Expression profiling reveals coordinated dysregulation of autophagy-associated proteins in marginal zone lymphoma and therapeutic implications

JINGSHU RUAN[1,2*], XIN ZHOU[2*], AI LI[1] and NINGNING SHAN[1]

[1]Department of Hematology, The Second Hospital of Shandong University, Jinan, Shandong 250033, P.R. China; [2]Department of Hematology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong 250021, P.R. China

Received July 10, 2025; Accepted November 12, 2025

DOI: 10.3892/ol.2025.15421

Abstract. Dysregulated autophagy and its therapeutic targeting have emerged as focal points in oncology research; however, specific studies investigating autophagy in marginal zone lymphoma (MZL) pathogenesis remain limited. The present study comprehensively characterized the expression profiles of key autophagy-related proteins in MZL, providing novel mechanistic insights and an experimental rationale for therapeutic intervention. Immunohistochemical analysis assessed the expression of Beclin-1, light chain (LC)3, sequestosome (SQSTM)1/p62 and Bcl-2 in formalin-fixed paraffin-embedded tissues from 16 patients with MZL compared with 16 reactive lymphoid hyperplasia (RLH) controls. MZL specimens exhibited significant autophagy pathway dysregulation, characterized by ~35-40% decreased expression of Beclin-1 and LC3 and 30-45% increased expression of SQSTM1/p62 and Bcl-2 compared with RLH tissues ($P<0.05$ for all proteins analyzed). The present findings delineate a distinct profile of autophagy dysfunction in MZL, highlighting aberrant Beclin-1, LC3, SQSTM1/p62 and Bcl-2 expression as potential disease biomarkers and therapeutic targets. This study provides a critical basis for elucidating the molecular mechanisms underlying MZL pathogenesis and underscores the therapeutic potential of modulating autophagy-related pathways.

Introduction

MZL is an indolent B-cell neoplasm thought to originate from post-germinal center marginal zone B cells, commonly presenting in the spleen, lymph nodes and mucosa-associated lymphoid tissues (MALT) (1). Histologically, the neoplastic cells typically display a monomorphic population of small-to-medium lymphocytes with slightly irregular nuclei, inconspicuous nucleoli and moderate amounts of pale cytoplasm (2,3). The pathogenesis of MZL is closely linked to chronic antigenic stimulation, frequently driven by infectious agents such as *Helicobacter pylori* in gastric MALT lymphoma. Additionally, recurrent molecular aberrations, including somatic hypermutation of immunoglobulin genes, specific chromosomal abnormalities [e.g., t(11;18), trisomies 3 and 18, and deletion 6q23], and mutations in genes such as Notch receptor 2 (NOTCH2), Kruppel-like factor 2 (KLF2), TNF alpha-induced protein 3 and TBL1X/Y related 1, are critical contributors to lymphomagenesis and disease progression (4,5). Current frontline therapies primarily employ anti-CD20 monoclonal antibodies (e.g., rituximab), often combined with chemotherapy regimens (e.g., bendamustine or CHOP variants), which substantially improve response rates and survival outcomes (6). Nevertheless, inherent and acquired chemoresistance and frequent disease relapse persist as significant clinical challenges, limiting long-term curability and highlighting the need for innovative therapeutic approaches (7). Consequently, targeting molecular pathways beyond conventional chemotherapy represents a pivotal research direction. In this context, dysregulated autophagy, a conserved lysosomal degradation pathway essential for maintaining cellular homeostasis, and its therapeutic potential have emerged as significant research areas in oncology. Aberrant expression of key autophagy-related proteins has been documented across multiple malignancies, including lymphoma (8), ovarian (9), lung (10), breast (11) and colorectal cancers (12), suggesting that this pathway may represent a therapeutic target. MZL constitutes roughly 5-10% of non-Hodgkin lymphoma cases globally, with an annual incidence estimated at 2-3 per 100,000 population (13,14). Although considered indolent, MZL typically follows a chronic, relapsing clinical course, characterized by median overall survival exceeding 10 years but frequent recurrence following conventional immunochemotherapy. Relapsed or refractory disease remains therapeutically challenging, emphasizing the urgent need for novel molecular targets and more effective treatments (5,15).

Correspondence to: Professor Ningning Shan, Department of Hematology, The Second Hospital of Shandong University, 247 Beiyuan Road, Jinan, Shandong 250033, P.R. China
E-mail: snning@126.com

*Contributed equally

Key words: marginal zone lymphoma, autophagy, beclin-1, LC3, SQSTM1/p62

Autophagy dysregulation has been implicated in various lymphoma subtypes, including diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL) and follicular lymphoma (FL), where reduced Beclin-1 or microtubule-associated protein 1A/1B-light chain 3 (LC3) expression and increased accumulation of p62 correlate with adverse prognosis and chemoresistance (16,17). These findings indicate that autophagy dysfunction may be a shared oncogenic mechanism across B-cell malignancies. Clinically, several agents targeting autophagy and apoptosis pathways, such as chloroquine, hydroxychloroquine and the Bcl-2 inhibitor venetoclax, have demonstrated encouraging efficacy in preclinical studies and early-phase clinical trials (18), further highlighting the therapeutic relevance of targeting this pathway. Although abnormal expression of primary autophagy-associated proteins such as Beclin-1, LC3 and p62 has been well-characterized in lymphomas like DLBCL, MCL and FL (19-21), their expression patterns in MZL have not yet been extensively studied. To bridge this knowledge gap and evaluate the therapeutic implications of autophagy modulation in MZL, this research examined the expression levels of crucial autophagy indicators, including Beclin-1, LC3, sequestosome (SQSTM)1/p62 and Bcl-2, in clinical tissue samples obtained from patients diagnosed with MZL.

