MultiClass Machine Learning-based Identification of Anoikis-related Genes Across Three Adult T-cell Leukemia/Lymphoma Subtypes

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Abstract

Introduction Adult T-cell leukemia/lymphoma (ATLL) is a type of cancer that originates from T-cells infected with the human T-cell lymphotropic virus type 1 (HTLV-1). Anoikis is a programmed cell death process that occurs when the contact between cells or the extracellular matrix is lost. We aim to identify the specific anoikis-related classifier genes for three ATLL subtypes, which could provide valuable insights into the molecular mechanisms underlying the disease's progression and potential targets for intervention.

Materials and Methods We conducted an analysis of differentially expressed anoikis genes (DEAGs) for identifying those associated with each subtype. Subsequently, we utilized multiclass support vector machine and logistic regression algorithms to recognize specific classifier anoikis-related genes distinguishing each ATLL subtype.

Results The results revealed the activation of several cancer- and anoikis-related pathways. Moreover, specific potential biomarkers were pointed out for each ATLL subtype: acute, with S100A9 and MAOA; chronic, with IL10, CDH1, and CYP3A4; and smoldering with BCL2L1 and SNAI2. These anoikis-related genes play a role in regulating cell adhesion and survival signaling which are crucial for maintaining normal cellular homeostasis.

Conclusion The findings not only contribute to our understanding of ATLL progression but also offer potential targets for developing more effective therapeutic strategies and improving treatment outcomes for patients with different subtypes.

Keywords
- human T-cell lymphotropic virus type 1
- adult T-cell leukemia/lymphoma
- asymptomatic carriers
- anoikis
- multiclass machine learning
- biomarker

Introduction

Anoikis is a form of programmed cell death that occurs when cells lose their attachment to the extracellular matrix (ECM) or to neighboring cells. It is a crucial process in maintaining tissue homeostasis and preventing the survival and spread of detached cells, particularly in normal development, tissue remodeling, and cancer.[1] This is triggered by the disruption of cell-ECM or cell-cell interactions, leading to the activation of specific signaling pathways.[2] Detached cells sense the loss of appropriate anchorage and undergo a series of intracellular events that ultimately result in cell death. Cancer cells can develop mechanisms to resist anoikis, allowing them to survive and proliferate at distant sites, leading to the formation of secondary tumors.[3]

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Adult T-cell leukemia/lymphoma (ATLL) is a rare and aggressive cancer that primarily affects T lymphocytes, a type of white blood cell involved in the immune response.[4] It is caused by infection with human T-cell lymphotropic virus type 1 (HTLV-1), a retrovirus transmitted through blood transfusions, sexual contact, and from mother to child during childbirth or breastfeeding. After infection, there is a long latency period before ATLL develops, usually spanning several decades. During this time, individuals may remain asymptomatic or experience mild symptoms.

There are different subtypes of ATLL, classified based on clinical features and prognosis. The main ones include acute, lymphoma, chronic, and smoldering, each with distinct characteristics and disease progression.[5]

Acute ATLL is characterized by a high level of abnormal lymphocytes in the blood, involvement of multiple organs, and aggressive disease progression. It typically presents with systemic symptoms such as fever, night sweats, weight loss, and organ dysfunction. Lymphoma-type ATLL presents as solid tumor masses in lymph nodes, skin, or other organs without significant blood involvement. It may resemble other types of non-Hodgkin lymphomas and exhibits variable clinical presentations and prognoses.

The chronic subtype is characterized by slow disease progression, milder symptoms, and longer survival compared to the acute subtype. It often involves skin lesions and may present with lymphocytosis (an increased number of lymphocytes) in the blood. However, chronic ATLL can progress to more aggressive forms over time.

Finally, smoldering ATLL is an indolent form, typically characterized by the presence of abnormal lymphocytes in the blood without significant symptoms or organ involvement. It may remain stable for extended periods or progress to more advanced stages.[6]

The symptoms of ATLL vary depending on subtype and disease stage. The most common are fatigue, lymphadenopathy (enlarged lymph nodes), skin lesions, hepatosplenomegaly (enlargement of the liver and spleen), and systemic symptoms such as fever, night sweats, and weight loss. Treatment approaches depend on subtype, stage, and individual patient factors,[7] and may include chemotherapy, targeted therapies, antiviral drugs, and stem cell transplantation.[8]

Understanding the mechanisms underlying anoikis resistance in ATLL is important for developing therapeutic strategies to combat metastasis and improve outcomes. This resistance can result from genetic alterations, dysregulation of signaling pathways, and changes in cell adhesion molecules.

