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Research Progress of Aplastic Anemia in Immune Dysfunction

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Abstract: Aplastic Anemia (AA) is an autoimmune disease mainly mediated by T cells. On the one hand, focusing on the current research status of different T lymphocytes in AA. On the other hand, because a variety of cytokines are involved in the occurrence, development and outcome of AA, the research progress of multiple cytokines (interleukin, interferon and tumor necrosis factor) in the pathogenesis of AA was analyzed at the same time. Facing the current status of recurrence and ineffective IST treatment in clinical treatment, we explore the role of mesenchymal stem cells from different tissues in immunity, and explore their potential therapeutic advantages may bring new ideas for clinical treatment. Exploring the pathogenesis of AA in multiple dimensions will bring about treatment ideas that will also be multi-dimensional.

1. Introduction

Human AA is divided into hereditary and acquired, and is an autoimmune disease characterized by severe pancytopenia and bone marrow failure (BMF). Inherited bone marrow failure syndrome (IBMFS) is a rare genetic disorder that is clinically well characterized and usually presents in childhood. Generally speaking, AA is considered to be acquired (Acquired Aplastic Anemia, aAA). Asia reports a higher incidence than Europe. It is generally believed that AA patients mainly occur in two age groups, the first is 15-25 years old, and the second is after the age of 60 [1]. AA severity is also classified according to the degree of peripheral cytopenia and myeloid hyperplasia: severe aplastic anemia (VSAA), severe aplastic anemia (SAA), and non-severe aplastic anemia (NSAA)[2,3]. In recent years, the incidence of AA has increased significantly, but its pathogenesis is still unclear [4]. For the research on the mechanism of AA immune disorder, most people believe that the immune system imbalance leads to the autoreactivity of T cells to destroy hematopoietic stem/progenitor cells [5]. The initial use of immunosuppressive therapy significantly improved the long-term survival of patients. However, with the relapse or poor efficacy of some patients, and in recent years, the therapeutic effect of immunosuppressive therapy in the treatment of AA has not made great progress. Therefore, we need to further explore the mechanism of AA immune

dysfunction, which is particularly important to better guide clinical treatment. This article summarizes the new research progress of aplastic anemia in immune function in recent years as follows.

2. The role of immune cell abnormalities in AA

2.1. T lymphocytes

AA is an immune-mediated disease. The disturbance of T cells in the immune system plays an important role in the occurrence and development of AA. At the same time, T lymphocytes are the main effector cells of cellular immunity [6]. Studies have found that patients with aplastic anemia not only have abnormal numbers of T cells in their bodies, but are also accompanied by significant changes in the distribution, phenotype and function of T cells. Some studies have confirmed that the abnormal immune function of AA is related to the abnormal proliferation of T cells, which may kill or inhibit hematopoietic stem and progenitor cells. T cells can be divided into three types according to their immune effects, namely Th, CTL and Treg, and can be divided into $CD4^+$ and $CD8^+$ T cells according to whether they express CD4 or CD8 molecules.

2.1.1. Helper T cells (Th)

(1) Th1 cells

Th1 cells are $CD4^+$ cells that mainly secrete IL-2, INF-γ, etc. [7]. Th1 cells are involved in the regulation of cellular immunity, assist in cytotoxic T cell differentiation and mediate cellular immune responses. Exogenous or neoantigens (toxins, drug exposure, viral infection, etc.) are processed by class II major histocompatibility complex (MHC) molecules and presented to helper T1 (TH1) cells by antigen-presenting cells. In the presence of a stimulus, the transcription factor T-bet binds to the interferon-gamma (IFN-gamma) promoter region and induces gene expression. It has been reported that the occurrence of AA is mainly attributed to the abnormal activation and proliferation of T cells, resulting in the excessive transformation of T cells into Th1 cells and the production of explosive inflammatory cytokines, such as IFN-γ and tumor necrosis factor (TNF)-α. Autoimmune responses can also directly destroy hematopoietic stem progenitor cells in the bone marrow through activated Th1 cells [8]. Evidence in most cases suggests that the disruption of self-tolerance leads to the infiltration of destructive Th1 cells into the bone marrow, where they target hematopoietic stem cells and damage stromal cells through the bypass effect [9]. Th1 polarization is common in most AA patients[30]. Constitutive expression of the transcriptional regulator T-bet is critical for Th1 polarization. Th1 cells can directly secrete IFN-γ, TNF-α and other cytokines to promote the occurrence of disease in AA. Th1 cells can also promote the activation of NK, CD8 and macrophages, and macrophages can further secrete IFN-γ, TNF-α, IL-6, IL-2 and other cytokines, and then mediate disease progression [8]. The overreaction of Th1 cells and the overproduction of IFN-γ became the main driving force for the development of AA. The overproduction of IFN-γ, TNF-α, and IL-2 suggests that hematopoietic cells may be destroyed through the Th1 cell response, as can the transcriptional upregulation of inflammatory cytokines such as TNF-α, Stat4, and IFN-γ [10].

