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Review Article

CYLD in Hematological Malignancies

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Tumor suppressor CYLD (Cylindromatosis) is a deubiquitinase, which was initially found in benign tumor cylindroma. Now it has been found that it plays an important role in regulating a variety of signaling pathways, participating in a variety of physiological and pathological processes, inducing apoptosis and inhibiting tumor formation. Its gene defect is closely related to the occurrence, pathogenesis and development of many kinds of tumors, such as Multiple Familial Trichoepithelioma (MFT), Familial Cylindroma (FC), Brooke-Spiegler Syndrome (BSS) and other skin tumors. In addition, the expression of CYLD is down regulated in lung cancer, breast cancer, colon cancer, hepatocellular carcinoma and other solid tumors [1-3]. At present, there are few studies on CYLD in hematological malignancies. As a deubiquitinase, CYLD regulates the proliferation, development and activation of lymphoid cells, and its expression is significantly inhibited in acute T-lymphoblastic leukemia and CLL [4,5]. Its role and significance in CML are unclear [6]. In recent years, down-regulation of CYLD has been found in multiple myeloma. This article reviews the role and significance of CYLD in hematological malignancies.

CYLD and Its Functions

Molecular structure of CYLD

The human CYLD gene is located on chromosome 16q12.1 and encodes a CYLD protein consisting of 956 amino acid residues. CYLD contains two important domains: Cytoskeleton-Associated Protein Glycine Conserved Domain (CAP-Gly) and C-terminal domain. In addition, CYLD also contains two proline-rich regions. The CAP-Gly domain is evolutionarily conserved and can directly interact with tubulin to regulate the cytoskeleton and cell movement. Spatially, the CAP-Gly domain can form a β-sheet structure, which can recognize and bind proline-rich proteins [7]. The C-terminal domain is responsible for encoding Ubiquitin Carboxyl-Terminal Hydrolase (UCH), which can remove polyubiquitin chains from protein substrates. It is an essential domain for deubiquitinating enzyme activity and can negatively regulate Nuclear Transcription Factors κb (NF-κB) signaling pathway and Mitogen-Activated Protein Kinase (MAPK) pathway [8]. CYLD deubiquitinating enzyme domain deubiquitinating signal molecules such as TRAFs, NEMO, Bcl-3, p53, SMADs and CAP-Gly domain regulating microtubules and changing the process of multimerization and acetylation , thus playing a regulatory role in cell proliferation, cell apoptosis, cell movement and cell differentiation.

CYLD Negatively Regulates NF-κB, TGF-β, JNK and Wnt /β-Catenin and other Signal Pathways

The transcription factor NF-κB signaling pathway is the most important pathway that regulates innate immunity, secondary immunity and inflammation. It regulates a variety of cell biological functions, such as cell proliferation, differentiation and apoptosis [9]. NF-κB is composed of five members: RelA(P65),RelB,c-Rel,p50/p105 and p52/p100, which can be combined in pairs to form homodimers or heterodimers, of which P50/P65 is the most common NF-κB form. Ubiquitination modification is one of the main molecular mechanisms regulating the activity of NF-κB signaling pathway [10]. Bcl-3 is a member of the IκB protein family and is a nuclear co-activator that can cooperate with P50 or P52 homodimer to perform transcriptional activation. JNK is a member of the Mitogen-Activated Protein Kinase (MAPK) family, an important signaling pathway in cells, and plays an important role in the formation and development of tumors.

CYLD removes K63-linked ubiquitination from the signal molecules such as RIP1, TRAFs, NEMO and Bcl-3 through its deubiquitination enzyme activity, thereby down-regulating multiple signal pathways including NF-κB, TGF-β and JNK. Under physiological conditions, it is also regulated by phosphorylation and ubiquitination. Therefore, the expression and activity of the CYLD protein are strictly regulated, which in turn regulates cell proliferation, apoptosis, cycle, invasion and other biological processes. It plays an important role in the occurrence of malignancies [11-12]. In addition, studies have found that loss of CYLD leads to the ubiquitination of hyper-Dvl protein and activation of the Wnt pathway, leading to overexpression of β-catenin, which may lead to tumorigenesis and/or tumor deterioration [13].

