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Review Article

Unraveling the complexity of follicular lymphoma: insights and innovations

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Abstract: This review discusses multiple aspects of follicular lymphoma (FL), including etiology, treatment challenges, and future perspectives. First, we delve into the etiology of FL, which involves a variety of pathogenic mechanisms such as gene mutations, chromosomal abnormalities, immune escape, immune system dysregulation, familial inheritance, and environmental factors. These mechanisms provide the context for understanding the diversity and complexity of FL. Second, we discuss the challenges faced when treating FL, particularly treatment resistance. Therapeutic resistance is a common problem in treatment, but by delving into the mechanisms of resistance, scientists have looked for strategies to combat it, including developing new drugs, improving treatments, and exploring combination therapy strategies. We also emphasize the breakthroughs in molecular biology, especially the study of targeting the BCL2 gene, which provides a new direction for targeted therapy in FL. Immunotherapy, small molecule targeted drugs, and individualized treatment strategies are also promising for the future treatment of FL. Finally, we look to the future, including research on therapeutic resistance, in-depth studies of genetics and gene expression, applications of gene editing and precision medicine, and clinical trials of new treatments. These lines of research offer additional opportunities for treating FL, and despite the challenges, the future is promising. This literature review provides comprehensive and integrated information for the in-depth understanding of FL and relevant treatment approaches.

Keywords: Follicular lymphoma, lymphatic system, Hodgkin lymphoma

Introduction

The lymphatic system is a part of the human body that includes tissues and cells such as lymph nodes, spleen, bone marrow, lymphatic vessels, tonsils and lymphocytes [1, 2]. This system plays a key role in maintaining the normal functioning of the immune system and helps the body fight infections and diseases [3]. Lymphoma is a malignant tumor that originates in the tissues and cells of the lymphatic system [4, 5]; it usually involves lymphocytes or related tissues that proliferate abnormally in the lymphatic system. Lymphomas are usually divided into two main categories: 1. Hodgkin lymphoma (HL), which usually involves specific types of malignant lymphocytes, called Reed-Sternberg cells, as well as peripheral lymphocytes. HL usually has characteristic pathological features, such as large multinucleated cells and a precise tissue configuration. 2. Non-Hodgkin lymphoma (NHL), which is a broader category of lymphoma that includes multiple subtypes derived from different types of lymphocytes. NHL is more common than HL, with varying pathologies and molecular biology, and thus different subtypes require different treatment strategies [5-8].

Follicular Lymphoma (FL) is a specific subtype of NHL and a type of B-cell lymphoma [9-11]. It originates from B lymphocytes, and its pathology is characterized by abnormal follicular structures and follicle-centered cells, which are its main features and the basis for diagnosis [9-13]. It is widely distributed in the human body and its schematic representation is shown in **Figure 1**. In general, it grows more slowly than other lymphoma subtypes, and the morphology of FL cells is usually relatively regular

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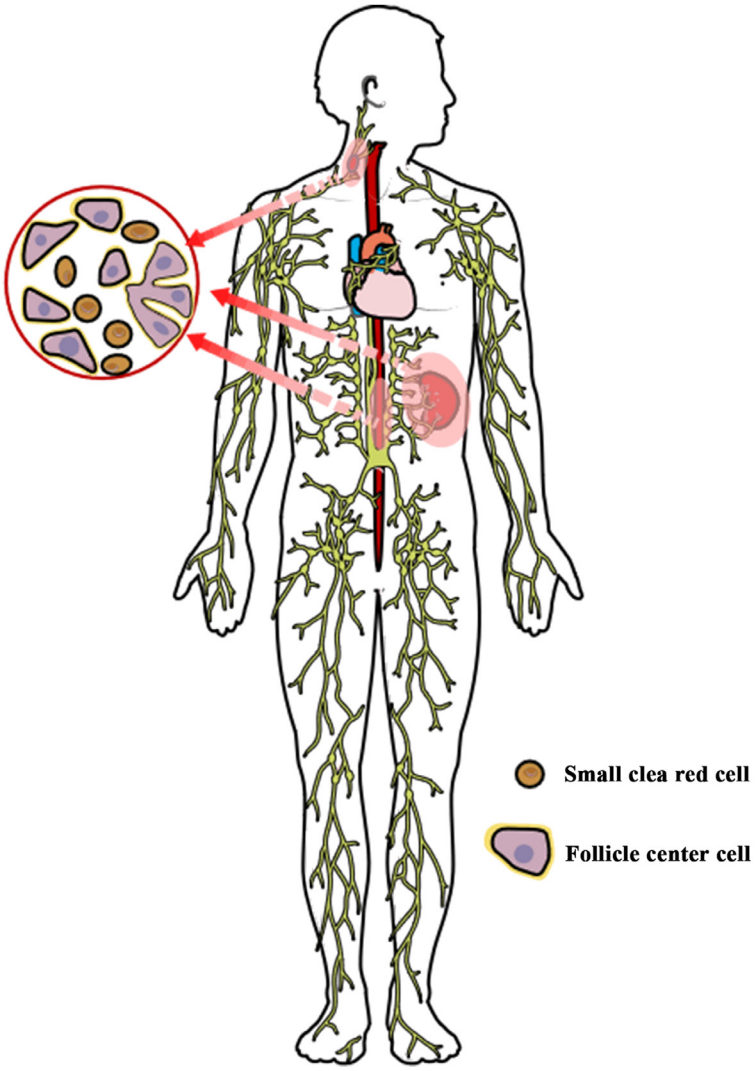

Figure 1. Schematic representation of the lymphatic system and the location of follicular lymphoma in the lymphatic system.

and not as heterogeneous as other lymphoma subtypes, thus early diagnosis can contribute significantly for disease control. FL has a series of distinctive pathological features and clinical manifestations, which can be further categorized according to a grading system [14-16]. According to the Gridding system, FL can be divided into the following three categories. Grade 1: FL has relatively regular follicular cells that proliferate slowly; Grade 2: FL has moderate follicular cell proliferation and regular cell morphology; Grade 3: FL has rapid follicular cell proliferation and irregular cell morphology. Grade 3 can be further subdivided into subtypes 3A and 3B. Together, the grading and clinical manifestations of lymphoma provide physicians with important diagnostic and therapeutic clues to help develop individualized treatment plans, which are of great clinical importance [17-20].

Clinically, patients with FL usually have enlarged lymph nodes as the main symptom, especially in the lymph nodes in the neck, abdomen and groin. Patients may also be accompanied by symptoms such as general malaise, persistent fatigue, low-grade fever, and weight loss, which are usually indicative of the presence of lymphoma. Additional symptoms such as excessive sweating, itching, skin lesions, or abdominal pain may also be present in different patients, and these symptoms depend greatly on the site of lymphoma involvement. Research has been conducted by clinicians as well as scientists for the prevention, process inhibition, and treatment of FL [21-23]. This study systematically reviews the clinical features, pathogenesis, diagnosis, and treatment of FL.

Pathologic and clinical characteristics

FL is a chronic disease that usually progresses slowly, and treatment strategies often depend on the patient's age, disease grade, and the presence or absence of symptoms; therefore, understanding the pathologic features and clinical manifestations of FL is very important for its treatment [24-26].

Pathologic features

As a follicular neoplastic disease, the main pathology of FL revolves around these two main features: Abnormal proliferation of lymphoid follicles: 1. FL includes the word "follicular" in its name, in part because the disease originates in the lymphoid follicular region, usually

the lymphoid follicles in the lymph nodes. Under normal circumstances, lymphoid follicles are part of the lymphoid tissue in which B cells produce antibodies in response to infection. In FL, however, the B cells in these lymphoid follicular areas begin to proliferate abnormally and form malignant tumors [27-29]; 2. B-cell source: The tumor cells in FL are usually part of B cells, a type of white blood cell of the immune system that produces antibodies in the body to fight infections and other foreign substances. In FL, these malignant B cells lose their normal growth and apoptosis (cell death) control mechanisms, causing them to divide and proliferate; 3. Surface Markers: Tumor cells in FL usually have specific surface markers such as CD19, CD20, and CD10. These markers are tools used in immunohistochemical studies to identify and classify lymphomas. They help determine the type and source of the tumor cells and help doctors make informed diagnosis.