(2) Bias of Th2 cells

Th2 cells mainly secrete IL-4, IL-6 and IL-10 [7]. It has also been reported that Th2 cells can produce interleukins IL-4, IL-5 and IL-13. In the bone marrow, an early and adequate Th2-biased immune response produces an inflammatory effect against bone marrow failure[31].

(3) Imbalance of Th17 cells

Th17 cells are characterized as a new subset of $CD4^+$ T cells that produce leukocyte IL-17 and

act as immune effectors in a variety of settings, including inflammation, infection, and autoimmunity. IL-23 can drive Th17 cells to promote the occurrence of autoimmune inflammation[11]. At present, Th17 cells can not only promote the development of bone marrow failure in AA mice, but also have been confirmed in AA patients[32].

(4) Imbalance of Th1/Th2 ratio

The balance between Th1 cells and Th2 cells is important for normal immune responses. In a healthy human body, Th1/Th2 cells remain in balance. Th1 responses often promote Th2 cell differentiation to maintain immune balance. However, in some cases, an overreaction of Th1 cells increases the Th1/Th2 ratio and upsets the balance. If this ratio cannot be corrected in time, immune-related diseases may occur [12]. Natural killer (NKT) cells also play an important role in regulating the balance between Th1/Th2. After NKT cells are activated in vitro, they will rapidly release a large number of Th1 and Th2 cytokines, thereby regulating the balance between Th1 and Th2. It is speculated that NKT may be involved in the occurrence of AA[33]. Studies have also shown that the imbalance of Th1/Th2 ratio and the increased secretion of Th1 cytokines IFN-γ and IL-2 in AA patients may activate $CD8^+$ T lymphocytes, increase the secretion of TNF-α, and accelerates the FAS/FASL-mediated apoptosis of myeloid progenitors, ultimately leading to hematopoietic failure.

(5) The ratio of Treg/Th17 cells is unbalanced

Treg and Th17 subsets have opposite roles in immune regulation. Both Treg/Th17 are $CD4^+$ T cell subsets. They inhibit each other physiologically, maintain dynamic balance, and play an important role in immune defense and immune self-stabilization. . The balance between Th17 cells and Treg cells is critical for maintaining immune balance. Th17 cells are important pathological factors involved in the pathogenesis of various autoimmune diseases and AA, and Tregs that control the overreaction of effector T cells are often reduced in immune-related diseases. Treg/Th17 cell disorder plays an important role in AA [13]. On the one hand, Li et al. pointed out that in chronic AA patients, bone marrow hematopoietic stem cells regulate Treg/Th17 balance by affecting the Notch/RBP-J/FOXP3/RORγt pathway [13], thereby affecting the development of the disease. On the other hand, Zhao et al. found that gingival-derived mesenchymal stem cells (GMSCs) significantly inhibited Th17 and increased Treg cells, resulting in hematological recovery and prolonged survival in AA mice [11].