Patients and methods

Study and control cohorts. The demographic and clinicopathological data of the patients are summarized in Table I. MZL cohort: Formalin-fixed, paraffin-embedded (FFPE) tissue blocks were analyzed from 16 patients with newly diagnosed, treatment-naïve MZL (11 males, 5 females; median age, 64.5 years; range, 45-78 years). All specimens were collected at initial diagnosis between January 2014 and December 2024 from Shandong Provincial Hospital Affiliated to Shandong First Medical University (Jinan, Shandong). Diagnoses were strictly confirmed according to current World Health Organization lymphoma classification criteria (1). Patients with previous radiotherapy or chemotherapy exposure were excluded. Subtypes included 10 nodal MZL, 4 MALT lymphomas and 2 splenic MZL. MZL cases were retrospectively identified from the pathology archives, and all newly diagnosed, treatment-naïve patients with adequate FFPE tissue and complete baseline data during the study period were included. The control cohort consisted of FFPE tissue blocks from 16 patients with RLH (12 males, 4 females; median age, 62 years; range, 50-75 years). RLH cases were consecutively identified from the pathology archives of the same center during the same period based on the availability of treatment-naïve FFPE tissue blocks, rather than being artificially matched to the MZL group. By including all eligible MZL and RLH cases from the same institution and time window, rather than arbitrarily selecting or artificially matching controls, the risk of selection bias was minimized. Baseline demographic and clinicopathological characteristics, including age, sex distribution and involved sites, did not differ significantly between the MZL and RLH groups.

Immunohistochemistry (IHC)

Antibodies and reagents. Anti-Beclin-1 antibody (cat. no. ab207612; Abcam) was used at a dilution of 1:100. Anti-SQSTM1/p62 antibody (cat. no. ab109012; Abcam) was used at a dilution of 1:2,000. LC3A/LC3B polyclonal antibody (cat. no. ab109012; Abcam) was used at a dilution of 1:200. Anti-Bcl-2 antibody (cat. no. ab2137583; Abcam) was used at a dilution of 1:500. HRP-conjugated goat anti-rabbit IgG (H+L) secondary antibody (cat. no. ab205718; Abcam) was applied at a dilution of 1:1,000. A diaminobenzidine (DAB) chromogen kit (cat. no. DA1010; Beijing Solarbio Science & Technology Co., Ltd.), 5% bovine serum albumin (BSA; Wuhan Boster Biological Technology, Ltd.) and 3% H_2O_2 (Wuhan Boster Biological Technology, Ltd.) were also utilized.

Experimental procedures. Tissue sections were first baked, deparaffinized, rehydrated and washed with PBS. Antigen retrieval was then performed via high-pressure treatment using EDTA buffer, after which slides were cooled to ambient temperature. Blocking of endogenous peroxidase activity was achieved by treating sections with 3% H_2O_2, and non-specific antigen-antibody interactions were minimized by incubating slides in BSA. Primary antibodies were applied overnight at 4˚C, and subsequently, slides underwent washing in PBS before incubation at 37˚C for 40 min with secondary antibodies conjugated to HRP. Following PBS washes, staining was visualized using DAB chromogen, counterstained with hematoxylin, differentiated and blued. Finally, slides were mounted with coverslips and neutral gum prior to imaging.

Quantitative analysis. Pathological assessments were independently performed by two blinded, experienced pathologists using optical microscopy (magnification, x400). For each specimen, five non-overlapping, randomly selected high-power fields were used for semiquantitative analysis. Protein expression levels were quantified using ImageJ software (1.54p; National Institutes of Health) to calculate the average optical density (AOD): AOD=Σ integrated optical density/Σ positive pixel area.

Statistical analysis. All statistical analyses were carried out using GraphPad Prism version 9.0 (Dotmatics). Expression differences of autophagy-related proteins between groups were assessed by applying unpaired two-tailed Student's t-tests. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Suppressed Beclin-1 expression in MZL tissues. Beclin-1 exhibited cytoplasmic granular (yellowish-brown) staining in both RLH and MZL tissues by IHC analysis. Quantitative evaluation demonstrated a significant reduction in Beclin-1 expression in MZL tissues (AOD=0.43±0.19) compared to RLH controls (AOD=0.50±0.21; P=0.0139) (Fig. 1).

Impaired autophagic flux in MZL via reduced LC3 expression. LC3 displayed characteristic cytoplasmic granular staining in all specimens (Fig. 2). Compared to RLH controls (AOD=0.32±0.09), MZL tissues showed significantly reduced LC3 expression (AOD=0.22±0.09; P<0.0001), indicating defective autophagosome formation.

Accumulation of p62 indicates autophagic dysfunction in MZL. Consistent with impaired autophagic flux, p62 expression

Table I. Demographic and clinicopathological characteristics of the study cohort.

Characteristic	MZL (n=16)	RLH (n=16)
Sex		
Male	11	12
Female	5	4
Median age, years (range)	64.5 (45-78)	62 (50-75)
Pathological diagnosis		
MALT	4	-
NMZL	10	-
SMZL	2	-

MZL, marginal zone lymphoma; RLH, reactive lymphoid hyperplasia; MALT, mucosa-associated lymphoid tissue lymphoma; NMZL, nodal marginal zone lymphoma; SMZL, splenic marginal zone lymphoma.

was significantly elevated in MZL tissues (AOD=0.37±0.13) compared with RLH controls (AOD=0.28±0.23; P=0.0017) (Fig. 3). Cytoplasmic granular accumulation (yellowish-brown staining) of this selective autophagy receptor was confirmed by IHC, suggesting defective substrate clearance as a potential mechanism underlying MZL pathology.

