

Research on the Related Molecular Mechanisms of Lung Metastasis of Adenoid Cystic Carcinoma

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Abstract

Adenoid cystic carcinoma, a common malignant tumor of the salivary glands, is characterized by its significant invasiveness, high recurrence rate, and frequent distant metastasis, especially to the lungs. The intricate mechanisms driving its metastasis currently lack specific therapeutic interventions, thus adversely affecting patient outcomes. Recent progress in molecular biology techniques has spurred numerous studies exploring the pivotal molecules and signaling pathways implicated in lung metastasis of adenoid cystic carcinoma. These investigations offer crucial insights into the metastatic processes and support the advancement of innovative targeted treatments. This review article delves into the molecular mechanisms associated with lung metastasis in adenoid cystic carcinoma.

Keywords

Adenoid Cystic Carcinoma, Lung Metastasis, Epithelial-Mesenchymal Transition, Tumor Microenvironment, Signal Pathway, Targeted Therapy

1. Introduction

Adenoid cystic carcinoma (ACC) is a malignant tumor arising from secretory glands, most commonly in the salivary glands, and is characterized by significant invasiveness, slow growth, and a high propensity for distant metastasis [1]-[5]. While lymphatic metastasis is relatively uncommon [6], distant metastasis, particularly to the lungs, is a frequent and devastating event, with an incidence reaching 47.8% [2] [3]. The prognosis for patients with metastatic disease is poor, with overall survival rates ranging from 23% to 40% [4]. Consequently, investigating the mechanisms underlying lung metastasis in ACC is imperative to improve pa-

tient survival rates.

ACC presents prominent inter- and intra-tumoral heterogeneity, which is closely correlated with its metastatic potential and clinical manifestations. Histologically, ACC is classified into tubular, cribriform and solid subtypes; the solid subtype exhibits the strongest invasiveness and highest risk of lung metastasis, while tubular-type tumors tend to have relatively indolent biological behavior. In terms of primary anatomical sites, ACC originating from minor salivary glands, tongue and base of tongue possesses a higher tendency for distant lung metastasis compared with tumors arising from parotid and submandibular glands. Such differences in histological pattern and primary location jointly shape the divergent metastatic behaviors of ACC, and also explain the inconsistent clinical outcomes and varied responses to molecular targeted therapy among different patient subgroups.

Recent research indicates that the development of lung metastasis is a complex, multi-step pathological process involving numerous factors [7]-[9]. These include the intrinsic characteristics of tumor cells, the tumor microenvironment (TME), angiogenesis, and intricate molecular regulatory networks. This review aims to systematically synthesize current knowledge on the molecular mechanisms associated with lung metastasis in adenoid cystic carcinoma, providing a comprehensive theoretical foundation for future clinical interventions and targeted therapy development.

2. Methods

This study was conducted as a narrative review. A comprehensive literature search was performed using the PubMed, Web of Science, and Scopus databases. The search strategy combined terms related to ACC (e.g., “adenoid cystic carcinoma”, “salivary gland cancer”) with terms related to metastasis (e.g., “lung metastasis”, “metastatic mechanisms”) and molecular biology (e.g., “molecular mechanisms”, “signaling pathways”, “gene expression”, “tumor microenvironment”). The search was limited to articles published in English up to October 2025. Literatures were categorized and summarized artificially based on research themes, without quantitative meta-analysis and standardized literature quality evaluation.

3. Results

The analysis of the literature reveals that ACC lung metastasis is driven by a coordinated, multi-level process involving the tumor cells themselves, their surrounding environment, and the molecular machinery that governs their behavior.

3.1. Intrinsic Biological Characteristics of Tumor Cells: The “Initiating Factors” of Metastasis

The inherent malignant phenotype of ACC cells provides the fundamental drive for metastasis. The cellular characteristics of ACC confer an “innate potential” to surpass the primary lesion, enabling infiltration and metastasis.

3.1.1. Cell Phenotypic Heterogeneity and Cancer Stem Cells (CSCs)

ACC tumor cell populations exhibit significant heterogeneity. A critical subpopulation driving metastasis is CSCs, which express markers such as CD44, CD133, and ALDH1. These cells possess enhanced self-renewal, differentiation, and anti-apoptotic properties, enabling them to survive therapeutic pressures. These stem-like cells can acquire motility through epithelial-mesenchymal transition (EMT), enter the circulation, and subsequently recolonize lung tissue via the reverse process, mesenchymal-epithelial transition (MET). Furthermore, highly invasive subpopulations within the tumor can directly facilitate metastasis by degrading the extracellular matrix (ECM) and invading blood vessels.