The Physiological and Pathological Effects of CYLD

The NF-κB signaling pathway is directly related to immune and inflammatory responses. The deubiquitinating enzyme CYLD negatively regulates the activity of NF-κB, and has important functions in both innate immunity and secondary immune response. In addition, CYLD has also been found to play a role in regulating osteoclast formation, bone internal environment balance, sperm formation, cell cycle progression and cell migration [14-17].

CYLD and Hematological Malignancies

CYLD and Multiple Myeloma (MM)

Multiple myeloma is a plasma cell malignant tumor. Its pathogenesis is complicated. There are many steps to transform normal plasma cells into aggressive myeloma cells, which often require multiple structural and quantitative genomic abnormalities. The most common genetic abnormalities include immunoglobulin heavy chain sites and genetic translocations such as CCND1, MMSET, CCND3, c-MAF or MAFB, and most of the remaining cases of MM are related to trisomies of chromosomes 3,5,7,9,11,15, 19 and 21. Other common genomic abnormalities in MM include RAS mutation activation, 6q, 8p, 13q, 16q or 17p deletion, or genetic changes involving the MYC gene family, most of which are related to the progression of MM disease to advanced stages; 15-20% of MM patients have all or part of the long arm of chromosome 16 missing, and often have a poor clinical prognosis [18-19].

Using single nucleotide polymorphism arrays for gene expression profiling and gene mapping, it was found that CYLD (16q12.1) is a potential determinant of poor prognosis in these cases [20]. CYLD gene deletion or mutation is more common in multiple myeloma. At present, studies related to the prognosis of multiple myeloma with CYLD have shown that myeloma patients with CYLD deficiency have a poor clinical prognosis [20]. In myeloma cell lines and primary MM, the expression of CYLD is highly variable. The low level of CYLD expression is related to the disease progression from MGUS to MM, and is related to the overall and progression-free survival of patients with MM; functional testings show that CYLD inhibits the proliferation and survival of MM cells [21].

However, the mechanism of CYLD as a tumor suppressor in the pathogenesis of MM is not yet clear. At present, it is generally believed that MM is an NF-κB dependent disease.

NF-κB signaling promotes the proliferation, survival and drug resistance of myeloma cells, and plays a central role in the pathogenesis of myeloma [22], NF-κB pathway related gene mutation and amplification are one of the most common genetic abnormalities in MM. The expression of NF-κB inhibitors such as A20, CYLD, IκBα and BIRC3 is inhibited, which is an important mechanism for myeloma cell survival. Among them, CYLD plays a leading role in the regulation of NF-κB [11]. H van Andel et al. believe that in primary MM, although CYLD is a negative regulator of NF-κB and Wnt/β-catenin signals, the low level of CYLD expression is strongly correlated with myeloma cell proliferation and Wnt gene expression signals, but not with NF-κB signal. The deletion of CYLD enhances the aggressiveness of MM cells by activating Wnt pathway [21].

During the progression of MM disease, MM cells continuously interact with the microenvironment to form a microenvironment that is conducive to tumor growth. The classic Wnt signaling pathway plays a dual role in the interaction between MM cells and the Bone Marrow (BM) microenvironment: (1) The BM microenvironment promotes the abnormal activation of the classic Wnt signal of MM cells, which in turn mediates the proliferation, migration and drug resistance of MM cells; (2) MM cells secrete Wnt antagonists, which lead to osteolytic lesions by blocking the differentiation of osteoblasts. The abnormal activation of Wnt signal is caused by the gene and epigenetic damage of Wnt regulatory components, these damages include the loss of tumor suppressor CYLD, promotor methylation of the Wnt antagonists WIF1, DKK1,DKK3, and sFRP1, sFRP2, sFRP4, sFRP5, as well as overexpression of the co-transcriptional activator BCL9 and the Rspondin receptor LGR4[23].

In addition, the interaction of Wnts and R-spondins with syndecan-1 (CD138) on the surface of MM cells also strongly promoted the activity of Wnt [23]. Therefore in MM, the absence of CYLD can promote the activation of the Wnt pathway, promote the proliferation of MM cells, and enhance the aggressiveness of MM cells by activating the Wnt pathway. The highly conserved Wnt signal transduction pathway plays a key role in regulating cell proliferation, differentiation, migration and stem cell self-renewal. Wnt signaling increases the adhesion of malignant plasma cells and bone marrow stromal cells by acting on the small GTPases that regulate the formation of the cytoskeleton, thereby enhancing drug resistance [24]. Di Marzo L and others also found that the adhesion of MM cells to bone marrow mesenchymal cells not only caused MM bone disease, but also played a key role in Cell-Adhesion-Mediated Drug Resistance (CAM-DR) [25].

