infection which related to uraemia-associated changes of the immune system (6,7).

A striking feature of the immune system in patients with ESRD is the remarkable decrease in numbers of cells of the lymphoid cell lineage (that is, T cells, B cells, NK cells and plasmacytoid dendritic cells) compared with those of the myeloid lineage (such as monocytes and PMNs), which might be increased in number. T cells and B cells from patients with ESRD have increased expression of proapoptotic molecules and are prone to activation-induced apoptotic cell death (3,4).

The proinflammatory milieu in ESRD patients is also closely associated with decreased cellular immunity although true causality is difficult to prove. For example, uraemia-induced activation of T cells leads to upregulation of cytokine receptors (including receptors for IL-2 and tumour necrosis factor [TNF]) but a subsequent decreased responsiveness of the activated cells to exogenous IL-2 or TNF a phenomenon known as tachyphylaxis (8,9). Other mechanisms leading to inflammation and decreased cellular immunity, such as activation-induced apoptosis and differential outgrowth of proinflammatory immune cell populations, are also important in uraemia-associated immune dysfunction (7).

TNF superfamily

The tumor necrosis factor (TNF) is a critical factor in eliciting rapid inflammatory events acting through two distinct receptors, TNFR1 and TNFR2 (10). Ligation of these receptors results in activation of caspases, E3:ubiquitin ligases, or both. Death domain containing receptors, such as TNFR1, recruit caspase 8, whereas lymphotoxin-b receptor (LT-bR) forms an E3 ligase liberating the nuclear factor k-light-chain-enhancer of activated B-cell (NF-kB)-inducing serine kinase (NIK) from ubiquitination and degradation (11). LT-bR signaling plays a key role in lymphoid organogenesis and homeostasis of lymphoid tissue microarchitecture. Herpes virus entry mediator (HVEM), TNFRSF14 acts as a molecular switch between proinflammatory and inhibitory signaling by serving as both ligand and receptor for multiple ligands (12). The cross-

utilization of ligands by HVEM, the LT-b receptor, and the two receptors for TNF create a network of signaling systems that together form a broader network of pathways regulating inflammation, innate and adaptive immune responses **(Fig. 1)**. The critical issue currently being addressed is interpreting these molecular pathways with physiological processes, particularly in the context of host defense **(13)**.

Several studies have suggested the existence of a functional cross-talk between TNFR1 and TNFR2, which is of great biological relevance. Due to the existence of a complex regulation network after the activation of the receptor, the final cellular response depends on the cellular context and the microenvironment conditions **(9,10)**.

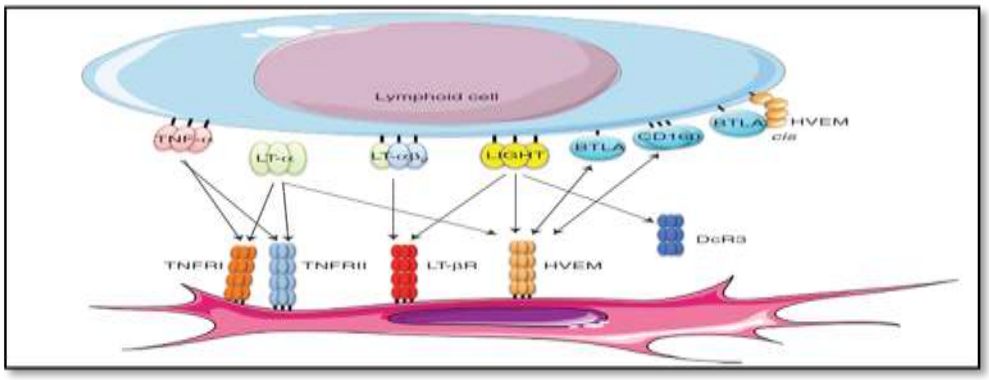

Figure (1): The lymphotoxin LIGHT-related network. The diagram depicts the binding interactions between cytokines and receptors related to lymphotoxins. The arrows define the specificity of the ligand–receptor interactions. Arrowheads define the directionality of signaling, with dual arrowheads defining bidirectional signaling. The TNF-related ligands include TNF-a, LT-a, LT-a1b2, and LIGHT (TNFSF14) and are shown as trimers in their membrane-bound form and expressed in lymphoid cells. Their cognate receptors, TNFRI, TNFRII, LT-bR, and HVEM (TNFRSF14), are expressed in stromal and myeloid cells. Decoy receptor-3 is secreted and also binds Fas ligand and TL1A (TNFSF25) (not shown). HVEM binds the Ig superfamily members BTLA and CD160, which form bidirectional-signaling pathways. BTLA and HVEM are coexpressed in lymphocytes forming a complex in cis.Not shown in this diagram are herpes virus proteins gD and UL144that signal viaHVEM or BTLA. DcR3, decoy receptor 3 **(13)**.