Generally, FL can be divided into different subtypes based on pathologic and histologic features, the most common types include follicular center lymphoma (FCL) and follicular marginal zone lymphoma (FMZL). There are some minor differences between these subtypes, such as cell morphology, location of lymphoid follicles, and expression of surface markers [29-32].

Pathologic typing

FLs are usually classified into different grades based on the density and morphologic features of the tumor cells within the lymph node. The grading system (G1, G2, and G3) commonly used is based on the Groupe d'Etude des Lymphomes Folliculaires (GELF) histologic score. G1 indicates a low number of tumor cells, G2 an intermediate number, and G3 a high number [33, 34]. The two main subtypes of FL, FCL and FMZL, have some differences in pathologic features [35, 36].

FCL

Abnormal proliferation within lymphoid follicles: One of the main pathologic features of FCL is the abnormal proliferation of B cells within lymphoid follicles. These B cells overpopulate the area of the lymphoid follicle, causing the area of the lymphoid follicle to become enlarged and filled with tumor cells. These follicles usually maintain a relatively regular shape, similar to that of normal lymphoid follicles, but the B cells within them lose their normal growth and apoptosis (cell death) control mechanisms. Tumor cells in the FCL usually express B-cell-associated surface markers such as CD19, CD20, and CD10. These markers help to determine the type and origin of the tumor cells [36-38].

FMZL

Abnormal proliferation in the marginal zone of lymphoid follicles: FMZL differs from FCL in that it shows an abnormal proliferation of B cells within the marginal zone of lymphoid follicles. Histologically, tumor cells in FMZL usually accumulate in the marginal region of the lymphoid follicle rather than in the center of the follicle. This feature helps to distinguish it from FCL. Tumor cells in FMZL usually express B-cell-associated surface markers, but are weak in CD10 expression, unlike FCL. This is an important feature that distinguishes these two subtypes pathologically [39-41].

FL subtypes as described in the 5th edition of the World Health Organization (WHO) classification of haematolymphoid tumors (WHO-HAEM5) [42]

Since the introduction of the WHO Classification of Lymphoid Tumors, 3rd edition, in 2001, it has become a worldwide reference standard for the development of basic principles for the diagnosis of lymphoid tumors [43]. WHO Classification 5 is a systematic evolution of the previous classification [44]. The grading system organizes diseases into categories, families/classes, entities/types and subtypes according to increased levels of specification. FL is the most common B-cell tumor in the Western world, second only to diffuse large B-cell lymphoma [45]. It is defined as a tumor in which the germinal center B-cells are composed of varying proportions of centrocytes and centrocyte-forming cells with at least a partial follicular growth pattern, according to the recommendations of WHO-HAEM5 and the International Consensus Classification [46]. The t(14;18) is considered to be the initiating event. In contrast, FLs with a different growth pattern or different cytology are very rare, as is the case for the more specific FL entities in WHO-HAEM5, such as follicular B-cell tumors in situ, duodenal-type follicular FL, pediatric-type follicular

FL, and primary cutaneous follicle-centered lymphomas. Therefore, WHO-HAEM5 proposed a novel concept to subclassify FL. Based on its frequency, approximately 85% of FL with a (partial) follicular growth pattern, consisting of centrocytes and centroblasts and containing t(14;18), is now referred to as classical FL (cFL) and is distinguished from rarer subtypes. Essentially, WHO-HAEM4R class 1, 2 and 3A FL will now belong to this entity.

Clinical characteristics and diagnostic methods

Clinical characteristics

Clinical signs and symptoms of FL can vary between individuals, but one of the most common symptoms is enlarged lymph nodes [47, 48]. Patients usually notice enlargement in the neck, armpits, groin, or other lymph node areas. These lymph node enlargements are usually painless and may be symmetrical, i.e., appearing on both sides of the body [5, 49-52]. Patients may feel lethargy, fatigue, and weakness due to chronic inflammation caused by the tumor, anemia, or other factors. Fatigue may interfere with daily life and the ability to work [53, 54]. Some patients may experience loss of appetite, leading to weight loss. This may be due to a tumor or systemic inflammation that interferes with the normal regulation of appetite and weight [55, 56]. Some patients with FL may experience fever, which is usually painless [17, 57]. In some cases, FL may cause skin lesions. One common skin lesion is nodular FL, which is a skin manifestation of FL that appears as small, lumpy nodules under the skin [58, 59]. In addition, an enlarged spleen is another common symptom that may cause pain or discomfort in the left upper abdomen. Enlargement of the spleen may be caused by the deposition of tumor cells in the spleen [9, 60]. FL can sometimes affect other organs such as the bone marrow, the gastrointestinal tract, the lungs, and other lymph node areas. This can lead to a range of symptoms and complications such as bone marrow suppression, abdominal pain, and breathing difficulties. Symptoms of FL can vary greatly from patient to patient, and some patients may have no noticeable symptoms [50, 61-65]. An illustrative diagram of the histologic features and typical clinical presentation of FL is shown in **Figure 2**. Therefore, diagnosis and treatment usually require a combination of information from a number of sources, including clinical presentation, pathology, and imaging. Some of the specific diagnostic methods are described below.

Diagnostic methods

When making a diagnosis of lymphoma (including FL), in addition to analyzing some of the clinical manifestations mentioned above, it is often necessary to further analyze the patient's histology, molecular genetics, and imaging information in clinical practice to ensure an accurate diagnosis for precise and effective treatment.

Histologic and immunohistochemical examinations

Histologic examination: Typically, the diagnosis of FL begins with a biopsy in which a sample of a lymph node or other lymphatic tissue is collected for microscopic examination. Histology reveals the appearance and arrangement of the tumor cells to determine if a lymphoma is present. FL is typically characterized by abnormal proliferation of B cells within lymphoid follicles [66-68].

Immunohistochemical tests: Immunohistochemical tests use antibodies to detect specific surface markers of tumor cells to determine their origin and type. In FL, commonly used antibodies include CD19, CD20, and CD10. Expression of these markers can help determine whether a B-cell lymphoma is present, as well as distinguish FL from other types of lymphoma [69-71].

Molecular diagnostic techniques

Advanced molecular genetics techniques such as polymorphic DNA analysis, FISH (fluorescence in situ hybridization), and PCR (polymerase chain reaction) are used to detect specific gene mutations or chromosomal abnormalities, leading to a more accurate diagnosis of FL and helping to distinguish between different subtypes [72-75]. Also, the search for FL-related molecular markers is an important way to aid in diagnosis. For example, overexpression of the BCL2 protein is often associat-