In recent years, the development of new drugs has made significant progress in the treatment of MM. In particular, the combined treatment strategies of immunomodulators, proteasome inhibitors, conventional chemotherapy and monoclonal antibodies have made substantial progress. However, despite the improvement in patient survival rate and quality of life, multiple myeloma is still incurable. The current median survival period is 8 years, mainly due to acquired drug resistance and disease recurrence. The proteasome inhibitor Bortezomib (BTZ) has a significant effect in MM. It specifically inhibits the activity of the proteasome

26S subunit, and can significantly reduce the degradation of nuclear factor κB(NF-κB) inhibitor (IκB).The combination of IκB and NF-κB can effectively inhibit the activity of NF-κB, inhibit the expression of genes related to cell proliferation, reduce the secretion of IL-6 and other myeloma cell growth factors and the expression of adhesion factors, and ultimately lead to myeloma cell apoptosis.

However, most patients inevitably face drug resistance and disease recurrence in the later stages of the disease. In BTZ-resistant Relapsed and Refractory Multiple Myeloma (RRMM), continuous activation of the NF-κB pathway is common, and CYLD is a negative regulator of the NF-κB pathway, and its deletion can lead to abnormal activation of the NF-κB pathway, suggesting that it may play a role in BTZ resistance. The application of the Immunomodulator (IMiD) lenalidomide not only improves the remission rate of MM patients, increases the depth of remission, but also significantly prolongs the survival time. However, they are also facing the dilemma of drug resistance. In MM, the absence of CYLD can promote the activation of the Wnt pathway and promote the proliferation of MM cells. The activation of Wnt pathway is related to the acquired cell adhesion mediated resistance of MM cells to traditional drug therapy (including doxorubicin and lenalidomide).

Therefore, in MM patients with deletion of CYLD, targeting Wnt pathway may be a promising therapeutic strategy: (1) it can increase the apoptosis of MM cells, to reduce the growth of tumor; (2) to reduce the level of DKK1 secreted by MM cells, so as to reduce osteolytic osteopathy and the subsequent bone related symptoms; (3) to reduce acquired Cell Adhesion Mediated Drug Resistance (CAM-DR) in MM, so as to increase the response to the established treatment regimes [26]. Harmen Van Andel et al. also believe that since Wnt signaling in MM cells is largely dependent on ligands, it can be targeted by drugs/antibodies acting on the upstream of the pathway to interfere with Wnt secretion, isolate Wnt, or block Wnt (CO) receptor [23]. The pathogenesis of multiple myeloma is complex. As an important tumor suppressor, the lack or low expression of CYLD is associated with the poor prognosis of MM. Currently, MM is still incurable, and drug resistance is a major problem. Bortezomib and lenalidomide are the first-line treatment for MM, and the follow-up treatment for resistant patients is a great challenge in clinic. According to the current relevant studies, the deletion of CYLD may be related to the acquired resistance of bortezomib, lenalidomide and adriamycin. Elucidating the regulation mechanism of its signaling pathway may provide a new way for molecular targeted therapy.

CYLD and Other Hematological Malignancies

The role and regulatory mechanism of CYLD in other hematological malignancies have not been well studied. At present, it is believed that there is either a loss of CYLD biallel gene or a post-translational mechanism to inhibit CYLD in tumor cells [27].

Adult T-Cell Leukemia/Lymphoma (ATLL)

ATLL is a peripheral T cell malignant tumor associated with Human T-Cell Leukemia Virus Type 1 (HTLV-1) infection. Patients with aggressive subtypes of ATLL have poor prognosis. Some studies suggest that the tumor inhibitory effect of CYLD may be due to its ability to switch ripk1 to death signal mode [27]. Xin Xu et al. observed that the baseline level of CYLD phosphorylation was increased in primary ATLL samples and cell line models, and CYLD phosphorylation could inhibit its deubiquitination function, resulting in increased ubiquitination of ripk1, providing a survival promoting signal for ATLL cells. IKK inhibitors (MRT67307 and TPCA) can reverse the phosphorylation of CYLD, reactivate CYLD and reduce the ubiquitination of RIPK1, resulting in the association of ripk1 with Death Inducing Signal Complex (DISC), thus triggering the death of ATLL cells. In the absence of CYLD, the ubiquitination of ripk1 was still increased after IKK blocking, but it was not associated with DISC. This study suggests that CYLD is a key regulator of ATLL cell survival, and inhibition of CYLD phosphorylation can be a new method for the treatment of ATLL patients [28].