Tumor necrosis factor superfamily protein 14 (TNFSF14), also called as LIGHT or CD258, is a 29-kD type II transmembrane protein expressed primarily on activated T lymphocytes and other immunocytes **(14)**. TNFSF14 plays an important role in immune and inflammatory responses and can exist in a soluble form by proteolytic cleavage **(13)**. Recently, TNFSF14 contributes to tissue remodeling and fibrosis, which are initiated by inflammatory conditions such as skin fibrosis, pulmonary fibrosis, and asthmatic airway remodeling, and rheumatoid arthritis **(15)**. TNFSF14 expression is induced by epithelial damage and directly increases the level of primary

human bronchial epithelial cells (hBECs) undergoing EMT and expressing matrix metallopeptidase-9 (16).

An evidence of the role of TNFSF14 pathway in kidney fibrosis development, indicating that disturbing the TNFSF14 signaling pathway can be a useful immunotherapeutic strategy for kidney fibrosis in humans (14).

Role of TNF superfamily in immunity, inflammatory response in HD

Decoy receptor 3 (DcR3), a member of the TNF receptor superfamily, is an antiapoptotic soluble receptor considered to play an important role in immune modulation. DcR3 may participate in immune suppression (17). Alternatively, DcR3 may have proinflammatory functions. An excessive inflammatory response to various forms of endothelial injury to an artery is characteristic of the atherosclerotic process. Atherosclerosis involves various inflammatory mediators including adhesion molecules, chemokines, and cytokines (18). DcR3 levels are elevated and have close associations with inflammation in hemodialysis patients. Serum DcR3 levels correlate with a clinical history of CVD and are an independent predictor of mortality. The association of DcR3 with mortality in hemodialysis patients may be explained, at least in part, by its proinflammatory effects (19).

TNF-like weak inducer of apoptosis (TWEAK, TNFSF12) is a member of the TNF superfamily of structurally related cytokines (20). The human TWEAK gene encodes a 249-amino acid type II transmembrane glycoprotein (30 kD). TWEAK may be expressed as a full-length, membrane-bound protein and as a 156-amino acid, 18-kD soluble protein, (sTWEAK) that results from proteolysis of TWEAK (21). TWEAK gene is expressed in many tissues, including brain, kidney, heart, arterial wall, monocytes and macrophages. In contrast, the expression of its receptor, fibroblast growth factor-inducible 14 (Fn14) is usually low in healthy tissues, including the normal vascular wall (22). Binding of TWEAK to Fn14 mediates different biologic effects, such as induction of cellular growth and proliferation, osteoclastogenesis, angiogenesis and, in an inflammatory microenvironment, stimulation of apoptosis (23). Moreover, TWEAK attenuates the transition from innate to adaptive immunity , activates nuclear factor kappa B signaling pathway, and induces the expression of different proinflammatory cytokines and cell adhesion molecules (21,24).

HD patients have lower sTWEAK levels and a lower range than controls with normal renal function. Within the HD population range, high sTWEAK plasma levels have additive effects to the high cardiovascular and all-cause mortality of HD patients with systemic inflammation through pathways that may relate to increased muscle wasting. Thus, the combined use of IL-6 and sTWEAK may help to identify a subpopulation of HD patients at particularly increased mortality risk (22).

Recently identified soluble circulating osteoprotegerin (OPG), a member of tumor necrosis factor receptor family, is the osteoclastogenesis inhibitory factor (OCIF). It acts as a "decoy" receptor for receptor activator of NF-kB ligand (RANKL) and antagonizes RANKL/RANK activity. This way OPG exerts the protective effect on bone, which is also important in hyperparathyroidism (25).

