# Immuno-oncology for B-cell lymphomas

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## Abstract

The goal of cancer immunotherapy is to restore and optimize the immune response against malignant clones through several stages, from recognition of tumor antigens to establishment of long-lived memory cell populations. Boosting the intrinsic anti-tumor immune responses of the patients' own, several types of "active immunotherapies" have been tried in many types of malignancies, inspired by successful experiences of immune checkpoint inhibition even in Hodgkin lymphoma. However, in B-cell non-Hodgkin lymphomas, clinical usefulness of such "active immunotherapies" is relatively unsatisfactory considering the remarkable advances in "passive immunotherapy," including CD19-targeting chimeric antigen receptor T-cell therapy. Understanding how tumor cells and immune cells interact and contribute to immune evasion processes in the tumor microenvironment (TME) is an important prerequisite for the successful restoration of anti-tumor immune responses. In this review, a recent understanding of the biology of the immune tumor microenvironment surrounding B-cell non-Hodgkin lymphomas will be introduced. In addition, novel therapeutic approaches targeting the immune microenvironment other than immune checkpoint blockade are discussed.

**Key Words** Lymphoma, T cell, Regulatory T cell, Immunotherapy, Vaccine

## INTRODUCTION

The core function of our immune system is to discriminate foreign substances from self-derived substances. According to the concept of "immune surveillance," the physiological function of the immune system also includes the ability to recognize and destroy transformed cells before they grow into tumors and kill established tumors [1]. However, tumors can evade or suppress immune responses in several ways by passing through various stages of "immunological editing" [2]. Recently, the ability of tumor cells to evade host immune defense mechanisms is considered one of the hallmarks of cancer [3]. The goal of cancer immunotherapy is to restore and optimize the immune response against malignant clones through several stages, from recognition of tumor antigens to establishment of long-lived memory cell populations. Understanding how tumor cells and immune cells interact and contribute to immune evasion processes in the tumor microenvironment (TME) is an important prerequisite for the successful restoration of anti-tumor immune responses. Several therapeutic modalities targeting these mechanisms, including immune checkpoint inhibition, have been deployed in our clinical practice as a standard treatment for selected types of lymphomas [4-7].

Non-Hodgkin lymphoma is a heterogeneous group of malignancies originating from mature lymphoid cells. The shape of the interaction between malignant and nonmalignant cells within the TME is also heterogeneous across histologic subtypes [8]. Understanding the distinct immunopathogenesis of lymphoma progression in the context of TME biology is critical for developing immunotherapies and identifying appropriate candidates for an established immunotherapeutic modality. Recent studies have demonstrated the characteristics of immune cells in the TME of lymphomas may be a druggable therapeutic target and biomarker for immunotherapy [9, 10]. However, until now, there has been no remarkable breakthrough in terms of "active immunotherapy," which optimizes the anti-lymphoma immune responses of the patients.

Herein, current knowledge regarding the immune microenvironment associated with B-cell non-Hodgkin lymphoma will be reviewed. This biologic insight into the TME provides us with fundamental concepts and mechanisms of future immunotherapies for lymphoma. In addition, recent advances in trials targeting immune microenvironments other than immune checkpoint blockade have been introduced.

# IMMUNE MICROENVIRONMENT OF B-CELL LYMPHOMAS

The cellular composition and immunological influence of the tumor microenvironment differ greatly across the histological entities of B-cell lymphoma. In general, the TME only has a limited role in aggressive and rapidly progressing lymphomas such as Burkitt lymphoma and lymphoblastic lymphomas, as the tumor masses largely consist of lymphoma cells and contain a low proportion of other types of immune cells. In contrast, TME seems to play a crucial role in low-grade B-cell lymphomas.

The relationship between B-cell non-Hodgkin lymphoma and the TME is split between the needs of the tumor cells for cytokine signaling by the TME and the needs of the tumor cells for immune escape. Similar to classical Hodgkin lymphoma (cHL), B-cell lymphoma cells are dependent on several cytokines of interleukin family derived from the surrounding microenvironment, such as IL-10, which promotes B-cell survival and induces an immunosuppressive milieu [11]. Likewise, IL-6 can contribute directly to the proliferation, migration, and invasion of B-cell lymphoma cells [12]. IL-6 can also activate and act via matrix metalloproteinases, another subgroup of enzymes that regulate the TME [13].

