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THE FUNCTIONAL ROLE OF TRANSFERRIN RECEPTOR – TfR1

The article presents modern data on the functional role of the transferrin receptor - TfR1. The information on the significance of this receptor in the functioning of various cells of the body is generalized, and the diverse role of this receptor depending on the type of cells and the stage of their activation is shown.

Keywords: receptor, transferrin, TfR1, CD71, iron, erythrocytes, lymphocytes, ferroptosis, oncology.

Transferrin receptor (TfR1) - CD71 is expressed on virtually all cells in the body. It is a multiligand receptor that is able to bind and transfer into the cell not only transferrin, but also various proteins, viruses, chemotherapy drugs, bacterial toxins, plant toxins, DNA, oligonucleotides, short inhibitory RNA (siRNA) and enzymes [4, 11, 32, 40, 47]. TfR1 is most strongly expressed on placental syncytiotrophoblasts, myocytes, basal keratinocytes, hepatocytes, endocrine pancreas, spermatocytes and immature erythroid cells, reticulocytes, hepatocytes, endothelial cells of the blood-brain barrier [30, 41]. Transferrin is an essential component of cell growth and metabolic processes that require iron, including DNA synthesis, oxygen sensitivity, and the G1 to S phase transition in the cell cycle, electron transport, mitogenic signaling pathways and, in turn, cell proliferation and survival [10, 12, 23]. Consequently, fast-growing cells require more iron for growth and actively proliferating cells have a much higher level of CD71 expression than cells at rest [33]. In research [36] It has been shown that CD71 and ki-67 (the nuclear protein of actively proliferating cells) have the same expression pattern after stimulation of CD4 + and CD8 + cells, which makes it possible to assess the level of activation of cell proliferative activity by the level of CD71 +, without intracellular staining of the ki-67 protein. Simultaneous increase in CD71 + and ki-67 levels has also been proven in malignant neoplasms [19].

Transferrin belongs to endogenous signaling proteins called alarmines. During the invasion of pathogens, alarms result from the breakdown of cells and the subsequent release of enzymes that break down proteins such as transferrin into fragments [38, 46]. At the cellular level, the expression of the transferrin receptor protein is interrelated with the expression of the ferritin protein through the interaction of proteins sensitive to iron, with the regulatory element of iron on the 5'-untranslated region of ferritin mRNA and regulatory elements of iron on the 3 '-translated region of the mRNA of the transferrin receptor. Expression of TfR1 increases, and expression of ferritin decreases at a low concentration of cytosolic iron, an increase in the level of cytosolic iron has the opposite effect [22]. Regulation of TfR1 expression is provided not only by the level of intracellular iron, but also largely by the oxygen status of the cell, the presence of reactive oxygen species, and hypoxia [26, 51]. Hypoxia leads to stabilization of hypoxia-inducible factor-1α (HIF-1α), the main regulator of transcription of genes responding to hypoxia, including the transferrin receptor gene [44]. HIF-1α then moves to the nucleus, where it binds to a hypoxia-inducible element in the promoter region of the transferrin receptor gene. Hypoxia increases the formation of reactive oxygen species, increases the cytosolic labile iron pool and TfR1 expression, while proliferation is activated, but not ferroptosis [39].

