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New insights into the mechanisms of the extracellular matrix and its therapeutic potential in anaplastic thyroid carcinoma

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Anaplastic thyroid carcinoma (ATC) is the most aggressive thyroid cancer, and it has a poor prognosis and high probability of metastatic recurrence. The long-term survival of cancer cells depends on their ability to settle in a favorable environment. Cancer cells interact with other cells in the tumor microenvironment to shape the "soil" and make it suitable for cell growth by forming an extremely complex tumor ecosystem. The extracellular matrix (ECM) is an essential component of the tumor ecosystem, and its biological and mechanical changes strongly affect tumor invasion, metastasis, immune escape and drug resistance. Compared to normal tissues, biological processes, such as collagen synthesis and ECM signaling, are significantly activated in ATC tissues. However, how ATC triggers changes in the properties of the ECM and its interaction with the ECM remain poorly characterized. Therefore, an in-depth study of the regulatory mechanism of the abnormal activation of ECM signaling in ATC is highly important for achieving the therapeutic goal of exerting antitumor effects by destroying the "soil" in which cancer cells depend for survival. In this research, we revealed the aberrant activation state of ECM signaling in ATC progression and attempted to uncover the potential mechanism of action of ECM components in ATC, with the aim of providing new drug targets for ATC therapy.

Keywords Anaplastic thyroid carcinoma, Extracellular matrix, Tumor microenvironment, Cancer-associated fibroblasts, Cancer therapy

Thyroid carcinoma is one of the most common malignant endocrine cancers, and its incidence is increasing annually[1]. Anaplastic thyroid carcinoma (ATC) is an extremely malignant subtype of thyroid cancer that accounts for approximately 2% of cases, with a median survival of only 3–7 months[2]. Conventional therapies have limited efficacy in patients with ATC, and ATC patients often have a poor prognosis due to tumor expansion and distant metastasis[3]. Most ATC patients are diagnosed with advanced-stage cancer and miss the opportunity for surgical treatment, and there are currently no efficacious treatments that increase the overall survival of ATC patients[4,5]. Therefore, it is necessary to understand the cellular mechanisms of ATC to develop effective therapeutic targets and improve the survival rate of patients with this malignancy.

The tumor microenvironment (TME) refers to the internal environment in which tumor cells arise and live, and it is a complex integrated system that contains cellular components, such as cancer cells, fibroblasts and inflammatory/immune cells, and non-cellular components, such as the extracellular matrix (ECM) and cytokines[6]. A growing body of evidence suggests that the TME is not a 'silent bystander' but rather an 'active promoter of oncogenesis' in the process of cancer development[7]. Hypoxia, chronic inflammation and immunosuppression are prominent features of the TME, and these components form a highly complicated molecular network that makes the microenvironment a "blind zone" for the body's anti-tumor immune response and immune intervention[8]. Recent immunotherapies, including immune checkpoint inhibitors, adoptive cellular immunotherapy, and cancer vaccines, restore and strengthen the ability of immune components in the TME to recognize and kill cancer cells, and these agents have shown superior therapeutic effects in the specific clearing of tumors compared to conventional therapies[9]. For patients with ATC, targeted blockade of programmed death-1/

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programmed death ligand-1 at immune checkpoints or the combination of molecularly targeted inhibitors and immunotherapy have shown promising therapeutic outcomes[10]. However, the high heterogeneity of individual tumors and the frequent occurrence of immune resistance limit the benefits of immunotherapy, and some patients do not benefit from it[11]. Understanding the mechanisms of immune regulation in the ATC microenvironment deepens our understanding of tumor cell behavior and aids in the development of new drugs to improve the antitumor efficacy of immunotherapy.

The ECM is a non-cellular component that provides biochemical components and fundamental structural support to tumor cells in the TME[12]. The main components of the ECM include collagen (approximately 90% of the ECM), fibronectin, elastin, laminin, hyaluronic acid, chondroitin sulfate, keratan sulfate, and heparan sulfate, and their quantity and cross-linking status are the main determinants of tissue stiffness[13]. The ECM is used as an intercellular filler, and it is an active substance and source of signaling molecules for intercellular communication, cell proliferation, and adhesion[14]. Active interactions between cancer cells and the TME often result in stiffening of the ECM, which leads to aberrant mechanotransduction and further malignant transformation during cancer progression[15]. The clinical application of ibrutinib, which is a small molecule compound that inhibits integrin (ECM receptor) signaling, for the treatment of lymphoid leukemias and lymphomas has demonstrated the feasibility of targeting aberrantly activated ECM in oncotherapy[16]. Notably, some studies have revealed the critical role of ECM remodeling in ATC cell metastasis[17]. Therefore, a comprehensive understanding of ECM derangement in the TME may help identify promising targets for ATC therapy.

In this study, we emphasize the significant role of ECM in ATC progression and its potential therapeutic targets for antitumor by summarizing the following knowledge: (1) the activation status of the ECM in ATC; (2) the potential function of the main components of the ECM in ATC; (3) the potential impact of the interaction between cancer cells and the ECM in the TME on ATC progression; and (4) potential therapeutic strategies targeting aberrant ECM signaling for ATC treatment.

Materials and methods

ATC data of public databases

The transcription data (GSE29265, GSE33630, GSE53072, and GSE65144) were downloaded from the Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo/).

Gene ontology (GO) and kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment analyses

Differentially expressed genes (DEGs) among the normal and ATC groups were displayed in the form of volcano plots by the "gplot" R package from Assistant for Clinical Bioinformatics (https://www.aclbi.com/static/index.html#/) platform. |Fold Change|> 2 and adjusted $p < 0.05$ were set as the statistical threshold value for differentially expressed genes. GO and KEGG pathway analyses were performed by the Assistant for Clinical Bioinformatics platform using ClusterProfiler package in R software, based on relevant cancer data in GEO database (GSE29265, GSE33630, GSE53072, and GSE65144). In the enrichment result, p less than 0.05 is considered to be a meaningful pathway.