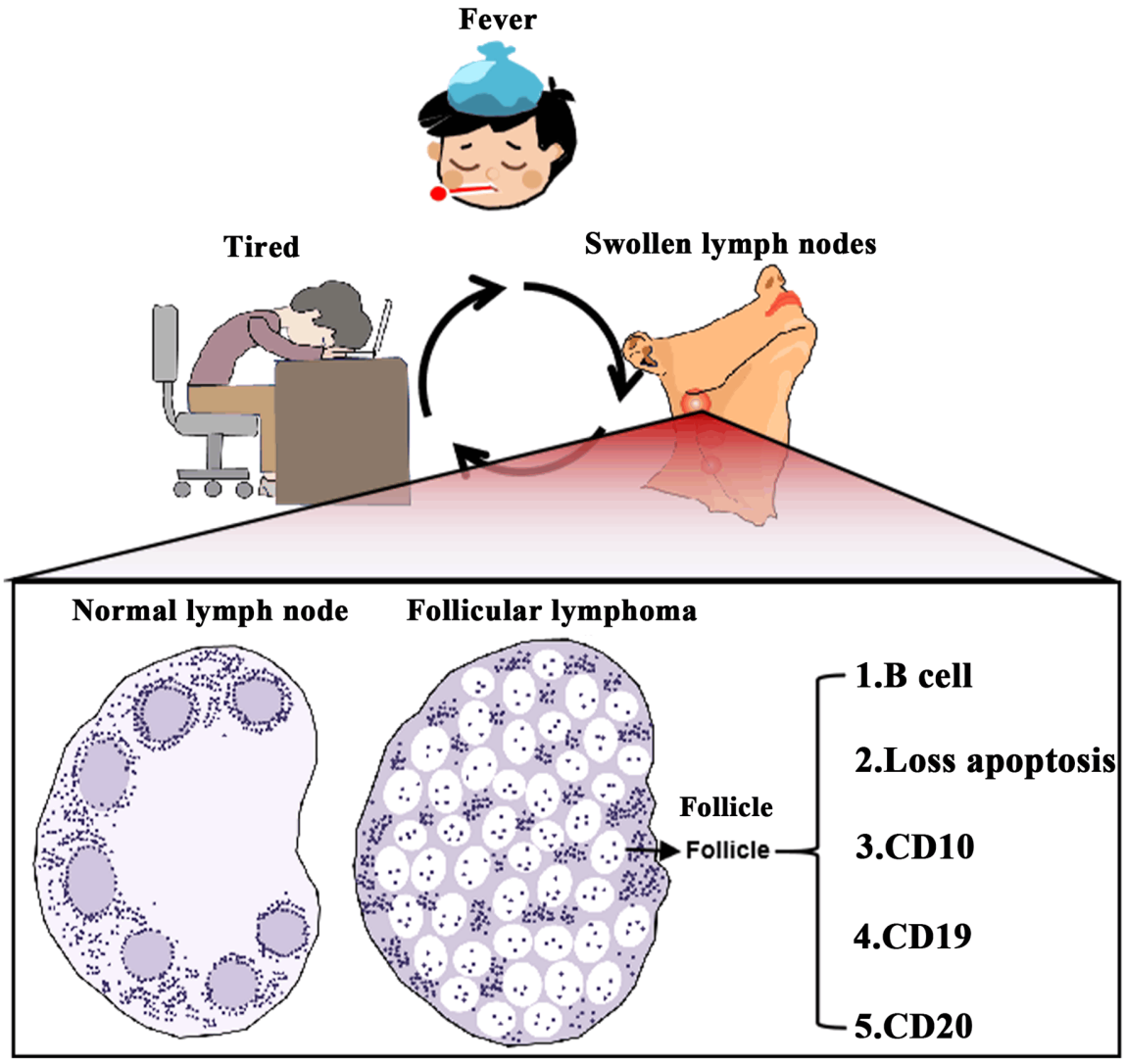

Figure 2. Example diagrams of FL histologic features and typical clinical presentations.

ed with the development of FL, so testing for BCL2 protein expression can be used as a secondary diagnostic tool [76-78]. The flow chart of immunohistochemical examinations and molecular diagnostic techniques is shown in **Figure 3**.

Diagnostic imaging

Imaging examinations for FL are similar to most tumor tests and are generally of the following types: 1. X-rays and CT scans can be used to assess the extent of lymph node enlargement and to detect whether other involved organs (e.g., spleen, lungs, gastrointestinal tract) are affected [79-83]; 2. Magnetic Resonance Imaging (MRI) can provide a detailed image that help evaluate the extent and depth of localized lesions [84-86]; 3. Positron emission tomography combined with computed tomography (PET-CT) can detect actively metabolizing lymphoma lesions and is critical for assessing response to treatment, grading, and monitoring residual lesions [87, 88].

By working in concert with multiple methods and analyzing histology, molecular genetics, and imaging results together, physicians are able to determine the type, grade, and extent of the disease and develop the most appropriate treatment plan for patients. This integrated approach helps ensure an accurate diagnosis and effective disease management.

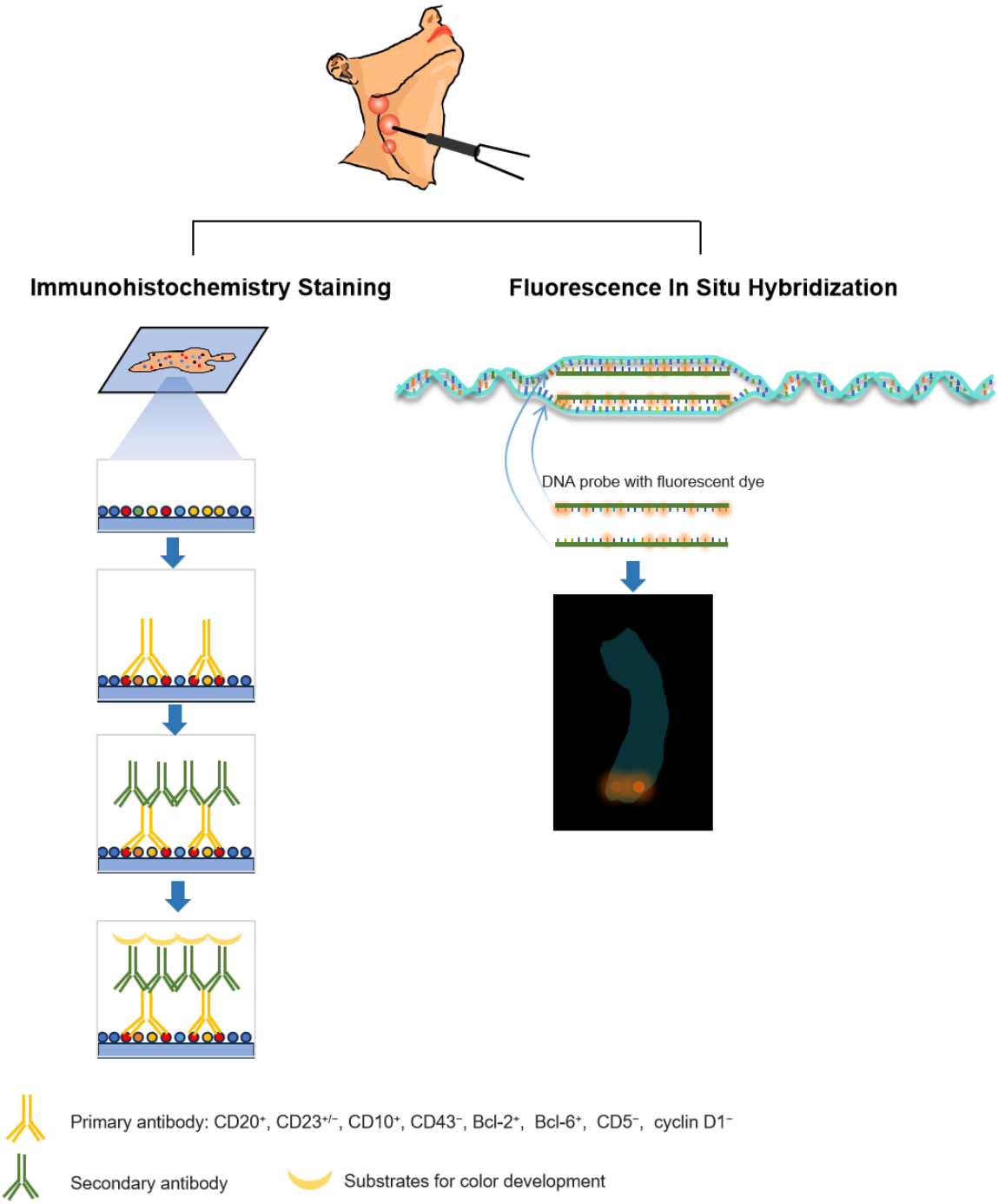

Figure 3. Flowchart of immunohistochemical tests and molecular diagnostic techniques.

Genomics and transcriptomics techniques

Genomics and transcriptomics techniques also play an important role in the diagnosis of FL [89]. While traditional diagnosis of FL usually relies on tissue biopsy and clinical presentation, these molecular biology methods provide more comprehensive and precise diagnostic support. 1. Subtype identification: Genomic and transcriptomic techniques can help identify different subtypes of FL. The subtypes may differ in their gene expression patterns, so by analyzing gene expression data, these techniques can be help differentiate and determine

a definitive diagnosis [90, 91]. 2. Risk assessment for disease progression: Genomic and transcriptomic techniques can be used to assess whether a patient's FL is characterized by a high risk for disease progression. By detecting expression patterns and specific mutations in certain genes, it is possible to predict whether a patient is prone to disease progression or recurrence. This can be very helpful in treatment selection after diagnosis and in monitoring patient progress [92, 93]. 3. Therapeutic target identification: By analyzing genomic and gene expression data, possible therapeutic targets can be identified for FL patients. This can help to develop more precise treatment strategies for individual patients, including medications that target specific genes [94, 95]. 4. Personalized therapy: Information from genomics and transcriptomics can be used to develop personalized treatment plans because they can help physicians better understand a patient's condition and potential response to treatment [92, 96].

