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PRACA POGLĄDOWA
REVIEW

# The role of matrix metalloproteinases in the pathophysiology of acute lymphocytic leukemia: A review

Anna Angelaki[1], Emma Arifagić[1], Eleni Zouganeli[1], Datis Kalali[2]

[1]School of Medicine and Dentistry, European University of Cyprus, Nicosia
[2]Medical School, University of Cyprus, Nicosia

## ABSTRACT

Acute lymphocytic leukemia (ALL) is a hematologic malignancy induced by the uncontrolled proliferation of lymphoid progenitor cells. It is the most frequent malignancy in the pediatric population and it requires prompt treatment. Thus, comprehending its pathophysiological mechanisms is of paramount importance. Matrix metalloproteinases (MMPs) are a group of enzymes that degrade components of the extracellular matrix and have been shown to promote the progression of leukemia. Moreover, polymorphisms of genes encoding these enzymes are known to contribute to higher susceptibility to various cancers and poorer prognosis. This narrative mini-review explores the role of MMPs in the pathophysiology of ALL, the association between the polymorphism of their respective genes and the risk of ALL carcinogenesis and metastasis, as well as the potential role of the enzymes as clinical markers and therapeutic targets in ALL.

KEYWORDS

acute lymphocytic leukemia, matrix metalloproteinases, *MMP* genes

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**Address for correspondence:** Datis Kalali, Medical School, University of Cyprus, Palaios dromos Lefkosias Lemesou No.215/6, 2029 Aglantzia, Nicosia, Cyprus, P.O.Box 20537 1678 Nicosia, Cyprus, tel. +35 22-8952557, e-mail: kalali.datis@ucy.ac.cy



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## Introduction

Acute lymphocytic leukemia (ALL) is a hematologic malignancy characterized by the clonal proliferation of immature lymphoid progenitor cells – predominantly of B or T cell origin – within the bone marrow, peripheral blood, and extramedullary sites [1]. It is the most common type of cancer in the pediatric population, but it can also manifest in adults, where the prognosis is generally less favorable [2]. As a rapidly progressing form of leukemia, ALL requires prompt and aggressive treatment, indicating the need for a better understanding of the biological mechanisms through which it progresses [1,3].

Matrix metalloproteinases (MMPs) are a group of enzymes within the large family of calcium-dependent zinc-containing endopeptidases; they play a crucial role in the remodeling of the extracellular matrix (ECM) and are involved in the degradation of various components of the ECM, including collagen, elastin, and glycoproteins [4]. MMPs are important for normal physiological processes such as tissue remodeling, wound healing, and embryogenesis, but they can also contribute to pathological conditions when their activity is dysregulated [5]. The overexpression of MMPs is associated with many types of cancer, as they can facilitate tumor invasion, metastasis, and inflammation [6,7]. Although MMPs are predominantly studied in solid tumors, they also play a role in hematologic malignancies, including leukemia [8,9].

This narrative mini-review aims to explore the role of MMPs in the carcinogenesis and progression of ALL.

## MMPs and ALL biology

While MMPs are crucial for physiological functions such as tissue reorganization, their overexpression has been associated with different malignancies [10]. Specifically, ALL patients with MMP-9 and MMP-14 overexpression in bone marrow biopsies have been found to show poorer prognosis and lower overall survival compared to other ALL patients [11]. Moreover, in bone marrow biopsies of ALL patients, a statistically significant correlation has been discovered between MMP-2 overexpression and the presence of extramedullary infiltration, suggesting that the latter enzyme is associated with ALL migration [12].