Results

ECM signaling is significantly activated in ATC tissues

The GEO is a shared repository for high-throughput microarray and next-generation sequence functional genomic datasets. To determine the status of activated ECM signaling in ATC, we downloaded and extracted transcriptome data and corresponding clinical information from the GSE29265, GSE33630, GSE53072, and GSE65144 datasets. Differentially expressed genes (DEGs) between ATC and normal tissue were identified, and enrichment analysis was performed as described previously[18]. Notably, the downregulated DEGs in the four GEO datasets were closely related to extracellular structure organization and extracellular matrix organization (Figs. 1, 2, 3, 4), which suggested that ECM signaling played a crucial role in ATC progression. The most significantly enriched terms for GSE29265 were organelle fission, nuclear division, mitotic nuclear division, extracellular structure organization, extracellular matrix organization, and chromosome segregation, as shown in Fig. 1. Similarly, the most significantly enriched terms for GSE33630 were extracellular structure organization, extracellular matrix organization, and cytokine–cytokine receptor interaction; the most significantly enriched terms for GSE53072 were Herpes simplex virus 1 infection, cytokine–cytokine receptor interaction, extracellular structure organization, and extracellular matrix organization; the most significantly enriched terms for GSE65144 were Herpes simplex virus 1 infection, cytokine–cytokine receptor interaction, extracellular structure organization, and extracellular matrix organization, and neutrophil degranulation, neutrophil activation involved in immune response, as shown in Figs. 2, 3 and 4, respectively. A distinguishing feature of ATC is its ability to easily shape the tumor stromal microenvironment. We listed several genes that exhibit aberrant expression in ATC tissues and are involved in modifying the ATC immune microenvironment in Table 1. Because of the important regulatory role of the ECM in the malignant phenotype of ATC, there is an urgent need to elucidate the mechanism of ECM remodeling in ATC.

The function of the main components of the ECM in TME

Cancer cells remodel the ECM by interacting with stromal cells to promote covalent intermolecular cross-linking and the massive deposition of supramolecular aggregates, such as fibrillar collagens, and this ECM remodeling promotes tumor progression and influences cancer cell invasion[25]. Most proteins in the ECM are categorized into two groups, fibrous proteins (including collagen, fibronectin, elastin, and laminin) and glycosaminoglycan proteins (consisting of hyaluronic acid, chondroitin sulfate, keratan sulfate, and heparan sulfate)[26].

