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Unraveling the Landscape of Rituximab Resistance in Diffuse Large B-Cell Lymphoma

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Abstract: Rituximab has profoundly improved outcomes for patients with Diffuse large B-cell lymphoma, yet the development of drug resistance continues to pose a serious clinical challenge, leading to treatment failure in 30–40% of cases. Previous studies have revealed several key resistance mechanisms underlying rituximab resistance, such as CD20 antigen expression and conformation, functional impairments in immune effector mechanisms such as antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), the establishment of an immunosuppressive tumor microenvironment (TME), and the activation of intrinsic tumor cell survival pathways. Despite these advances, the resistance landscape of rituximab in diffuse large B-cell lymphoma is not fully mapped; for instance, the roles of ferroptosis and non-coding RNAs remain to be elucidated. This review will summarize these mechanisms to help provide insights that will aid in the development of novel therapeutic strategies and facilitate more personalized approaches to overcome resistance and improve patient outcomes.

Keywords: CD20; Diffuse Large B-cell lymphoma; Resistance Mechanisms; Rituximab.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is derived from cancerous mature B cells, which is the most common type of Non-Hodgkin lymphoma (NHL), and there is great heterogeneity [1]. Rituximab combined with chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone), known as R-CHOP, is the standard treatment regimen for DLBCL. About 60% of patients are cured through this first-line therapy. However, Other patients may experience recurrence or be incurable, mainly due to drug resistance[2]. Rituximab resistance involves multiple mechanisms. It begins with inefficient antibody binding to CD20. This extends to impaired complement activity and disrupted immune cell recruitment. Broader factors include an immunosuppressive tumor microenvironment (TME)and the cancer cells' own survival traits. Therefore, it is very important to draw a complete network map of drug resistance. This will help us understand the biological mechanism of treatment failure and design more effective treatment strategies.

2. CD20 and Rituximab

CD20 is a transmembrane protein encoded by the MS4A1 gene. As a ubiquitous B cell marker, it exists on the surface of almost all mature B cells, but is missing on plasma cells and their precursors[3].There is significant heterogeneity in CD20 expression. There are differences in the expression levels of patients with the same lymphoma type, and even the expression levels of different tumor cells in individual patients are different[4]. This diversity has direct clinical significance: high expression of CD20 is associated with better survival outcomes, and its expression level directly affects the efficacy of anti-CD20 antibodies.

Rituximab is a chimeric monoclonal antibody. It combines a human IgG1 constant region with a mouse variable region[5].As a landmark treatment for B-cell lymphoma, it specifically targets the CD20 antigen and has been approved for the treatment of a variety of B-cell malignant tumors and related diseases. Clinical evidence showed that rituximab can significantly improve the progression-free survival (PFS) and overall survival (OS) of patients with chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), and DLBCL[6].This antibody exerts therapeutic effects through a variety of mechanisms, including complement-dependent cytotoxicity (CDC), antibody-dependent cytotoxicity (ADCC),antibody-dependent cellular phagocytosis (ADCP), and direct induction of apoptosis[7].Studies have confirmed that ADCC is a key mechanism of action in the treatment of lymphoma[8].

3. Mechanisms of Resistance to Rituximab

The mechanisms of rituximab resistance involve multiple aspects. Aberrant CD20 expression affects its binding to the antibody. Impairment of the effector mechanisms weakens ADCC and CDC effects. The tumor microenvironment (TME) and intrinsic cellular properties establish an immunosuppressive environment. All these processes are influenced by host-specific factors. The following sections will elaborate in detail.

3.1. Alterations in CD20 Expression

3.1.1. Downregulation of CD20 Expression

Downregulation of CD20 serves as a key determinant of resistance to CD20-directed antibody therapy. This downregulation is commonly mediated by multi-layered regulatory pathways, including transcriptional, post-transcriptional, post-translational, and epigenetic levels.