Indeed, MMP-2 and MMP-9 are known to promote the migration, infiltration, and dissemination of leukemic cells into extramedullary tissues, thereby worsening disease development [13]. MMPs contribute to the remodeling of the bone marrow microenvironment, which is vital for the survival of leukemic cells. By degrading extracellular matrix components such as laminin, fibronectin, and collagen, they help establish a supportive environment for these cells [14]. More specifically, MMP-2 is known to degrade type I collagen, promoting the migration of leukemic cells [15]. Furthermore, MMP-9 has the potential to degrade type IV collagen – an essential element of osseous tissue – and at the same time activate inflammatory factors, including interleukin 1-beta (IL-1β) and transforming growth factor-β, which are known to promote proliferation and drug resistance in ALL [6,16,17]. MMP-14 is known to degrade laminin, an essential component in the adhesion of ALL cells to the basement membrane; its cleavage therefore promotes the motility of malignant cells.

In addition to ECM degradation, MMP activity is closely linked to intracellular signaling cascades. In detail, MMP-mediated ECM cleavage can activate the mitogen-activated protein kinase/extracellular signal--regulated kinase (MAPK/ERK) pathway, enhancing leukemic cell proliferation and survival [18]. Moreover, MMP-driven release of cytokines such as IL-1β can potentially activate the nuclear factor-kappa B (NF-κB) signaling pathway, contributing to chemoresistance and microenvironmental modulation [17]. It is worth mentioning that MMPs also facilitate angiogenesis, establishing an environment that promotes the survival and proliferation of leukemic cells [19]. More specifically, MMP-1 and MMP-9 have been shown to promote angiogenesis in the environment of ALL cells [13].

Nevertheless, these associations may be influenced by other variables, such as the patient's age, leukemia subtype, and treatment regimen. No studies stratifying MMP expression findings by these variables have been conducted yet, making it ambiguous whether MMP overexpression is an independent prognostic factor. Figure 1 summarizes the role of MMPs in the pathophysiology of ALL.