3.1.2. The Driving Role of EMT

EMT is a critical process linking molecular regulation to metastatic behavior [4] [10]. In ACC, EMT is characterized by the loss of epithelial markers like E-cadherin and a gain of mesenchymal markers such as N-cadherin and vimentin, leading to loss of cell polarity and enhanced migratory capacity. Key molecules, such as the transcriptional repressor BMI-1, facilitate EMT, thereby promoting ACC infiltration and metastasis [7].

3.2. Regulation by the Tumor Microenvironment (TME): The “Soil” for Metastasis

The TME, comprising stromal cells, ECM, and cytokines, creates a supportive niche for metastatic cells, both at the primary site and in distant organs like the lungs, where a pre-metastatic niche (PMN) is established [11].

3.2.1. Role of Stromal Cells

Cancer-Associated Fibroblasts (CAFs): CAFs play a central role in promoting metastasis [12]-[14]. As the predominant stromal cells [15], they remodel the ECM by secreting matrix metalloproteinases (MMPs) and cytokines like IL-6 and TNF- α , facilitating tumor cell invasion [12]. CAFs also promote chemotactic migration of ACC cells via the CXCL12/CXCR4 axis. **Importantly**, CAFs-derived extracellular vesicles (CAFs-EVs) show explicit pulmonary tropism, which is an ACC lung-metastasis-specific characteristic rather than a universal metastatic trait [14]. These EVs enhance lung vascular permeability by upregulating VEGFR1, recruit bone marrow-derived cells, and remodel the ECM via periostin (POSTN), thereby preparing the PMN [13] [14].

Immune Cells: The ACC microenvironment is often immunosuppressive. M2-type macrophages secrete factors like VEGF and EGF, enhancing tumor cell invasion and metastasis. Regulatory T cells (Tregs) suppress effector T cell activity via IL-10 and TGF- β , creating an immune-tolerant environment that allows tumor cells to evade surveillance. For regulatory T cells (Tregs), direct evidence supporting their role in ACC lung metastatic immune escape remains scarce. The conclusion that Tregs suppress effector T cell activity via IL-10 and TGF- β to form an immune-tolerant microenvironment for tumor cell immune evasion is an inferential conclusion summarized from pan-tumor metastasis theories.

3.2.2. Reshaping of the Extracellular Matrix (ECM)

ECM remodeling is intricately linked to ACC invasion. CAF-secreted MMPs degrade ECM components, disrupting tissue barriers and facilitating tumor cell intravasation. Degradation products, such as collagen fragments, can further activate pro-survival pathways like PI3K/Akt in tumor cells. The altered ECM can also influence tumor cell behavior through integrin-mediated signaling.

3.2.3. Cytokine and Chemokine Networks

A complex signaling network mediates communication between ACC cells and the TME. Angiogenic factors, particularly VEGF, are significantly upregulated in metastatic ACC and enhance vascular permeability and angiogenesis, facilitating tumor cell intravasation [9]. The CXCL12/CXCR4 chemokine axis is a core mechanism mediating ACC lung tropism: Lung tissue highly expresses CXCL12, which specifically recruits ACC cells with high CXCR4 expression to migrate toward the lung, a tissue-specific effect distinct from general metastasis promotion. Inflammatory cytokines like IL-6, IL-8, and TNF- α activate pathways such as STAT3 and NF- κ B, promoting tumor cell proliferation, invasion, EMT [16], and further increasing vascular permeability.

3.3. Angiogenesis and Circulating Tumor Cells (CTCs): The “Pathway” for Dissemination

To reach the lungs, tumor cells must utilize and create vascular pathways.

3.3.1. Tumor Angiogenesis and Vasculogenic Mimicry (VM)

Tumor angiogenesis within the primary lesion provides a physical channel for metastasis. ACC exhibits robust angiogenic capabilities, primarily driven by the VEGF/VEGFR pathway. Additionally, ACC cells can form vascular-like structures themselves through VM, independently of endothelial cells, further promoting tumor cell dissemination.