In summary, genomics and transcriptomics technologies provide more information about molecular features in the diagnosis of FL, which can help to understand patient condition, predict the risk of disease progression, identify therapeutic targets, and develop personalized treatment plans. These approaches are expected to improve the diagnosis and treatment of FL, and enhance the survival and quality of life of patients.

Possible pathogenic mechanisms

The pathogenesis of FL is a complex and multifactorial process, and although it is not yet fully understood, some research progress has been made. Several factors are involved, including chromosomal abnormalities and gene mutations, immune system dysregulation, environmental factors, and familial inheritance. These factors interact with each other to promote the abnormal proliferation and spread of lymphoma cells.

Chromosomal abnormalities and gene mutations

Chromosomal abnormalities and gene mutations are an important part of the pathogenesis of FL. Most notable is a rearrangement on chromosome 14 involving the BCL2 gene. This event leads to overexpression of BCL2 protein by B cells, which inhibits the process of apoptosis in normal cells, allowing lymphoma cells to survive longer in vivo [97-99]. In addition, other gene mutations in Myc, BCL6, and PAX5 may also play a key role in the development of FL. These mutations cause lymphoma cells to lose normal cell cycle control, which drives their abnormal growth and division [100, 101].

BCL2 gene rearrangement is a key finding in the pathogenesis of FL. In patients with FL, a specific rearrangement of the BCL2 gene has been identified, a finding that has important biological and therapeutic implications. The BCL2 gene encodes a protein called BCL-2, which acts in normal cells to inhibit or slow down the process of apoptosis. Thus, overexpression of BCL-2 can result in the inability of cells to die according to the normal apoptotic program, which promotes the survival and expansion of malignant lymphocytes.

Specifically, BCL2 gene rearrangements in FL patients typically involve a translocation event between chromosomes 14 and 18, commonly referred to as t(14;18)(q32;q21). This chromosomal abnormality results in a fusion between the BCL2 gene and the immunoglobulin heavy chain (IgH) gene, linking the regulatory sequences of IgH to the BCL2 gene, thereby contributing to the abnormally high expression of BCL-2 in B cells. Due to the overexpression of BCL-2 protein, malignant B cells can escape the natural process of apoptosis and have a prolonged survival cycle, which contributes to the development and growth of FL [101-104].

In addition to the rearrangement of the BCL2 gene, mutations in other genes have been found to have an important role in the development of FL. These genes include IRF8, CREBBP, EZH2, etc., which may be involved in regulating biological processes such as cell proliferation, differentiation, and survival. Mutations in these genes may lead to malignant proliferation and abnormalities in lymphocytes, promoting the development of FL [13, 105, 106].

In addition, chromosomal abnormalities are also very common in FL patients, a typical example of which is the t(14;18) chromosome translocation. This chromosomal abnormality is associated with overexpression of the BCL2 gene and the pathophysiology of FL [78, 107,

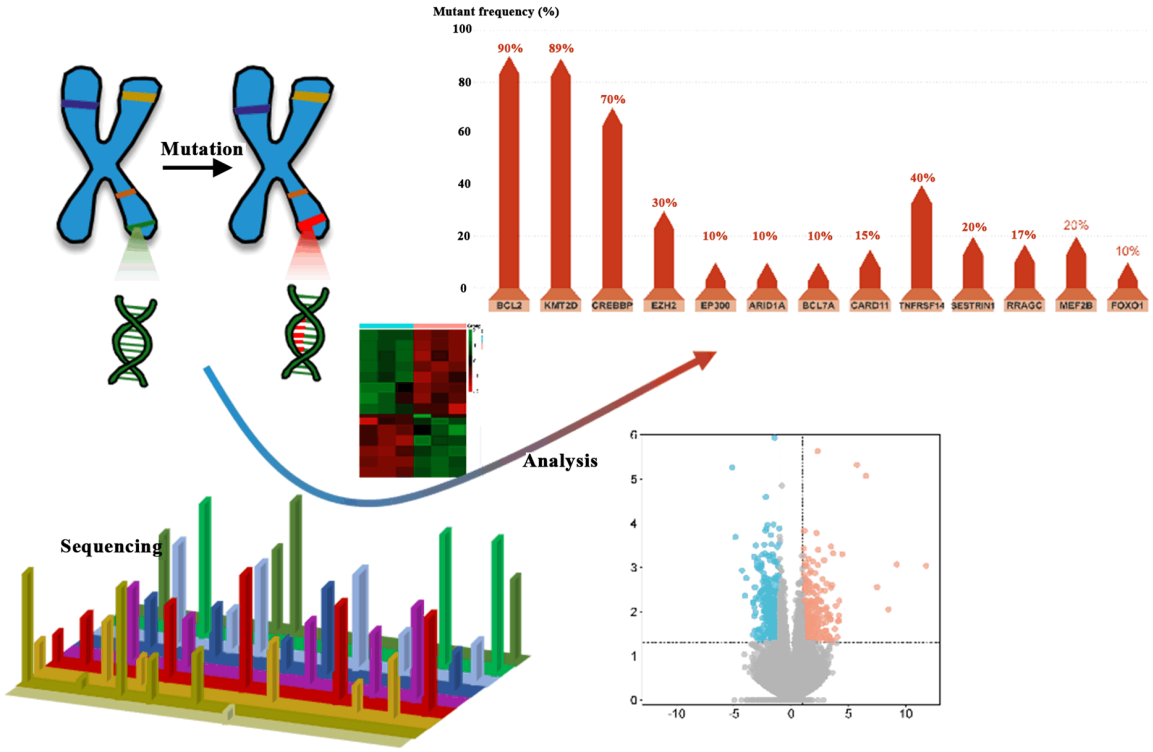

Figure 4. Schematic of the most commonly mutated genes and chromosomes in FL.

108]. These chromosomal abnormalities information has contributed to a better understanding of the pathogenesis of FL and has also provided clues for the development of therapeutic strategies, particularly through the intervention of drugs targeting abnormal genes such as BCL-2. The distribution of mutations and some of the most common mutations in FL are given in **Figure 4**. In-depth studies of these mutations and chromosomal abnormalities can help provide more precise and effective treatments for FL patients.

Immune system dysregulation

Immune system dysregulation has also been linked to the pathogenesis of FL. The immune system plays a vital role in maintaining the body's immune balance and fighting against infections. It recognizes and attacks foreign substances, pathogens, and abnormal cells in the body to ensure health and homeostasis. However, studies have found that dysregulation of the immune system may be associated with the development of FL [105, 109].

Additionally, a prolonged state of immunosuppression may increase the risk of developing FL. This condition is usually associated with immunosuppressive therapy after undergoing organ transplantation. After organ transplantation, patients are required to take immunosuppressive drugs to prevent the immune system from attacking and rejecting the transplanted organ. However, these medications suppress the normal functioning of the immune system and reduce its ability to monitor and remove abnormal cells. This increases the risk of developing lymphomas such as FL, as malignant lymphocytes may escape the monitoring of the immune system and cannot be removed in time [110-113].

Autoimmune diseases have also been found to be associated with the development of FL. Autoimmune diseases are a group of diseases in which the immune system abnormally attacks its own normal tissues and cells, leading to inflammation and damage. Some studies have shown that certain autoimmune diseases, such as rheumatoid arthritis or lupus erythematosus, may increase the risk of developing FL. This may be related to the dysregulation of the immune system in people with autoimmune diseases, making it difficult for immune cells to

effectively monitor and remove malignant lymphocytes.

Likewise, immunodeficiency diseases may play a role in the development of FL. Immunodeficiency diseases leave individuals with a compromised or dysfunctional immune system that is unable to fully perform its normal defense functions. This condition may allow malignant lymphocytes more opportunities to escape monitoring and removal by the immune system, thus promoting the development of FL [114-116].

In conclusion, immune system dysregulation may be a key factor in the development of FL. Normal functioning of the immune system maintains the body's immune homeostasis, but dysregulation of the immune system may increase the risk of developing FL. This includes organ transplant patients receiving immunosuppressive therapy, patients with autoimmune diseases, and patients with immunodeficiency disorders. These conditions may interfere with the immune system's ability to monitor and remove malignant lymphocytes, thus providing an opportunity for FL to develop.