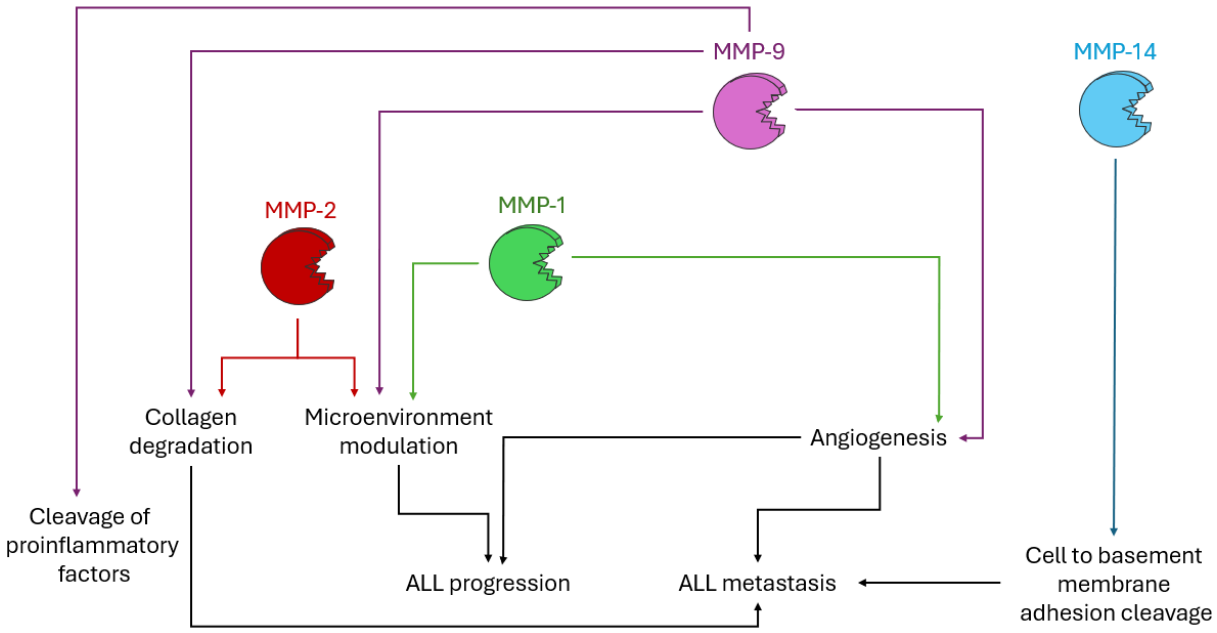


**Fig. 1.** Role of matrix metalloproteinases (MMPs) in the pathophysiology of acute lymphocytic leukemia (ALL)

## Gene polymorphisms of MMPs and ALL

Polymorphisms of genes coding for MMPs have been shown to play a potential role in ALL carcinogenesis and metastasis, as illustrated in Table I. Specifically, the MMP-2 -1306C>T, the MMP-9 -1562C>T, and the MMP-7 -181A>G polymorphisms have been shown to be associated with the pathophysiology of ALL. While all three polymorphisms are linked to an increased risk of carcinogenesis, it is important to note that the *MMP-2* and *MMP-9* polymorphisms are also associated with a higher risk of metastasis, whereas the *MMP-7* polymorphism does not show this correlation, indicating that the MMP-2 and MMP-9 enzymes may play a more significant role in leukemia progression and metastasis than MMP-7 [20,21,22]. This hypothesis can be supported by the fact that MMP-2 and MMP-9 have exhibited a better ability to degrade the bone microenvironment and osseous tissue [23,24].

The latter polymorphisms were studied in case-control studies with relatively small cohorts (N < 300). Lin et al. [20] investigated MMP-2 -1306C>T and MMP-9 -1562C>T in an adult population with a mean age of 48.0 ± 8.1, whereas the other studies were conducted among pediatric populations. All studies were conducted in China and Taiwan with Asian majority populations. Notably, the MMP-9 -1562T allele is relatively common in Asian populations, but rare in Caucasian populations, which may explain differences in the results [25]. Thus, validation in prospective, multi-ethnic cohorts is required before firm conclusions can be reached.

**Table I.** Polymorphisms of matrix metalloproteinase (MMP) genes in acute lymphocytic leukemia (ALL)

| Polymorphism | Genetic model | Genotype correlated with ALL | Increased risk of carcinogenesis | Increased risk of metastasis | References |
|---|---|---|---|---|---|
| MMP-2 -1306C>T | Dominant | CT + TT | ✓ | ✓ | [17] |
| MMP-7 -181A>G | Dominant | AG + GG | ✓ | ✗ | [20] |
| MMP-9 -1562C>T | Dominant | CT + TT | ✓ | ✓ | [17,19] |

## Discussion and conclusions

The findings discussed in this review highlight the significant role of MMPs in the pathophysiology of ALL. Among the various MMPs, MMP-1, MMP-2, MMP-7, MMP-9, and MMP-14 have been found to be associated with ALL progression. Despite these insights, several questions remain unanswered. For instance, while correlations between MMP expression and prognosis have been established, the causal relationship between specific MMPs and ALL progression needs to be elucidated through functional studies.

From a therapeutic perspective, targeting MMP activity in ALL presents an intriguing opportunity. The inhibition of MMPs has been explored in solid tumors, with mixed success, but their potential in hematologic malignancies remains underexplored [26,27]. Previous attempts to use small-molecule MMP inhibitors in solid tumor clinical trials were largely disappointing due to a lack of selectivity, off-target effects, and dose-limiting musculoskeletal toxicities, which limited their long-term tolerability [28]. The development of targeted inhibitors capable of selectively blocking the activity of key MMPs, such as MMP-2 and MMP-9 – without disrupting physiological functions – represents a promising avenue for therapeutic intervention. As research in this field continues to evolve, integrating MMP-focused strategies into existing treatment paradigms could pave the way for more precise and effective approaches to ALL management. Additionally, MMP expression profiling could serve as a prognostic tool, helping to stratify patients based on their risk of metastasis and resistance to treatment, as already suggested in other diseases [29].

