FUNCTION OF CELLULAR IMMUNE FACTORS

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Introduction. Cellular immunity is mediated by cells of both specific and nonspecific defense: specific cells include helper T lymphocytes (CD4+) and cytotoxic "killer" T lymphocytes (CD8+), which are highly specialized for destroying virions as well as virus-infected cells. Nonspecific cells include macrophages and NK cells. The function of cellular immune factors is associated with suppression of viral replication, migration, and retention of macrophages, lymphocytes, and inflammatory cells at the site of infection.

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In addition, components of cellular immunity cause lysis of infected cells, releasing intracellular viruses for subsequent neutralization by antibodies, and also influence neighboring healthy cells, preventing their infection. For example, interferon production leads to increased synthesis of MHC-I, complement components C2 and C4, lymphotoxin, and other factors. Direct cytotoxicity is mediated by the close contact of T killer cells with the surface of infected cells, which are recognized through the presence of virus-specific membrane antigens [10,11,12,13,14].

Special studies of cellular immunity in patients with recurrent herpes infections have shown its insufficiency even during the inter-recurrence period. The activity of cellular immunity is a critical factor in preventing disease development and promoting recovery during infection. The importance of cellular immunity in resistance to viral infections is particularly evident in individuals with congenital T-cell defects, following thymectomy, irradiation, severe secondary immunodeficiencies (such as AIDS or oncopathology), immunosuppressive therapy, and similar conditions [1,2,3,4,5].

The T-cell branch consists of two main lymphocyte subpopulations: CD4+ (constituting approximately two-thirds of peripheral blood T cells) and CD8+ TCR+ (T-cell receptor-positive) [6,7,8].

According to modern concepts, human CD4+ T cells can be divided into two major functional phenotypes (analogous to murine T helpers): Th1 cells (inflammatory

T cells) and Th2 cells (conventional T helpers). Some researchers also describe Tr3 cells, first identified in mice with experimental autoimmune encephalomyelitis during oral antigen presentation. These cells predominantly produce transforming growth factor beta (TGF-β), a potent inhibitor of Th1 cells at local sites of inflammation, particularly in the brains of affected mice, which underlies the observed regression of key inflammatory signs [15,16,17,18,19,20].

The main criterion for differentiating T helper cells is their participation in the induction of either a predominantly cellular (Th1) or humoral (Th2) immune response. The induction of a particular Th-cell subset is determined by a combination of co-stimulatory molecules expressed by the antigen-presenting cell and the cytokine signals received by the T helper cell [9,10,11,12].

Understanding the mechanisms of isolated stimulation and suppression of Th1 and Th2 cells has practical applications. For example, IL-4 and IL-5 are involved in the induction of IgE synthesis in individuals with allergic diseases. Knowing that Th2 cells are suppressed by Th1 cytokines can allow, in certain cases, the achievement of tolerance to allergens [13,14,15].

CD8+ T lymphocytes represent a subpopulation of T cells that can also be divided into inducer and effector cells: the former predominantly produce a Th1-like cytokine profile (Tc1 cells, cytotoxic), while the latter display a Th2-like profile (Tc2 cells) (Table 3). Similarly, CD8+ T cells with a Th3-like cytokine profile have been described (Janeway, Ch. A., Travers, P., 1996).

The specific action of CD8+ cytotoxic T lymphocytes is mediated through the release of perforins, granzymes A and B, membrane-contact signals via Fas (CD95): FasL, mTNF (membrane-bound TNF) — TNF RI/II type, and secretion of cytokines such as TNF-α, TNF-β, IFN-γ, and TGF-β.

The prevailing cytokine profile of CD8+ T cells is Th1-like, primarily IFN-γ, TNF-α, and TNF-β, which strongly stimulate macrophages and NK cells. This phenotypic dominance is explained by the fact that naive CD8+ T cells, during differentiation (prior to antigen stimulation), are predisposed to develop into Tc1 cells. Regarding their main effector function — cytotoxicity — Tc2 cells are less effective than Tc1 cells, although they mediate cytotoxicity through similar perforin- and FasL-dependent pathways [16,17,18].

Given the distinctive cytokine secretion patterns of Tc1 and Tc2 cells, their ability to influence B cells and immunoglobulin production was of interest. It was initially assumed that CD8+ T cells directly lyse target B cells; however, an in vitro mechanism of “bypass helper activity” has been described. For example, stimulation with immobilized anti-CD3 antibodies caused Tc2 cells to focus their lytic activity toward the contact side with the plastic, while the opposite side could interact with B cells via CD40–CD40L signaling (switching IgM to IgG) and secrete IL-4, IL-5, IL-6, and IL-

13. In terms of helper activity strength, T cells are ranked as follows: Th2 > Th1 > Tc2 > Tc1. Thus, the main effect of CD8+ T cells on B cells is lytic, directed against infected B cells, while CD4+ T cells provide a helper effect (Mosmann, T. R., et al., 1997).

Similar to the Th1–Th2 system, Tc1 cells can influence Tc2 activity, and vice versa. Importantly, IL-4 from Th2/Tc2 cells suppresses the ability of Tc1 cells to produce IL-2 (and other Th1 cytokines) and proliferate in response to antigen stimulation, without affecting their cytotoxicity. Conversely, IL-2 from Th1 cells or exogenous IL-2 can induce proliferation of Tc1 cells. This establishes a balanced system of CD8+ effector phenotypes [19,20,21,22,23].

A critical aspect of persistent viral infections is the reduction of both specific and nonspecific immune responsiveness. The hypothesis of viral immunosuppression was proposed at the beginning of the 20th century.

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