Renal bone disease is one of the most common potentially debilitating complication affecting patients with chronic renal failure. It cannot be explained simply by vitamin D deficiency and/or parathyroid hormone (PTH) hypersecretion, since bone remodeling process is affected by numerous local modulators: cytokines, receptors and growth factors (26). A new insight into the regulation of bone metabolism in recent years has been made by study of receptor activator of nuclear factor (NF)-κB (RANK)/RANK ligand (RANKL)-osteoprotegerin (OPG) system. In short, RANKL, also known as tumor necrosis factor-related activation-induced cytokine (TRANCE), osteorotegerin ligand (OPGL) or osteoclast differentiation factor (ODF), is a membrane-associated protein on osteoblasts lineage cells, that binds to RANK receptor located on osteoclasts to stimulate osteoclastogenesis, thus activating mature osteoclasts and inhibiting the apoptosis of these cells. Soluble circulating OPG, or osteoclastogenesis inhibitory factor (OCIF) is a member of tumor necrosis factor receptor family and acts as a decoy receptor for RANKL and antagonizes RANKL/RANK activity. In this way OPG exerts an important protective effect on the bone, which was shown also after administration of OPG to postmenopausal osteoporotic women (24).

It was observed increase level of OPG in hemodialysis patients might protect bone against intensive bone loss in this type of secondary hyperparathyroidism but it is not likely that this is mediated by increased bone formation (27).

A high circulating OPG level is reported to be a risk factor for upregulated inflammatory markers, disturbed immune response, vascular calcification and mortality in HD patients (28).

TNF-related apoptosis-inducing ligand in hemodialysis patents

TRAIL and its receptor system are expressed widely in a variety of cells of the innate and adaptive immune system (29). As the name suggests, TRAIL induces apoptosis through its death receptors 4 (DR4; TRAIL-R1) and 5 (DR5; TRAIL-R2) (30). On the other hand, the anti-apoptotic property of TRAIL is also associated with binding to decoy receptors (DcR1; TRAIL-R3 and DcR2; TRAIL-R4) and the soluble decoy receptor (osteoprotegerin). TRAIL and its receptor system therefore appear to regulate immunity by maintaining a fine balance between apoptotic and antiapoptotic actions (31).

Emerging evidence has also demonstrated that TRAIL is involved in atherosclerosis and cardiovascular disease (CVD) which are deeply linked to immune and inflammatory processes coupled with dyslipidemia (28). In vivo studies have clearly shown that TRAIL acts as an anti-

atherogenic factor (32). Cross-sectional and longitudinal studies in humans also suggest anti-atherogenic functions of TRAIL (33).

A low TRAIL level was associated with disrupted immune response to infections and was a predictor of all-cause and infectious mortality in male HD patients independent of other risk factors. They suggested that serum TRAIL can predict poor prognosis in HD patients (34).

Clinical implications

If premature ageing of the immune system in patients with ESRD was directly related to uraemia or inflammation, one would expect a reversal of T and B cell lymphopenia and a reduction in numbers of CD^{4+}, CD^{28-} T cells and $CD14^{+}$, $CD16^{++}$ monocytes after kidney transplantation. However, several studies have shown no effect of kidney transplantation on these cell populations, although a rapid decrease in the levels of proinflammatory cytokines, such as IL-6 and TNF, was observed. Treatment with immunosuppressive medication and incomplete restoration of renal function also influences the function and composition of the immune system after kidney transplantation (35-38).

The relative importance of each uraemia-associated immune cell dysfunction cannot be established with certainty. However, it is now clear that severe impairment in the generation of fully differentiated, antigen-specific T helper cells as a result of uraemia explains the reduced T-cell-dependent vaccination responses of patients with ESRD (39,40). The lack of maintenance of serological vaccination responses in these patients might be related to increased activation-induced apoptosis of both memory T and B cells. However, the cellular and long-lasting serological response to a highly potent antigenic challenge, indicates that adequate responses can be achieved in these patients when their immune system is optimally stimulated. Defective T-cell responses might also explain the substantially increased risk of tuberculosis in patients with ESRD (41).

Therefore, anti-TNF-α drugs can stabilize renal function in patients with chronic kidney disease based on the difference in the annual change of eGFR, suggesting that anti-TNF-α drugs might be a potential treatment option for patients with CKD. Although there is currently no validated indication of anti-TNF-α treatments in kidney diseases, TNF-α inhibitors may be a therapeutic option in patients with CKD (42).

CONCLUSION:

A proinflammatory environment and functional deficiencies in nearly all innate and adaptive immune cell populations are linked to progressive loss of renal function.

The increased susceptibility of individuals with ESRD to viral and bacterial infections, their poor vaccine responses, and their increased risk of malignancies may be explained by the combined impact of increased immune cell activation and reduced immune cell function.

Particularly remarkable immunological similarities between elderly people in good health and those with ESRD point to the possibility of early immunological ageing in ESRD patients.

We believe that further research is still necessary to clarify the prognostic and therapeutic role of TNFRs in clinical nephrology.

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