Therefore, in this study, we employed several multiclass machine learning (ML) algorithms to identify specific anoikis-related classifier genes for three ATLL subtypes.

Materials and Methods

Datasets, Merging, and Preprocessing

In this study, we obtained four microarray datasets from the Gene Expression Omnibus (GEO) database. These datasets contained gene expression data from ATLL samples and asymptomatic carrier (AC) subjects. Specifically, we downloaded the microarray datasets GSE33615 and GSE55851,[9] which include gene expression data from ATLL samples, as well as GSE29312 and GSE29332,[10] which comprise gene expression data from AC subjects.

The samples were derived from whole blood or peripheral blood mononuclear cells (PBMCs). We merged the expression values for each condition separately, resulting in a total of 23 samples from individuals with chronic and 29 with acute ATLLs, as well as 10 samples from the smoldering subtype, and 37 samples from ACs. No new human subjects were directly involved in this research. The combined gene expression data consisted of 14,887 genes. To address potential batch effects, we utilized the "removeBatchEffect" function from the Limma package. Additionally, the data were log2-transformed and subjected to quantile normalization to ensure comparability and enhance analysis accuracy.

Identification of Differentially Expressed Genes and Anoikis

We utilized the Limma package within the R (R Foundation for Statistical Computing) environment to identify the genes that are differentially expressed between ACs and ATLL subtypes. We considered genes with Benjamini-Hochberg false discovery rate (FDR) adjusted *p*-values of less than 0.05 as differentially expressed genes (DEGs). To determine the differentially expressed anoikis-related genes (DEAGs), we found the common genes between DEGs and 756 aniokis-related genes obtained from the GeneCard website (Weizmann Institute of Science, https://www.genecards.org/). Then, we determined the DEAGs with $\log FC > 1$ for further analysis.

Multiclass Machine Learning Algorithms

Multiclass classification is a type of machine learning problem where the goal is to classify instances into one of three or more options.[11] Several algorithms can be used for multiclass classification, including logistic regression (LR) and support vector machine (SVM). Multiclass classification can be challenging when dealing with imbalanced datasets, where some classes have significantly fewer instances than others. To address this, techniques such as oversampling can be employed.[12]

The SVMs are powerful classification tools known for their robustness and tendency to avoid overfitting, often performing well across various applications.[13,14] Although they are inherently binary classifiers, they can be extended to multiclass problems by decomposing the task into multiple binary classification problems. In the one-vs-rest approach, k SVM models are built, where k is the number of classes. The m-th SVM is trained with examples from the m-th class labeled as positive and all other examples labeled as negative. Another approach, multiclass SVM, directly formulates the problem to optimize classification across multiple classes, often using fast algorithms in the linear case. This method uses a feature vector derived from the input features and the class label to build a two-class classifier. At test time, the classifier assigns the class with the highest score.[12]

Multiclass logistic regression generalizes the model to handle problems with more than two classes. Traditional

logistic regression models binary outcomes by mapping class labels to 1 (positive) or 0 (negative) and predicting the probability of belonging to class 1. By default, logistic regression is not suitable for multiclass classification but can be adapted by decomposing the problem into multiple binary classification tasks using one-vs-rest or one-vs-one strategies.[15] Alternatively, LR can be extended to directly predict probabilities for multiple classes simultaneously.

In the present study, we applied the multiclass SVM and LR algorithms to identify the best anoikis-related classifier genes distinguishing several ATLL subtypes. By comparing the results from both models, we identified genes consistently selected as classifiers.

Results

Identification of DEGs and DEAGs

We identified 11,179 DEGs for the acute ATLL subtype, 10,650 for the chronic subtype, and 10,801 for the smoldering subtype. Next, we determined the common DEGs with log fold change > 1 across all ATLL subtypes compared to ACs as controls, and intersected these with known anoikis-related genes. Consequently, we identified 361 common DEAGs (►**Fig. 1**, ►**Supplementary data file 1**). These DEAGs for all subtypes and ACs were then used as input features for the subsequent classification step.