## Follicular lymphoma

Specifically, follicular lymphoma (FL) also requires the supporting structures of the follicular architecture to maintain its survival; the need for these structures is lost in the process of transformation to overt DLBCL, as shown by a lack of dependence on G$\alpha$13-dependent signaling [14, 15]. FL is rich in T-cells, constituting up to 50% of the total cell count. Among them, follicular helper T (Tfh) cells, a CD4$^+$ T cell subset of recently defined functional entities, plays a major role [16, 17]. Tfh cells provide vital survival signals for FL cells as they do for non-neoplastic germinal center cells by secreting various effector cytokines, including IL-2 and interferon-$\gamma$ [18]. Stromal cells, such as cancer-associated fibroblasts, secrete several chemokines, such as CXCL12 and CXCL13, which are required for trafficking and retention of various immune cells [19, 20]. Macrophages also promote the growth and survival of FL tumor cells via the CD40 axis [21] and can activate the B-cell receptor functionally [22]. Conversely, FL tumor cells exploit immune escape and immune silencing mechanisms to foster their survival; although not expressing PD-L1 themselves, increased numbers of PD-L1-expressing macrophages and PD1$^+$ CD4$^+$ and CD8$^+$ T cells are noted in FL [23]. The induction and promotion of Tfh cells also helps to create an immunosuppressive milieu in addition to providing growth stimulation and survival signals for FL cells, as mentioned above [18]. Furthermore, Tfh cells induce the migration of regulatory T (Treg) cells, further promoting the silencing and attenuation of the immune system [24]. FOXP3$^+$ CD4$^+$ Treg cells are known to have a negative prognostic impact and at a higher risk of transformation in FL, which is explained by their immunosuppressive abilities [25]. They not only act on their own but also cooperate with M2 macrophages present in the TME. The complexity of the importance and predictive value of the TME in FL is further complicated by the impact of different therapeutic approaches. The addition of rituximab to therapy seems to neutralize the negative prognostic role of macrophages [26].

## Diffuse large B cell lymphoma

In diffuse large B-cell lymphoma (DLBCL), little is known about the interaction between lymphoma cells and cellular components of the TME. Activation of the B-cell receptor in DLBCL is mainly due to mutations in *MYD88, CD79B, BCL10, CARD11, CD79A* and; other mechanisms of tumor promotion are active, such as activation of *JAK-STAT* signaling due to *SOCS1* and *STAT6* mutations, and immune escape due to *B2M, CIITA, CD58, CREBBP*, and *EP300* mutations, such that DLBCL cells seem to be less dependent on the TME [27-29]. However, there is also evidence that some DLBCL subgroups are dependent on TME interactions [28, 29]. CXCR5$^+$CD4$^+$ T-cells in peripheral circulation support tumor growth and survival in an IL-10 dependent manner [30]. Moreover, DLBCL tumor cells display *IL10RA* or *IL10RB* gene amplifications in some aggressive cases, suggesting that the IL-10/IL-10 receptor pathway can be a potential therapeutic target in selected cases of DLBCL [31]. DLBCL cells are also known to regulate their microenvironment by secreting vascular endothelial growth factor (VEGF) and recruiting VEGF-receptor-positive macrophages [32, 33]. Intriguingly, the survival of DLBCL cells *in vitro* was improved by co-culturing with neutrophils [34]. This is thought to be achieved by the secretion of a proliferation-inducing ligand (APRIL), a ligand of the tumor necrosis factor family [34], physiologically activating several vital proteins related to B-cell survival, such as B-cell maturation antigen. APRIL has also been shown to be a negative prognostic marker for DLBCL [35]. Conversely, DLBCL cells can attract neutrophils by IL-8 secretion and induce the formation of neutrophil extracellular traps [36], which in turn leads to the activation of Toll-like receptor-induced pathways inducing NF-κB, STAT3, and p38 related signaling [36].

The PD-1/PD-L1 axis is currently one of the most popular drug targets for immune checkpoint inhibition and is important in many types of lymphoma. The clinical usefulness of PD-1 blocking monoclonal antibodies has been suggested in several types of non-Hodgkin lymphomas, which are associated with specific genetic alterations leading to overexpression of PD-L1 protein [10, 37]. However, from an immunological perspective, PD-L1 expression can be induced by factors other than genetic overexpression [38]. The expression of PD-1 and PD-L1 is controlled by various types of biological stimuli [39, 40] and represents an immunological potential or degree of exhaustion of T cells responsive to tumor antigens [41-43]. Advances in understanding the mechanisms and immunologic significance underlying PD-1/PD-L1 regulation have led to a more fine-tuned appli-

cation of checkpoint inhibition therapy for B-cell non-Hodgkin lymphoma.

## TARGETING THE IMMUNE MICROENVIRONMENT IN B-CELL LYMPHOMAS

For progression, lymphomas need to avoid immuno-surveillance while preserving the pro-lymphomatogenic functions of nearby immune cells. In line with this concept, genetic and immunohistochemical signatures of non-tumor cells in the neoplastic tissue currently represent the best predictors for B-cell non-Hodgkin lymphoma patients' prognosis [44, 45]. These findings suggest that specific immune cell subsets infiltrating tumors could be a good target to offset the poor prognosis.