Elevated anti-apoptotic Bcl-2 expression in MZL. IHC demonstrated cytoplasmic Bcl-2 accumulation (granular yellowish-brown staining) in all tissues. MZL tissues displayed significantly increased expression (AOD=0.28±0.09) compared to RLH controls (AOD=0.19±0.15; P<0.0001) (Fig. 4), indicating enhanced survival signaling typical of lymphomagenesis. This molecular alteration represents a potential therapeutic target.

Discussion

Autophagy is a key catabolic process that maintains balance in cells via the lysosomal breakdown of damaged organelles and protein aggregates, as well as redundant components in the body (22). Autophagy is a dynamic process that occurs in five sequential steps (22-24), which can result in dysfunctions in various key steps. At the initiation of autophagy, signaling pathways that involve mTOR complex 1 (mTORC1) lead to the inhibition of unc-51 like autophagy activating kinase 1/2 complexes that inhibit the initiation of autophagy (25). At the vesicle nucleation step, Bcl-2:Beclin-1 complexes inhibit autophagosome formation via the inhibition of Beclin-1/VPS34 retromer complex component complexes (26-28). Furthermore, in pathologic scenarios, there is a possibility of defective autophagy, leading to a reduction in the usual physiological roles of autophagy, which in turn contributes to cancer development. Dysautophagy in cancer allows cancer cells to adapt in a host that is under various pathologic stresses, including hypoxia as well as starvation (29,30).

Autophagy's role remains particular in the context of tumorigenesis, having a dual role that seems contradictory in nature (31-34). Autophagy is a tumor suppressor mechanism that eliminates dysfunctional organelles, misfolded proteins, as well as reactive oxygen species, thereby maintaining genomic stability and preventing tumorigenesis. However, in already present malignancies, dysfunctional/mutated autophagy pathways are known to promote tumor survival during metabolic, as well as hypoxic stresses, thereby leading to increased tumor progression as well as resistance (35,36). These data observed in MZL cases in the current study, showing dysfunctional Beclin-1 and reduced LC3 expression levels, as well as increased p62 accumulation, are possibly suggestive of a transition from a protective to a dysfunctional form of autophagy, leading to survival in the tumor microenvironment (37). Furthermore, certain known mutations in MZL will possibly interact with the autophagy pathways. *NOTCH2* mutations leading to increased B-cell survival as well as B-cell activation possibly lead to a reduction in autophagy as a result of increased mTOR, as well as NF-κB pathways in those downstream pathways. Furthermore, mutations in KLF2 leading to a reduction in KLF2 activity possibly result in increased NF-κB pathways in a possibly perpetually increased phase of activity, leading to alterations in metabolism of cells, as well as functioning as known modifiers of the process of autophagy (38,39). Therefore, dysfunctional autophagy observed in MZL is possibly a result of a multitude of these mutations affecting the pathways.

As increasing studies have focused on MZL, the intricate relationship between autophagy and MZL pathogenesis has slowly been revealed. Autophagy plays a role in MZL development and progression through various pathways, such as B-cell receptor signaling modulation, tumor microenvironment modulation, increased drug resistance, as well as crosstalk between tumor suppressor pathways (40,41). Goldsmith *et al* (42) revealed that autophagy supports metabolic rerouting in RAS-mutant cancer cells. Poillet-Perez *et al* (43) also found that autophagy suppresses T-cell immunity functions by attenuating stimulator of interferon response cGAMP interactor 1 pathway activity, whereas hepatocyte-specific autophagy deficiency moderately increased T-cell immunity against tumors. Furthermore, in 2024, Choi *et al* (44) found that myeloid-specific deficiency of autophagy reduced tumor-associated macrophages, increasing the accumulation of myeloid-derived suppressor cells. However, the mechanism of disrupted autophagy in MZL pathogenesis remains to be fully elucidated.

Beclin-1 inhibits tumor initiation under physiological circumstances. Conversely, in a tumor microenvironment, Beclin-1 expression is reduced. This leads to a failure in the formation of autophagosomes, thereby increasing the susceptibility of cells to transformation and tumorigenesis. Jiang *et al* (10) confirmed that Beclin-1 expression is significantly reduced in non-small cell lung cancer tissues compared with normal lung tissues. Pattingre and Levine (45) observed that Beclin-1 haplo deletion resulted in reduced autophagy in B lymphocytes. This further increased the susceptibility of mice to spontaneous B-cell lymphoma. It was revealed that B-cell lymphomas often display high Bcl-2 expression. This not only prevents apoptosis but also has a role in increasing B-cell lymphoma by functioning as a negative regulator of Beclin-1 expression-initiated autophagy (46). Furthermore, in the present analysis, it was discovered that