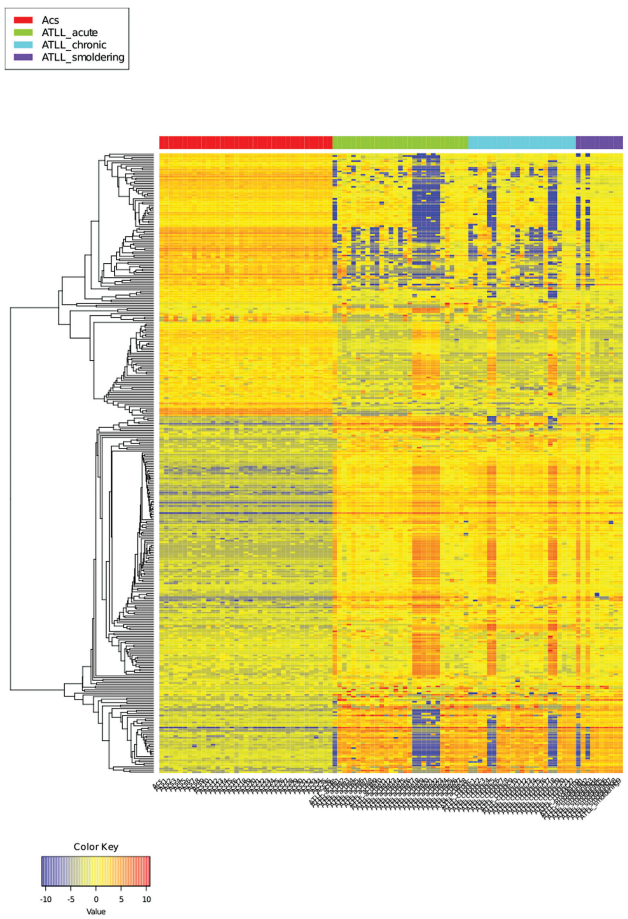

Fig. 1 Heatmap illustrating the expression levels of the common DEAGs for all ATLL subtypes and ACs.

Determining Anoikis-Related Genes Biomarkers

We applied two multiclass machine learning algorithms, multiclass SVM and LR, to identify the best classifier genes distinguishing all ATLL subtypes from ACs. The dataset was split into training and testing sets with a 70:30 ratio. Subsequently, both machine learning methods were applied, and the top five classifier genes were identified for each subtype, which can be found in ►**Table 1**.

The confusion matrices and classification reports demonstrate the performance of multiclass SVM (►**Fig. 2A**) and multiclass LR (►**Fig. 2B**) models in distinguishing between various ATLL subtypes and ACs. Precision shows how many of the predicted positive cases were correct, recall indicates how many of the actual positive cases were identified, and the F1-score combines precision and recall into a single measure of accuracy. The results were similar for both models. They correctly classified all 9 ACs, achieving 100% precision, recall, and F1-score for this class. The ATLL_acute model accurately identified 7 out of 8 samples, with one misclassification into ATLL_smoldering. Furthermore, ATLL_chronic was also well-distinguished, with 5 correct classifications out of 6, while ATLL_smoldering showed slightly lower performance, with only 2 out of 3 samples correctly classified but a single misclassification from ATLL_acute. The average precision, recall, and F1-score across all classes were 0.89, 0.93, and 0.90, respectively.

Gene Enrichment Analysis

The identified genes by two models have been enriched in several gene ontology (GO) biological process (►**Fig. 3**) and KEGG pathways as identified in ►**Fig. 4**. As it is indicated, the DEAGs of ATLL_acute were enriched in P53 signaling pathway, endocrine resistance, microRNAs in cancer, proteoglycans in cancer, rap1 signaling pathway, PI3K-Akt signaling pathway, and pathways in cancer.

Table 1 The best five classifiers identified by multiclass SVM and LR

ML algorithms	Genes
multiclass SVM	ACs: C5AR1, ROCK2, PTHLH, ISM1,IL1B ATLL_acute: S100A9,MMP2, IGFBP3, MAOA, ITGB3 ATLL_chronic: IL10, CDH1, SNAI1, CYP3A4, SPTA1 ATLL_smoldering: BCL2L1, MET, HOXA10, CLU, SNAI2
multiclass LR	ACs: CEACAM3, ROCK2, MMP2, SNAI1, SPTA1 ATLL_acute: S100A9, CDKN2A, MET, MAOA, EPHA2 ATLL_chronic: IL10, CDH1, HOXA10, CYP3A4, NMU ATLL_smoldering: BCL2L1, IGFBP3, ISM1, ITGB3, SNAI2

Abbreviations: AC, asymptomatic carrier; ATLL, adult T-cell leukemia/lymphoma; LR, logistic regression; ML, machine learning; SVM, support vector machine.
Note: The common genes are expressed in bold.

