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"HOST THERAPY" STRATEGY FOR TUBERCULOSIS AND ELIMINATION OF THE IMPORTANCE OF INTERFERON - GAMMA IN THE PATHOGENESIS AND THERAPY OF TUBERCULOSIS INFECTION

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Annotation. The possibilities of immunotropic drugs should be used in conditions of constantly changing properties of the pathogen (genotype, virulence, resistance to anti-tuberculosis drugs) with a prolonged, complication-prone and relapsing course of the disease with the formation of secondary immunological insufficiency requiring correction. As an adjunct to chemotherapy, HDT can be administered at the beginning of a standard treatment regimen to correct a general immunological imbalance or towards the end of treatment to enhance "host immunity" to prevent potential recurrence.

Keyword. Host-directed therapy, tuberculosis, mycobacterium tuberculosis, immunomodulation, interferon-gamma, pathogenesis of tuberculosis, immunotherapy, host immune response.

The high hopes of phthisiologists for the successful treatment of MDR/XDR tuberculosis (TB) patients are associated with highly effective drugs, unique in their mechanism of action – bedaquiline, delamanid, linezolid, which are especially important for short-term treatment regimens. However, MBT also develops resistance to these drugs. The emergence of MBT resistance to any new compound with anti–tuberculosis activity is a manifestation of biological adaptation to survival, which can negatively affect the effectiveness of tuberculosis treatment, especially with MDR/XDR. According to Arrigoni R, et al. (2022), due to the growing number of MDR-MBT strains, the possibilities of using natural and biological drugs such as probiotics, polyphenols, antimicrobial peptides and interferon-gamma (IFN-γ) have recently been intensively studied.

When developing tuberculosis drug chemotherapy regimens, the human body's own reserves are practically not taken into account, while protective immune reactions constantly occur in conditions of continuous struggle with the metabolic activity of MBT. The strategy of "host therapy" (HDT – host-directed therapy) is aimed at strengthening immune mechanisms that limit the growth of MBT, the progression of inflammation, and damage to lung tissue.

HDT does not directly target pathogens, which avoids the expansion of their drug resistance. In this case, an increase in the effectiveness of treatment is achieved by using auxiliary means aimed at enhancing responses in infected host immune cells, that is, pro-inflammatory or anti-inflammatory cytokines and immuno-metabolic processes are regulated.

The review examines in detail the application points and mechanisms of action of various drugs aimed at protecting host cells during the development of tuberculosis infection. Some anti-tuberculosis drugs have the ability to influence the kinetics of pro-inflammatory or anti-inflammatory cytokines. However, the most significant approach to changing the immunological profile in the process of tuberculosis inflammation and its treatment is the use of immunotropic drugs, the importance of which has increased with the increasing prevalence of MDR/XDR tuberculosis and low treatment success. The article highlights the central role of cytokine IFN-γ in the host body's response to MBT, related to the functions of macrophages and cytokine regulation of the immune response, and suggests numerous application points for HDT for the use of recombinant IFN-γ.

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The biological properties of MBT, especially virulence, affect the parameters of immunity, and the outcome of the tuberculosis process is determined by the state of the lymphocyte-macrophage link of the immune system and the production of cytokines that coordinate immunocompetent cells during the immune response. To facilitate survival in macrophages, MBTs rearrange energy metabolism, disrupting the main functions of mitochondria for the production of ATP and reactive oxygen species. Switching metabolism to glycolysis and the production of pro-inflammatory cytokines are an integral part of the macrophage's ability to elicit an effective immune response against MBT. A cytokine with pleiotropic properties acting on all key points in tuberculosis infection is type II interferon (interferon-gamma (IFN-γ)). IFN-γ stimulates hundreds of genes in macrophages and induces antimicrobial effector responses, including inducible nitric oxide synthase, the nitric oxide and oxygen pathway, phagocytosis, and autophagy. Nitric oxide produced by IFN-γ-activated macrophages induces apoptosis of infected macrophages by activating caspase, which ultimately leads to permeability of the outer membrane of mitochondria and the release of cytochrome C. The authors refer to experimental studies on the use of caspase inhibitors, as a result of which it was found that the growth of MBT in infected macrophages limits NO-induced apoptosis mediated by IFN-γ rather than direct toxicity of NO.

Under the action of IFN-γ, macrophages are activated, acquiring the M1 phenotype, which has a greater bactericidal ability, and accumulate in the primary infection site. Stimulated by IFN-γ macrophages produce large amounts of IL-12, which induces the differentiation of CD4+ Th0 T-lymphocytes into Th1, stimulates their proliferation, and inhibits Th2 cell proliferation.

IFN-γ synthesis is carried out by CD4+ Th1 lymphocytes, cytotoxic CD8+ T lymphocytes, natural killer (NK) cells, macrophages, dendritic cells, and B lymphocytes. Neutrophils can be an auxiliary source of IFN-γ. In patients with tuberculosis, neutrophils produce two types of interferons: type 1 interferons, which contribute to the progression of the disease, and IFN-γ, which stimulates the destruction of MBT by switching signaling pathways.