MS4A1 gene transcription is strictly regulated by specific promoter elements. The promoter contains several key regulatory sites: an E-box motif, a "PU.1/PiP" binding site, and a BAT box. The BAT box serves as a binding site for transcription factors OCT1, OCT2, and their coactivator

BOB.1/OBF.1, which plays a crucial role in CD20 expression in mature B cells[9].The "PU.1/PiP" site is bound by ETS transcription factors like PU.1 in CD20-positive cells. Its downregulation directly correlates with CD20 loss during the process of plasma cell differentiation, because its mutation nearly abolishes MS4A1 promoter activity[10]. In CLL and NHL B cells, PU.1 positively regulates CD20 transcription. Farnesyltransferase inhibitors promote the binding of PU.1/OCT2 to the MS4A1 promoter, activating transcription[11]. Conversely, FLT3 inhibits PU.1, reducing CD20 expression in CLL cells[12]. Bryostatin-1 upregulates CD20 through MEK1/ERK1/2-mediated activation of ELK1 and ETS1, with potential involvement of NF-κB.[11]A genome-wide screen identified CHD4 and MBD2 as activators of MS4A1, while CREM and the cAMP signaling pathway suppress its expression[13]. FOXO1 acts as a transcriptional repressor of MS4A1. Its mutation-activated expression is associated with poor prognosis in rituximab-treated DLBCL patients[14]. Notably, although MYC and CD20 typically increase simultaneously during B-cell activation and MS4A1 is a direct MYC target gene, MYC silencing paradoxically upregulates CD20 expression in Burkitt lymphoma[15].

Some evidence has confirmed that epigenetic mechanisms regulate the expression of CD20 in B-cell Non-Hodgkin lymphoma (B-NHL). DNMT and HDAC inhibitors can stimulate the expression of CD20 and enhance the efficacy of anti-CD20 therapy in patients, but their specific mechanisms still need to be studied further. DNMT inhibitors effectively restore MS4A1 mRNA transcription and surface CD20 expression in relapsed CD20-negative B-NHL patients[16]. At the molecular level, Tomita et al. found that curcumin A treatment significantly upregulated CD20 mRNA and protein in CD20-negative lymphoma cells **via a mechanism involving** the dissociation of the Sin3A-HDAC1 corepressor complex from the MS4A1 promoter and the acetylation of related histone. Shimizu et al. further discovered that HDAC inhibitors like valproic acid induce high acetylation of the MS4A1 promoter while activating transcription factor SP1[17]. However, the clinical effects of HDAC inhibitors are different in different tumor types. The VALFRID study confirmed that valproic acid can upregulate the CD20 expression of DLBCL patients[18], while the PREVAIL study did not observe this effect in CLL. This may be because valproic acid simultaneously recruits the repressor EZH2 to the MS4A1 promoter[19]. In order to improve the therapeutic effect, researchers have developed subtype-specific HDAC inhibitors. Among them, the HDAC1/4 inhibitor entinostat can effectively upregulate the expression of CD20[20]; while HDAC6 inhibitors enhance anti-CD20 antibody efficacy by promoting MS4A1 mRNA translation[21]. Recent studies have identified two novel resistance mechanisms: PDK4 induces rituximab resistance by inhibiting CD20 expression through HDAC8 phosphorylation, and the long non-coding RNA CHROMR is highly upregulated in drug-resistant DLBCL, potentially regulating CD20 via HDAC3 phosphorylation[22]. Targeting these pathways shows promise for overcoming drug resistance.

At the post-transcription level, 5'-UTR variable splicing has a key regulatory role in the expression of CD20. There are four 5'-UTR splicing variants (V1-V4) in CD20 mRNA; among them, the V1 variant significantly inhibits translation efficiency because it contains uORFs and a stem ring structure, and the V3 variant supports high-efficiency protein synthesis. B-cell activation or EBV infection can induce the conversion of V1 to V3, thus enhancing the expression of CD20. On the contrary, the conversion of V3 to V1 was observed in patients with follicular lymphoma that relapsed after mosunetuzumab treatment, which directly leads to the loss of CD20 protein and causes drug resistance[23].