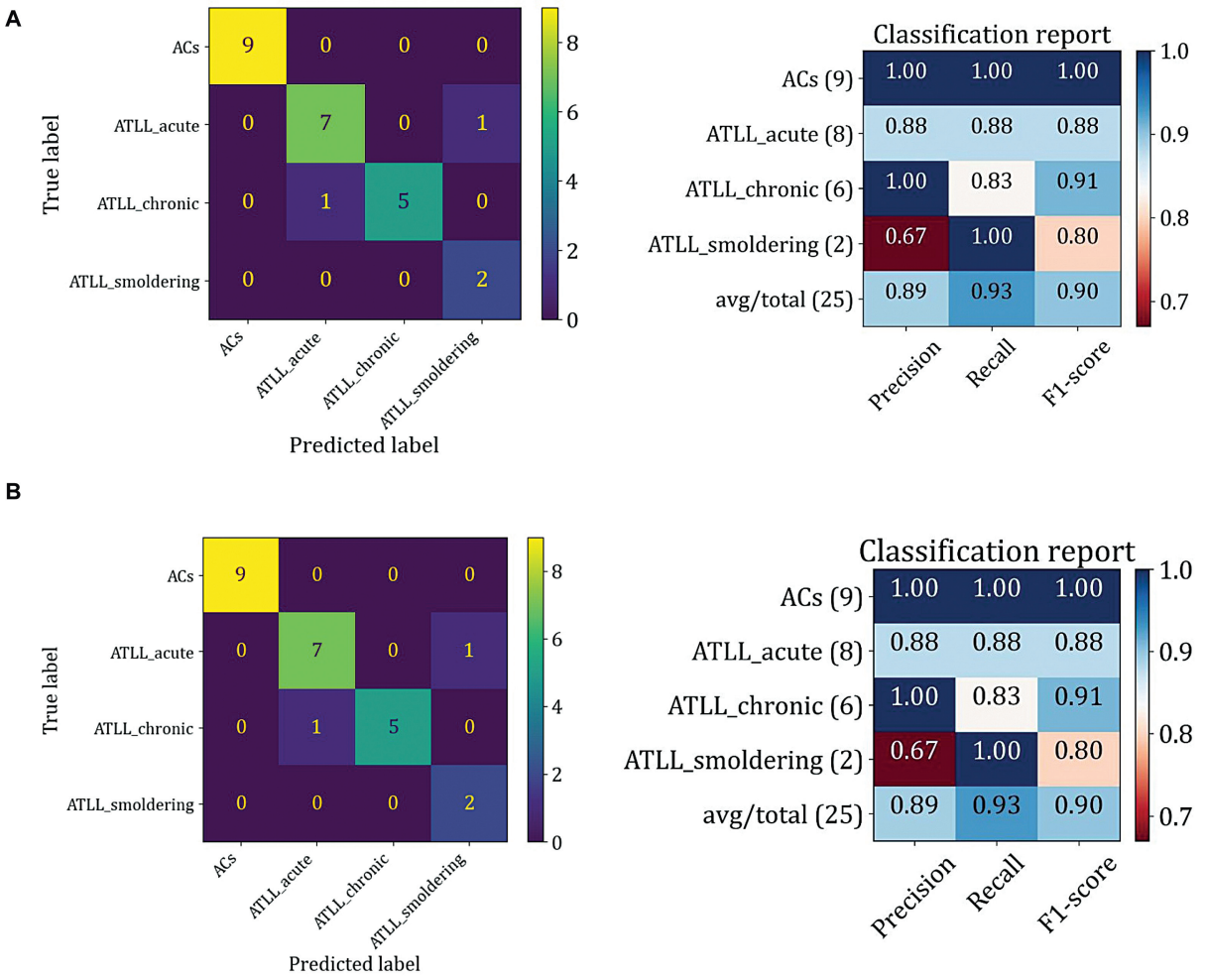

Fig. 2 Confusion matrixes and classification reports—including precision, recall, and F1-score—obtained from multiclass (**A**) SVM and (**B**) LR.