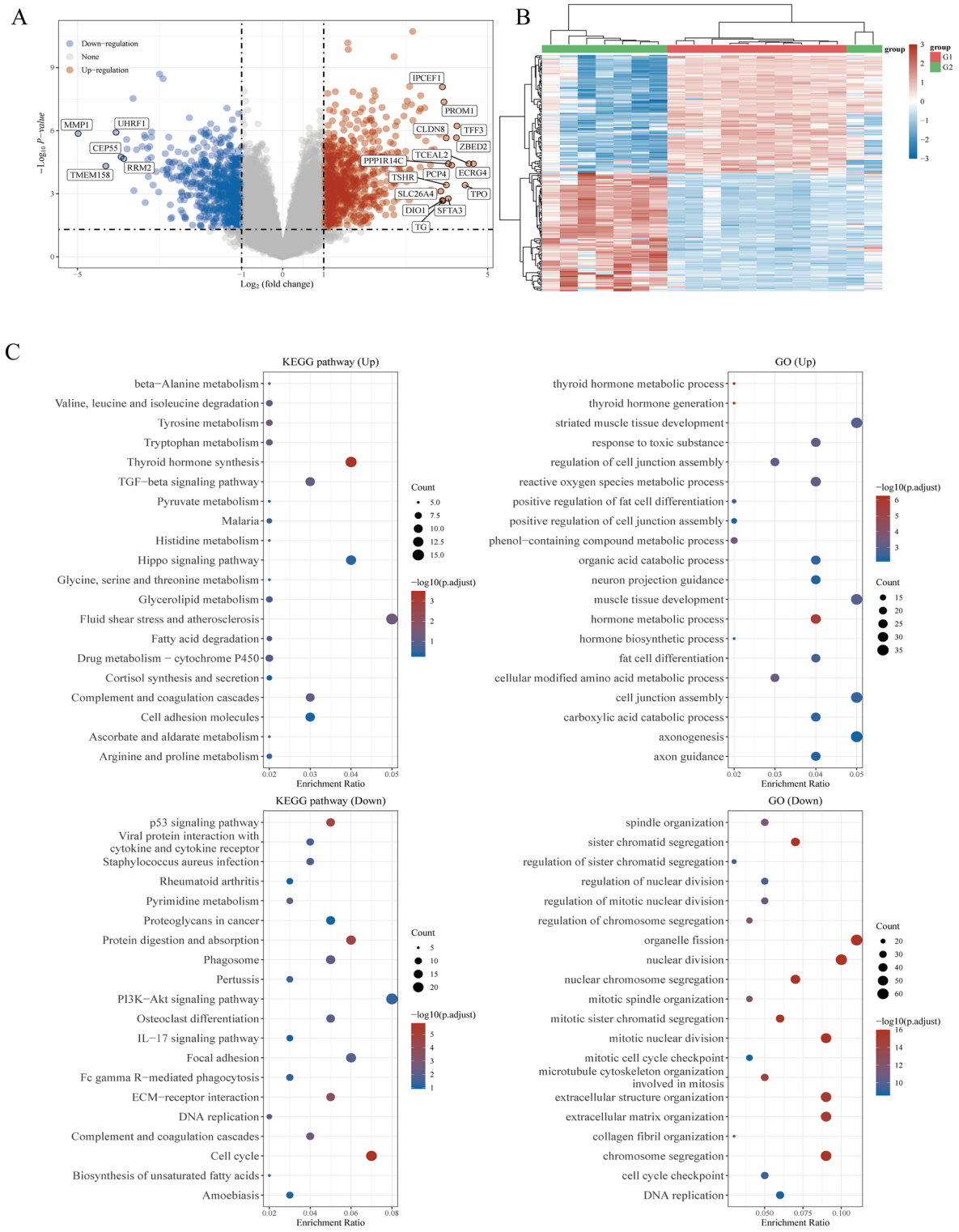

Fig. 1. Differentially expressed genes and enrichment analysis between ATC and normal tissues based on the GSE29265 dataset. A-B Volcano map (**A**) and heatmap (**B**) of differentially expressed genes was constructed on normal and ATC group. (**C**) The most significantly enriched terms for GSE29265 were organelle fission, nuclear division, mitotic nuclear division, extracellular structure organization, extracellular matrix organization, and chromosome segregation.

Collagen

Fibroblasts primarily produce collagen, which is located in bones, tendons and skin[27]. Collagen accumulate in and

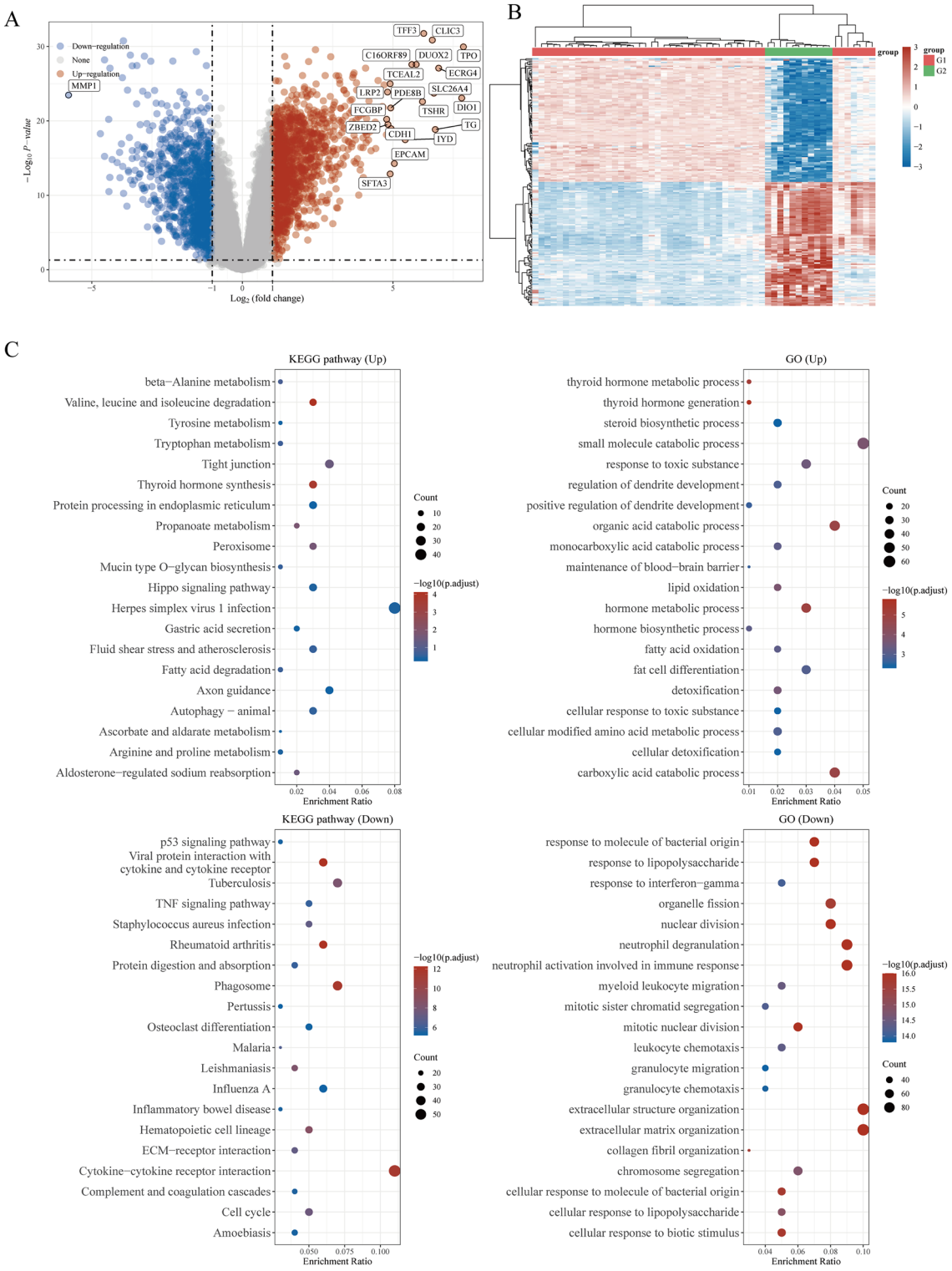

Fig. 2. Differentially expressed genes and enrichment analysis between ATC and normal tissues based on the GSE33630 dataset. A-B: Volcano map (**A**) and heatmap (**B**) of differentially expressed genes was constructed on normal and ATC group. (**C**) The most significantly enriched terms for GSE33630 were extracellular structure organization, extracellular matrix organization, and cytokine–cytokine receptor interaction.