Alternative approaches may help overcome these limitations. For example, antibody-based inhibition of MMPs may offer greater specificity and may reduce systemic toxicity compared to broad-spectrum inhibitors, as tested in some other malignancies [30]. Moreover, RNA interference technologies and antisense oligonucleotides may be able suppress MMP expression at the transcriptional level [31]. Such approaches may provide a more favorable safety profile and could be combined with conventional therapies to prevent resistance and disease relapse, but further research is certainly required in the field.

Future studies should prioritize mechanistic investigations to determine how MMPs interact with the leukemic microenvironment at a molecular level. Clinical research is also essential to assess whether MMP expression levels correlate with specific ALL subtypes, treatment responses, and long-term prognosis. Additionally, genetic studies exploring the impact of MMP polymorphisms on leukemia risk and progression in diverse populations could further enhance our understanding of disease susceptibility and outcomes.

Beyond their role in risk stratification, MMP polymorphisms may also carry potential clinical utility as predictive biomarkers. For instance, the MMP-2 -1306C>T and MMP-9 -1562C>T variants have been associated with not only ALL susceptibility, but also prognosis, suggesting a role in predicting treatment responses [20]. Because MMPs regulate extracellular matrix remodeling and activate cytokine pathways that drive drug resistance, genotyping of these polymorphisms could help identify patients more likely to experience treatment resistance or relapse, guiding the selection of more intensive or targeted therapies [6,10]. Furthermore, as MMP activity is linked to tissue remodeling and inflammatory responses, genetic variants might also influence chemotherapy-related toxicities, such as musculoskeletal complications or inflammatory side effects – though this hypothesis warrants clinical validation [32]. Thus, incorporating *MMP* genotyping into molecular risk assessment could provide both prognostic and predictive value, complementing existing stratification strategies in ALL management.

**Authors' contribution**

Study design – A. Angelaki, D. Kalali
Data collection – A. Angelaki, E. Arifagić, E. Zouganeli, D. Kalali
Manuscript preparation – A. Angelaki, E. Arifagić, E. Zouganeli, D. Kalali
Literature research – A. Angelaki, D. Kalali
Final approval of the version to be published – D. Kalali

## REFERENCES


**1.** Chang JH, Poppe MM, Hua CH, Marcus KJ, Esiashvili N. Acute lymphoblastic leukemia. Pediatr Blood Cancer. 2021;68 Suppl 2:e28371. doi: 10.1002/pbc.28371.

**2.** Sasaki K, Jabbour E, Short NJ, Jain N, Ravandi F, Pui CH, et al. Acute lymphoblastic leukemia: A population-based study of outcome in the United States based on the surveillance, epidemiology, and end results (SEER) database, 1980–2017. Am J Hematol. 2021;96(6):650–658. doi: 10.1002/ajh.26156.

**3.** Rafei H, Kantarjian HM, Jabbour EJ. Recent advances in the treatment of acute lymphoblastic leukemia. Leuk Lymphoma. 2019;60(11):2606–2621. doi: 10.1080/10428194.2019.1605071.

**4.** Van Doren SR. Matrix metalloproteinase interactions with collagen and elastin. Matrix Biol. 2015;44–46:224–231. doi: 10.1016/j.matbio.2015.01.005.

**5.** Kapoor C, Vaidya S, Wadhwan V, Hitesh, Kaur G, Pathak A. Seesaw of matrix metalloproteinases (MMPs). J Cancer Res Ther. 2016;12(1):28–35. doi: 10.4103/0973-1482.157337.

**6.** Kalali D. The Role of the Matrix Metalloproteinase-9 Gene in Tumor Development and Metastasis: A Narrative Review. Glob Med Genet. 2023;10(2):48–53. doi: 10.1055/s-0043-1768166.

**7.** Juchniewicz A, Kowalczuk O, Milewski R, Laudański W, Dzięgielewski P, Kozłowski M, et al. MMP-10, MMP-7, TIMP-1 and TIMP-2 mRNA expression in esophageal cancer. Acta Biochim Pol. 2017;64(2):295–299. doi: 10.18388/abp.2016_1408.