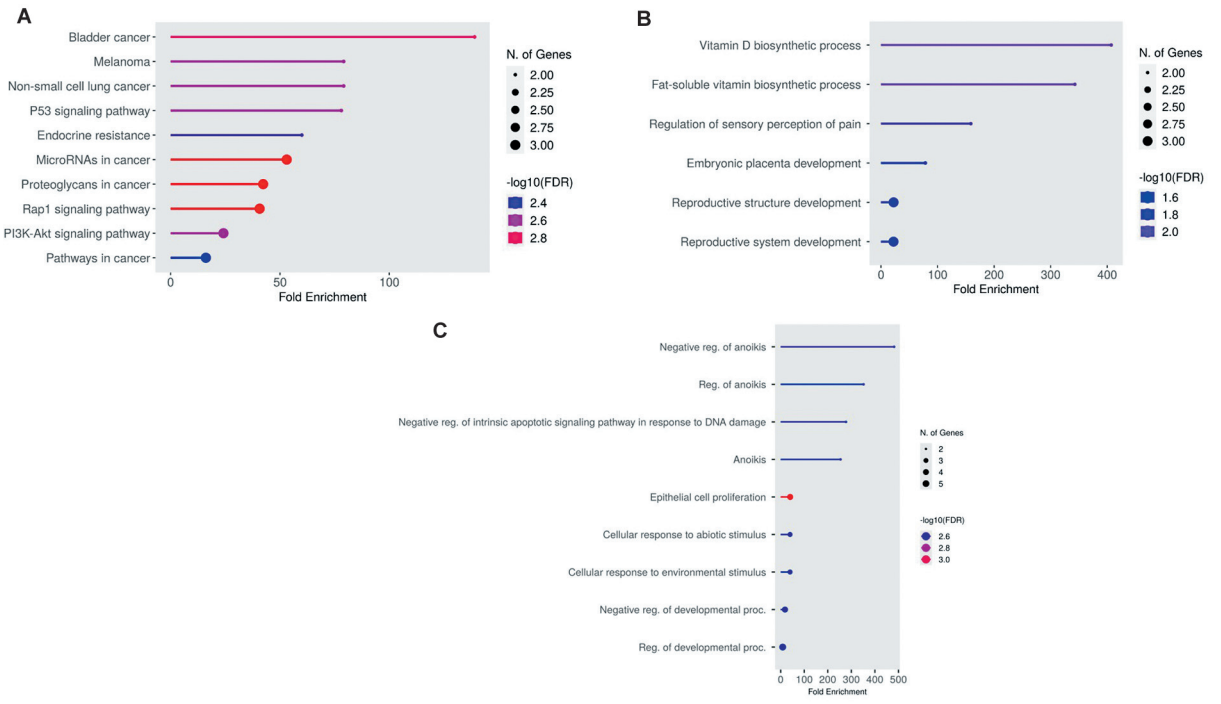

Fig. 3 Top gene ontology (GO) biological processes enriched by anoikis-related genes in (**A**) acute, (**B**) chronic, and (**C**) smoldering ATLL subtypes.

