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HOT TOPICS

Cytokines and the pathogenesis of HIV infection

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Cytokines are hormones of the immune system that are essential for important functions such as cell proliferation, differentiation and survival. They play an important role in both health and disease states. In this context, they have enormous therapeutic potential for treating patients through either the use of recombinant cytokines, soluble cytokine receptors, or neutralizing antibodies. For example, antibodies and soluble receptors that neutralize TNF have revolutionized the treatment of arthritis [1] and Crohn diseases [2].

In 1986, the existence of a dichotomy in the profile of cytokines secreted by T cell subsets (type 1 Helper T cells, T_H1 *versus* type 2 Helper T cells, T_H2) was proposed [3]. This dogma dominated for nearly two decades. T_H1 cells are characterized by the secretion of IL-2 and gamma-IFN. They are involved in cell-mediated immunity and represent a defense against intracellular pathogens including viruses and other microbial pathogens. Several, chronic inflammatory diseases such as multiple sclerosis and diabetes are associated with an exacerbated T_H1 response. The second subset, T_H2, is characterized by the production of IL-4, IL-5, IL-9, and IL-13. These are essential for defense against large extracellular pathogens such as parasites, and play a role in allergy responses [4]. The balance between two major cytokines secreted mainly by antigen-presenting cells (APCs), IL-10 and IL-12, that counteract each other, was considered to be critical in the development of T_H1/T_H2 cells [5-7]. Whereas IL-12 is essential for T_H1 development, IL-10 inhibits such differentiation by inhibiting IL-12 production and in turn favors T_H2 cells. Similarly, it was shown that there is a similar balance for gamma-IFN and IL-4 in the differentiation of T_H1 *versus* T_H2 cells, respectively. Therefore, environmental factors were considered to be critical in the establishment of T cell immunity.

Numerous reports in the 80-90s demonstrated that there was a deficit in cell-mediated immunity during HIV infection [8, 9]. Similarly, in non-human primate models of SIV infection that progresses to AIDS [10], a clear defect of T_H1 cells was shown [11, 12]. However, this defect was not compensated for by the expansion of T_H2 as is classically observed during parasite infections [13, 14], but was seen to be associated with abnormal programmed cell death or apoptosis [11, 15]. Finally, the dysregulation in the balance of IL-10 and IL-12 during AIDS was considered central in the progressive deterioration in cell-mediated immunity [14, 16-18]. Moreover, it has been shown that the same cytokines (IL-10 and IL-12), which control T helper cell differentiation and proliferation, were involved in dysregulated T cell apoptosis during HIV infection [14, 19, 20].

Among Type I cytokines that use the common cytokine receptor-gamma-chain, including interleukin-2 (IL-2), IL-4, IL-7, IL-9 and IL-15 [21], several have been reported to modulate *in vitro* apoptosis [20, 22-25], and have been evaluated *in vivo* either in HIV-infected patients or in SIV-infected monkeys to rectify cell-mediated immunodeficiency, as well as being tested as adjuvants in HIV-1-DNA vaccine regimens.

With the advent of the new century, other factors have been seen to be clearly involved in the control of the balance of T cell differentiation (see review [26]). In fact, it was observed that a component of IL-12, the IL-12p40 subunit, was also a component of IL-23 (together with IL-23p19) that stimulated cells to produce a newly identified cytokine named IL-17A (CTLA-8) [27, 28], revealing a new branch in the T cell lineage [29]. Therefore, naive T cells can differentiate during a primary antigen response into additional, polarized subsets such as regulatory T cells (Treg) [30] or T_H17 (see review [31]). Commutation between Treg *versus* T_H17 cell differentiation is determined by the presence of inflammatory cytokines such as IL-6, IL-1β and IL-21, concomitantly with the presence of TGF-β. In particular, higher levels of TGF-β have been observed during the acute and chronic phase of pathogenic SIV-infection of rhesus macaques [32-34].

This special issue of *European Cytokine Network* summarizes the recent advances in cytokine studies in the field of HIV infection, and the experimental trials performed during the past decade on immune-based immunotherapies to correct immunodeficiency.

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