

Medicine

Cytokines and Lymphoma

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Currently lymphoma is mainly treated with combination chemotherapy, hematopoietic stem cell transplantation, immunotherapy, and new targeted therapy, but treatment-related drug resistance, recurrence, extranodal and central infiltration, and leukemic transformation are still clinical problems that need to be solved urgently. Studies have shown that cytokines are expressed to varying degrees in lymphoma patients, which are significantly related to the progression of lymphoma, poor prognosis, chemotherapy response, and drug resistance. It has been confirmed that interleukin 6 (IL-6) and IL-10 are highly expressed in all types of lymphoma, and IL-10 is highly expressed in cerebrospinal fluid of central nervous system lymphoma, and both of them indicate poor prognosis. This review discusses the role of cytokines in the development and potential treatment of lymphoma.

Keywords: Cytokines; Lymphoma; Immunotherapy; Lymph Nodes; Outcomes

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LYMPHOMA ranks tenth in the mortality rate of all malignant tumors (1). The heterogeneity of lymphoma makes it highly variable in clinical manifestations and prognosis (2). Although great breakthroughs have been made in its treatment, extranodal infiltration, leukemic transformation, chemotherapy-related drug resistance, and recurrence are still clinical problems that need to be overcome urgently. Cytokines participate in the regulation of lymphatic development through a complex and strictly regulated network system (3, 4). When this regulation is out of balance, it will lead to lymphatic hypoplasia and pathological changes. In lymphoma, cytokines can promote or inhibit tumor by activating corresponding signaling pathways, such as interleukin (IL)-6, IL-10, and tumor necrosis factor α (TNF- α) etc., and increased expression in patients can promote its occurrence and development (5). For instance, IL-21 can

induce direct apoptosis of B-cell non-Hodgkin's lymphoma (B-NHL) expressing IL-21 receptor (IL-21R), resulting in an anti-tumor effect (6).

Expression and function of different cytokines in lymphoma

Interleukins

ILs are produced by lymphocytes, macrophages, etc., and play important roles in transmitting information, regulating immunity, inflammatory response, and mediating the activation, proliferation and differentiation of T cells and B cells (7). According to molecular structure and signal transduction, it is divided into six categories: IL-1 family, IL-2 family, IL-12/IL-6 family, IL-10 family, IL-17 family and unclassified IL. The expression levels

of different ILs vary among lymphomas.

IL-2 Family

IL-2 is a multifunctional cytokine that plays an important role in lymphocyte homeostasis (8). IL-2 effectively interacts with functional receptors to recruit the γ chain, induce the reverse phosphorylation of JAK3 and JAK1, activate the JAK-STAT signaling pathway, PI3K and MAPK signaling pathways, participate in the regulation of target gene transcription, enhance cell proliferation, and promote glycolysis (9). The amplification of IL-2 signaling pathway can enhance the expression of its receptor complex, leading to the invasion and malignant transformation of lymphoma (10). In classical Hodgkin's lymphoma (cHL), Hodgkin Reed-Sternberg (HRS) cells can produce soluble IL-2R α , which binds to IL-2 and prevents IL-2 from interacting with T cells and natural killer (NK) interaction, NK cell lysis failure, leading to immune escape of tumor cells (11, 12). Elevated serum levels of soluble interleukin-2 receptor (sIL-2R) in patients with follicular lymphoma are associated with poor prognosis (13) and may indicate disease recurrence or progression (14). In relapsed and refractory peripheral T-cell lymphoma and diffuse large B-cell lymphoma (DLBCL), high levels of sIL-2R were significantly associated with poor response to chemotherapy and poor survival (15, 16).

IL-12/IL-6 Family

IL-6 is a member of the hematopoietic cytokine family and is a (21-28) \times 10³ glycosylated protein (17). When combined with the IL-6 receptor, it recruits the signal transducer gp130 to form a high-affinity IL-6R complex (IL-6/IL-6R/gp130 complex). The signal activated by the receptor complex is mediated through the Janus tyrosine kinase (JAK)-STAT, Ras/Raf/MAPK, and PI3K pathways, and is involved in the regulation of cell cycle-related genes, tumor angiogenesis, local tumor inflammatory response and self-renewal of cancer stem cells, etc. (18). It has been reported that the expression level of IL-6 in the serum of all types of lymphoma is higher than that of normal people (19), and in the advanced stage and when metastasis occurs, the level of IL-6 in the peripheral serum of patients is significantly increased (20). A retrospective cohort study of children with Hodgkin's lymphoma (HL) treated with ABVD found that IL-6 expression in background cells was an independent predictor of treatment failure in children with HL (21). IL-35, an immunosuppressive cytokine member of the IL-12 family, is overexpressed in DLBCL tumor cells, and high expression of IL-35 is significantly associated with low overall survival (OS) rate in patients receiving traditional CHOP chemotherapy (22).

