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Cytokines Network and Influenza Virus Infection

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Abstract

Influenza virus is the common trigger for cytokines. Excessive cytokine response can lead to different extent pulmonary injury while defending pathogens, which depends on the pathogenicity of the virus and the strength of host response. Insight of the host reaction and the kinetics of cytokines network response can guide the clinical diagnosis and treatment, which can help reduce the mobility and the mortality.

Keywords: Cytokine; Influenza virus; Lung injury

Cytokines play an important role in innate immune system recognition and rapid clearance of pathogens in mammalian at the cost of causing tissues injury, which also can regulate the innate immunity and adapt immunity [1]. Adequate cytokine activation enhances the ability of defending pathogens. However, excessive activation of the cytokine responses may destroy the homeostasis and lead to pathological inflammatory consequences [2].

An inflammatory response flaring out of control is known as "cytokine storm". The term of "cytokine storm" was first coined by Ferrara JL to describe their observations in graft-versus-host disease (GVHD) [3], after which it began to appear more frequently in the scientific researches about acute lung injury induced by the influenza A viruses. Previous researches show that influenza A viruses were the most common pathogens during respiratory infection which can induce different cytokines profiles in lung tissues and have a significant influence on patients' prognosis [4]. Different subtypes of influenza A viruses can raise various network of cytokines, even in the same species.

The cytokines can act as pro-inflammatory or anti-inflammatory in the host response, and the advent of pro-inflammatory cytokines usually accompanied with consistent presence of anti-inflammatory cytokines [5]. Once the balance between anti- and pro- inflammatory response was broken, it would have irreparable consequences.

The cytokines including IL-1β, IL-1Ra, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-13, IL-17, G-CSF, GM-CSF, IFN-α, IFN-β, IFN-γ, TNF-α, IP-10, MCP-1, MIP-1α, MIP-1β, RANTES, keratinocyte-derived chemokine (KC) [6-9], which were reported to aroused to some extent in the serum samples of patients infected with influenza A virus, and most of which can recruit macrophages, neutrophils and other polymorphonuclear cells to inflammatory sites [2,10]. Previous studies showed that pro-inflammatory cytokines TNF-α, IL-6, IP-10 are excessively elevated in infections caused by highly virulent subtypes such as H5N1,2009 pandemic influenza A virus (H1N1) [11,12], which are consistent with findings in SARS [8,13], compared to the seasonal influenza. On 31 March 2013, an explosive human infection with a novel reassortant avian influenza H7N9 virus has recently been reported in China. Researchers also grasped the significant increased levels of IL-6,IP-10,TNF-α and MCP-1 in the serum gathered from H7N9 patients[14]. Similarly, significant increase of IL-6 and TNF-α was probed in the H1N1 with bacterial co-infection group [15], indicating that TNF-α, IL-6, IP-10 may be the key contributors in virus mediated severe respiratory diseases, which would lead to Acute Lung Injury(ALI) or Acute Respiratory Distress Syndrome (ARDS) and add the morbidity and mortality. On the other hand, anti-inflammatory cytokine appears somewhat later as the body attempts to control the acute systemic inflammatory response. For example, IL-10 is a cytokine with pleiotropic effects in immunoregulation and inflammation, which can downregulate the expression of Th1 cytokine and can recruit fibrocytes into the lung [16,17].

The expression of cytokine is associated with the condition of the patients. The IL-6 is lower in small-for-gestational-age (SGA) neonates / appropriate-for-gestational-age (AGA) neonates/children than in the adults [18,19]. Additionally, the pessimistic emotions were correlated with lower Th1 cytokine (IL-2, IFN-γ) expression during virus stimulation, whereas optimism contributes to greater cytokine responses. It appeared to be more common than those between mood and the Th2 cytokine response [19]. Furthermore, compared to non-asthmatic patients, asthmatic patients also show higher level of IL-5, histamine, protease during virus infection, which are allergic [20,21].

The amplified situation of cytokine expression was proved by multiple researches, but the mechanisms remain unclear. It is known that influenza virus may escape the cytokines' antiviral effects and consistent replicate [22], the increased viral load may mount host cytokine response, such as IL-1Ra, IL-6, MCP-1, TNF-α and IP-10 [6, 23], and cause hypercytokinemia. Moreover, as the cytokines secreted, it appears to have secondary stimulation. For example, when treated with TNF-α, differentiated astrocytes can express IL-6 as well as other cytokine; it is not the case in turn [24]. IFN-γ can stimulate the delivery of IP-10 and MIG, and they can modulate the Th1 cellular immune response in influenza infection [25,26]. Likewise, IFN-α, IFN-γ, IL-1β can affect the secretion of IL-6 and IL-12 to various degrees as well [27-29].

There are many complete researches about the relationship between cytokines, and some cytokine regulators are already licensed for human use, such as IL-2 and interferon (IFNs) [30]. Nevertheless, it is limited in guidance on the control of the cytokine storm, and the threaten caused by influenza A virus still exist. Base on that, scientists turn to study the effect of different cell types on initiation and amplification of the cytokine storm that follow virulent influenza infection. It shows

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that diversified types of cells have capacities for secreting cytokines, including macrophages, neutrophils, though fibrocytes and endothelial cells [5]. Previous studies show that the sphingosine-1-phosphate (S1P) signaling system acted as immune response modulator is related to cytokine amplification during influenza virus infection [31]. Infected mice treated with the AAL-R, a promiscuous S1P receptor agonist [32], or the $S1P_1$-receptor specific agonist, CYM-5442 show suppression of early inflammatory cells recruitment through dampen cytokine production by lung endothelial cells [33]. The achievement provides insight into immune cell trafficking and immune responses points to a new shield for cytokine storm.

In summary, monitoring the change of those key cytokines as biomarkers, such as IL-6, TNF-α, while improving the efficiency of virus detection goes a long way towards evaluating the disease severity of flu patients and guiding physicians to institute immunomodulatory treatment accompanied by antiviral treatment. In the process of research on the network and the kinetics of cytokines responses, comprehending the critical part of host reaction should be attached to more importance.

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