2.1.2. Regulatory T cells (Tregs)

Tregs are a special lineage of T cells that play an indispensable role in regulating immune unresponsiveness to self-antigens and immune responses detrimental to the host [14]. It has been reported that the abnormal number and function of Treg in peripheral blood of AA patients has become the main reason for the disease of AA patients. Moreover, recent studies have confirmed that T cells (Tregs) are reduced in AA patients [15]. It has also been reported that Tregs can maintain an appropriate level of immune self-tolerance and are a subset of T cells that inhibit T cells [16]. On the one hand, the function of Tregs in aAA is impaired and will be unable to suppress effector T cells [17]. On the other hand, a decrease in the number of Tregs correlates with the severity of the disease in aAA, and an increase in the number of Tregs can predict a better response to immunosuppressive therapy (IST) [17]. Therefore, the state of Tregs is not only one of the forming factors of AA patients, but also has certain guidance for the treatment of AA patients.

2.1.3. Cytotoxic T cells (CTLs)

Cytotoxic lymphocytes (CTLs) play a key role in SAA. CTLs, Th1, Th17, mDCs (myeloid dendritic cells) and dysfunctional Tregs mediate the occurrence of SAA [18-20]. Among them,

overactivated CTLs play an important role in the pathogenesis of SAA, but the specific mechanism needs to be further explored.

2.2. Natural Killer (NK) Cells

According to the expression level of CD56, NK cells can be divided into CD56dim $CD16^+$ and CD56 bright $CD16^-$ subsets. Cooper et al first suggested that CD56 bright NK cells have an "immunomodulatory role". Because, compared with CD56dim NK cells, they can increase cytokine production and reduce cytotoxicity. CD56 bright $CD16^-$ plays an immunoregulatory role by secreting cytokines such as IFN-γ, TNF-α, IL-10 [34]. Liu et al. [35] found that the proportion of CD56 bright NK cells decreased in SAA, while Li et al. [21] found that the proportion of CD56 bright NK cells increased in NSAA. Moreover, the more severe the anemia of the patient, the higher the proportion of CD56 bright NK cells in the body, which indicates that the proportion of CD56 bright NK cells is related to the severity of the disease. CD56 bright NK cells can also produce a large number of proinflammatory cytokines and participate in the pathogenesis of AA. Li et al. [21] also demonstrated that CD56 bright NK cells can play an immunoregulatory role when the immune status of the body changes.

Natural killer T (NKT) cells are a distinct subtype of T lymphocytes that co-express the alpha/beta T cell receptor (TCR) along with surface markers of NK cells. Most NKT cells express an invariant TCRα chain, consisting of the Vα14-Jα281 fragment in mice and the Vα24-JαQ fragment in humans, and associated with a limited set of Vβ genes [22]. The main function of NKT cells is to induce the rapid release of a large number of cytokines, including IL-4 and IFN-γ. IFN-γ helps Th1 cells to produce cytokines to defend against various pathogens and prevent tumorigenesis, while IL-4 promotes Th2 responses and inhibits Th1-mediated autoimmune responses. Since NKT cells can induce a large amount of cytokines compared to T cells or NK cells after being stimulated, Miyake Sachiko et al. reported that NKT cells can inhibit Th1-mediated autoimmune diseases. As for whether it is completed by mediating IL-4 to be explored. A sphingosine truncated analog (α-GC), OCH, has been shown to preferentially induce Th2 cytokines from NKT cells. NKT cells, as important immune regulators that balance Th1/Th2, may play an important role in the pathogenesis of AA. Qiao et al. demonstrated that in CByB6F1 mice, the specific activation of NKT cells by OCH can reverse the pathogenic Th1 to the protective Th2, thus exerting a protective effect on immune-mediated BMFS [23]. Therefore, the state of NK cells plays a very important role in the occurrence and treatment of AA, and further research is needed.