IL-10 Family

IL-10 is mainly produced by Th2 cells and has obvious negative immune regulation effect (23). By inhibiting the secretion of IL-2 and interferon (IFN)- γ and the activity of Th1 cells, IL-10 can damage the body's immune surveillance system against tumors, induce tumor cells to evade the body's immune killing, and promote tumor cell proliferation and dissemination (24). The expression level of IL-10 is closely related to the curative effect and prognosis of lymphoma. The serum IL-10 level of untreated NHL patients was significantly higher than that of the

normal control group, and the higher the serum IL-10 level of the patients, the lower the response rate of the patients during treatment and the shorter the OS time (25). IL-10 has a significant advantage in the diagnosis of central system lymphoma (CNSL). IL-10 levels in cerebrospinal fluid for CNSL showed that the overall sensitivity of IL-10 in cerebrospinal fluid for the diagnosis of CNSL was 81%, the specificity was 97%, the area under the curve (AUC) was 0.95, and the increase of IL-10 level in cerebrospinal fluid was negatively correlated with progression-free survival (PFS) (26, 27). At the same time, the ratio of IL-10/IL-6 in cerebrospinal fluid is an important way to distinguish CNSL from central nervous system infection (28). Likewise, elevated levels of intraocular IL-10 or an IL-10/IL-6 ratio > 1.0 can be used as reliable biomarkers for the diagnosis of primary intraocular lymphoma (29).

IL-17 Family

IL-17 is mainly produced by activated Th17 cells and is a type of pro-inflammatory cytokine (30). IL-17A activates the STAT3/GIV signaling pathway to make tumor cells produce pro-angiogenic factors and promote the proliferation of new blood vessels in the tumor microenvironment (31). An immunohistochemical study of living CHL specimens found increased expression of IL-17 in HRS cells and surrounding T lymphocytes in 40% of classical HL specimens and correlated with tumor burden (32, 33). In DLBCL patients, IL-17A can promote the proliferation of tumor cells and inhibit their apoptosis by inhibiting the expression of p53, leading to poor prognosis (34). However, another study found that IL-17 inhibited tumor growth in a T-cell-dependent manner in cutaneous T-cell lymphoma; the levels of Th17 cells and IL-17AF in the tumor microenvironment of some NHL patients were significantly reduced, but the reasons and effects It is not yet clear (35), this difference in IL-17 may be related to the activation of different cytokines in different lymphoma types and their microenvironment, and further research is needed.

IFN

According to their different sources and physical and chemical properties, IFN can be divided into type I IFN, including IFN α , IFN β , IFN ϵ , IFN κ , IFN ω ; type II IFN, namely IFN γ ; and type III IFN. Type I IFN has powerful antitumor and antiviral effects (36). Among them, IFN- α can induce tumor cell apoptosis through the Fas-Fas pathway and plays an important role in tumor immunotherapy (37). IFN- γ is highly expressed in HL tissue cells and tumor HRS cells and has a potential impact on the prognosis of patients (38). In children with ALK-positive anaplastic large cell lymphoma (ALCL), high levels of IFN- γ were significantly associated with high tumor stage, poor initial general condition, and low 3-year PFS rate (39).

TNF- α

TNF- α can specifically bind to tumor cell receptors, inhibit the expression of p53 protein itself, enhance cytotoxicity, and ultimately accelerate cell apoptosis (40). However, high levels of TNF- α will increase the risk of NHL (41). Higher TNF- α levels in DLBCL are significantly associated with patients with B symptoms, poor prognosis and shorter PFS (42), and increased

TNF gene expression in lymphoma patients is associated with complications such as fever and malignant transformation (43).