around tumors during tumorigenesis progression and contribute to the promotion of tumor cell growth, metastasis, and drug resistance[28,29]. Notably, whether collagen deposition is a promoter or inhibitor in ATC progression remains controversial. Some collagens restrain cancer progression via multiple mechanisms, including inhibition

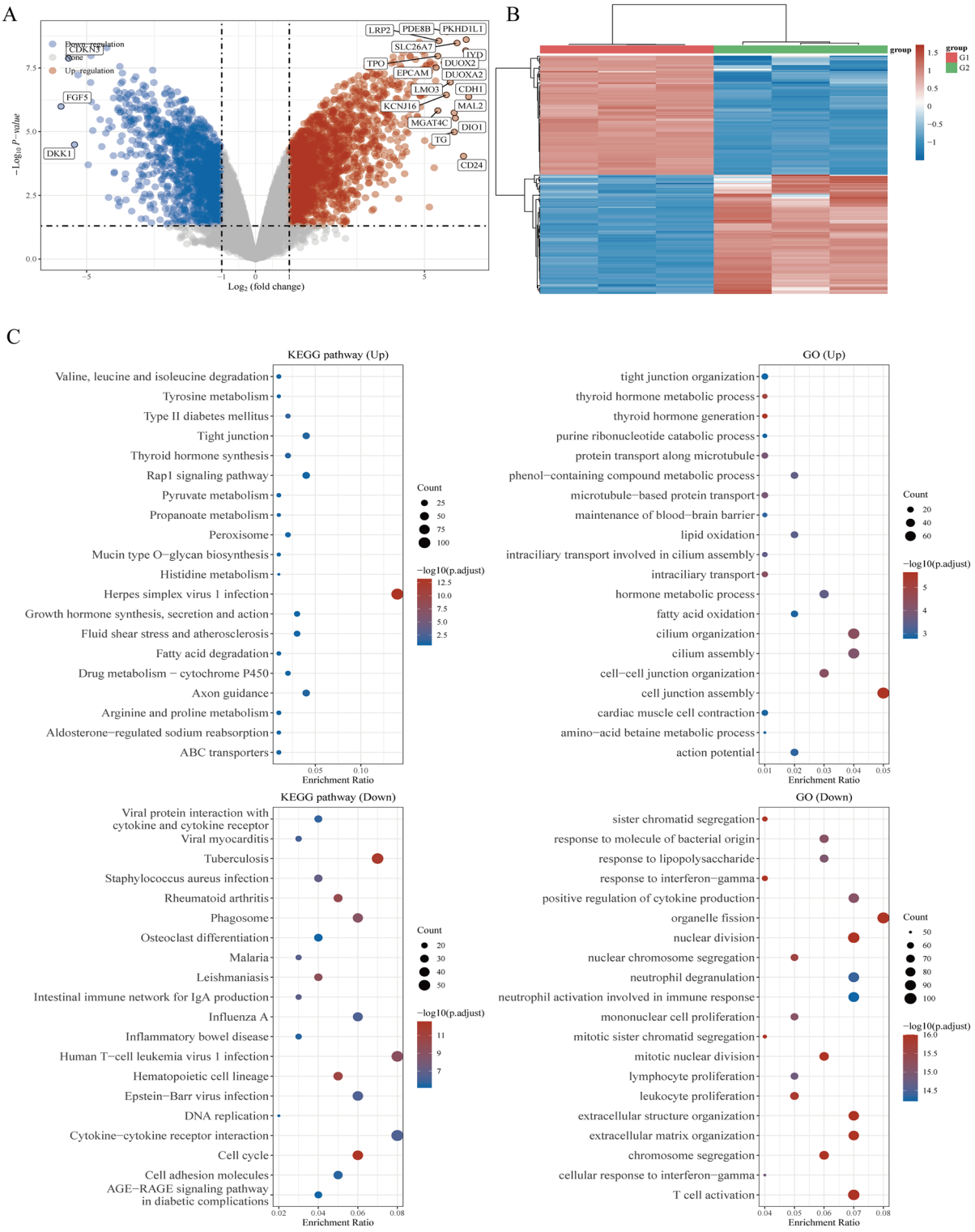

Fig. 3. Differentially expressed genes and enrichment analysis between ATC and normal tissues based on the GSE53072 dataset. A-B: Volcano map (**A**) and heatmap (**B**) of differentially expressed genes was constructed on normal and ATC group. (**C**) The most significantly enriched terms for GSE53072 were Herpes simplex virus 1 infection, cytokine–cytokine receptor interaction, extracellular structure organization, and extracellular matrix organization.

of tumor proliferation by promoting cancer cells to enter and remain in a dormant state. Cancer cells in collagen-deficient tumors produce increased levels of chemokines to attract myeloid-derived suppressor cells (MDSCs),