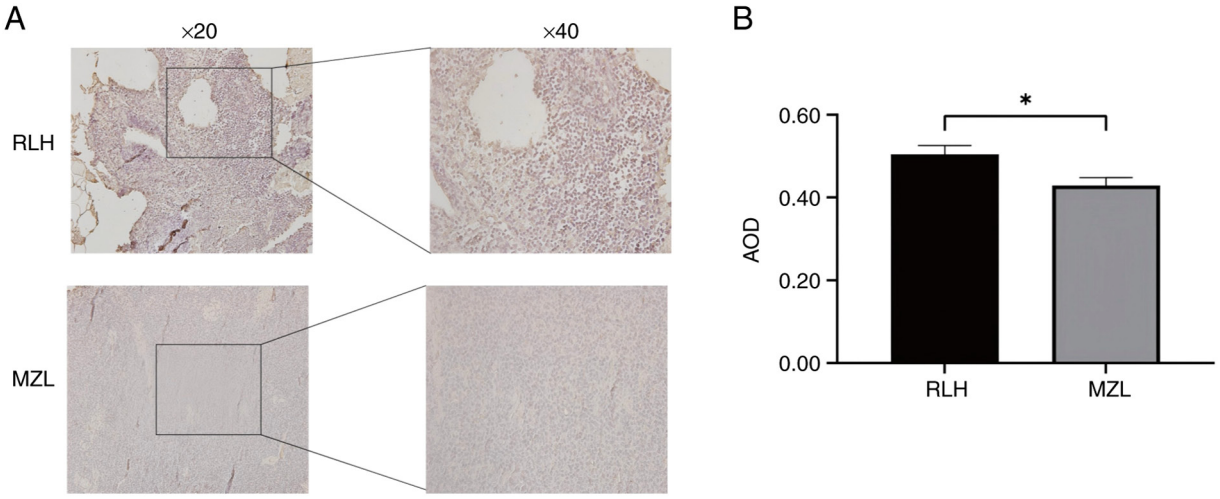

Figure 1. Beclin-1 protein expression in MZL and RLH tissues. (A) Representative immunohistochemical staining for Beclin-1 in MZL and RLH samples. (B) Statistical comparison of Beclin-1 expression between MZL and RLH tissues (analyzed by unpaired t-test. *P<0.05). MZL, marginal zone lymphoma; RLH, reactive lymphocyte hyperplasia; AOD, average optical density.

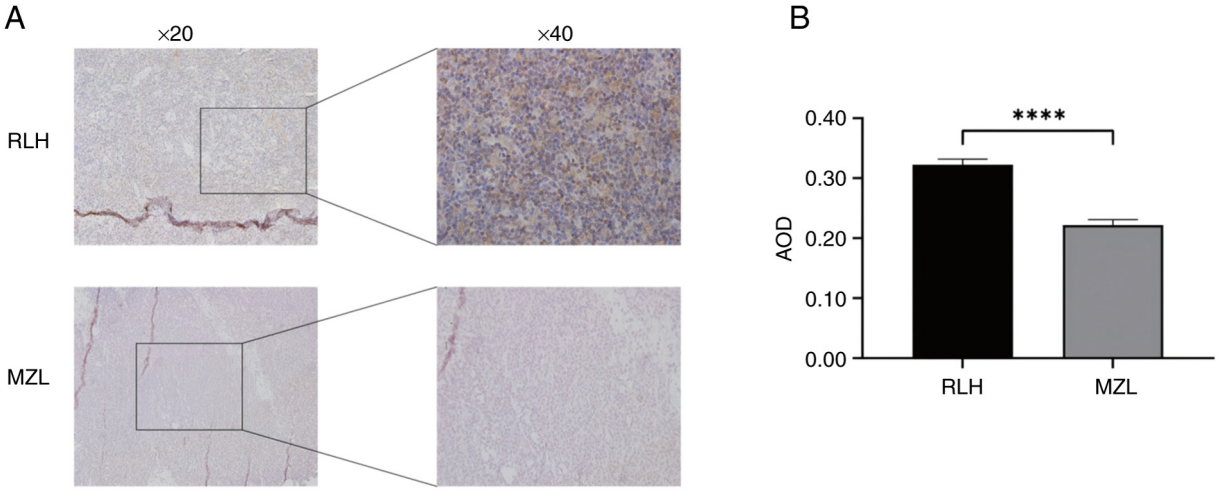

Figure 2. LC3 expression is significantly decreased in MZL tissues. (A) Representative immunohistochemical images showing LC3 staining in RLH and MZL samples (left panel: Magnification, x20; overview. Right panel: Magnification, x40; detailed view). (B) Statistical analysis demonstrating significant differences in LC3 expression between MZL and RLH groups (unpaired t-test, ****P<0.0001). LC3, light chain 3; MZL, marginal zone lymphoma; RLH, reactive lymphocyte hyperplasia; AOD, average optical density.

Beclin-1 was downregulated, whereas Bcl-2 was upregulated in MZL patients' tissue, suggesting that there is a problem in the formation of vesicles in MZL-related autophagy. In addition, it may be speculated that the abnormal expression of Beclin-1 and Bcl-2, regulated by the tumor microenvironment, leads to phagophores in MZL, making it impossible to remove metabolic waste in the form of autophagosomes, paving a way towards the transformation of cancerous cells in MZL. However, the current results indicated that this autophagy-related, Bcl-2-targeted hypothesis needs further clarification due to insufficient data supporting the use of Bcl-2 inhibitors in MZL. Nevertheless, some small molecules of Bcl-2 inhibitor drugs like ABT-199 (47) and ABT-263 (48) are already in the clinical trials phase. Furthermore, the present results demonstrate that Bcl-2 inhibitors have promising potential utility in patients MZL as a treatment drug. Future mechanistic and preclinical studies are warranted to determine whether modulating phagophore formation via Bcl-2 inhibition can influence MZL progression.