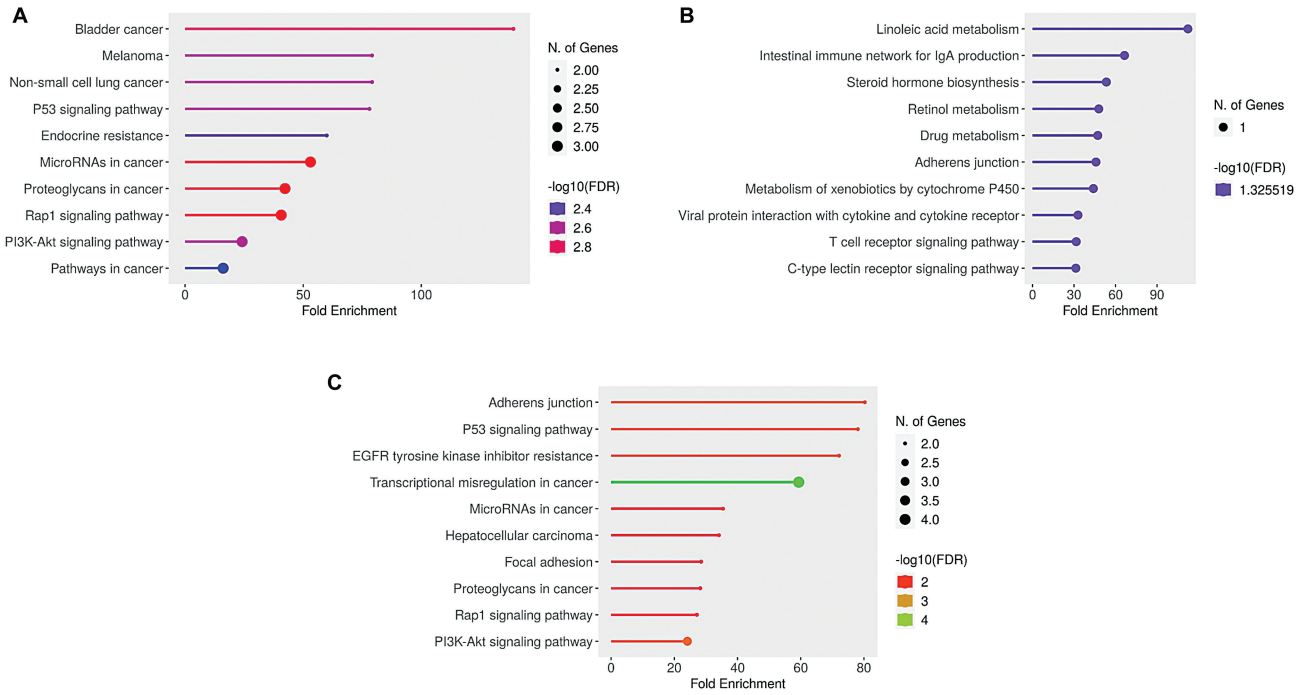

Fig. 4 Top biological passways enriched by anoikis-related genes in (**A**) acute, (**B**) chronic, and (**C**) smoldering ATLL subtypes.

Steroid hormone biosynthesis, drug metabolism and retinol metabolism, adherens junction, metabolism of xenobiotics by cytochrome P450, viral protein interaction with cytokine and cytokine receptor, T cell receptor signaling pathway, and C-type lectin receptor signaling pathway have been enriched by ATLL_chronic DEAGs.

The DEAGs of ATLL_smoldering were enriched in P53 signaling pathway, EGFR tyrosine kinase inhibitor resistance, transcriptional misregulation in cancer, microRNAs in cancer, focal adhesion, proteoglycans in cancer, rap1 signaling pathway, and PI3K-Akt signaling pathway.

Most of the identified pathways and BP terms are related to cancer development and viral infection, which are two characteristics of all ATLL subtypes.

Determination of Major Aniokis-Related Genes for Each ATLL Subtype

In the next step, we identified the common genes detected by both multiclass algorithms. These genes could be considered major anoikis-related biomarkers for each subtype. The ATLL_acute included S100A9, which is involved in the IL-17 signaling pathway, and MAOA, associated with serotonergic and dopaminergic synapse pathways as well as amino acid metabolism (►**Fig. 5A**).

In ATLL_chronic, the highlighted genes were IL10, which participates in viral protein interaction with cytokine and cytokine receptor, T cell receptor signaling, FoxO signaling, JAK-STAT signaling, and cytokine-cytokine receptor interaction; CDH1, involved in cell adhesion molecules, hippo signaling, rap1 signaling, and cancer pathways; and CYP3A4, related to drug metabolism and chemical carcinogenesis (►**Fig. 5B**).

Finally, for ATLL_smoldering, BCL2L1 was identified, linked to NF-kappa B signaling, apoptosis, human T-cell leukemia virus 1 infection, PI3K-Akt signaling, and cancer pathways, along with SNAI2, which is associated with adherens junction and hippo signaling pathways (►**Fig. 5C**). These genes may serve as valuable biomarkers for differentiating subtypes and represent potential therapeutic targets in future research.

Discussion

The accurate classification of ATLL subtypes is crucial for tailoring effective therapeutic strategies, as each subtype exhibits distinct genomic profiles and clinical outcomes. In our study, we explored the expression patterns of anoikis-related genes across three major ATLL subtypes—acute, chronic, and smoldering—using multiclass SVM and LR models. We identified several differentially expressed genes that serve as potential classifiers for each subtype.

We identified S100A9 and MAOA as the most significant DEAGs distinguishing the acute ATLL subtype.