3. Research progress on the role of cytokines in AA

3.1. Interleukin (IL)

3.1.1. IL-2

Interleukin 2 (IL-2) is a T cell growth factor that has been shown to regulate immune responses in vitro. Severe combined immunodeficiency (SCID) has been reported to be associated with a complete deficiency of IL-2, which is associated with reduced $CD4^+CD25^+$ Th cell function and immune homeostasis, leading to autoimmune disease. Therefore, IL-2 is both an immunostimulatory factor and an immunosuppressive factor, which can effectively control the immune system's response to autoimmunity and adaptive immune responses. The use of immunosuppressive agents against the IL-2 receptor, such as mycophenolate mofetil, rapamycin or monoclonal antibodies, can effectively reduce cytotoxic T cell activity against HSCs [8]. Rajib De et al. [24] demonstrated that elevated IL-2 levels are associated with AA disease. Therefore, the

increase or decrease of IL-2 will have a negative effect on the body, and its normal level is particularly important for the treatment of AA.

3.1.2. IL-18 and its receptors

IL-18, a member of the IL-1 family, was initially identified as an inducer of IFN-γ production in T cells and NK cells, and was secreted by macrophages and dendritic cells (DCS). Notably, the biological activity of IL-18 is mainly regulated by its enzymatic processing rather than at the transcriptional level. The IL-18 receptor (IL-18R) is mainly expressed on CTLs. IL-18 binds to IL-18R to recruit IL-18Rβ chain, which initiates downstream signaling through primary response 88 (MyD88), NF-κb and activating protein 1 (AP-1) of myeloid differentiation. IL-18 cooperates with IL-12 to activate NK cells, induce INF-γ production and other type 1 cytokines in response to pathogens, thereby promoting Th1 polarization and CTL responses. It has been reported that IL-18 is also a pro-inflammatory cytokine, and its activation of NK cells is closely related to its dose. It has also been reported that the level of IL-18 in serum of AA is higher than that of NSAA and the normal control group [37]. The more severe the disease, the higher the IL-18. This may be because IL-18R is mainly located in CTLs, and the level of CTLs is also related to SAA as mentioned above. Wu et al. found that [25] IL-18R was also expressed on human HSPCs, and the test also found that the serum level of IL-18 in SAA patients was higher. They believe that IL-18 has a direct effect on HSPCs, thereby inhibiting hematopoiesis in AA patients. Therefore, they further experimentally demonstrated that IL-18 has a direct regulatory effect on human HSPCs, and may be beneficial to helper T cell signaling, and may inhibit progenitor cell proliferation and/or myeloid differentiation. Therefore, it can be boldly guessed here that the localization of IL-18R may be closely related to the severity of the disease. The more accurate the localization of IL-18R and targeted treatment, the less distant or even complete cure of the disease will be.

3.2. Interferon

IFN-γ can act as an inflammatory signal to stimulate immune responses through NF-κB signaling. About 30% of AA patients have elevated serum INF-γ, and the expression of INF-γ is detected in the bone marrow of most acquired AA patients. Studies have found that there are high levels of IFN-γ in peripheral blood mononuclear cells of AA patients [26]. IFN-γ protein may also be involved in the pathogenesis of AA through the T-bet/IFN-γ signaling pathway, inflammatory factors (such as TNF-α, IL) or cytokines (CD4, CD8). IFN-γ protein inhibits early and late hematopoiesis and induces programmed cell death. In AA, increased Fas expression is induced by IFN-γ, which in turn promotes the apoptosis of hematopoietic stem cells [26]. In a mouse model of bone marrow failure with activated CTLs, IFN-γ inhibits hematopoiesis and promotes the destruction of hematopoietic cells by increasing apoptosis. IFN protein, one of the negative effector cytokines, is highly expressed in CTLs of SAA patients. On the one hand, sustained IFN exposure can damage hematopoietic stem cells and hematopoietic progenitor cells through direct and indirect effects. On the other hand, IFN signaling can also induce the proliferation of hematopoietic stem cells and reduce their own capacity, thereby limiting the function of hematopoietic stem cells and promoting their exhaustion [26]. Lin et al. [27] found that deletion of Sirt1, an NAD+-dependent protein deacetylase, caused abnormal IFN-γ, which in turn caused SAA.