Dysregulation of autophagy is often found in the elongation process of the vesicle, in which LC3 is a crucial component. In this process, LC3 is targeted to the autophagosomal membrane, where it monitors autophagy activity, as well as targeting the components of the core autophagy process to the phagophore membrane. It has been irrefutably shown that lack of LC3 leads to a marked reduction in the efficiency of autophagosome formation and fusion with lysosomes (49-51). In addition, the process of bringing key components of autophagy to the phagophore membrane is regulated by LC3 in a p62/SQSTM1-mediated way. p62 binds to ubiquitinated target proteins, directing them towards the autophagosomal membrane via a specific interaction with LC3. Importantly, this is possible as p62 itself is a target of autophagy. As such, p62 accumulation is expected

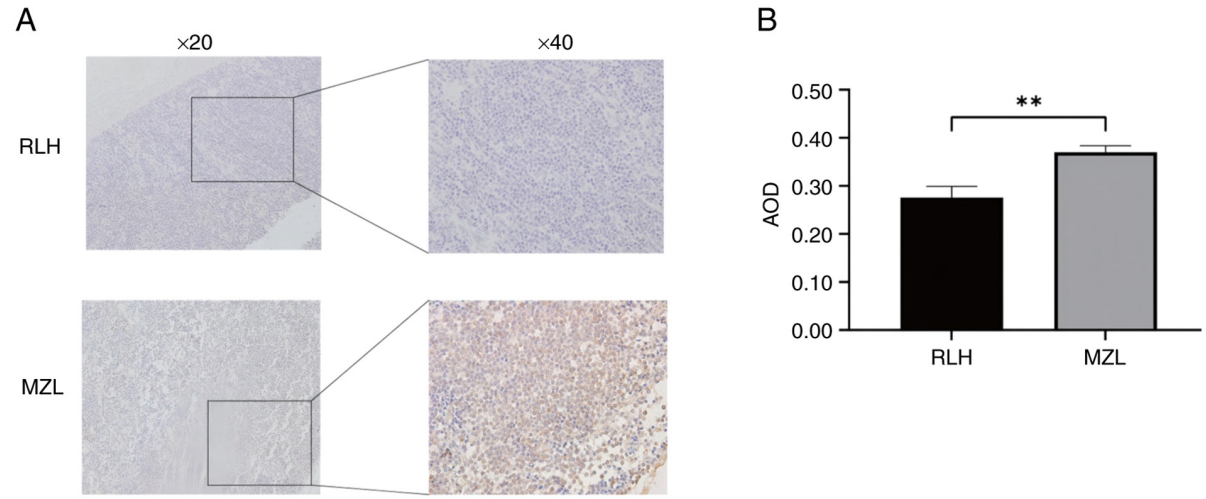

Figure 3. Elevated expression of p62 in MZL tissues compared to RLH controls. (A) Representative images of p62 immunohistochemical staining in MZL and RLH samples. (B) Statistical comparison of p62 expression between MZL and RLH groups (unpaired t-test, **P<0.01). MZL, marginal zone lymphoma; RLH, reactive lymphocyte hyperplasia; AOD, average optical density.

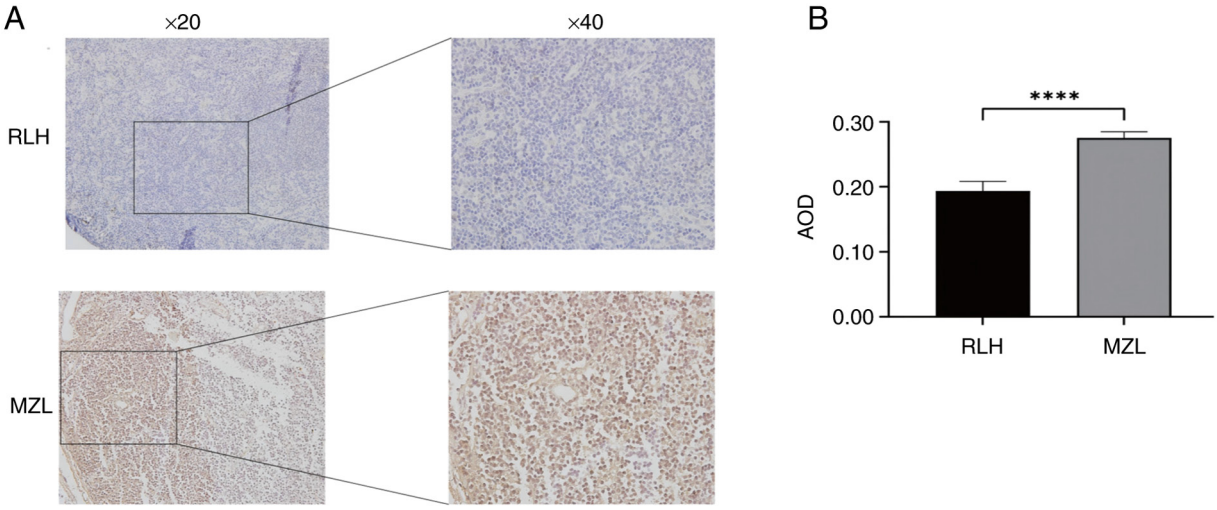

Figure 4. Bcl-2 expression is significantly increased in MZL tissues. (A) Representative IHC staining of Bcl-2 in MZL and RLH samples (left panel: Magnification, x20; overview. Right panel: Magnification, x40; detailed view). (B) Statistical comparison of Bcl-2 expression between MZL and RLH groups (unpaired t-test, ****P<0.0001). MZL, marginal zone lymphoma; RLH, reactive lymphocyte hyperplasia; AOD, average optical density.

in most cases of dysfunctional autophagy activity (52,53). This results in the activation of mTOR and NF-κB pathways that initiate tumorigenic processes. This suggested that in autophagy-deficient animal models, p62 overexpression is observed, increasing oxidative stress in conjunction with increased tumorigenic activity (54,55). This is also observed in the present analysis: LC3 is downregulated, while p62 is increased in MZL tumor tissues. Together, these alterations support the present hypothesis that excessive p62 accumulation, combined with LC3 repression, reflects a block in phagophore/autophagosome formation and membrane growth, thereby contributing to tumor-promoting autophagy dysfunction in MZL. Future studies will involve transgenic strategies that aim to increase LC3 expression in conjunction with p62 inhibition strategies via small molecule drugs that inhibit p62 accumulation to provoke a positive response in MZL by overcoming phagophore membrane maturation.

