Immunomodulators: interleukins, interferons, and the OKT3 monoclonal antibody

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Introduction

The term cytokines includes interleukins, chemokines, growth factors, colony stimulating factors, and tumor necrosis factors (TNF). These molecules are involved in cell injury and repair, inflammation and its regulation, and apoptosis.

In the first part of this chapter, we review the renal toxicity of the cytokines currently in clinical use. In the second part, we describe the cytokine-mediated nephrotoxicity associated with the use of the OKT3 monoclonal antibody in transplant recipients.

Cytokine associated renal dysfunction is regularly observed in the setting of sepsis syndrome or systemic inflammatory response syndrome. Systemic inflammatory response syndrome is often used as a model for evaluating the renal effects of various cytokines. During systemic inflammatory response syndrome, it has been observed that even in the absence of systemic hypotension, acute tubular necrosis can occur. Certain cytokines are released during systemic inflammatory response syndrome that mediate peripheral vasodila-
tion in the absence of systemic hypotension. The renal response to peripheral vasodilation is renal vasoconstriction and reduced renal blood flow. One can appreciate that in the setting of renal ischemia, it is difficult to conclusively attribute the etiology of acute tubular necrosis to the direct nephrotoxic effects of cytokines much less any individual cytokine among the cascade of mediators which produce the shock syndrome. The cytokine release syndrome associated with OKT3 administration, as discussed later in this chapter, is similar to systemic inflammatory response syndrome. In both syndromes, TNF-α is the initiator or central mediator of the cytokine cascade.

The crucial role of TNF-alpha in cytokine-associated renal dysfunction

Tumor necrosis factor α (TNF-α) is a pro-inflammatory cytokine which augments its own production and the synthesis of other inflammatory mediators. It stimulates the pyrogen, IL-1β and regulates genes coding for other inflammatory mediators such as IL-1, IL-6, IL-8, and macrophage inflammatory protein. Endotoxin is the most studied stimulator of TNF-α but other cytokines, various phospholipases and protein kinases, and some toxic agents also participate in its activation. There are two TNF-α receptors and two distinct families of adaptor proteins or TNF-α receptor-associated factors that can activate different cytosolic signaling cascades (death domain homologs and signaling pathways such as mitogen-activated protein kinase and extracellular signal-regulated kinase) leading to activation of a variety of nuclear transcription factors, especially NF-kappaB [1]. The plasticity of this system helps to explain the number and complexity of TNF-α activities (Table 1).

TNF-α and interleukin-1 (IL-1) are the two major cytokines implicated in the pathogenesis of systemic inflammatory response syndrome. Inhibition of these cytokines with anti-cytokine antibodies or receptor deficient knockout mice is associated with prevention of renal injury, but the mechanism may be simply preventing hypotension. The data do not support a direct role of IL-1 in the pathogenesis of acute renal failure.

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**Table 1. TNF-α actions [2].**

1. Induces synthesis of active proteins by causing changes in gene expression.
2. Induces both cell necrosis and cell apoptosis
3. Mitogenic for fibroblasts, hepatocytes, smooth muscle cells, and lymphocytes.
4. Increases natural killer, endothelial, macrophage/monocyte, neutrophil, and lymphocyte cell activity.
5. Stimulates production of adrenocorticotropic hormone and thyroid stimulating hormone.
6. Stimulates muscle cell glycolysis and glycogen synthesis
7. Stimulates synovial fluid synthesis of prostaglandine-D2, plasminogen activator, collagenase, hyaluronic acid
8. Major role in inflammation by providing cell signals and regulating genes that code for IL-1, IL-6, IL-8, macrophage inflammatory protein, granulocyte macrophage-colony stimulating factor, intercellular adhesion molecule 1 (ICAM-1), and endothelial leukocyte adhesion molecule 1 (ECAM-1)

**Table 2. Tumor necrosis factor-mediated renal diseases [3].**

1. Ischemia and reperfusion-induced acute tubular necrosis
2. Endotoxin induced acute renal failure
3. Renal injury models such as aminonucleoside-induced nephropathy and Adriamycin-induced nephropathy
4. Anti-glomerular basement membrane glomerulonephritis
5. Immune complex glomerulonephritis
6. Focal proliferative and exudative glomerulonephritis
7. Lupus nephritis
8. Diabetic nephropathy