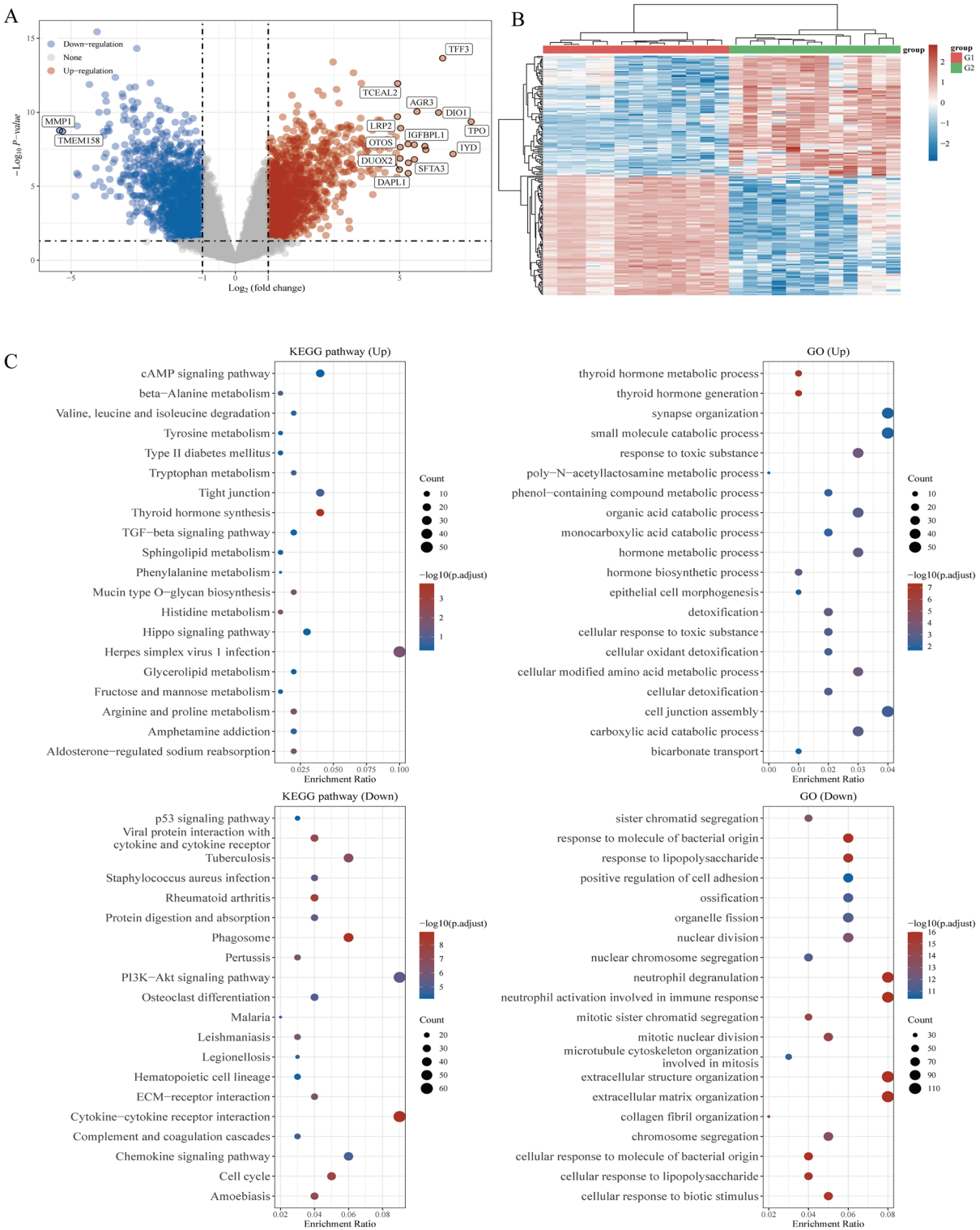

Fig. 4. Differentially expressed genes and enrichment analysis between ATC and normal tissues based on the GSE65144 dataset. A-B: Volcano map (**A**) and heatmap (**B**) of differentially expressed genes was constructed on normal and ATC group. (**C**) The most significantly enriched terms for GSE65144 were Herpes simplex virus 1 infection, cytokine–cytokine receptor interaction, extracellular structure organization, and extracellular matrix organization, and neutrophil degranulation, neutrophil activation involved in immune response.

which induce an immunosuppressive microenvironment to limit the effectiveness of immunotherapy[30,31]. As a major component of the ECM, the quantity and post-translational modifications of collagen often change

Gene name	Differential expression in ATC	Biological processes/cellular functions	References
METTL3	↓	increased the abundance of the immunosuppressive Tregs and terminally exhausted T cells	19
SIGLEC15	↑	interacted with T cells by immunosuppressive signals such as CXCL12-CXCR4	20
CD1d	↑	a receptor for NKT cells	21
PPARGC1A	↑	inhibited immune cell infiltrations	22
TLR4	↑	shaped the immunosuppressive microenvironment	23,24

Table 1. Aberrant genes in ATC immune microenvironment.

dramatically during cancer progression, which enable the construction of a complex collagenous mesh that has a fundamental impact on the behavior of cancer cells and other cells in the TME[32,33]. Collagen degradation is primarily governed by matrix metalloproteinases (MMPs). MMP-1, MMP-8, MMP-13, and MMP-14 cleave fibril-forming collagens I, II, and III, and MMP-2 and MMP-9 cleave denatured collagens and collagen IV[34]. Several collagen subtypes and MMPs are strongly associated with the development and progression of thyroid cancer, which suggests that remodeling of the ECM is a key feature of the TME that promotes the malignant processes of thyroid cancer and collagen subtypes and MMPs are candidate therapeutic targets and biomarkers for advanced stages of this malignancy[35–37].

A recent single-cell transcriptomics study revealed that excessive activation of collagen and collagen-interacting receptors were critical processes in the malignant transformation of ATC[38]. Current studies elucidated the role of collagen in the ATC process from two main perspectives. One perspective is collagen synthesis and degradation. Many genes involved in collagen degradation affect the progression of ATC by altering collagen deposition[39,40]. The second perspective is the activation of cancer-associated fibroblasts (CAFs). Knockdown of CREB3L1 remodeled the tumor stromal microenvironment, and the presence of CAFs inhibited the growth of ATC spheroids and the metastasis of ATC cells[41]. Collagen is also produced from a subset of tumor cells[42]. We hypothesized that the state of collagen in ATC was a dynamic process, with alterations in components and content as cancer cells proliferate, expand and migrate. However, TAM-modified collagen also triggers signals that affect the interaction between cancer cells and surrounding mesenchymal cells or immune cells. There is also a great deal of variation in the collagen that borders or encapsulates the interior and exterior of the tumor tissue. The dynamic changes and differences in collagen, and the different sources of production, obscure its role in cancer progression. Therefore, constructing an intelligent model to reveal the progression status of ATC based on dynamic changes in collagen may be an effective approach.