Environmental and familial genetic risks

Although the exact cause of FL is unknown, certain environmental factors, such as exposure to pesticides, solvents, organic solvents, and asbestos, have been proposed as possibly being related to the development of FL. It has been suggested that prolonged exposure to such toxic substances may lead to serious health problems and, in addition to FL, malignant diseases such as lung cancer and mesothelioma are often associated. Although the link between the environment and these diseases is widely recognized, its connection to FL is not yet clear and needs to be further explored [117, 118].

Meanwhile, patients with a family history of FL may have a relatively high risk of developing FL, especially if there are multiple cases of FL in the family. However, a family genetic history does not necessarily result in a person developing FL, but rather increases the likelihood of developing FL. The impact of family genetic history varies depending on the number of FL cases in the family and the degree of relationship. Family predispositions may be caused by one or more genetic factors, but again, these factors are not yet fully understood [117, 119].

Treatment strategies

Many medical professional organizations and associations have published treatment guidelines for FL, and most of these guidelines provide detailed recommendations and strategies that designed to help doctors and patients make appropriate treatment decisions. For example, the guidelines on FL treatment issued by the Leukemia & Lymphoma Society (LLS) emphasize that treatment recommendations for different groups of FL patients should take into account factors such as grading, severity of disease, age, and overall health status. The LLS guidelines emphasize the importance of individualizing treatments to meet patients' specific needs. Another know guideline is published by the International Lymphoma Study Group (ILSG). Similarly, the guidelines typically include information on treatment options, testing and follow-up, response to treatment, and survival and prognosis.

Treatment options

According to treatment guidelines, the choice of treatment is usually based on: grading and severity of lesions, age, overall health status, symptoms and clinical presentation, disease distribution, and treatment goals. **Figure 5** briefly illustrates the decision tree given in the treatment guidelines for individual cases.

Radiotherapy

Radiotherapy is a localized treatment that uses high-energy X-rays or ionizing radiation to damage or kill malignant lymphocytes by precisely targeting the area of localized lymph node enlargement in order to reduce the size of the tumor or to relieve symptoms. This treatment is indicated for patients who cannot receive systemic chemotherapy or for those with localized disease. The treatment procedure is performed under the supervision of a radiation oncologist, usually requires multiple irradiations, and may be accompanied by some temporary side effects. A combination of other treatments may be necessary for widely distributed FL or in cases where systemic therapy is required [77, 120].

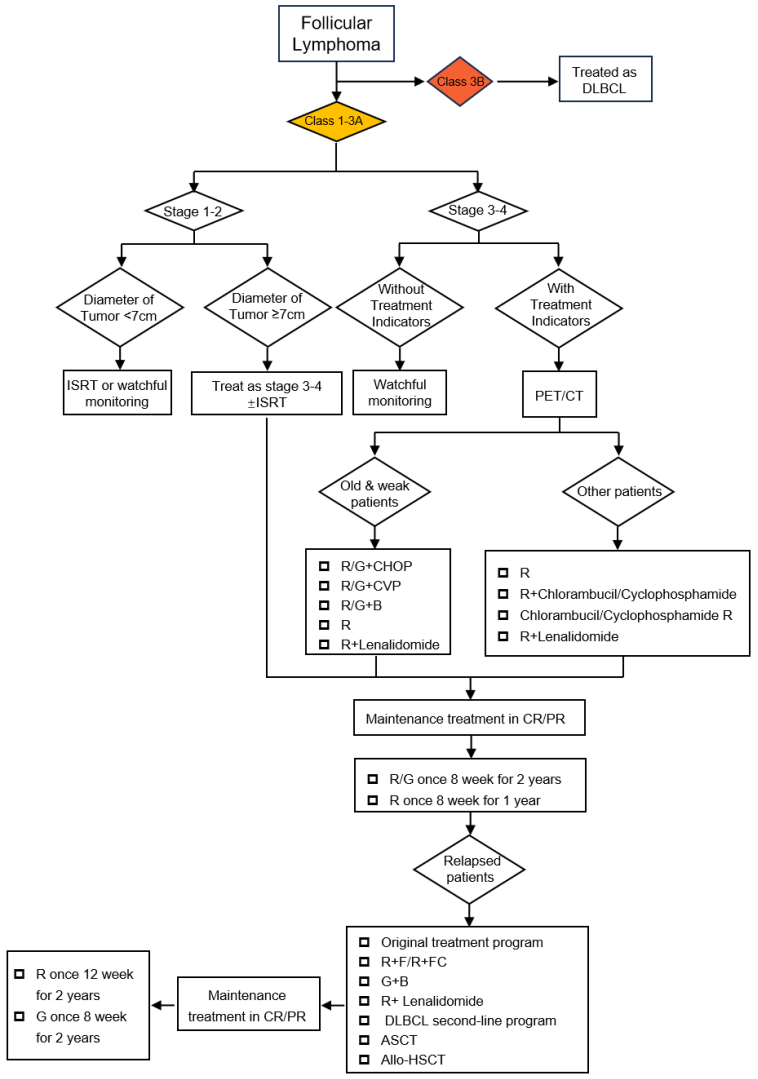

Figure 5. Schematic diagram of the decision tree for treatment guidelines. FL: follicular lymphoma; DLBCL: diffuse large B-cell lymphoma; ISRT: involved site in radiation therapy; R: Rituximab; G: obinutuzumab; CHOP: cyclophosphamide + hydroxydaunorubicin + oncovin + prednisone; CVP: cyclophosphamide + vincristine + prednisolone; B: Bendamustine; CR: complete remission; PR: partial remission; F: fludarabine; FC: fludarabine + cyclophosphamide; ASCT: autologous hematopoietic stem cell transplantation; allo-HSCT: allogeneic hematopoietic stem cell transplantation.

Chemotherapy

Chemotherapy is a common treatment for FL, especially for patients who require systemic therapy. It involves the use of a combination of chemotherapeutic agents, such as cyclophosphamide, doxorubicin, vilutide, and vincristine, which interfere with the growth and division of cancer cells through different mechanisms, including inhibiting DNA synthesis, decreasing the rate of cell division, and inducing apoptosis, thereby controlling the progression of the disease.

Chemotherapy is usually indicated for FL patients who require systemic therapy, especially those with widely distributed lesions or unrestricted lymph node enlargement. The treatment process consists of a cyclical regimen in which the patient receives the drug for a certain period of time, followed by a rest period, and this cycle is repeated several times to achieve optimal treatment results. Chemotherapy drugs can be given orally or intravenously, depending on the treatment regimen and the patient's condition.

Although chemotherapy is very effective in controlling the progression of FL, reducing the size of the tumor, and relieving symptoms, it is accompanied by a series of side effects including nausea, vomiting, hair loss, immune system suppression, and anemia, but these side effects are usually temporary and can be alleviated with medication management or supportive therapy [76, 121-123].

Targeted therapy

Targeted therapy is a more effective and less toxic treatment for FL that interferes with the growth and division of cancer cells through specific molecular or protein targets. Generally speaking, the commonly used targeted therapeutic agents for the treatment of FL are CD20 antibodies and BTK inhibitors. Rituximab is one of these targeted therapeutic agents widely used in FL treatment. It is an anti-CD20 monoclonal antibody that directs the immune system to attack FL cells by binding to the CD20 antigen on the surface of B cells. This treatment is known as immunotherapy and its mechanism is to destroy cancer cells by activating the

body's immune response. Usually, rituximab is used in combination with chemotherapy drugs to improve the effectiveness of the treatment [124-126]. Another important targeted therapy is BTK (Bruton's tyrosine kinase) inhibitors such as Ibrutinib and Acalabrutinib. These drugs inhibit FL cell growth and division by interfering with the signaling pathway in B cells by inhibiting BTK enzyme activity within the B cells. BTK inhibitors are usually used as oral medications for some FL patients, especially those who do not respond well to or cannot tolerate chemotherapy. These targeted therapies play a key role in the treatment of FL. They have fewer toxic side effects and can largely improve the quality of life of patients while limiting the progression of the disease [127-130].