The present findings provide compelling evidence that MZL exhibits coordinated dysregulation of core autophagy machinery. Significant downregulation of Beclin-1 (P<0.05) and LC3 (P<0.0001), key regulators of autophagosome initiation and maturation, alongside elevated expression of the autophagy receptor p62 (P<0.001) and anti-apoptotic Bcl-2 (P<0.0001), highlights impaired autophagic flux as a potential hallmark of MZL pathobiology. Differential expression of LC3, p62, Bcl-2 and Beclin-1 between MZL tissues and RLH tissues could help in the precise identification of MZL. Future studies could aim at the development of a multiplexed IHC antibody kit that will help in the precise identification of MZL, as there is a lack of a specific biomarker in the field that will prompt the clinician to initiate appropriate treatment strategies. Besides Bcl-2 inhibition, other strategies targeting the phenomenon of autophagy in hematologic malignancies are under investigation (56,57). These include mTOR pathway

inhibitors (everolimus, rapamycin), which inhibit the initiation of autophagy through mTORC1 pathway modulation, and agents that target autophagy, such as chloroquine and hydroxychloroquine, which inhibit the fusion of the autophagosome with the lysosome. Exploring these agents, individually or in rational combinations, may provide further therapeutic avenues for MZL.

The present study also has several limitations. Firstly, the sample size is small, even if considering the subtypes of MZL: Nodal, MALT and spleen involvement. Due to this small sample size, certain parameters could not be studied in a subtype analysis. Secondly, this analysis was mostly done by IHC. IHC is appropriate to characterize protein localization in clinical specimens, which, however, lack any molecular confirmation. It is proposed that analysis involving western blotting analysis or certain genetic studies in a large series of specimens could provide new perspectives. Lastly, survival data are not available in this analysis. This makes certain parameters, including survival outcomes, impossible to analyze in this particular experiment. Furthermore, since certain studies involve alterations in a particular group of genes, as also observed in this experiment, in a variety of lymphomas as well as certain solid cancers, this pattern of alterations is more of a supporting factor than a confirmatory one.

In conclusion, the present analysis identified a distinct molecular signature of autophagic dysfunction across MZL subtypes, characterized by significant suppression of Beclin-1 ($P<0.05$) and LC3-II ($P<0.0001$) expression, coupled with pathological accumulation of p62 ($P<0.001$) and Bcl-2 ($P<0.0001$). Collectively, these results provide preliminary evidence that coordinated dysregulation of key autophagy-associated proteins, specifically reduced Beclin-1 and LC3 expression and increased accumulation of p62 and Bcl-2, may represent a distinct molecular hallmark of MZL pathobiology. Although these findings offer valuable insights into the potential role of autophagy in MZL, they should be interpreted as hypothesis-generating rather than definitive. Validation through larger, independent cohorts and complementary functional studies will be necessary to confirm these observations and explore their therapeutic implications.

Acknowledgements

Not applicable.

Funding

The study was supported by a grant from the Taishan Youth Scholar Foundation of Shandong Province (grant no. tsqn201812140).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JSR designed the study. AL performed the analysis and interpretation of images. NS performed the analysis and interpretation of data. XZ performed the analysis and interpretation of data, and contributed to manuscript drafting and critical revisions of the intellectual content. XZ and NS confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All methods were carried out in accordance with relevant guidelines and regulations. The study was approved by the Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University (approval no. NSFC:NO.2022-209; approval date, March 1st, 2024). Written informed consent for participation in this study, including the use of their tissue samples for scientific research, was provided by the participants' legal guardians/next of kin.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD and Jaffe ES: The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127: 2375-2390, 2016.
2. Juárez-Salcedo LM and Castillo JJ: Lymphoplasmacytic lymphoma and marginal zone lymphoma. Hematol Oncol Clin North Am 33: 639-656, 2019.
3. Zucca E, Arcaini L, Buske C, Johnson PW, Ponzoni M, Raderer M, Ricardi U, Salar A, Stamatopoulos K, Thieblemont C, *et al*: Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 31: 17-29, 2020.
4. Rodríguez-Sevilla JJ and Salar A: Recent advances in the genetic of MALT Lymphomas. Cancers (Basel) 14: 176, 2021.
5. Rossi D, Bertoni F and Zucca E: Marginal-zone lymphomas. N Engl J Med 386: 568-581, 2022.
6. Coiffier B, Thieblemont C, Van Den Neste E, Lepeu G, Plantier I, Castaigne S, Lefort S, Marit G, Macro M, Sebban C, *et al*: Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 116: 2040-2045, 2010.
7. Luo C, Wu G, Huang X, Ma Y, Zhang Y, Song Q, Xie M, Sun Y, Huang Y, Huang Z, *et al*: Efficacy and safety of new anti-CD20 monoclonal antibodies versus rituximab for induction therapy of CD20+ B-cell non-Hodgkin lymphomas: a systematic review and meta-analysis. Sci Rep 11: 3255, 2021.
8. Kyriazopoulou L, Karpathiou G, Hatzimichael E, Peoc'h M, Papoudou-Bai A and Kanavaros P: Autophagy and cellular senescence in classical Hodgkin lymphoma. Pathol Res Pract 236: 153964, 2022.
9. Ying H, Qu D, Liu C, Ying T, Lv J, Jin S and Xu H: Chemoresistance is associated with Beclin-1 and PTEN expression in epithelial ovarian cancers. Oncol Lett 9: 1759-1763, 2015.
10. Jiang L, Liang X, Liu M, Wang W, Ma J, Guo Q, Han L, Yang C and Nan K: Reduced expression of liver kinase B1 and Beclin1 is associated with the poor survival of patients with non-small cell lung cancer. Oncol Rep 32: 1931-1938, 2014.
11. Wu T, Li Y, Gong L, Lu JG, Du XL, Zhang WD, He XL and Wang JQ: Multi-step process of human breast carcinogenesis: A role for BRCA1, BECN1, CCND1, PTEN and UVRAG. Mol Med Rep 5: 305-312, 2012.