Other components of the ECM

The content of fibronectin in the ECM is low. However, its role in tumor transformation should not be ignored, primarily because fibronectin connects various structural proteins to form an integrated matrix. Fibronectin also recognizes and binds integrins on the cell membrane and induces integrin attachment, which profoundly impacts intracellular signaling. Fibronectin binds directly to growth factors, such as insulin-like growth factor (IGF), fibroblast growth factor (FGF), transforming growth factor-β (TGF-β), hepatocyte growth factor (HGF), and platelet-derived growth factor (PDGF)[43–46]. Elastin is the main component of elastic fibers that maintains the toughness and strength of tissues by resisting tissue deformation or rupture together with collagen[47,48]. Laminin and collagen form the components of the basement membrane, which is involved in the process of vascular maturation[49,50]. Hyaluronic acid (HA) is a high molecular weight glycosaminoglycan that mechanically increases the elastic viscosity of the ECM[51]. HA also acts as a sieve to impede and immobilize large molecular particles that may be recognized by many types of cells during cell movement, invasion, proliferation and inflammation[52,53]. Despite the current lack of evidence confirming the role of these components of the ECM in the ATC process, their roles cannot be ignored. A recent study revealed that thyroid cancer cells cultured in different dimensional states differed significantly in hypoxia, ECM, cytoskeleton, thyroid-specific proteins, and thyroid transcription factors[54]. Three-dimensional spheroids from patients with thyroid cancer showed a decrease in the expression of thyroid differentiation markers[54]. Based on the essential role of ECM components in maintaining the spherical morphology of cancer cells, we hypothesized that these components played a crucial role in the malignant progression of ATC.

Fibroblasts

Fibroblasts directly produce structural macromolecules, such as collagen, fibronectin, and laminin, and secrete many enzymes involved in the modification and degradation of these structural macromolecules, such as lysyl hydroxylases and MMPs, to play a central role in the formation and renewal of the ECM[55,56]. Fibroblasts are highly flexible cells that convert signals from multiple sources, including TGF-β, tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1, repeated mechanical stretching, and repeated mild heat shocks, into alterations in ECM components[57,58]. Cancer-associated fibroblasts (CAFs), which originate primarily from mesenchymal cells and resident fibroblasts, are among the most important cell components in the TME of most solid tumors and are activated and reprogrammed in response to paracrine factors and cytokines produced and released by tumor cells[59]. Many studies suggest that fibroblast-mediated collagen remodeling within the TME facilitates the progression of thyroid cancers, and increased expression of CAFs is a risk factor for worse thyroid cancer clinicopathological features[60–62]. CAFs and senescent thyroid cancer cells co-occur in various histotypes of BRAF-driven thyroid tumors and localize at the tumor invasive front, which suggests that crosstalk between CAFs and

thyroid cancer cells plays an essential role in the invasive process of thyroid tumors[63]. There is some evidence that the inhibition of the CAF-like properties of ATC cells via the blockade of ECM signaling, which remodels the tumor stromal microenvironment and drives malignancy in ATCs, may be a novel strategy for suppression of the malignant transformation of ATCs[41]. Fibroblasts are one of the major cell types in the TME, and targeting fibroblasts to block cell−cell communication in ATC cells is an immunotherapeutic opportunity[64].

Interaction of the ECM with TME components

Most cancers exhibit greater matrix stiffness (depending on the ECM components and proportions) than their corresponding normal tissues. Therefore, ECM stiffness is a unique feature and promising therapeutic target[65,66]. However, we hypothesize that the interaction of the ECM with cancer cells, stromal cells, and immune cells in the complex molecular regulatory network of the TME is the key to unraveling the malignant process of ATC. Chemokine-chemokine receptor interactions, such as the TGF-β/Smad2/3 and CXCL12/CXCR4 signaling pathways, are the most significant drivers of the transformation of normal fibroblasts to CAFs and macrophages to the M2 type of macrophages, which further facilitate ECM deposition and cancer malignancy[67]. This interaction also directly or indirectly affects ECM stiffness. Overall, the production of ECM components and enzymes is further accelerated when tumor cells receive external signals from growth factors. In contrast, some enzymes that catalyze ECM degradation are inhibited in the TME[67]. Notably, the upregulation of MMP activity in a stiffened TME also increases vascular proliferation, invasion, and neovascular branching[68]. The ECM acts as a reservoir for growth factors, and ECM degradation contributes to the release of growth factors and cytokines that facilitate cancer progression. However, the motility of cancer cells is activated when the local matrix is degraded, which further confirms the complexity and dynamics of the ECM regulatory network.

The ECM in the TME promotes the proliferation, migration and vascularization of cancer cells and the transformation of tumor cells to cancer stem cells (CSCs). Cancer cells hijack surrounding stromal cells, immune cells, inflammatory cells, and the ECM is a vehicle for inducing cancer cell expansion. The specific pathways and mechanisms involved have been detailed previously[67]. The ECM acts as a physical barrier and compresses micro blood vessels or causes them to leak, which partially reduces the efficacy of chemotherapies and immune therapies[66,69]. The negative effect of the ECM on the infiltration of tumor-killing immune cells in the TME is also well understood. The tumor-killing immune cells are more inclined to migrate during the ECM-rich encapsulation of tumors. ECM-rich tumors create a hypoxic environment that allows enhanced glycolytic metabolism and acidification, which further induces an immunosuppressive microenvironment[70]. ECM proteins also directly enhance the activity of Tregs to induce cancer cells to express more PD-L1, or drive M2 polarization, which inhibits $CD8^+$ T-cell-mediated anti-tumor immune responses[71,72]. Altogether, these results suggest that the cross-talk between the ECM and microenvironmental cells largely controls cancer progression. Therefore, we hypothesize that aberrantly activated ECM signaling appears to be critical for the rapid expansion of ATC cells.