CD71 + on tumor cells. The level of TfR1 expression by malignant cells is many times higher than that of normal cells of the body. It has been shown that TfR1 expression can correlate with tumor stage or cancer progression, and an increase in the TfR1 level on transformed cells is a poor prognosis in various types of cancer [33, 43, 49]. Recently, there has been a lot of research on the use of the transferrin receptor to «capture» tumor cells. The use of TfR1 for the isolation of malignant cells has an advantage over other methods, mainly based on the detection of epithelial cell adhesion molecules, because as an affinity target, it can separate almost any type of cancer cells, regardless of the origin of the disease, including non-epithelial [1, 33]. The transferrin receptor is an attractive target for targeted therapy [24, 42]. On the one hand, due to constant recirculation, TfR1 is used to deliver drugs directly to malignant cells; on the other hand, antibodies are actively used that block its natural function, which leads directly to the death of cancer cells [2, 34]. The drugs used for chemotherapy are toxic to the body due to their rapid diffusion and accumulation in the body, which leads to high intoxication. Through the use of TfR, drug delivery is significantly improved, which makes it possible to increase their intracellular concentration. This results in more efficient tumor targeting and enhances overall therapeutic efficacy. In addition, some drugs are conjugated with transferrin, which also allows the delivery of active substances directly to the cancer cell, preventing their degradation in the extracellular space. This significantly increases the safety of their use and patient survival. However, the problem of using drugs aimed at blocking the function of the transferrin receptor, or blocking the functioning of cells, indirectly through TfR1, is that virtually any cell in the body expresses the TfR1 receptor to a greater or lesser extent. Thus, when using drugs by means of TfR1, for the treatment of patients with malignant neoplasms, it is necessary to assess the harm / benefit ratio.

CD71 + erythroid cells (EC). High expression of transferrin receptors is characteristic of early precursors of erythrocytes in the intermediate phase of normoblasts, after which the expression decreases in the phase of reticulocytes [18, 35, 37, 45]. Maturation to erythrocytes results in loss of transferrin receptor expression in combination with suppression of the hemoglobin synthesis mechanism. Most mature erythrocytes do not express CD71. A high level in the circulation of CD71 + EC in newborns and in various pathologies of hematopoiesis, oncological processes. The detection of high concentrations of CD71 + EC in newborns, which have an immunosuppressive

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effect, allows a new look at the problem of «failure» of immune protection in newborns. EC CD71 + suppress innate, anti-infectious and tumor immunity [6]. Removal of these cells from the circulation restores resistance to neonatal infections, but, for example, the introduction of EC CD71 + in adult patients leads to the suppression of anti-infectious protection [17]. CD71 + erythroid cells - like other immunomodulatory cells such as Tregs - can use a variety of mechanisms to mediate immune regulation. They can suppress or modulate immune cell function through soluble factors such as TGF-β, arginase-2, cytokines and reactive oxygen species through cell-cell interactions (e.g. PD-1: PDL-1 / PDL-2, VISTA) [14].

A decrease in the level of CD71 + erythroid cells leads to an increase in the activation of immunocompetent cells in the intestine and the synthesis of pro-inflammatory cytokines (IL-6, TNFα) [15]. CD71 + cord blood erythroid cells suppress the proliferation of CD4 + and CD8 + cells [9]. The immunosuppressive role of CD71 + erythroid cells in relation to anti-infectious / innate immunity is balanced by the need to suppress active inflammation in the intestine as a result of active colonization by microflora in the first months of a child's life. Thus, a decrease in the activity of immunity in newborns can be considered as a physiological norm aimed at the formation of successful adaptation to new conditions. A similar immunoregulatory effect of CD71 + -ECs is exerted during pregnancy and is likely to play a decisive role in gestation and the formation of fetal and maternal tolerance. Maternal CD71 + erythroid cells suppress an aggressive allogeneic response against the fetus, such as a decrease in TNF-α and IFN-γ production through arginase-2 and PD-1 / PDL-1 activities. Their depletion leads to the failure of gestation due to the immunological rejection of the fetus. Similarly, fetal liver CD71 + erythroid cells exhibit immunosuppressive activity [8]. Expression of the transferrin-1 receptor and ferroportin was found on the placental syncytiotrophoblast and was polarized such that TfR1 was on the apical maternal membrane and ferroportin was on the basal fetal membrane, consistent with unidirectional iron transport from mother to fetus. Ferritin is highly expressed in the stroma, suggesting that fetal tissue can store and store iron. A decrease in CD71 + erythroid cells leads to the formation of inflammatory reactions due to a decrease in the production of IL-4 and IL-10, against the background of an increase in the concentration of TNF-α and IL-6 in the tissues of the placenta [8]. A decrease in the level and dysfunction of CD71 + erythroid cells was noted in patients with inflammatory bowel disease during pregnancy. Dysfunction of CD71 + erythroid cells contributes to the formation of a pro-inflammatory environment in the gastrointestinal tract, dysbiosis, a decrease in the level of Tregs is characteristic, against the background of a high concentration of IL-6 and TNF-α [31].