Autologous stem cell transplantation (ASCT)

ASCT is one of the novel treatments for FL, which is typically used to treat relapsed or refractory FL. Often, doctors may choose to treat patients with ASCT based on their gender, age, and other characteristics, when traditional therapies are no longer appropriate, or when FL shows rapid progression or is accompanied by severe symptoms. The ASCT process includes the following steps [131-134]:

1. Stem cell collection: Prior to ASCT, the patient's autologous stem cells are collected from the bone marrow or peripheral blood. This usually involves the use of drugs to stimulate the proliferation of stem cells, which are then separated from the blood through a decellularization process. These autologous stem cells will be used in subsequent treatments to rebuild the hematopoietic system.

2. High-dose chemotherapy: Prior to stem cell harvesting, patients receive high doses of chemotherapy drugs that kill malignant lymphocytes but also damage the normal hematopoietic system. This is a very powerful treatment, so patients need to undergo stem cell harvesting prior to receiving high-dose chemotherapy in order to use autologous stem cells during treatment.

3. Stem cell transplantation: At the end of high-dose chemotherapy, the previously collected autologous stem cells are reimplanted into the body. This helps to re-establish the normal hematopoietic system while reducing the toxic side effects caused by high-dose chemotherapy. The goal of autologous stem cell transplantation is to restore the patient's hematopoietic function so they can cope with the cytotoxicity during treatment.

It is important to note that the use of ASCT usually requires close monitoring, as the patient's immune system can be significantly compromised during treatment. This procedure may result in low blood counts for a period of time, so patients will need to receive anti-infective therapy and supportive care to alleviate treatment-related discomfort and complications.

CAR-T cell therapy

CAR-T cell therapy is another emerging therapeutic approach that is also highly specialized for the management of relapsed or refractory FL. For some patients with refractory or recurrent FL, when other therapeutic options are not effective, the patient's own T-cells can be utilized and genetically engineered to transform them into CAR-T cells (Chimeric Antigen Receptor T-cells), which are able to recognize and attack the FL cells for therapeutic purposes. Similar to stem cell transplantation, the steps of CAR-T cell therapy include the following three phases: 1. T-cell collection: The patient's T-cells are collected, usually by means of peripheral blood; 2. CAR-T cell engineering: The collected T-cells are genetically engineered in the laboratory to enable them to recognize and attack FL cells through the introduction of CAR genes; 3. CAR-T cell therapy: The engineered CAR-T cells are expanded and then re-implanted into the patient's body. Once in the body, CAR-T cells can seek out and destroy FL cells. **Figure 6** illustrates the detailed workflow of CAR-T cell therapy. Similarly, this treatment is also accompanied by some important adverse effects such as cytokine release syndrome and neurotoxicity, so close monitoring and management is required [135-138].

Other strategies

Guideline strategies for monitoring and follow-up of treatment response, and prognostic factors also play a key role in the management of FL. Ongoing regular observation and assessment of disease status is required to ensure effective disease control and to respond promptly to any relapse or adverse reactions to

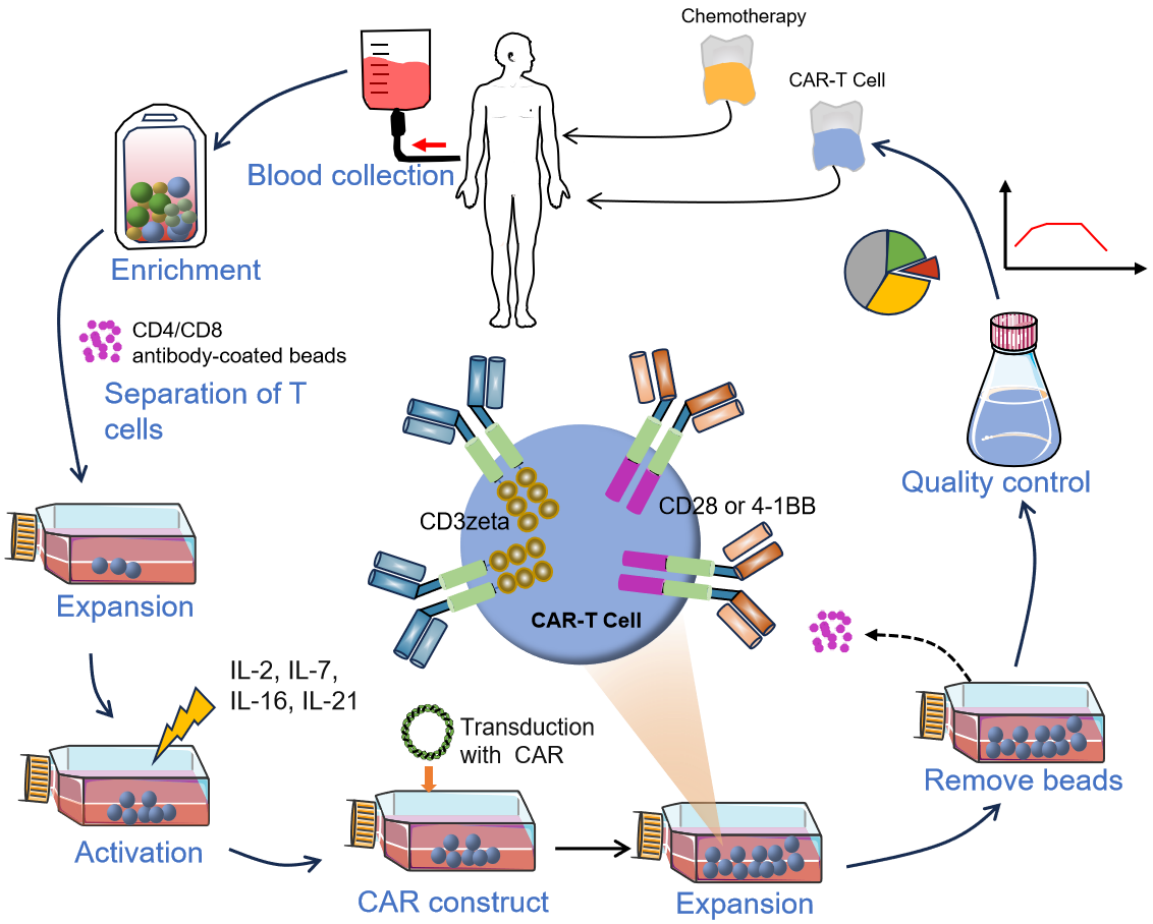

Figure 6. Detailed workflow diagram of CAR-T cell therapy and steps for processing CAR structures and patient T cells.

treatment. Follow-up visits provide regular medical observation and evaluation of patients on a specific schedule and frequency to monitor FL through physical examination, imaging, blood tests, and evaluation of response to treatment and prognostic factors to assess the effectiveness of treatment and the need for adjustments to the treatment program [139-141].

Challenges and progress

Despite the great efforts and research dedicated to the treatment of FL, a variety of problems and difficulties remain in the treatment of FL. These problems include, but are not limited to, FL drug resistance, relapse after treatment, and toxic side effects during treatment, which pose a great challenge to the clinical treatment of FL.

Challenges and problems

Drug resistance

Resistance is the ability of a disease to produce a reduced response to a therapeutic agent or to no longer respond to it. In FL therapy, this resistance may be due to a variety of mechanisms, including variation in the molecular targets of the drug, changes in intracellular signaling pathways, and immune escape mechanisms. 1. Changes in intracellular signaling pathways: A variety of signaling pathways within the FL cell may undergo changes that diminish its response to therapeutic drugs. These pathways include those for cell proliferation, survival, and resistance to apoptosis. When these pathways are altered, FL cells may be able to evade the effects of the drug [142, 143]; 2. Mutation of the molecular target of the drug: The effects of certain therapeutic drugs depend on their spe-