CD4+ Th1 lymphocytes, which produce large amounts of IFN-γ, TNFa, and IL-2, play a major regulatory role in the development of the immune response and type of tuberculous inflammation (productive or exudative). CD8+ T lymphocytes, in addition to producing IFN-γ and other pro-inflammatory cytokines, have direct cytotoxic activity against infected macrophages. However, as the CD8+ infection progresses, mitochondrial function in T cells is disrupted, dependence on glycolysis increases, and immune failure occurs due to a lack of bioenergy. Weakening of the immune response is the main condition for the development of the disease, and subsequently causes a delayed development of regression of specific changes and a prolonged course of the infectious process against the background of complex antibacterial therapy, even when using maximum doses of medications.

The productive type of tuberculous inflammation is characterized by relatively high levels of CD4+, CD8+-T-lymphocytes and pro-inflammatory interleukins (IL -β, IL -2, IL - 12, TNFa, IFN-γ). A decrease in the number of CD4+, CD8+ lymphocytes, the concentration of IFN-γ, and the predominance of the synthesis of anti-inflammatory cytokines (IL-4, -5, -S, -8, -10, -13) are characteristic of the exudative type of inflammation [1].

The results of studies analyzing the concentration of IFN-γ in the blood and its production in vitro in tuberculosis patients are contradictory. It has been shown that 89% of patients with newly diagnosed infiltrative tuberculosis have a reduced ability of blood cells to synthesize IFN-γ against the background of increased synthesis of anti-inflammatory IL-4 and IL-10, which is explained by depletion of lymphocyte-macrophage cells resulting from interaction with MBT [4]. Marked inhibition of IFN-γ production by peripheral mononuclears when stimulated by BCG antigen and

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whole blood cells in response to ESAT-S antigen was observed in patients with infiltrative tuberculosis with severe, progressive and complicated course of the disease. In patients with a favorable process, these indicators differed slightly from practically healthy individuals, due to a decrease in the functional activity of immunocompetent cells in severe patients [18].

The prevalence of the process and drug resistance of MBT has a significant effect on the level of secretion of endogenous IFN-γ and its production in response to mycobacterial antigens. As demonstrated in the study [42], MDR patients produced lower levels of IFN-γ upon ESAT-S stimulation (553 ± 11 pg/ml) compared with patients with drug-sensitive tuberculosis (1179 ± 163 pg/ml, $p < 0.05$). When studying immune parameters in patients with progressive fibrotic cavernous tuberculosis, a decrease in IFN-γ was found, which is more pronounced in cases of damage to both lungs [8]. According to the authors, the decrease in its production during the chronic unfavorable course of the disease is explained by the functional depletion of antigen-specific T cells or the suppression of MBT functional activity of T lymphocytes.

At the same time, studies [14] found that the induction of lymphocytes in vitro by cytokines IL-12/IL-27 led to an increase in IFN-γ secretion in infiltrative tuberculosis by 2.1 times, and in disseminated tuberculosis by 3.0 times compared with its baseline level. IFN-γ hypersecretion was associated with a low content of a subpopulation of T-lymphocytes with an intracellular content of IFN-γ (CD3+IFN-γ+) and an increase in the proportion of interferon-producing cells without the phenotypic marker of T cells (CD3-IFN-γ+). Similar results were obtained by the authors of another study [20], which concluded that IFN-γ hypersecretion was combined with a decrease in the total number of T-lymphocytes and the number of T-lymphocytes with intracellular IFN-γ content in the blood of patients. At the same time, the number of CD3-negative cells (CD3-IFN-γ+) increased significantly, especially in disseminated drug-resistant pulmonary tuberculosis. It was established [3] that hypersecretion of IFN-γ lymphocytes in vitro against the background of an increase in the number of (CD3-IFN-γ+) cells suggests that the main cytokine-producing cells in tuberculosis are not T lymphocytes, but NK cells. Previously, a similar conclusion was made by a number of authors who believed that an increase in the number of NK cells and an increase in their cytokine-producing activity is aimed at compensating for the insufficient functional activity of CD4+ lymphocytes, however, IFN-γ produced by NK cells does not have the specific effects of its T-lymphocytic homologue [2, 6, 21].

The individual genetic characteristics of a patient can significantly influence the response of target cells to IFN-γ. Back in 1993. Experimental studies have shown that mice with IFN-γ deficiency are more susceptible to M.tuberculosis infection, and the process is generalized [41, 34].Differences in the histological pattern during the initial phase of infection between control mice and mice with an altered IFN-γ gene, regardless of the method of infection, are described. Important differences included previously increased accumulation of granulocytes and more rapid and pronounced interstitial pneumonia in mice with a defective gene without significant differences in the amount of MBT seeded from the lungs [60]. As shown in the article [31], children with rare mutations in the IFN-γ genes were very susceptible to BCG and non-tuberculosis mycobacterial infections.

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