Colony-stimulating factor (CSF)

CSF-1 and its receptors promote tumor cell proliferation and survival through autocrine or paracrine methods (44). Under pathological conditions, macrophages can be recruited through activation initiated by binding of CSF-1 to the CSF-1 receptor (CSF-1R) and secrete growth factors that contribute to tumor growth or metastasis, resulting in higher disease recurrence rate (45). In HL, high expression of CSF-1R in non-HRS cells often indicates a poor prognosis in uniformly treated patients (46).

Growth factors

Growth factors generally refer to a class of cytokines that can stimulate cell growth and regulate cell growth and differentiation (47). Among them, vascular endothelial growth factor (VEGF) is one of the important factors of tumor angiogenesis, which can provide the required oxygen and nutrients for tumor tissue and determine the activity of tumor proliferation (48). In NHL, VEGF is expressed in both cell lines and tumor tissues, and high serum VEGF-A levels are associated with poor prognosis in NHL (49); whereas in aggressive lymphomas, VEGF levels are associated with shorter OS, whereas in classical In HRS cells of type HL, VEGF-A and its receptors are also highly expressed (50).

Chemokine (CXC)

CXC is a class of cytokines that can drive the directional movement of target cells (51). Tumor cells produce CXC in an autocrine or paracrine manner and promote the expression of important growth-promoting genes of cell cycle proteins (such as D1, Fos, heparin-binding epidermal growth factor (HB-EGF), by activating the MAPK-ERK signaling pathway, Promote tumor cell proliferation and survival (52, 53). In DLBCL, expression of chemokine receptor (CXCR) 4 is involved in the spread of malignant B-cell lymphoma and is a marker of poor prognosis (54). CXCR7 is a good prognostic factor for DLBCL patients, which may be related to its inhibition of CXCR4-mediated signal transduction (55).

Cytokine-Targeted Therapy

In recent years, new drugs targeting cytokines and their signaling pathways have made some achievements in the treatment of lymphoma patients. Studies have shown that in primary effusion

lymphoma, tocilizumab reduces VEGF mRNA expression and IL-6-induced VEGF production by inhibiting STAT3 phosphorylation and STAT3 binding to the VEGF promoter, thereby reducing peritoneal effusion formation, and play a therapeutic role (56). IFN is recommended in the treatment of cutaneous T-cell lymphoma, and its therapeutic effect is time- and dose- dependent, and the effect is better when a large dose is used continuously (57). G-CSF is widely used in chemotherapy-induced febrile neutropenia. The monocyte count on the 8th day of chemotherapy was the lowest point in hematology, at which point G-CSF could be used for prevention (58). Cytokines also play a role in chemotherapy resistance. Studies have found that in DLBCL treated with R-CHOP chemotherapy, rituximab can induce tumor cells to secrete IL-6, promote Th17 and Treg cells to secrete IL-17A, and IL-17A can inhibit the expression of p53 in vitro (59); and in turn, it prevents rituximab-induced apoptosis and promotes the proliferation of DLBCL cells, leading to rituximab resistance (60). Ibrutinib is a small molecule tyrosine-based enzyme inhibitor (BTK). Acquired BTK mutations release cytokines such as IL-6 and IL-10 through continuous ERK1/2 activation, resulting in ibrutinib resistance (61). The production of drug resistance and can protect BTK normal tumor cells through a paracrine mechanism to reduce the curative effect, the use of IL-6, IL-10 antibodies can eliminate this protective effect, which provides an opportunity for the use of targeted cytokine drugs to overcome its resistance (62, 63). In B lymphoma, IL-24 can change the expression of multidrug resistance genes by down-regulating the GTP-RhoA-ERK signaling pathway, thereby enhancing the sensitivity of chemotherapy drugs (64). Therefore, chemotherapy combined with targeted cytokine therapy is expected to reduce the drug resistance of lymphoma patients to chemotherapy and achieve better therapeutic effect.

Conclusion

In lymphoma, IL-2, IL-6, IL-10, VEGF, etc. can promote its development, while IL-17, IFN, TNF, etc. may have dual effects of promoting and inhibiting. However, the mechanism of these effects in lymphoma and the exact impact on the disease are not completely understood. Studies have shown that cytokines are closely related to the occurrence, development, and treatment of lymphoma. Finding a new target for the treatment of lymphoma in the role of lymphoma, bringing hope for the cure of lymphoma. ■

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