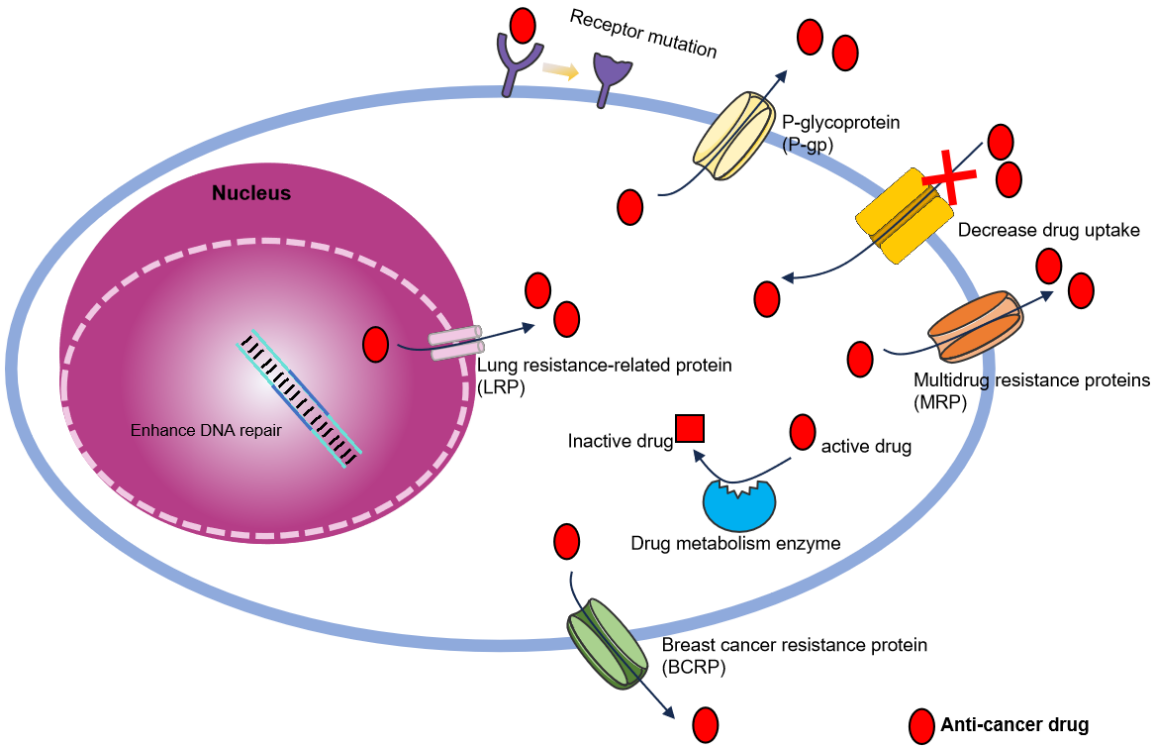

Figure 7. Network diagram of interactions between drugs and resistance mechanisms.

cific molecular targets in FL cells. If these molecular targets are mutated, the drug may not bind to them as expected, leading to drug failure [142, 144]; 3. Immune escape mechanisms: FL cells can adopt a number of immune escape strategies, for example, by altering their surface antigens to reduce recognition by the immune system. This makes it difficult for immune cells to attack FL cells, thus diminishing the effectiveness of immunotherapy [145, 146]; 4. Multi-drug resistance: FL cells may develop resistance to multiple drugs, which may be due to the compounding effect of multiple intracellular resistance mechanisms [147, 148]. **Figure 7** describes the interactions between drugs and resistance mechanisms.

Understanding these resistance mechanisms can help researchers and physicians develop more targeted therapeutic strategies, such as the use of different drug combinations, targeted therapies, or switching therapies at specific time points, to overcome resistance and improve treatment outcomes. This is an unavoidable but practical problem that affects therapeutic efficacy and requires a great deal of time and effort to explore and investigate.

Post-treatment relapse

Post-treatment recurrence is a frequent problem not only in the treatment of FL, but also in the treatment of other tumors. Despite the fact that the disease is under control or even in remission after the initial treatment, the disease may recur or progress after treatment in some patients. This may be due to failure to completely eradicate the disease cells, disease resistance, or other reasons. Post-treatment relapse or progression usually requires a re-evaluation of the treatment plan, which may require changing the treatment strategies to targeted therapy, radiotherapy, autologous stem cell transplantation, etc. This procedure greatly increases patients' treatment cycle, resulting in a serious decline in their quality of life, increased use of healthcare resources, as well as more cost and suffering [139, 149, 150].

Toxic side effects of treatment

As with the treatment of most tumors, adverse events can be caused by the therapeutic agents or the treatment itself. In general, common adverse events include [151-154]: 1. Diarrhea,

nausea and vomiting: Chemotherapy drugs usually stimulate the vomiting center, causing patients to experience nausea and vomiting; 2. Fatigue: Fatigue is a common adverse event during FL treatment, and patients may feel weak and have low energy; 3. Low blood cell counts: Chemotherapy drugs may adversely affect the hematopoietic system, resulting in lower white blood cell, red blood cell, and platelet counts. This may increase the risk of infection, anemia, and bleeding; 4. Infections: Due to the suppressive effect of chemotherapy drugs on the immune system, patients are susceptible to the threat of infections; 5. Toxic rashes: Some chemotherapy drugs may cause skin reactions such as rashes, itching, or dryness. These toxic side effects seriously increase the psychological burden of patients in the course of treatment and reduce their quality of life in the course of treatment. Due to the mechanisms of the treatment modality and therapeutic agents, these toxic side effects seem to be unavoidable at present. However, we expect that as research deepening, a treatment program with minimal toxic side effects and good therapeutic effects will be found.

Progress and development

Although the prevention, detection, and treatment of FL face multifaceted challenges and remain deficient, scientists and clinicians have made significant strides. This progress includes a deeper understanding of the pathogenesis of FL, the discovery of new molecular markers, the development of precise molecular diagnostic tools, and the emergence of innovative therapeutic strategies. In terms of prevention, although there are no clear-cut prevention strategies, researchers are working to identify possible environmental factors and genetic risks for developing FL, which help to develop more targeted prevention strategies. As for detection, based on the latest molecular biology techniques, researchers are continuously improving diagnostic methods for FL, including the application of genomics and transcriptomics, which can help to more accurately identify disease subtypes and thus provide a more precise basis for treatment selection. Particularly in terms of treatment, the emergence of innovative therapeutic strategies such as immunotherapy, small molecule targeted drugs, and individualized therapeutic strategies has provided patients with more treatment options. These approaches have not only improved treatment efficacy but also mitigated treatment-related adverse events, which offers new hope for the treatment of FL.

Immunotherapy

Immunotherapy holds great promise for the treatment of FL, as it utilizes the patient's own immune system to fight cancer cells, offering many potential advantages. As previously described, CAR-T cell therapy has shown significant therapeutic benefits in some FL patients. This treatment involves harvesting a patient's T-cells and then genetically engineering them in the lab to express the CAR receptor, which recognizes FL cells and destroys them. The engineered CAR-T cells are then re-implanted into the patient's body, and this approach has already showed favorable therapeutic outcomes in some patients with recurrent FL. Currently, scientists are trying to reduce the toxicity and increase the durability of CAR-T cells, which will be a new hope for FL treatment. Meanwhile, immune checkpoint inhibitors are another attempt by scientists. They are a class of drugs that unlock the suppression of the immune system by cancer cells, thereby increasing the aggressiveness of the immune system. These drugs have shown potential in FL treatment, particularly in patients who have high expression of the target proteins of immune checkpoint inhibitors (e.g., PD-1 and PD-L1). Future studies should focus on determining the optimal conditions for the use of immune checkpoint inhibitors, including monotherapy or combinations with other therapies [155-158].

Overall, immunotherapy holds great promise in the treatment of FL and has already led to some encouraging results. Combing immunotherapy with other therapeutic approaches, such as chemotherapy, radiotherapy, or targeted therapies, enables multiple attacks on tumor cells. This strategy enhances therapeutic efficacy, reduces toxic side effects, lowers the treatment burden on patients' body, and improves both patient survival and quality of life.

Small molecule targeted drugs

The development of small molecule targeted drugs in the treatment of FL represents an

exciting research direction. The mechanism of action of these drugs is to intervene in specific molecular signaling pathways required for the growth and survival of cancer cells, resulting in a more targeted fight against FL cells. For example, BTK inhibitors and BCL2 inhibitors, which we discussed earlier, intervene in the growth and division of FL cells and the restoration of the normal apoptotic process by controlling the signaling pathways of B cells, respectively, so that FL cells cannot escape apoptosis. Some drugs have been put into market use while some are still in clinical trial stages, but such drugs offer new therapeutic prospects for patients who are difficult to treat. Researchers of small molecule targeted drugs are still searching for new targets by exploring different molecular pathways and biomarkers to more precisely target patients' disease subtypes. Efforts are also being made to mitigate adverse effects and improve the therapeutic safety of these drugs. The development of small molecule targeted drugs represents an important advancement in the field of FL treatment, and they are expected to provide patients with more effective and personalized treatment options to improve survival and quality of life.