Receptors for the ECM in TME

Receptor proteins are important factors for ECM communication with the surrounding environment[73]. Many ECM-associated receptor proteins, including integrin, discoidin domain receptors (DDRs), CD44, and receptor for hyaluronan-mediated motility (RHAMM), are highly upregulated in many solid tumors and correlate with malignancy and poor prognosis[74,75]. Notably, inhibitors or antibodies against these receptors have been widely used in preclinical and clinical studies[76]. Cancer cells respond to their surroundings by sensing ECM-mediated mechanical stress or molecular stimuli via unidirectional (receptors sense ECM stiffness then transmit this signal to cells) or bidirectional (cells sense signals received by receptors and transmit signals through receptors) signaling driven by receptor proteins[77]. Notably, these receptors have a distinct division of labor, and different subtypes receive the corresponding ECM signals. For example, DDR1 binds to collagen types I and IV, and DDR2 interacts with collagen types I, II, and X. HA is the major ligand for membrane-bound RHAMM[67]. The binding of lymphocytes to fibronectin is also facilitated by CD44, which is critical for lymphocyte infiltration into the TME[78,79]. A preclinical trial demonstrated that recombinant fibronectin CH296 stimulated T cells to achieve robust tumor suppression in patients with advanced cancer[80], which suggesting that blockade of ECM-cancer cell crosstalk is a potential anti-cancer strategy. This meticulous cross-linking constitutes a complex network of ECM-cancer cell interactions. We hypothesize that cancer cells hijack the ECM in the TME to sense changes in their surroundings and use it as a territory to send aggressive signals to surrounding or distant cells or organs. Cancer cells wrap surrounding normal cells via the ECM to form a tumor environment and construct an immunosuppressive microenvironment that is conducive to cancer cell expansion. We hypothesize that the rapid expansion of ATC is closely related to the dysregulation of ECM receptor signaling.

Matrix components as potential therapeutic targets for ATC

Drugs that inhibit collagen synthesis (halofuginone, Fresolimumab) or induce collagen degradation (collagenases) have been investigated extensively in animal and preclinical studies[81,82]. Mechanistically, these drugs weaken the stiffness of the ECM and contribute to more efficient drug delivery to solid tumors[83–85]. Several strategies aimed at modulating the number or activity of MMPs or approaches that indirectly increase the synthesis of collagenases also contribute to cancer therapy[86]. A number of drugs that use ECM components as therapeutic targets (e.g., 4-methylumbelliferone, which was designed to facilitate greater penetration of anticancer drugs into the interior of solid tumors) or that use ECM components as targets for precise drug delivery (BC-1, L19) also offer new opportunities for solid tumor therapy[67]. However, these methods have some drawbacks. The degradation of collagen releases many growth factors, and whether this release exacerbates the inflammatory response of tumors is not known, Whether ECM degradation contributes to cancer cell invasion must be further investigated. We postulated that the inhibition of collagen cross-linking is a novel strategy for inhibiting the

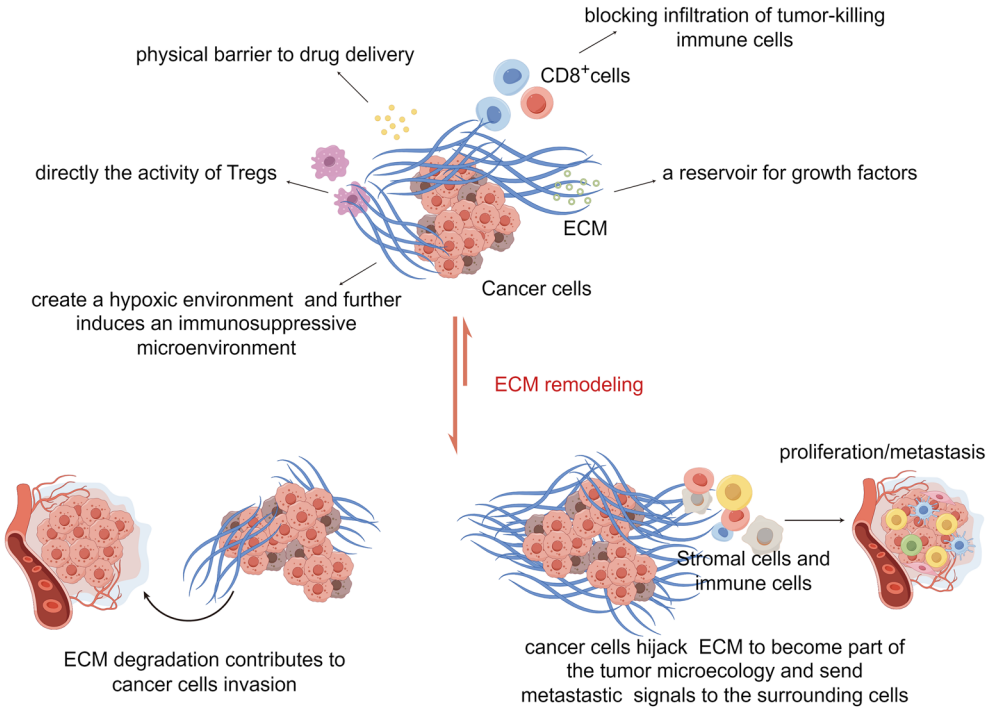

Fig. 5. Schematic representation of the mechanisms underlying the potential role of the extracellular matrix in the tumor microenvironment (generated by FigDraw).

progression of ATC. Lysyl oxidase (LOX, an ECM-remodeling enzyme) catalyzes collagen cross-linking and is frequently upregulated in thyroid cancer[87]. Several clinical trials confirmed the use of an anti-LOXL2 monoclonal antibody (simtuzumab) with no clinically significant effect in patients with pulmonary or hepatic fibrosis[88,89]. However, this unexpected negative result may be related to an ineffective antibody, and other members of the LOX family may be more appealing candidates for cancer treatment.