3.3.2. Survival and Colonization of CTCs

Circulating tumor cells (CTCs) are tumor cells that have entered the bloodstream. Regarding the mechanisms of CTC immune escape and their shielding by platelets or leukocytes, direct experimental and clinical evidence specific to ACC remains insufficient. The prevailing conclusion—that CTCs survive shear stress and immune attack by expressing anti-apoptotic proteins such as Bcl-2 [17] and Survivin, and by forming protective complexes with platelets and leukocytes—is largely inferential, derived from general research on tumor CTCs. Upon reaching the lung capillaries, CTCs extravasate into the lung interstitium. With support from the lung microenvironment, they can undergo MET, restoring their epithelial phenotype and proliferating to form metastatic colonies.

3.4. The Molecular Regulatory Network: The “Core Switch” of Metastasis

All aspects of ACC lung metastasis are governed by a complex molecular network,

where aberrant gene and protein expression, along with dysregulated signaling pathways, act as the primary driving forces.

3.4.1. Key Genes and Proteins

Oncogene Activation: The MYB-NFIB fusion gene is a pivotal initiating event in ACC, activating downstream pro-angiogenic and pro-invasive targets [18]. Other oncogenes like NOTCH1 and EGFR synergistically promote proliferation, invasion, and metastasis via pathways like PI3K/Akt and MAPK. For example, the specific downstream target gene HES [19] of the NOTCH signaling pathway functions as an oncogene by promoting ACC cell proliferation, inhibiting apoptosis, and enhancing metastatic and invasive capabilities. Under hypoxic conditions, HIF-1 α transcriptionally activates genes like NID1, forming a “HIF-1 α -NID1-PI3K/AKT-EMT” axis that specifically drives ACC lung metastasis (lung-tropism mechanism) [20] [21]. Furthermore, the overexpression of oncogenic genes such as IGFBP2, PIM1, and spindle and kinetochore-associated complex subunit 1 (SKA1) can promote invasion and metastasis by inducing EMT and participating in the cell cycle process [22]. Beyond protein-coding genes, microRNAs (miRNAs)—short non-coding RNA transcripts—also exert pro-tumor effects in ACC; prominent oncogenic miRNAs including miR-21 [17] and miR-130a [23] initiate oncogenic signaling transduction, potentiate ACC proliferative and metastatic phenotypes, and confer apoptosis resistance to tumor cells. Additionally, Epiregulin, released by EVs and belonging to the epidermal growth factor (EGF) family of peptide growth factors, can induce ACC cells to adopt a metastatic phenotype [6] [24]. It also enhances angiogenic capacity and increases endothelial cell permeability [8]. Furthermore, Epiregulin significantly influences the pre-transfer microenvironment from a distance [2] [8] [25]. Overexpression of oncogenic proteins such as MYB, EN1 [26], and PKD1 [27] promotes metastasis by inducing EMT or activating downstream pathways.

Tumor Suppressor Gene Dysregulation: The inactivation of tumor suppressors is equally critical. Loss of PTEN [17] [28] and p53 function increases cell migration, invasion, and survival. Another significant category of regulatory molecules comprises tumor suppressor circRNAs and miRNAs. CircRNAs can modulate tumor behavior and influence the migration and invasion of ACC through various signaling pathways [29] [30]. Epigenetic silencing, such as the promoter hypomethylation of EN1 or the targeting of RUNX3 by miR-23b-3p, contributes to the disruption of tumor suppressor networks. Similarly, reduced expression of tumor-suppressive miRNAs like miR-125a-5p [31] leads to the upregulation of EMT drivers such as Snail [32] and ZEB1 [16] [33], facilitating metastasis. Moreover, the reduced expression of NDRG2 correlates with unfavorable prognoses in patients, and its functional deficiency further diminishes the inhibitory effect on the metastasis of ACC cells [34].

3.4.2. Key Signaling Pathways

Several signaling pathways act as central hubs, integrating upstream signals to

drive the metastatic cascade.

PI3K/AKT Pathway: This is a principal conduit for ACC metastasis, activated by various upstream molecules like NID1, EN1, and Epiregulin, and negatively regulated by PTEN. It promotes the cell cycle, EMT, and angiogenesis.

Notch Signaling Pathway: Highly expressed in ACC, the Notch pathway, via its active fragment NICD1, forms a complex with MYB to activate oncogenic targets like MYC, driving tumor stem cell differentiation and lung metastasis [4] [7] [19].

Retinoic Acid (RA) Signaling Pathway: This pathway acts as an endogenous inhibitor of ACC metastasis. RAR α suppresses EMT and cancer stem cell-like properties. Its inactivation can lead to excessive activation of the Notch1-MYB-MYC pathway, accelerating lung metastasis [7].