Future prospects

The future of treating FL is promising, and despite the challenges that remain. One prominent challenge is treatment resistance, a common problem in therapy. Understanding the mechanisms of therapeutic resistance is critical, as it can help scientists find strategies to combat it. This may include the development of new drugs with different targets or mechanisms that can overcome resistance, or reduce the occurrence of resistance by decreasing the resistance mechanisms. In addition, improving existing treatments to increase their durability or finding new combination treatment strategies could reduce the development of resistance. Research on treatment resistance will provide FL patients with better treatment options in a more cost-effective and efficient way.

Another exciting prospect is the in-depth research in genetics and gene expression. Scientists will continue to explore the genomes and transcriptomes of FL patients to reveal important factors associated with disease progression and treatment response. This molecular analysis will help identify unique subtypes and provide more information for developing individualized treatment strategies. Doctors will be able to select the optimal treatment plan for patients based on their genetic information, combined with clinical diagnosis, thereby improving treatment outcomes and reducing over-treatment. This will also help scientists to develop new drugs to target specific genes or molecules.

In addition, gene editing and precision medicine will provide new possibilities for future treatments. With the continuous development of gene editing technology, treatments for FL will be more precise and may even repair genetic abnormalities associated with the disease. We show in **Figure 8** the application of gene editing technology exemplified by CRISPR-Cas9. This offers new hope for patients whose disease cannot be effectively controlled by medication, and it marks the dawn of the era of precision medicine. The application of precision medicine will also further personalize treatment, ensuring that each patient receives the most appropriate treatment for their particular situation.

The exploration of FL prognostic factors has never stopped, but there is still no optimal prognostic model to accurately predict patients with early disease progression. How to prospectively combine existing prognostic models with innovative approaches to design new prognostic prediction systems to accurately predict patients with early-progressing FL in the initial treatment is a direction for future research. First-line treatment of FL with mertuzumab showed high remission and MRD-negative rates. Epcoritamab in combination with R2 regimen and Epcoritamab maintenance therapy have emerged in first-line FL treatment. Survival of relapsed-refractory FL needs to be further improved, but there is still no standardized treatment plan, and the choice of salvage treatment plan needs to be evaluated individually and comprehensively; novel bispecific antibodies have significant efficacy in patients with relapsed-refractory FL, and to a certain extent, they can overcome the poor prognosis of high-risk patients; CAR-T therapy has provided a therapeutic option for patients with FL in multiple lines of therapy; the emergence of new

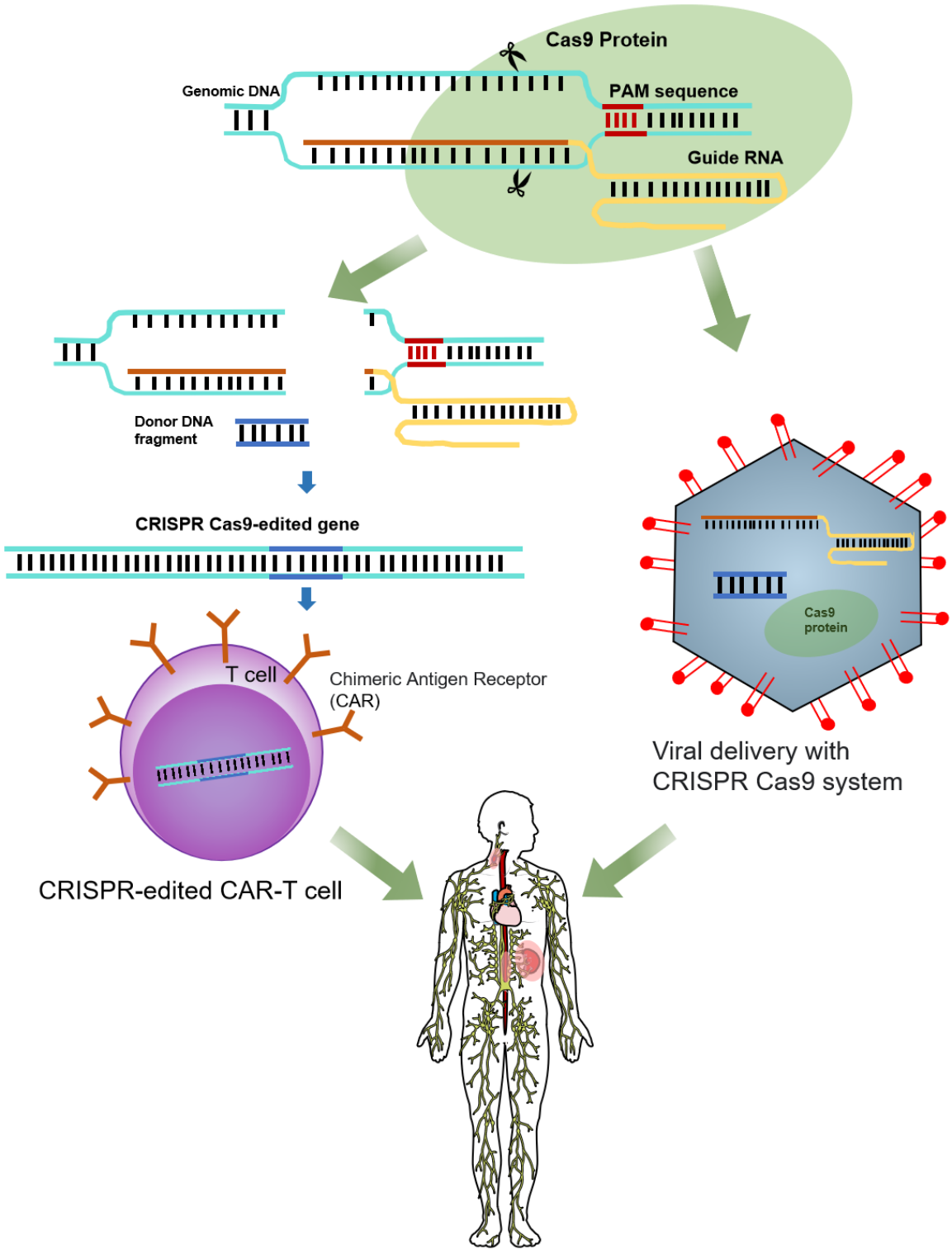

Figure 8. Schematic of the application of gene editing technology using CRISPR-Cas9 as an example.

drugs with different targets has improved the efficacy of FL. However, how to combine with other mechanism drugs to further improve the prognosis of FL still needs to be explored.

Clinical trials of new treatment strategies will continue to advance the field of FL therapy. More treatments will enter clinical trials, including targeted drugs, immunotherapies and gene

editing. By participating in these trials, patients will have access to yet-to-be-approved treatments and provide scientists with more information about treatment strategies. In the future, the treatment of FL will become more diverse, and individualized treatment strategies will become the norm, ensuring the best possible outcome for each patient. We have reason to believe that through research on treatment resistance, in-depth studies of genetics and gene expression, the application of gene editing and precision medicine, and clinical trials of new therapeutic strategies, we can expect to make more progress in the treatment of FL and bring a better future for patients.

Conclusion

FL is a complex type of lymphoma, with its treatment and research involving multiple dimensions. Its pathogenesis is intricate, and in terms of etiology, we highlight the possible pathogenic mechanisms of FL. These interconnected mechanisms add to the diversity of disease progression, underscoring the importance of precise therapeutic strategies. We further explore the therapeutic challenges and opportunities. Therapeutic resistance is a common problem, but scientists are working to understand its mechanisms to develop more effective treatment strategies. In addition, breakthroughs in various research areas, especially those targeting the BCL2 gene, have provided new directions for targeted therapy for FL. More in-depth research on the mechanisms of treatment resistance, searching for new therapeutic strategies, in-depth exploration of genetics and gene expression in FL patients, development of more individualized treatment strategies, application of gene editing and precision medicine, and promotion of clinical trials of new therapeutic approaches will be important directions for research in the future. While challenges remain, these efforts represent a promising blueprint for the future of FL treatment, providing more opportunities to improve patient outcomes. We also hope that this article will help clinicians gain a deeper understanding of FL, enabling them to better assess their patients' health during the treatment process. This knowledge will support the development of more effective and personalized treatment strategies.

Disclosure of conflict of interest

None.

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