The S100A9 calcium-binding protein is expressed in myeloid cells, cancer cells, and tumor stroma, acting as a damage-associated molecular pattern (DAMP) that promotes inflammatory signaling and tumor progression.[16,17] Primary tumor cells also secrete proinflammatory factors like VEGF-A, TGF-β, and TNF-α, which induce the selective expression of chemoattractants S100A8 and S100A9, thereby facilitating the homing of tumor cells to premetastatic sites.[18] The S100A9 protects cells from anoikis, thereby aiding metastasis, as shown in skin cells.[19,20] In acute ATLL, S100A9 likely helps HTLV-1-infected T-cells survive during circulation by

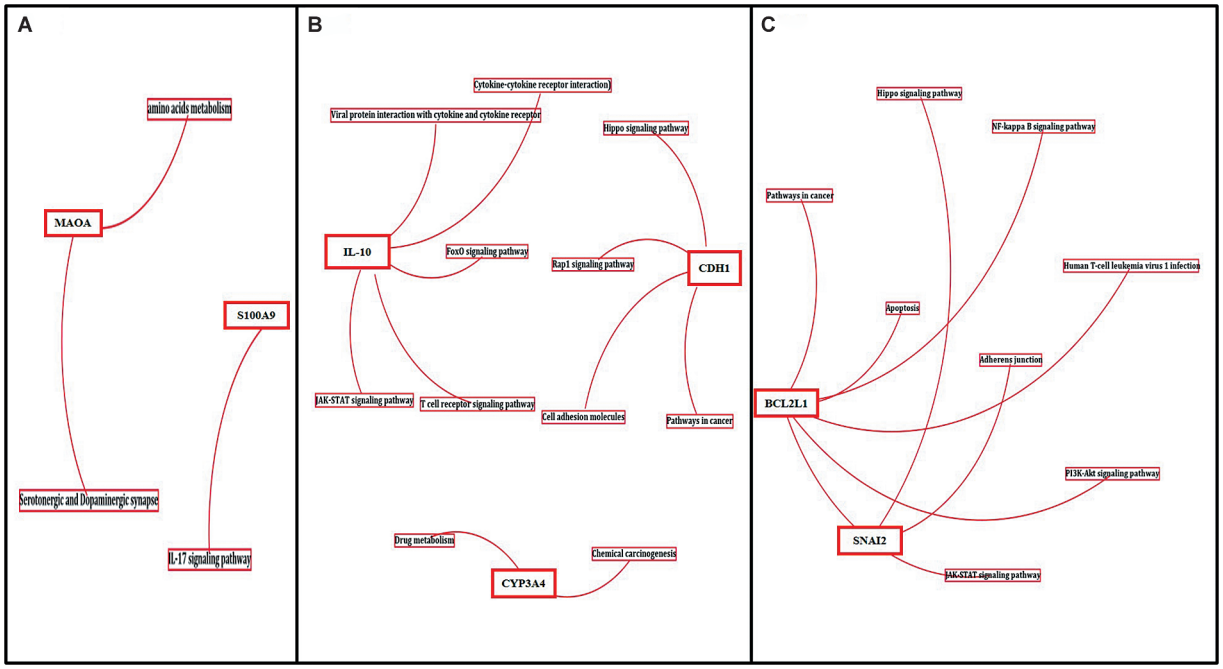

Fig. 5 Illustration of the key pathways associated with specific anoikis-related genes identified in **(A)** acute, (**B**) chronic, and (**C**) smoldering ATLL subtypes.

resisting anoikis, contributing to disease progression and poor prognosis. Additionally, S100A9-driven inflammatory cytokines may worsen chronic inflammation, promoting tumor growth and immune suppression. However, its precise role in ATLL remains unclear and warrants further study.

The MAOA mitochondrial enzyme degrades biogenic amines, including neurotransmitters like dopamine, norepinephrine, and serotonin, thereby regulating cellular signaling and oxidative stress.[21,22] While it has neurological functions, it also plays diverse roles in cancer. For example, in hepatocellular carcinoma MAOA is downregulated and linked to increased metastasis, suggesting a tumor-suppressive role.[22] In ATLL, its involvement in anoikis resistance could relate to its regulation of cellular stress responses. Anoikis involves oxidative stress and mitochondrial dysfunction, and MAOA's enzymatic activity generates reactive oxygen species (ROS),[23] which may paradoxically support cancer cell survival by activating survival pathways under stress conditions.

In chronic ATLL, three anoikis-related genes were identified: IL-10, CDH1, and CYP3A4. The first, IL-10, is an immunoregulatory cytokine that suppresses inflammation and Th1 responses.[24] Elevated levels are common in ATLL and are associated with HTLV-1-infected T-cell proliferation.[25] Furthermore, IL-10 may protect ATL cells from spontaneous apoptosis, as shown by its ability to reduce apoptosis in human T cells.[25] It also enhances cell survival by inhibiting apoptosis rather than directly inducing cell division, and targeting IL-10 signaling could disrupt anoikis resistance and immune evasion in ATLL, representing a potential therapeutic approach.