12. Wang L, Zhang H, Sun M, Yin Z and Qian J: High mobility group box 1-mediated autophagy promotes neuroblastoma cell chemoresistance. Oncol Rep 34: 2969-2976, 2015.
13. Cheah CY, Zucca E, Rossi D and Habermann TM: Marginal zone lymphoma: Present status and future perspectives. Haematologica 107: 35-43, 2022.
14. Fiorentino V, Pizzimenti C, Pierconti F, Lentini M, Ieni A, Caffo M, Angileri F, Tuccari G, Fadda G, Martini M and Larocca LM: Unusual localization and clinical presentation of primary central nervous system extranodal marginal zone B-cell lymphoma: A case report. Oncol Lett 26: 408, 2023.
15. Zucca E, Rossi D and Bertoni F: Marginal zone lymphomas. Hematol Oncol 41 (Suppl 1): S88-S91, 2023.
16. Ye J, Zhang J, Zhu Y, Wang L, Jiang X, Liu B and He G: Targeting autophagy and beyond: Deconvoluting the complexity of Beclin-1 from biological function to cancer therapy. Acta Pharm Sin B 13: 4688-4714, 2023.
17. Nicotra G, Mercalli F, Peracchio C, Castino R, Follo C, Valente G and Isidoro C: Autophagy-active beclin-1 correlates with favourable clinical outcome in non-Hodgkin lymphomas. Mod Pathol 23: 937-950, 2010.
18. Avsec D, Djordjevič AT, Kandušer M, Podgornik H, Škerget M and Mlinarič-Raščan I: Targeting autophagy triggers apoptosis and complements the action of venetoclax in chronic lymphocytic leukemia cells. Cancers (Basel) 13: 4557, 2021.
19. Valente G, Morani F, Nicotra G, Fusco N, Peracchio C, Titone R, Alabiso O, Arisio R, Katsaros D, Benedetto C and Isidoro C: Expression and clinical significance of the autophagy proteins BECLIN 1 and LC3 in ovarian cancer. Biomed Res Int 2014: 462658, 2014.
20. Zhang S, Huang F, Wang J, You R, Huang Q and Chen Y: SQSTM1/p62 predicts prognosis and upregulates the transcription of CCND1 to promote proliferation in mantle cell lymphoma. Protoplasma 262: 635-647, 2025.
21. McCarthy A, Marzec J, Clear A, Petty RD, Coutinho R, Matthews J, Wilson A, Iqbal S, Calaminici M, Gribben JG and Jia L: Dysregulation of autophagy in human follicular lymphoma is independent of overexpression of BCL-2. Oncotarget 5: 11653-11668, 2014.
22. Li-Harms X, Milasta S, Lynch J, Wright C, Joshi A, Iyengar R, Neale G, Wang X, Wang YD, Prolla TA, *et al*: Mito-protective autophagy is impaired in erythroid cells of aged mtDNA-mutator mice. Blood 125: 162-174, 2015.
23. Glick D, Barth S and Macleod KF: Autophagy: Cellular and molecular mechanisms. J Pathol 221: 3-12, 2010.
24. Yu L, Chen Y and Tooze SA: Autophagy pathway: Cellular and molecular mechanisms. Autophagy 14: 207-215, 2018.
25. Alers S, Löffler AS, Wesselborg S and Stork B: Role of AMPK-mTOR-Ulk1/2 in the regulation of autophagy: Cross talk, shortcuts, and feedbacks. Mol Cell Biol 32: 2-11, 2012.
26. Levine B, Sinha S and Kroemer G: Bcl-2 family members: Dual regulators of apoptosis and autophagy. Autophagy 4: 600-606, 2008.
27. Usman RM, Razzaq F, Akbar A, Farooqui AA, Iftikhar A, Latif A, Hassan H, Zhao J, Carew JS, Nawrocki ST, *et al*: Role and mechanism of autophagy-regulating factors in tumorigenesis and drug resistance. Asia Pac J Clin Oncol 17: 193-208, 2021.
28. Kang R, Zeh HJ, Lotze MT and Tang D: The Beclin 1 network regulates autophagy and apoptosis. Cell Death Differ 18: 571-580, 2011.
29. Vitto VAM, Bianchin S, Zolondick AA, Pellielo G, Rimessi A, Chianese D, Yang H, Carbone M, Pinton P, Giorgi C and Patergnani S: Molecular mechanisms of autophagy in cancer development, progression, and therapy. Biomedicines 10: 1596, 2022.
30. Rangel M, Kong J, Bhatt V, Khayati K and Guo JY: Autophagy and tumorigenesis. FEBS J 289: 7177-7198, 2022.
31. Russell RC and Guan KL: The multifaceted role of autophagy in cancer. EMBO J 41: e110031, 2022.
32. Levy JM and Thorburn A: Autophagy in cancer: Moving from understanding mechanism to improving therapy responses in patients. Cell Death Differ 27: 843-857, 2020.
33. Chavez-Dominguez R, Perez-Medina M, Lopez-Gonzalez JS, Galicia-Velasco M and Aguilar-Cazares D: The double-edge sword of autophagy in cancer: From tumor suppression to pro-tumor activity. Front Oncol 10: 578418, 2020.