**8.** Hatfield KJ, Reikvam H, Bruserud Ø. The crosstalk between the matrix metalloprotease system and the chemokine network in acute myeloid leukemia. Curr Med Chem. 2010;17(36):4448–4461. doi: 10.2174/092986710794183033.

**9.** Thorns C, Bernd HW, Hatton D, Merz H, Feller AC, Lange K. Matrix--metalloproteinases in Hodgkin lymphoma. Anticancer Res. 2003;23(2B): 1555–1558.

**10.** Mustafa S, Koran S, AlOmair L. Insights Into the Role of Matrix Metalloproteinases in Cancer and its Various Therapeutic Aspects: A Review. Front Mol Biosci. 2022;9:896099. doi: 10.3389/fmolb.2022.896099.

**11.** Schneider P, Costa O, Legrand E, Bigot D, Lecleire S, Grassi V, et al. In vitro secretion of matrix metalloprotease 9 is a prognostic marker in childhood acute lymphoblastic leukemia. Leuk Res. 2010;34(1):24–31. doi: 10.1016/j.leukres.2009.07.039.

**12.** Kuittinen O, Savolainen ER, Koistinen P, Möttönen M, Turpeenniemi--Hujanen T. MMP-2 and MMP-9 expression in adult and childhood acute lymphatic leukemia (ALL). Leuk Res. 2001;25(2):125–131. doi: 10.1016/S0145-2126(00)00104-1.

**13.** Klein G, Vellenga E, Fraaije MW, Kamps WA, de Bont ES. The possible role of matrix metalloproteinase (MMP)-2 and MMP-9 in cancer, e.g. acute leukemia. Crit Rev Oncol Hematol. 2004;50(2):87–100. doi: 10.1016/j.critrevonc.2003.09.001.

**14.** Verma D, Zanetti C, Godavarthy PS, Kumar R, Minciacchi VR, Pfeiffer J, et al. Bone marrow niche-derived extracellular matrix-degrading enzymes influence the progression of B-cell acute lymphoblastic leukemia. Leukemia. 2020;34(6):1540–1552. doi: 10.1038/s41375-019-0674-7.

**15.** Ries C, Loher F, Zang C, Ismair MG, Petrides PE. Matrix metalloproteinase production by bone marrow mononuclear cells from normal individuals and patients with acute and chronic myeloid leukemia or myelodysplastic syndromes. Clin Cancer Res. 1999;5(5):1115–1124.

**16.** Pérez-Figueroa E, Sánchez-Cuaxospa M, Martínez-Soto KA, Sánchez--Zauco N, Medina-Sansón A, Jiménez-Hernández E, et al. Strong inflammatory response and Th1-polarization profile in children with acute lymphoblastic leukemia without apparent infection. Oncol Rep. 2016;35(5):2699–2706. doi: 10.3892/or.2016.4657.

**17.** Mostufi-Zadeh-Haghighi G, Veratti P, Zodel K, Greve G, Waterhouse M, Zeiser R, et al. Functional Characterization of Transforming Growth Factor-β Signaling in Dasatinib Resistance and Pre-BCR$^+$ Acute Lymphoblastic Leukemia. Cancers. 2023;15(17):4328. doi: 10.3390/cancers15174328.

**18.** Fei J, Guo Y. MAPK/ERK Signaling in Tumorigenesis: mechanisms of growth, invasion, and angiogenesis. EXCLI J. 2025;24:854–879. doi: 10.17179/excli2025-8479.

**19.** Quintero-Fabián S, Arreola R, Becerril-Villanueva E, Torres-Romero JC, Arana-Argáez V, Lara-Riegos J, et al. Role of Matrix Metalloproteinases in Angiogenesis and Cancer. Front Oncol. 2019;9:1370. doi: 10.3389/fonc.2019.01370.

**20.** Lin CM, Zeng YL, Xiao M, Mei XQ, Shen LY, Guo MX, et al. The Relationship Between MMP-2 -1306C>T and MMP-9 -1562C>T Polymorphisms and the Risk and Prognosis of T-Cell Acute Lymphoblastic Leukemia in a Chinese Population: A Case-Control Study. Cell Physiol Biochem. 2017;42(4):1458–1468. doi: 10.1159/000479210.