3.3. Tumor necrosis factor and its receptor

Activated macrophages produce TNF-α. TNF-α can upregulate the cellular receptor Fas, enhance the sensitivity of cells to apoptosis, and induce excessive apoptosis of hematopoietic

stem/progenitor cells. TNF-α and IFN-γ synergistically regulate the expression of T cell receptor (TCR) and FAS receptor, promote the differentiation of CTLs from $CD8^+$ precursors (Tc cells), and destroy altered autologous cells [8]. CD27, a member of the tumor necrosis factor receptor (TNFR) superfamily, can transmit costimulatory signals, and T cell activation requires signals provided by costimulatory factors in addition to antigen-induced signals. One of the best-characterized co-stimulatory factors is CD28. CD28 costimulatory signaling promotes T cell proliferation and differentiation through coordinated antigen recognition [28]. CD27 is expressed on T cells, B cells, NK cells and hematopoietic stem cells, and the only characteristic ligand for CD27 is CD70. CD70 is a member of the TNF superfamily and is expressed on activated T cells, B cells, dendritic cells and NK cells. The CD27-CD70 co-stimulatory pathway contributes to the proliferation and survival of activated T cells and positively regulates T cell effector function and memory responses [36]. Zhao et al. [29] found in VSAA and SAA patients that increased $CD8^+CD27^+$ T cells exhibited a cytotoxic effector phenotype by increasing the ratio of perforin, and demonstrated for the first time that CD27 is responsible for abnormal T cell activation in AA one.

4. Potential treatments

4.1. Bone marrow mesenchymal stem cells (MSCs)

MSCs do not express class II histomajor compatibility complex (MHC) or lymphatic costimulatory molecules and have low immunogenicity and are easy to collect, so they have great prospects for clinical application. Mesenchymal stem cells from AA patients lack the ability to downregulate T cell initiation, proliferation, and cytokine release. It has been reported in the literature that the number of Th17 cells in AA patients is increased, and the number of Treg cells is decreased, and Th17 cells are involved in the early pathophysiological process of AA disease. Li et al.[13] reported that the infusion of MSCs into AA patients modulated the regulation of Th17/Treg cell balance in AA patients through the Notch/RBP-J/FoXP3/RORγt pathway, which in turn led to IL-2, IL-2, IL-2, and IL-2 in serum and bone marrow in vivo. INF-γ and TNF-α decreased, the percentage of Th1 and Th17 cells were significantly decreased, and Treg cells were significantly increased, thereby reducing the anemia of refractory and relapsed AA patients and achieving the purpose of treatment.

4.2. Human gingival tissue-derived mesenchymal stem cells (GMSCs)

Compared with other cells, GMSCs have the advantages of stronger repairability, faster proliferation, no potential tumorigenesis risk, and strong immune ability. Zhao et al. [11] demonstrated that GMSCs inhibited the secretion of IL-17A and IL-6, but increased the level of the anti-inflammatory cytokine IL-10. Correspondingly, it was found that GMSCs inhibited Th1 and Th17 cells in AA mice, while promoting the expansion of $CD4^+$ Tregs, and it has been widely demonstrated that IL-10 and/or Tregs have significantly inhibited inflammatory and autoimmune responses. Therefore, they believe that GMSCs also have immunosuppressive ability against immune-mediated BMF. Further research confirmed that GMSCs transplantation can treat immune-mediated aplastic anemia BMF by inhibiting Th1 and Th17 cells and enhancing the differentiation of $CD4^+Foxp3^+$ regulatory T cells ($CD4^+$Tregs), so as to achieve the purpose of therapy.

5. Conclusions

In summary, the pathogenesis of immune dysfunction in aplastic anemia is complex and diverse, mainly focusing on T lymphocyte immune cells and their related cytokines and other factors

affecting the disease process. At present, immunotherapy is still the mainstream treatment measure, and its efficacy is beyond doubt, but there are also some potential treatment methods and gene detection adjuvant treatment plans that are more promising. This paper also provides new ideas for treatment based on immune mechanism, in order to help the in-depth study of the mechanism and the treatment of patients. Therefore, we should strengthen the multi-dimensional in-depth research on immune dysfunction, so as to clarify its pathogenic mechanism, to find better and more comprehensive new ideas for immunotherapy, to better improve the cure rate, prolong the survival rate, and slow down the disease. progression rate, reducing recurrence and mortality.

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