The number of erythroid cell precursors CD71 + increases significantly in patients with COVID-19, especially in moderate to severe disease [16, 25]. The high level of these cells is partly due to the strong immunosuppressive effect that forms in patients with COVID-19. CD71 + ECs are vulnerable to infection with SARS-CoV-2, due to the high expression of angiotensin-converting enzyme 2 (ACE2), which is used by the virus to attach and invade the cell, so the virus can spread through the bloodstream, causing local inflammation in the tissues. Immature erythrocytes CD71 + play an important role in the pathogenesis of HIV, due to the presence on their membrane of a large number of CD35 adhesion receptors and DARC chemokine receptor, which are the main target molecules for HIV. Immature CD71 + erythrocytes promote the persistence and transmission of HIV to uninfected CD4 + T cells [5]. In hepatocellular carcinoma tissues, intratumoral CD45 + CD71 + erythroid cells are able to suppress the activity of T cells due to the generation of reactive oxygen species, IL-10 and TGF-β by paracrine and intercellular contact, which plays an important immunosuppressive role in the tumor microenvironment and serves as a marker for predicting hepatocellular recurrence carcinomas [29].

The role of CD71 + on somatic cells. Expression of TfR1 on somatic cells plays a decisive role in the early stages of development. Thus, deletion of the TfR1 gene causes severe muscle atrophy, growth retardation, metabolic disorders and premature death. Deletion of TfR1 in adults is not so critical and does not affect survival, but it causes skeletal muscle atrophy and motor functional disorders similar to muscle atrophy observed after denervation [50]. A decrease in TfR1, but an increase in the level of the Slc39a14 protein on the cell membrane promotes labile iron accumulation in skeletal muscles, which leads to the activation of ferroptosis (FP) in old skeletal muscles [48]. Ferroptosis, the process of cell death caused by cellular metabolism and iron-dependent lipid peroxidation [20, 52]. Ferroptosis does not depend on the activation of caspases, the release of cytochrome C, an increase in intracellular calcium and other mediators of programmed cell death [21]. Ferroptosis is associated with diseases such as ischemic organ damage, cancer, and neurological diseases. The transferrin receptor can be a specific marker of ferroptosis. Ferroptosis is fatal for virtually all types of tumor cells, and the regulation of its activity is considered as one of the promising options for treating tumors [13, 53]. The transferrin receptor is activated in beta cells of the pancreas in the first weeks of the postnatal period, surface expression of CD71 is regulated in a glucose-dependent manner. Beta cells express higher levels of several other genes involved in iron metabolism, and iron deprivation significantly impairs beta cell function. With a deficiency of glucose in the beta cells of the pancreas, the expression of CD71 + increases. CD71 - is a postnatal beta-cell-specific marker and plays a central role in iron metabolism in the functioning of beta cells [3]. However, high expression of CD71 in the mesangium is responsible for the progression of IgA nephropathy. CD71 functions as a mesangial IgA receptor, binding of CD71 to circulating immune complexes (CICs) containing IgA1 leads to the deposition of CICs on the glomerular mesangium [7, 27]. SIgA bound to the apical CD71 + receptor on the surface of enterocytes avoids lysosomal degradation; this process ensures the transcytosis of bound proteins [28].

Conclusion. The function of the transferrin receptor is diverse, due to its ability to bind substances of various natures and transport them across the cell membrane. The use of TfR in the targeted treatment of cancer patients, actively studied in recent years, is a rather promising direction and is justified from the point of view of high expression of TfR by tumor cells. This method significantly reduces the toxic effect of drugs, but the question remains about how such drugs affect healthy cells in the body, which also express TfR. The emergence of new data on the functional immunoregulatory role of CD71 + erythroid cells allows a new look at the issue of the functioning of the immune system in children. Thus, new perspectives are opening up in studying the issue of «failure» of immunity in children and solving the issue of the need for immunostimulating therapy at an early age.