### Targeting FOXP3^{+} regulatory T cells

In particular, $CD4^+CD25^{hi}FOXP3^+$ Treg cells, a subset of $CD4^+$ T cells with potent suppressive activity, have a negative effect on immune surveillance by the TME in B-cell non-Hodgkin lymphoma [25]. Although the drug has not been specifically evaluated in patients with B-cell lymphoma, anti-CCR4 monoclonal antibody (mogamulizumab) successfully decreased the frequency of circulating Treg cells and evoked anti-tumor immune responses in humans [46]. Furthermore, the anti-CCR4 monoclonal antibody showed significant anti-lymphoma clinical activity for cutaneous T-cell lymphoma irrespective of the CCR4 expression level [47], suggesting the significance of Treg cell depletion in the treatment of lymphoma.

### Targeting immune checkpoint for T cell activation

Recently, in addition to Treg cell inhibition, several strategies capable of modulating T-cell functions have become available, allowing preclinical and in some cases clinical evaluation of the anti-lymphoma effects of promotion of T-cell co-stimulation. Agonistic monoclonal antibodies directed against the co-stimulatory molecules OX40 (CD134), glucocorticoid-induced TNF-related protein (GITR), and 4-1BB (CD137), have been used to boost antitumor T-cell functions. In preclinical models of lymphoma, T-cell modulation by anti-OX40, -GITR, and -CD137 monoclonal antibodies has been shown to significantly improve the therapeutic efficacy of several immunotherapeutic modalities, including anti-tumor vaccination and monoclonal antibody therapy [48].

### Modulating NK cell activity

Another straightforward way to redirect immune cells against lymphoma clones within the tumor microenvironment is to modulate NK cell activity to enhance the effector functions of monoclonal antibody drugs. One of the major mechanisms of action of therapeutic monoclonal antibodies in lymphoma is antibody-dependent cell-mediated cytotoxicity (ADCC), whereby NK cells are redirected to the targeted tumor cells through Fc receptors of the antibody drugs. The possibility of further co-stimulation of ADCC cellular media-

tors via immunomodulatory monoclonal antibodies was hypothesized to synergize with anti-tumor monoclonal antibodies. Since the co-stimulatory molecule 4-1BB is upregulated on NK cells upon Fc receptor engagement [49], agonistic anti-4-1BB monoclonal antibodies have been investigated in combination with anti-lymphoma monoclonal antibodies to increase anti-tumor ADCC. Agonistic anti-4-1BB monoclonal antibodies significantly improved the anti-lymphoma effects of anti-CD20 monoclonal antibodies in preclinical models [49, 50]. Recently, through a first-in-human study, utomilumab in combination with rituximab demonstrated clinical activity in patients with B-cell non-Hodgkin lymphoma [51].

### Immunomodulating agents

Because of their immunomodulatory properties, thalidomide and its derivatives have also been exploited to target the microenvironment in B-cell non-Hodgkin lymphomas. In addition to their potential to directly interfere with tumor growth and induce apoptosis in tumor cells, these agents promote anti-tumor immunity, including monoclonal antibody-mediated ADCC and anti-angiogenic effects. Lenalidomide has been the most widely investigated drug in this category, showing significant single-agent anti-lymphoma activity in clinical trials [52-54]. However, in combination with standard rituximab-containing chemotherapy, lenalidomide failed to demonstrate a universal benefit against diffuse large B-cell lymphoma [55, 56].

## CONCLUSION

Novel curative therapeutic approaches for B-cell lymphoma are urgently required. Inducing and optimizing the intrinsic potential of the immune system to control lymphoma is an attractive approach. The availability of specific antigens and the easy accessibility of the immune system to tumors are crucial prerequisites for such immunotherapy. Even though "active" immunotherapy through anti-tumor vaccination theoretically represents the ideal modality of immunotherapeutic for inducing anti-tumor immunity and controlling the recurrence of disease, the possibility to activate effective endogenous immune responses has proven challenging even in lymphoma patients. Other approaches targeting lymphoma by "passive" (adoptive) T-cell therapy have been actively investigated with promising results, including the recent clinical successes of chimeric antigen receptor T cell therapy.

To develop better immunotherapy for B-cell lymphoma, the immunobiological network underlying the lymphoma TME should be finely dissected, and the pathogenic roles of the components need to be clearly documented. It also seems clear that if active and adoptive immunotherapy as well as immunomodulatory monoclonal antibodies may not show optimal activity as single agents, they can be exploited in rational combinations to maximize the probability of a clinical benefit. Significant advancements in the develop-

ment and application of immunotherapy against B-cell lymphomas will provide us with curative options in the near future.

## Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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