3.1.2. Conformation Changes of CD20

The conformation of CD20 on the cell membrane significantly affects the binding and function of antibodies. Teeling et al. confirmed that the anti-CD20 antibody identification conformation epitope depends on the three-dimensional structure of the antigen, which is maintained by a lipid double-layer environment. The destruction of the membrane structure significantly weakens the antibody binding and CDC effect[24]. The Winiarska team found that statins changed the configuration of CD20 by consuming cholesterol, which decreased antibody binding ability and weakened the CDC and ADCC effects at the same time[25]. The Intramembrane CD20conformation and lipid interactions are crucial for antibody efficacy.

3.1.3. Loss and Internalization of the CD20 Membrane Protein

The dynamic loss of membrane surface proteins is also a factor contributing to drug resistance, such as the “shaving” phenomenon and antigen regulation mechanisms. The “shaving” phenomenon refers to the removal of CD20-antibody complexes by monocytes or macrophages via FcγRI-dependent endocytosis, resulting in loss of surface CD20 expression[26]. This phenomenon can be avoided by incorporating intravenous immunoglobulin into the treatment regimen. Antigen-dependent regulation is an energy-dependent process involving cytoskeletal remodeling to internalize and degrade CD20-mAb complexes. Transfection of FcγRIIb into originally negative Ramos cells significantly enhanced rituximab internalization in a dose-dependent manner[27]. Further studies revealed that the degree of antigen regulation was particularly pronounced in CLL patients during rituximab therapy, whereas it was relatively lower in follicular lymphoma and DLBCL cells[28].

3.2. Mechanisms of Action

3.2.1. Impaired ADCC

ADCC is an immune response. The target cell antigen is recognized by the Fab region of the antibody, and its Fc region binds to Fcγ receptors on immune effector cells. This activates the immune cell to release cytotoxins and kill the target cell.

NK cells are the main effector cells for ADCC, mainly exerting their effects through the $CD56^{dim}$ NK cell subset. This subset possesses a relatively high level of activated FcγRIII receptor (CD16). This receptor transmits regulatory signals downstream through the immune receptor tyrosine motif (ITAM). The ADCC effect mediated by NK cells is highly dependent on the recognition ability of the FcγRIII receptor for the Fc segment of IgG[29]. The ADCC effect is significantly affected by the polymorphism of the FcγRIIIa gene. The affinity of antibody Fc fragments depends on the genotype of 158 sites (V/V, V/F, or F/F), and this genotype directly regulates NK cell cytotoxicity[30]. The V/V genotype is associated with high affinity, while the F/F genotype is associated with low affinity. Patients with the V/V or V/F genotypes, especially in the GCB subtype of DLBCL, can still elicit a stronger ADCC response and achieve better clinical efficacy even with a lower dose of rituximab[31].

The resistance to rituximab may also be related to the low expression of CD16 on NK cells. Studies indicated that in both newly diagnosed and rituximab-treated patients with DLBCL, the expression of CD16 on NK cells, including the CD56 ^{dim} population, was significantly lower than that in the control group. This low expression led to impaired degranulation function of NK cells and weakened the ADCC effect[32]. Inhibitory killer cell immunoglobulin-like receptors (KIRs) are mainly expressed by NK cells and regulate NK cell response by recognizing human leukocyte antigen class I molecules (HLA I) present on tumor cells. Some KIRs inhibit the degranulation of NK cells by binding to HLA[33]. Studies have shown that upregulation of B-cell HLA-I can confer resistance to NK cell-mediated ADCC in lymphoma patients[34]. A study investigated the clinical response to rituximab in 74 patients with NHL and revealed that low KIR ligand levels and high KIR-positive NK cells were associated with enhanced rituximab efficacy[35]. Furthermore, it has been demonstrated that the changes in B-cell membrane lipid rafts in patients receiving statin treatment can induce in vitro resistance to ADCC[25].