Other Key Pathways: The JAK2/STAT3 pathway mediates inflammatory signals (e.g., IL-6 from CAFs) to induce EMT [13]. The RhoG/Rac1 cascade regulates cytoskeletal reorganization and cell movement, enhancing ACC cell migration and invasion [25]. The MAPK/ERK, STAT3, and Wnt/ β -catenin pathways are also implicated, regulating EMT, angiogenesis, and cell survival.

4. Discussion

Lung metastasis in ACC is not a linear event but a complex, dynamic process orchestrated by a multi-level regulatory network. This review synthesizes the current understanding into a framework where intrinsic tumor cell factors (the “seed”), the supportive TME (the “soil”), and the vascular system (the “pathway”) are all governed by a core molecular regulatory network (the “switch”). The imbalance between oncogenes (e.g., MYB) and tumor suppressors (e.g., PTEN, RUNX3, PIM1) forms the molecular foundation. These alterations funnel through key signaling hubs like PI3K/AKT and JAK2/STAT3 to drive critical biological processes, most notably EMT, ultimately enabling metastasis.

Despite significant progress, several research limitations and clinical challenges remain.

4.1. Limitations of Current Research

***In Vitro* Reliance and Lack of Validation:** Many findings are based on single cell lines and lack validation in large clinical cohorts, failing to capture tumor heterogeneity. Furthermore, some mechanistic insights, such as the anti-anoikis role of MRPL23-AS1 [3], are primarily derived from *in vitro* experiments and require confirmation in *in vivo* models like nude mouse lung metastasis assays.

Incomplete Mechanistic Depth: The dual roles of molecules like TGF- β 1 remain poorly explored [9]. The precise regulatory details of pathways, such as how HES1 promotes proliferation [19], and the potential synergistic or antagonistic effects among different miRNAs are not fully understood.

4.2. Challenges in Clinical Translation

Lack of Specificity in Targeted Drugs: Existing multi-target drugs like

celecoxib can lead to undesirable side effects, highlighting the need for more specific inhibitors.

Unstandardized Biomarkers: Potential biomarkers like MRPL23-AS1 and CDH11 lack standardized detection methods and unified clinical cutoffs for diagnosis and prognosis.

Limited Clinical Trial Data: The efficacy and safety of potential therapeutic agents targeting these pathways require rigorous validation in clinical trials, which are difficult to conduct due to the rarity of the disease and limited sample sizes. For instance, the PI3K/AKT pathway is activated by multiple upstream molecules including NID1 and EN1; preclinical studies have verified that selective PI3K/AKT inhibitors suppress EMT and pulmonary metastasis in ACC, yet all candidate agents targeting this pathway are confined to preclinical research with no finished phase I/II clinical trials specific to ACC. Similarly, γ -secretase inhibitors against the Notch1-MYB axis exert anti-metastatic activity in ACC xenograft models, and combinatorial treatment with RA agonists produces synergistic inhibitory effects on this signaling axis, but all such therapeutic interventions are still restricted to preclinical investigation.

4.3. Future Directions

To overcome these challenges, future research should focus on: 1) elucidating the cross-regulatory relationships among signaling pathways using systems biology approaches to identify core regulatory nodes; 2) developing highly specific inhibitors against key targets (e.g., PIM1, CAFs-EVs) and exploring combination therapies (e.g., targeted therapy + immunotherapy) to overcome resistance; 3) conducting multicenter clinical studies to validate biomarkers like miR-338e5p/3p for early metastasis detection [35]; and 4) investigating strategies to disrupt the formation of the pre-metastatic niche and intercellular communication within the TME.

5. Conclusion

In conclusion, the poor prognosis of patients with ACC can be attributed to local invasive growth and distant metastasis. The former contributes to a high recurrence rate, even following extensive tumor resection [36], while the latter is a primary factor complicating treatment and significantly contributes to the low survival rate among ACC patients [8] [16] [37]. Lung metastasis in ACC is a multifaceted process driven by a complex interplay of tumor cell-intrinsic properties, a permissive tumor microenvironment, and a dysregulated molecular network. While current research has laid a crucial theoretical foundation, a deeper, more integrated understanding of this network is essential. Such insights will pave the way for the development of novel targeted therapies and combination strategies, ultimately aimed at improving the dismal prognosis for patients with metastatic ACC.

Conflicts of Interest

The authors declare that they have no competing interests.

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