34. Ahmadi-Dehlaghi F, Mohammadi P, Valipour E, Pournaghi P, Kiani S and Mansouri K: Autophagy: A challengeable paradox in cancer treatment. Cancer Med 12: 11542-11569, 2023.
35. Pizzimenti C, Fiorentino V, Ruggeri C, Franchina M, Ercoli A, Tuccari G and Ieni A: Autophagy involvement in non-neoplastic and neoplastic endometrial pathology: The state of the art with a focus on carcinoma. Int J Mol Sci 25: 12118, 2024.
36. Pandey A, Goswami A, Jithin B and Shukla S: Autophagy: The convergence point of aging and cancer. Biochem Biophys Rep 42: 101986, 2025.
37. Debnath J, Gammoh N and Ryan KM: Autophagy and autophagy-related pathways in cancer. Nat Rev Mol Cell Biol 24: 560-575, 2023.
38. Pizzimenti C, Fiorentino V, Franchina M, Martini M, Giuffrè G, Lentini M, Silvestris N, Di Pietro M, Fadda G, Tuccari G and Ieni A: Autophagic-related proteins in brain gliomas: Role, mechanisms, and targeting agents. Cancers (Basel) 15: 2622, 2023.
39. Pizzimenti C, Curcio A, Fiorentino V, Germanò A, Martini M, Ieni A and Tuccari G: Immunoexpression of autophagy-related proteins in a single-center series of sporadic adult conventional clival chordomas. Oncol Lett 29: 32, 2025.
40. García Ruiz O, Sánchez-Maldonado JM, López-Nevot MÁ, García P, Macauda A, Hernández-Mohedo F, Veiga J, Figuerola J, Videvall E and Martínez-de la Puente J: Autophagy in Hematological Malignancies. Cancers (Basel) 14: 5072, 2022.
41. Buchner M and Müschen M: Targeting the B-cell receptor signaling pathway in B lymphoid malignancies. Curr Opin Hematol 21: 341-349, 2014.
42. Goldsmith J, Levine B and Debnath J: Autophagy and cancer metabolism. Methods Enzymol 542: 25-57, 2014.
43. Poillet-Perez L, Sharp DW, Yang Y, Laddha SV, Ibrahim M, Bommareddy PK, Hu ZS, Vieth J, Haas M, Bosenberg MW, *et al*: Autophagy promotes growth of tumors with high mutational burden by inhibiting a T-cell immune response. Nat Cancer 1: 923-934, 2020.
44. Choi J, Park G, Lee SSY, Dominici E, Becker L, Macleod KF, Kron SJ and Hwang S: Context-dependent roles for autophagy in myeloid cells in tumor progression. bioRxiv 16: 2024.07.12.603292, 2024.
45. Pattingre S and Levine B: Bcl-2 inhibition of autophagy: A new route to cancer? Cancer Res 66: 2885-2888, 2006.
46. Xu HD and Qin ZH: Beclin 1, Bcl-2 and autophagy. Adv Exp Med Biol 1206: 109-126, 2019.
47. Minson A, Tam C, Dickinson M and Seymour JF: Targeted agents in the treatment of indolent b-cell non-hodgkin lymphomas. Cancers (Basel) 14: 1276, 2022.
48. Warren CFA, Wong-Brown MW and Bowden NA: BCL-2 family isoforms in apoptosis and cancer. Cell Death Dis 10: 177, 2019.
49. Lamark T and Johansen T: Mechanisms of selective autophagy. Annu Rev Cell Dev Biol 37: 143-169, 2021.
50. Schaaf MBE, Keulers TG, Vooijs MA and Rouschop KMA: LC3/GABARAP family proteins: Autophagy-(un)related functions. FASEB J 30: 3961-3978, 2016.
51. Galluzzi L and Green DR: Autophagy-independent functions of the autophagy machinery. Cell 177: 1682-1699, 2019.
52. Shaid S, Brandts CH, Serve H and Dikic I: Ubiquitination and selective autophagy. Cell Death Differ 20: 21-30, 2013.
53. Amaravadi R, Kimmelman AC and White E: Recent insights into the function of autophagy in cancer. Genes Dev 30: 1913-1930, 2016.
54. Moscat J and Diaz-Meco MT: p62: A versatile multitasker takes on cancer. Trends Biochem Sci 37: 230-236, 2012.
55. Wei H, Wang C, Croce CM and Guan JL: p62/SQSTM1 synergizes with autophagy for tumor growth in vivo. Genes Dev 28: 1204-1216, 2014.
56. Feng Y, Chen X, Cassady K, Zou Z, Yang S, Wang Z and Zhang X: The role of mTOR inhibitors in hematologic disease: From bench to bedside. Front Oncol 10: 611690, 2020.
57. Ali ES, Mitra K, Akter S, Ramproshad S, Mondal B, Khan IN, Islam MT, Sharifi-Rad J, Calina D and Cho WC: Recent advances and limitations of mTOR inhibitors in the treatment of cancer. Cancer Cell Int 22: 284, 2022.