3.2.2. Impaired CDC

Rituximab primarily induces B-cell lysis through CDC. Specifically, the C1 complex binds to rituximab-coated target cells and initiates the complement cascade. This cascade culminates in the assembly of a membrane attack complex (MAC) on the target cell membrane, resulting in membrane integrity loss and cell lysis. Downregulation of C1qA, a key initiator of the complement system, directly impairs complement-mediated CDC effect. Research indicated that C1qA expression is regulated by m6A RNA methylation, a process in which the methyltransferase METTL3 and the reader protein YTHDF2 suppress C1qA protein translation by reducing its mRNA stability, thereby impairing complement recognition and activation. Restoring C1qA expression enhances rituximab sensitivity[36].Additionally, tumor cells achieve immune evasion by upregulating multiple complement regulatory proteins, including the membrane-bound proteins CD46, CD55, and CD59. These proteins respectively inhibit the assembly of C3 and C5 convertases and the formation of the MAC, ultimately suppressing the progression of the complement cascade[37].Research by Sandra Lara et al. indicated that lymphomas with high CD20 expression and low CD59 expression were more sensitive to rituximab, and neutralizing CD59 can reverse drug resistance in two-dimensional culture[38]. In certain patients with high tumor burden, excessive depletion of complement components leads to impaired complement-dependent CDC effect. Klepfish et al.demonstrated that the CDC effect of rituximab was restorable by supplementing exogenous complement, like fresh frozen plasma[39].

The integrity of the cell membrane is essential for CDC efficacy, and disruptions in its composition or structure can confer resistance. Lipid rafts, as dynamic microdomains rich in cholesterol and sphingolipids on the cell membrane, play an important role in signal transduction. Rituximab binds to CD20 and induces antigen-antibody complexes to aggregate onto lipid rafts[40].Research indicates that GM1 ganglioside downregulation in CLL and MCL cells compromises sensitivity to rituximab-mediated CDC[41].What is more, elevated α2-6-linked sialic acid on primary CLL cells, driven by increased α2-6-sialyltransferase activity, is associated with CDC resistance. Enzymatic removal of terminal sialic acid effectively restores the CDC effect triggered by rituximab[42].

3.3. Altered Tumor Microenvironment（TME）

Anti-CD20 monoclonal antibodies remold the tumor microenvironment (ME), which fosters an immunosuppressive niche composed of diverse cellular and molecular components that contribute to rituximab resistance.

At the cellular level, the Fc fragment of anti-CD20 monoclonal antibodies activates myeloid cells (such as monocytes/neutrophils) to produce reactive oxygen species (ROS) via the NOX-2 pathway, thereby suppressing NK cell activity and attenuating ADCC[43].NK cells exhibit heightened sensitivity to reactive oxygen species (ROS)-mediated oxidative stress, particularly to hydrogen peroxide (H_2O_2), resulting in diminished cellular activity and severely impaired cytotoxic function. Lower peroxiredoxin-1 (PRDX1) levels in these cells are associated with better NK cell function[44].Antioxidants can only partially restore the ADCC effect of mononuclear cell blocking, indicating that there are other mechanisms of action.[43]Interestingly, rituximab treatment itself disrupts the immune balance in tumors. It will trigger Th17 cells and IL-17+Foxp3+ regulatory T cells to release IL-17A. This cytokine then prevents the death of DLBCL cells[45].

Rituximab interferes with IL-10 signaling at the molecular level. This inhibitory effect reduces the activation of STAT3. The decrease in STAT3 levels leads to reduced BCL-2 production. Ultimately, this process induces chemotherapy resistance[46].Mesenchymal stem cells (MSCs) have dual functions in the tumor microenvironment: they protect malignant B cells by reducing CD20 expression through direct contact, while simultaneously promoting treatment resistance by secreting IL-6 and increasing IL-17A levels[47].Stromal cells can enhance CD20 expression in CLL through chemokine signaling[4].Fibroblasts expressing CD40L trigger rapid internalization of CD20, resulting in decreased surface CD20 levels[48]. TGF-βsignaling induces binding of SMAD2/3 to the MS4A1 gene, which inhibits CD20 production in Ramos cells[49]. Lymphoma-derived galectin-1 (gal-1) impairs phagocytic function of macrophages[50]. Tumor-derived extracellular vesicles carry specific microRNAs that promote drug resistance. These vesicles suppress TNFAIP3 expression by delivering miR-125b-5p, though their complete mechanism requires further clarification[51].

