The role of TNF in lung immunopathogenesis during influenza infection

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Abstract
Influenza is a highly contagious respiratory disease. Yearly epidemics and pandemics account for high morbidity and mortality worldwide. Lung immunopathology is a major factor causing death following influenza. The classically proinflammatory cytokine TNF plays a dual and biphasic role at different times postinfection. While it does have pro-immune roles in the beginning stages, TNF acts as a negative type 1 immune regulator at later points of infection. TNF controls the level of immune activation and has a key role in preventing lung immunopathology and aberrant tissue remodeling.

Keywords: influenza virus, lung immunopathology, TNF, tissue remodeling

Introduction
Acute pulmonary influenza infection is a very common and highly contagious respiratory disease. Annual worldwide influenza epidemics account for a significant number of deaths, particularly in high risk populations such as children, the elderly, and people with chronic illness. The influenza viruses are responsible for more than 100,000 hospitalizations and 20,000 deaths each year in the United States alone. Influenza viruses of varying pathogenicity not only cause annual epidemics, but also continue to cause unpredictable and perilous worldwide pandemics. These include the 1918 influenza pandemic that killed over 50
It is well established that lung immunopathology is one of the main causes of influenza-related morbidity and mortality. Recent studies using experimental animal models have significantly enhanced our understanding of the complex mechanisms involved in the immunopathogenesis during influenza infection. This involves acute inflammatory responses including the role of cytokines and chemokines.

Current studies together suggest that carefully selected targeting of certain cytokine pathways may improve influenza immunopathology without negatively affecting viral clearance, which would be the ideal treatment. However, cytokine biology is complex, as most cytokines are required at proper levels and at specific times in the immune response, and any deviation from this well-controlled expression can cause complications such as extensive lung immunopathology. Also, proper expression of immunoregulatory cytokines is essential in the return to homeostasis during the resolution phase of influenza infection.

TNF plays an important immunoregulatory role during influenza immunopathogenesis. This finding adds to recent studies that have discovered immune suppressive roles for the classically proinflammatory cytokine [9-10, 11]. It has been found that TNF is not required for influenza clearance and thus plays a redundant role in the early times of the infection, as immune responses are effectively initiated to clear the virus in TNF-deficient hosts. However, these same responses that successfully clear the virus are excessive and prolonged, culminating in lung immunopathology. Therefore, it has been shown that TNF plays a differential and biphasic role during the course of primary influenza infection. In the early phase of infection, it is proinflammatory, and may in fact contribute to the 'cytokine storm' and immunopathology, seen particularly in cases of highly pathogenic influenza. However, TNF is immunoregulatory in later phases of infection after viral clearance. This role is in agreement with the pleiotropic nature of TNF and with its role in apoptosis, which is reflected in the reduced T cell contraction following viral clearance in our model [12, 13]. Recent evidence has also shown an antifibrotic activity of TNF in various models, including idiopathic pulmonary fibrosis (IPF) [14, 15]. Interestingly, it has been also found that TNF is anti-fibrotic during influenza infection, through suppression of profibrotic chemokine MCP-1 expression. Thus, it has been identified that the dysregulated MCP-1 and in turn TGF-1 responses represent an important molecular mechanism in aberrant tissue repair and heightened immunopathology in influenza.

TNF depletion has been widely implemented as a means to counter inflammatory conditions in humans [16-17]. It is needed caution for clinical use of such therapeutics as they may worsen influenza-associated immunopathology during flu seasons or epidemics.

Interestingly, a study found that treatment of RA patients with etanercept (a soluble TNF receptor) led to increased peripheral T cell reactivity to microbial antigens that included influenza [17]. Several studies have also indicated that TNF blockade with infliximab (a monoclonal antibody) increases T cell reactivity [18, 19]. As such, it has been suggested that in autoimmune diseases in which TNF blockade is therapeutic (RA, Crohn’s disease, psoriasis) the overproduction of TNF is part of the innate immune response and released by macrophages, rather than by T cells such as in diseases where neutralization of TNF worsens disease severity (MS, diabetes, mouse models of EAE and lupus) [12, 13, 16].

However, to date there is little evidence showing that patients treated with TNF inhibitors exhibit more frequent or severe influenza infections. Clinical trials of the safety and immunogenicity of influenza vaccination in patients with RA have shown that the vaccine induces an adequate humoral response and does not induce clinical exacerbation of RA [20, 21]. There is a lack of reports of influenza illness itself in RA patients being treated with TNF inhibitors [22]. However, as mentioned above, TNF deficiency may have stimulating effects on T cell activity against microbial antigens and may assist in the generation of CTLs to clear the infection, as was shown in TNF inhibitors model.

Thus, an adequate humoral response following immunization and influenza viral clearance following infection may occur in patients under TNF deficiency, which is in agreement with our model. However, the question still
remains about the fate of such patients at later times post-infection after the virus is cleared which is when TNF acts as a negative regulator preventing lung immunopathology. Also, RA patients are concurrently on glucocorticoid immunosuppressive therapy used to control the disease, which may mask the effect of TNF deficiency, where TNF deficient mice had excessive inflammatory responses including cytokine and chemokine expression that led to fibrosis and immunopathology.

Conclusion

Nevertheless, influenza patients on TNF inhibiting medication should be more closely monitored, including at later stages after the virus has been cleared and the lung architecture is returning to homeostasis, in order to prevent complicating lung disease that may occur under TNF deficiency.

References

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