**21.** Kuo CC, Tsai CW, Chang WS, Shen TC, Tzeng HE, Li CH, et al. Contribution of Matrix Metalloproteinase-9 rs3918242 Genotypes to Childhood Leukemia Risk. Anticancer Res. 2020;40(10):5751–5756. doi: 10.21873/anticanres.14591.

**22.** Pei JS, Chou AK, Hsu PC, Tsai CW, Chang WS, Wu MF, et al. Contribution of Matrix Metalloproteinase-7 Genotypes to the Risk of Non--solid Tumor, Childhood Leukemia. Anticancer Res. 2017;37(12):6679–6684. doi: 10.21873/anticanres.12126.

**23.** Li X, Jin L, Tan Y. Different roles of matrix metalloproteinase 2 in osteolysis of skeletal dysplasia and bone metastasis (Review). Mol Med Rep. 2021;23(1):70. doi: 10.3892/mmr.2020.11708.

**24.** Chen D, Zhang X, Guo Y, Shi S, Mao X, Pan X, et al. MMP-9 inhibition suppresses wear debris-induced inflammatory osteolysis through downregulation of RANK/RANKL in a murine osteolysis model. Int J Mol Med. 2012;30(6):1417–1423. doi: 10.3892/ijmm.2012.1145.

**25.** Zhang Z, Wu X, Cai T, Gao W, Zhou X, Zhao J, et al. Matrix Metalloproteinase 9 Gene Promoter (rs 3918242) Mutation Reduces the Risk of Diabetic Microvascular Complications. Int J Environ Res Public Health 2015;12(7):8023–8033. doi: 10.3390/ijerph120708023.

**26.** Szczygielski O, Dąbrowska E, Niemyjska S, Przylipiak A, Zajkowska M. Targeting Matrix Metalloproteinases and Their Inhibitors in Melanoma. Int J Mol Sci. 2024;25(24):13558. doi: 10.3390/ijms252413558.

**27.** Almutairi S, Kalloush HM, Manoon NA, Bardaweel SK. Matrix Metalloproteinases Inhibitors in Cancer Treatment: An Updated Review (2013–2023). Molecules. 2023;28(14):5567. doi: 10.3390/molecules28145567.

**28.** Boucher B. Matrix metalloproteinase protein inhibitors: highlighting a new beginning for metalloproteinases in medicine. Metalloproteinases In Medicine. 2016;3:75–79. doi: 10.2147/MNM.S119588.

**29.** Yang H, Bueso-Ramos CE, Pierce SA, Wei Y, Fang Z, Nguyen M, et al. Expression Profiles of Matrix Metalloproteinases (MMPs) and Tissue Inhibitors of Metalloproteinases (TIMPs) in Myelodysplastic Syndromes (MDS): Level of MMP-9 Is Associated with Improved Prognosis in MDS Patients. Blood. 2012;120(21):3845. doi: 10.1182/blood.V120.21.3845.3845.

**30.** Fischer T, Riedl R. Inhibitory Antibodies Designed for Matrix Metalloproteinase Modulation. Molecules. 2019;24(12):2265. doi: 10.3390/molecules24122265.

**31.** Zhi YH, Song MM, Wang PL, Zhang T, Yin ZY. Suppression of matrix metalloproteinase-2 via RNA interference inhibits pancreatic carcinoma cell invasiveness and adhesion. World J Gastroenterol. 2009;15(9):1072–1078. doi: 10.3748/wjg.15.1072.

**32.** Tune BXJ, Sim MS, Poh CL, Guad RM, Woon CK, Hazarika I, et al. Matrix Metalloproteinases in Chemoresistance: Regulatory Roles, Molecular Interactions, and Potential Inhibitors. J Oncol. 2022;2022:3249766. doi: 10.1155/2022/3249766.