T-Cell Acute Lymphoblastic Leukemia (T-ALL)

T-ALL is an aggressive hematologic malignancy. Teresa Da et al. found that Notch-Hes1-CYLD-NF-κB axis plays an important role in the maintenance of T-ALL. After silencing the target gene Hes1 of Notch or over expressing the target gene CYLD of Hes1, the ability of Notch1 to induce T-ALL disappeared [29]. Espinosa L found that the expression of CYLD was significantly inhibited in primary T-ALL. Hes1, as the target gene of notch, maintains the activation of NF-κB by repressing the deubiquitinase CYLD, a negative IKK complex regulator. IKK inhibition is a promising choice for targeted therapy of T-ALL [30]. An earlier domestic study found that miR-19 was highly expressed in T-ALL patients and cell lines. Ectopic expression of miR-19 inhibited the expression of CYLD, while miR-19 inhibitor induced the expression of CYLD protein and decreased the expression of NF-κB, which may provide a potential therapeutic target for T-ALL [4].

Chronic Lymphocytic Leukemia (CLL)

The loss of CYLD expression was also observed in CLL. A domestic study detected the expression of CYLD mRNA in 125 patients with CLL by PCR. Compared with normal B cells, the expression of CYLD mRNA in CLL cells was significantly down regulated. The Overall Survival rate (OS) of patients with high expression of CYLD was longer (10-year OS: high CYLD: 94.74%, low CYLD: 52.71%; P = 0.0534). For patients with IGHV gene mutation, high CYLD was also associated with better OS (10-year OS: high CYLD: 100%, low CYLD: 66.67%; P = 0.0547). This study shows that CYLD plays a role as a tumor suppressor

in the pathogenesis of CLL [5]. Subsequently, this team found that the Wnt inhibitor Ethacrynic Acid (EA) could induce apoptosis and necrosis of primary CLL cells, and proved that EA could inhibit the recruitment of DNA promoter by LEF1 and restore the expression of CYLD in CLL cells. EA may be a promising drug for the treatment of CLL [31].

Chronic Myeloid Leukemia (CML)

The role and significance of CYLD in CML is still unclear. It has been reported that CYLD negatively regulates Wnt/β-catenin signaling pathway through deubiquitination of Dvl protein [13]. A recent study in CML came to a different conclusion. Ceyda caliskan et al. evaluated the mRNA expression of three CML cell lines, and the sequencing results showed that there was no mutation in the coding sequence of CYLD gene; after Dvl silencing, the expression of CYLD decreased; after Dvl protein over expression, the expression of CYLD increased. These data suggest that there are more complex mechanisms of mutual regulation in CML cell lines [6].

lymphoma

At present, there are few studies on CYLD in lymphoma patients. An early study on Hodgkin's lymphoma suggested that STAT6 was a potential transcription target, and RGMa, CHD2 and CYLD were identified as candidate tumor suppressor genes of classical Hodgkin's Lymphoma (cHL) [32]. In order to determine whether the CYLD mutation plays a role in the pathogenesis of CHL, Schmidt a et al. sequenced the CYLD gene in CHL cell lines. The results showed that the biallelic CYLD mutation is rarely involved in the pathogenesis of cHL [33]. There are few reports of CYLD in non-Hodgkin's lymphoma. At present, only a few cases have been reported. A female patient with aggressive non-Hodgkin's lymphoma presented with multiple cylindromas of the capillitium. Her mother also suffered from a mild form of late-onset cylindromas. Genotyping from peripheral blood showed that c.2465insAACA mutation in exon 17 of CYLD gene was detected in the patient and her mother, which led to frameshift [34].

Summary and Prospect

CYLD regulates many signaling pathways and plays an important role in the occurrence and development of many diseases. At present, most of the CYLD mutations have been reported in solid tumors, but there are few studies in hematological malignancies. The absence of CYLD may provide prognostic guidance for some hematological malignancies. Currently, the regulatory mechanism of CYLD on cell function still needs to be further explored. Elucidating the regulatory mechanism of its signaling pathway may provide a new way for molecular targeted therapy of hematological malignancies.

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