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THERAPEUTIC APPROACHES TO RESTORING THE ANTIATHEROGENIC FUNCTION OF HIGH DENSITY LIPOPROTEINS

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A low level of high density lipoproteins (HDLs) in blood plasma is considered to be an important risk factor for the development of atherosclerosis. The antiatherogenic function of HDLs is associated with their participation in the reverse transport of excess cholesterol from peripheral tissues to the liver. In addition, they have antioxidant, anti-inflammatory, antithrombotic and anti-infectious properties, which also contribute to their atheroprotective effect. Recent studies have shown that the structure and composition of HDLs can change under various pathological conditions, thus leading to the appearance of dysfunctional HDLs, which cannot perform protective functions in the body. This review is devoted to the analysis of modern approaches aimed both at increasing the level of HDLs in blood plasma and at maintaining and restoring their native functional properties.

Keywords: high density lipoproteins, approaches to increase antiatherogenic function.

Introduction. Large epidemiologic studies have demonstrated an inverse relationship between the concentration of serum cholesterol (Chol) in high density lipoproteins (HDLs) and the risk of developing cardiovascular diseases (CVDs). Each increase in the concentration of HDL-Chol by 0.026 mmol/l decreases the risk of developing coronary heart disease (CHD) by 2–3% [56]. In this connection, various approaches were devised to increase the HDL-Chol level. However, recent studies, particularly those where the transfer of Chol esters (eChol) was estimated using an inhibitor of cholesteryl ester transfer protein (CETP), revealed that an increase only in the level of HDL and HDL-Chol does not prevent cardiovascular diseases [48]. At present, the research interest is focused on estimating the functional state of HDL and HDL-Chol rather than their level.

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The main antiatherogenic function of HDLs is related to the reverse Chol transport (RCT); in addition, they possess antioxidant, anti-inflammatory, antithrombotic and anti-infectious functions, which also determine their atheroprotective action [6,8]. HDLs enhance the production of nitric oxide (NO), stimulate proliferation and migration of endothelial cells, and suppress inflammation and apoptosis processes [39]. HDL-associated enzymes paraoxonase 1 (PON-1), lecithincholesterolacyltransferase (LCAT), platelet-activating factor acetylhydrolase (PAF-AH), and myeloperoxidase (MPO) are responsible for the antioxidant functions [45]. Antidiabetic [22,38] and cardioprotective functions of HDLs are discussed [6].

The aim of this review is to analyze therapeutic approaches to restoring the native structural-functional properties of HDLs. Among such approaches are physical exercise and low-calorie diet, CETP inhibitors, and raising the level of apolipoprotein A-I (apoA-I) with the use of recombinant HDLs (rHDLs) or apoA-I mimetic peptides.

Physical exercise. Regular physical exercises and diet not only increase the level of HDL-Chol but also improve the functional properties of lipoprotein particles, particularly HDLs [29]. Different researchers have demonstrated that the HDL level significantly increases after a training load. Sportsmen showed a higher maximum oxygen consumption (VO_2max), concentrations of HDL-Chol and apoA-I in blood plasma were also higher; along with this, the efficacy of RCT increased due to a growth in the amount of large mature α1-HDL particles that deliver Chol esters to the liver [29,20]. In women with obesity, physical exercise for 9 weeks (5 sessions a week) reduced their body weight and decreased the concentration of triglycerides (TG) and apoB; therewith, the content of total Chol, LDL-Chol and HDL-Chol did not change. However, RCT has improved; this was estimated from the HDL ability to remove $^{(14)}$C-Chol from the human monocyte/macrophage line THP-1 [42]. In marathoners, the concentrations of LDL-Chol, apoB and TG did not differ from the control group of patients with a sedentary lifestyle. However, marathoners had higher levels of HDL-Chol and apoA-I; therewith, an increase in the transfer rate of labeled lipids (Chol, eChol, TG, and phos-