3.4. Intrinsic Characteristics of Tumor Cells

Changes in the apoptosis pathway can affect the therapeutic response of rituximab. Drug-resistant cells usually show abnormal activation of p38 MAPK, NF-κB, ERK1/2, and AKT signaling pathways, accompanied by overexpression of a variety of anti-apoptotic proteins[52]. Following rituximab exposure, B cells can develop resistance through NF-κB overactivation. This pathway upregulates anti-apoptotic proteins like Bcl-2 while suppressing pro-apoptotic factors, including Bax and Bak[53]. Studies showed that the combination of rituximab with Bcl-2 inhibitors such as oblimersen was highly effective on follicular lymphoma, achieving an overall response rate of 60% even in patients with rituximab-refractory disease or after a failed autologous stem cell transplant[54]. The new generation of sequencing technology confirms that the activation of p38 MAPK (especially the p38δ subtype) is related to rituximab resistance, and deferasirox may be an effective strategy to overcome such resistance[55]. In CLL, anti-apoptotic

proteins such as Mcl-1 and XIAP are crucial to control apoptosis induced by rituximab, and overexpression of these proteins directly leads to drug resistance[53]. Recent studies found that the heat shock protein Mortalin (HSPA9/GRP75) induces drug resistance through dual mechanisms: activating the AP-1 transcription factor to promote cell proliferation, also suppressing apoptosis by inhibiting the FAS death receptor via YY-1. Animal experiments demonstrated that knocking out mortalin significantly enhances the anti-tumor activity of rituximab[56]. Beyond traditional apoptotic pathway abnormalities, a novel form of cell death—ferroptosis—is associated with the efficacy of rituximab. This study first provided evidence that rituximab triggers ferroptosis in DLBCL via the CDC pathway[57], a process primarily mediated by the SLC7A11/GPX4 axis[58]. Experiments demonstrated that the ferroptosis inhibitor Fer-1 effectively rescues cellular viability, whereas the inducer RSL3 synergistically enhances rituximab-mediated suppression of proliferation[57]. This provided a novel theoretical basis and therapeutic directions for developing treatments to reverse drug resistance in DLBCL. Notably, tumor cells develop resistance to rituximab by altering their metabolic processes and target characteristics. Hexokinase II (HKII) has been demonstrated to both promote glycolysis and inhibit mitochondrial apoptosis, and its overexpression is associated with rituximab resistance in aggressive lymphomas[59]. Downregulation of the L-type calcium channel α-1C subunit (CACNA1C) simultaneously reduces rituximab-induced apoptosis susceptibility and decreases CD20 membrane expression, leading to drug resistance[60].

3.5. Host-Related Factors

Host factors act as an independent layer influencing response to rituximab therapy and are also a key reason for individual variations in treatment efficacy. Some patients develop human anti-chimeric antibodies (HACA) against the murine components of rituximab, with subsequent accelerated drug clearance and treatment failure[61]. Furthermore, some authors have noted that vitamin D deficiency impairs NK cell function, which may be associated with rituximab-mediated ADCC resistance[62].

4. Summary

Rituximab resistance remains a major obstacle to long-term survival in DLBCL, driving a shift from traditional chemotherapy toward multi-target combination strategies. The new generation of anti-CD20 antibodies (such as obinutuzumab) enhances ADCC/ADCP effects through Fc segment glycosylation. Antibody-drug conjugates (such as polatuzumab Vedotin) target CD79b, thereby circumventing CD20-related resistance mechanisms. Rituximab combined with BCL-2, BTK, or PI3K inhibitors can reverse apoptosis resistance and abnormal signaling. Bispecific antibodies directly activate T cells for killing by bridging CD3 on T cells and CD20 on tumor cells. CD19 CAR-T offers a novel cellular immunotherapy for patients with relapsed/refractory disease. In summary, advancing the mechanistic understanding of rituximab resistance, combined with the integrated application of novel antibodies, targeted agents, and cellular immunotherapies, holds significant promise for improving outcomes in treatment-resistant DLBCL.

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