As for CDH1, it encodes E-cadherin, a transmembrane glycoprotein critical for cell-cell adhesion in epithelial tissues. Loss this glycoprotein's expression enhances cancer cell invasiveness and anoikis resistance by reducing dependence on ECM adhesion.[26] In ATLL, CDH1's role is less clear but may involve modulating cell adhesion or signaling pathways that influence survival in suspension.

The CYP3A4 liver enzyme is involved in drug metabolism and detoxification that can influence cancer progression by metabolizing endogenous compounds and chemotherapeutic drugs, potentially affecting cell stress responses and apoptosis.[27] Although its role in anoikis is not well-defined, it may contribute by regulating oxidative stress and lipid metabolism, which are important for cell survival when detached. In ATLL, CYP3A4 may help HTLV-1-infected T-cells resist anoikis by mitigating metabolic and oxidative stress during circulation and by metabolizing signaling molecules or drugs that affect survival and drug resistance.

Both BCL2L1 and SNAI2 were identified as the best DEAGs classifiers for ATLL_smoldering. As an anti-apoptotic protein from the BCL-2 family, BCL2L1 promotes cell survival and is a potential target in cancer treatment to induce apoptosis.[28] Studies on ATLL show BCL2L1 is upregulated by HTLV-I and -II due to the tax protein activating survival pathways like NF-κB.[29] In smoldering ATLL, BCL2L1 helps HTLV-1-infected T-cells resist anoikis by preventing mitochondrial apoptosis, which allows the cells to survive without ECM attachment. It also stabilizes mitochondrial integrity, counteracting proapoptotic signals and helping malignant T-cells persist, potentially leading to more aggressive disease subtypes.

As for SNAI2, it is a zinc-finger transcription factor of the SNAIL family, primarily known for promoting EMT by repressing E-cadherin, which reduces cell-cell adhesion and enhances migratory and invasive cancer cell phenotypes critical for metastasis.[30,31] Studies show that SNAI1 can recruit HDAC1 to suppress SNAI2 transcription during EMT.[32] In ATLL,

especially the smoldering subtype, SNAI2 may contribute to anoikis resistance and disease progression through noncanonical EMT-like mechanisms, since this tumor arises from lymphoid rather than epithelial cells.

The anoikis-related gene profiles identified in this study reflect the biological divergence and clinical behavior of ATLL subtypes. The acute tumor is marked by aggressive progression and associated with the presence of S100A9 and MAOA, which may drive inflammatory signaling via S100A9/RAGE/TLR4 interactions, as well as oxidative stress modulation through MAOA activity, collectively enhancing survival of HTLV-1-infected T-cells under nonadherent conditions.

Chronic ATLL with intermediate clinical outcomes features IL-10, CDH1, and CYP3A4, suggesting reliance on IL-10, altered adhesion dynamics via CDH1-linked pathways, and metabolic/redox adaptation (CYP3A4-mediated detoxification).

Finally, smoldering ATLL, characterized by indolent disease with latent progression risk, engages BCL2L1 and SNAI2, pointing to dependencies on both. These distinct molecular patterns provide a framework for subtype-specific prognostic stratification and therapeutic targeting.[33]

To validate our computational model's findings on ATLL subtype-specific gene profiles, future studies should focus on experimental validation through several approaches. These include gene editing techniques in relevant cell lines to directly confirm the functional roles of candidate genes; in vitro functional assays to assess effects on cell survival, proliferation, and anoikis resistance; in vivo animal model experiments to evaluate the efficacy of targeted therapies based on these gene profiles; and comprehensive analysis of patient-derived samples to verify gene expression patterns and correlate them with clinical outcomes. Collectively, these strategies would provide robust biological validation and support the development of precision therapeutic interventions for this disease.

Conclusion

Anoikis-related genes have the potential to serve as biomarkers for classifying different subtypes of ATLL. These genes can contribute to the activation of multiple pathways involved in the progression of these various subtypes. It is worth noting that the most important anoikis-related genes and their impact on ATLL development may vary among subtypes. Therefore, extensive studies incorporating large cohorts of patients and integrated molecular analyses are necessary to identify reliable biomarkers and gain a comprehensive understanding of the molecular mechanisms underlying this differentiation.

Authors' Contributions

MZG: bioinformatics, statistical analysis, data interpretation, writing of the manuscript. EA: investigation, writing of the manuscript. All authors approved the final manuscript.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article and its ►**Supplementary information files**.

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Conflict of Interests

The authors have no conflict of interests to declare.

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