Significant breakthroughs in the past decade have been made in controlling cancer progression via targeted cell–ECM interactions. Collagen, proteoglycans, and glycoproteins also form ECM in the bone marrow and lymph nodes. However, unlike solid tumors, leukemia (so-called "liquid carcinoma") cells form only temporary connections to the ECM in structured niches within the bone marrow and lymphoid organs[90]. Ibrutinib (an inhibitor of bruton tyrosine kinase) controls integrin α4β1-mediated adhesion to fibronectin, VCAM-1, and chemotaxis signals mediated by CXCL12-, CXCL13-, and CCL19-induced signaling, and it has been approved for patients with chronic lymphocytic leukemia (CLL)[91]. The RHAMM-HA interaction facilitates cell motility, but the RHAMM-R3 peptide vaccine triggered anti-cancer immune responses in CLL patients[92,93]. These results reveal that targeting cell-ECM interactions is a highly viable approach against malignant tumors, including ATCs.

Conclusion

ATC is a rare subtype of thyroid carcinoma and is extremely aggressive. Treating ATC in the traditional manner of treating differentiated thyroid tumors is ineffective in most cases, and due to the highly aggressive and recurrent properties of ATC, its therapeutic options are mainly palliative. Therefore, there is an urgent need to find new therapeutic approaches, and targeted therapy in the ATC microenvironment may be a new way[94]. Polymorphonuclear neutrophils (PMNs) are critical effector cells that orchestrate the inflammatory response in TME. PMNs contain and release an excess of mediators, including granular enzymes [e.g., myeloperoxidase (MPO), pentraxin-3 (PTX3) and matrix metalloproteinase-9 (MMP-9)], and neutrophil extracellular traps (NETs), and those seem to correlate with malignancy and severity of progressive thyroid tumor[95]. Cristinziano et al.[96] discovered that conditioned media with ATC cell lines induced the release of NETs, and thus targeting neutrophil activation may contribute to inhibiting ATC proliferation. In addition, the combination of BRAF inhibitors and immunotherapy in ATC is a promising therapeutic approach to maximize treatment efficacy. For example, combination therapy with the BRAFV600E inhibitor PLX4720 and an anti-PD-L1 or anti-PD-1 antibody significantly improved mouse survival, and the reduction in tumor volume was associated with an increase in the number and activity of effector immune cells[97]. Moreover, the interaction of ECM with cancer cells not only facilitates tumor development and progression, but also largely controls most of the characteristic hallmarks of tumorigenesis, providing new opportunities for the treatment of ATC.

Cancer progression is driven by continuous interactions between cancer cells, the ECM, and other cell types present in the TME. ECM components contribute significantly to the microenvironment of most individual cells in the body, and their dysregulation is closely linked to the development of many diseases, including cancer. However, the therapeutic role of EMT in thyroid cancer is often underestimated. The main challenge lies in

the current lack of materials that accurately mimic the ECM in vitro due to its complex physical and biological properties, and the delicate interactions between different components of the ECM. There is a lack of systematic comparisons of differences in specific ECM components in different cancers, which is an essential step for the development of specific therapeutic and sensitive detection strategies. Therefore, current applications of the ECM in cancer primarily include adjuvant therapy for immunotherapy or are considered an imaging tool for tumors, and its central role in tumor therapy remains unexplored.

ATC is a subtype of thyroid cancer that occurs in a small percentage of patients but has a high degree of malignancy and poor patient prognosis. Clinically, it generally manifests as a fast-growing goiter or nodule that is firm to the touch and adheres resolutely to the underlying structures. We revealed the important role of ECM components in the malignant transformation of ATC, which suggested that ECM components were promising therapeutic targets. We hypothesized that cancer cells wrapped and hijacked the ECM to become part of the tumor microenvironment, which promoted the sending of signals of their own aggression to surrounding or distant tissues or organs and altered the state of the surrounding environment to form an immunosuppressive microenvironment that was conducive to the growth of cancer cells. Therefore, ATC undergoes significant infiltration and metastasis at an early stage.

During the malignant transformation of ATC, a variety of immune cells that were previously capable of tumor killing are transformed into promoters that advance the malignant progression of the tumor, including but not limited to the transformation of $CD8^+$ T cells to depleted T cells and the polarization of macrophages to M2-type macrophages. These results suggest that cancer cells must release some signal or pressure to promote a decrease in immune cell activity in the TME. We hypothesize that the continuous interactions between the ECM and cancer cells play a crucial role in this process. Therefore, sufficient attention should be given to ECM-cancer cell interactions in future studies to reveal their key mechanisms in the process of cancer immunosuppression, which will provide new opportunities for the treatment of ATC (Fig. 5).

Data Availability

The original data contributing to the findings presented in the study were obtained from Assistant for Clinical Bioinformatics (https://www.aclbi.com/static/index.html#/). Further inquiries may be addressed to the corresponding author.

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Author contributions

X.J.K. conceived and designed the study, performed the data analysis and interpretation. X.J.K., S.Y.Y., and C.X.X. wrote the manuscript. All authors reviewed the manuscript.

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