Mechanisms of Chemotherapy Resistance and Treatment Strategies in Pulmonary Adenosquamous Carcinoma

Zuo Zhancheng*, Xu Yixing*, Peng Dexing

Capital Medical University, Beijing, 100069, China

Abstract: Chemoresistance of pulmonary adenosquamous carcinoma is a complex, dynamic process influencing its multifactorial evolution. The underlying mechanisms include classical overexpression of drug efflux pumps, escape from anticancer treatment by histological transformation and stem-cell features in tumor cells driven by plasticity, and dysregulation of the KEAP1/NRF2 and NF-κB signaling pathways. Differences and interactions between individual histological components (adenocarcinoma vs squamous carcinoma) have been described in these processes; together they constitute major roadblocks against therapy. Future directions for research need to address on dynamic monitoring of resistance evolution using multi-omics analysis and serial biopsy before and after treatment in order to determine combination therapeutic strategies targeting of specific resistant mechanisms, such as coordinating chemotherapy with pathway inhibitors (i.e., NF-κB inhibitors), anti-angiogenic agents or immunotherapy that not only overcome disease resistance but ultimately lead to improved clinical outcomes in patients with pulmonary adenosquamous carcinoma.

Keywords: Pulmonary adenosquamous carcinoma; Lung neoplasms; Drug resistance; Chemotherapy

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1. Introduction

A non-small cell lung cancer, pulmonary adenosquamous carcinoma is a relatively uncommon but very aggressive mixed subtype which poses a serious challenge in therapy, especially when it develops resistance to chemotherapy. Chemotherapy is one of the pillars of treatment of lung cancer at an advanced stage though drug resistance is likely to arise, causing the disease to progress and fail the treatment. Explaining the underlying molecular mechanisms is thus very important to formulate effective therapies thereafter. The study of resistance mechanisms in pulmonary adenosquamous carcinoma has grown over traditional chemotherapeutic drug efflux and enhanced DNA repair concepts to include acquired mutations in driver genes, histological subtype transformation, and adaptive tumor microenvironment changes in the past few years. This review, based on recent clinical case reports and basic research, systematically examines the resistance mechanisms that arise in pulmonary adenosquamous carcinoma following chemotherapy and subsequent multi-line therapies and addresses current treatment options and biomarkers, clinical decision-making, and future research.

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Corresponding Author

Zuo Zhancheng (2006-), Male, Han ethnicity, Heilongjiang Province. Student. Currently studying for a bachelor's degree. At Capital Medical University. Lung cancer.

Xu Yixing (2006-), Male, Han ethnicity, Nanyang, Henan Province, None, Bachelor's degree, Capital Medical University,Research Progress on Histological Transformation from Lung Adenocarcinoma to Squamous Cell Carcinoma.

About the Author

Peng Dexin (2006–), Male, Han Chinese, Daxing'anling Prefecture of Heilongjiang Province, No position, Bachelor's degree, Capital Medical University, Research direction: Tumor and Lung Cancer.

2. Cellular and Molecular Pathways of Chemotherapy Resistance

(1) Histological subtype transformation

Transformation to histological subtype is not only realized after targeted therapy (including EGFR-TKIs) but also may take place following chemotherapy which can influence the response of the tumor to alternative treatment regimens. It has been reported in clinical cases that the patients of lung adenocarcinoma can progress to pure squamous cell carcinoma following first-line chemotherapy and adjuvant chemotherapy, which indicates that squamous transformation might be a mechanism linked with resistance to cytotoxic drugs [1]. More complicated patterns of transformation are simultaneous transformation of adenocarcinoma to both squamous cell carcinoma and small cell lung cancer. This case has taken place following EGFR-TKI resistance even though this further corroborates histological transformation as a universal way of acquired resistance [2]. It is important to note that although the majority of cases of histological transformation include driver gene mutations (i.e., EGFR/ALK), cases without driver gene mutations have been also reported, suggesting that histological transformation is not limited to particular genetic events [1].

(2) Cancer stem cells, and tumor cell plasticity

Cancer stem cells, characterized by self-renewal, proliferation, and potential to differentiate as well as inherent resistance to chemotherapy, are believed to play critical roles in tumor recurrence and drug resistance. cancer stem cells(CSCs) express a set of biomarkers associated with stem cell-related processes that directly or indirectly mediate chemotherapy resistance. CSC biomarkers found in lung cancer are: CD133, CD44, EpCAM, ALDH1A1, ABCG2, and transcription factors, including Oct-4, Sox2, and Nanog [3]. Studies have demonstrated that chemotherapy enriches CRIPTO, a lung tumor stem cell marker, and selects and expands CRIPTO-positive lung cancer stem cells resulting in increased CRIPTO expression. CRIPTO levels balance dynamically affect tumor progression and stability. It is this plasticity that allows tumor cells to respond to therapeutic pressure (through histological transformation), and thus acquire resistance to drugs and avoid therapy [4].

(3) Mutations in acquired genes and coexisting mutations

New acquired gene mutations, which are developed following chemotherapy, may result in resistance to future treatments, such as immunotherapy. One case report was of a patient with initially driver gene-negative adenosquamous carcinoma who was treated with nivolumab because of high PD-L1 expression. Following the failure of treatment, genetic testing showed a newly acquired EGFR exon 21 p. L858R mutation. This observation indicates that EGFR L858R could be an acquired resistance mechanism to nivolumab; perhaps by the process of clonal enlargement of tumor cells with exon 21 L858R, which were not detectable prior to therapy, but became detectable after therapy with nivolumab. Nevertheless, this process still needs to be confirmed by simple experimental and clinical research [5]. The presence of coexisting gene mutations like TP53 which are common with EGFR mutations in cases could enhance genomic instability and encourage the emergence of resistant clones [6].

(4) Multidrug resistance-associated proteins are expressed

Amplification of multiple membrane transporter proteins is an archetypical example of chemotherapy resistance by increasing drug efflux and decreasing intracellular drug levels. The membrane transporter superfamily comprises of P-glycoprotein, multidrug resistance-associated protein, and lung resistance protein. MRP expression in untreated lung cancer is tissue specific: the rate of expression is greater in adenocarcinoma-based specimens (47%), and positively correlates with the degree of tumor differentiation, and lower in squamous cell carcinoma and small cell lung cancer [11]. But in a different study, high expression of MRP gene in NSCLC has been detected in squamous cell carcinoma and is strongly linked with a poor prognosis following

chemotherapy [12]. The expression of lung resistance protein in squamous cell carcinoma is associated with the opposite of the expected; high expression of LRP is negatively related to response to platinum-based chemotherapy, indicating that LRP-positive patients respond less. Co-expression phenomena (including P-gp which is mostly co-expressed with LRP) occur frequently in lung squamous cell carcinoma and have the potential to collectively enhance a greater drug-resistant phenotype [13].

(5) Metabolic enzymes and resistance to drug metabolism

The variation in intracellular enzyme levels of drug-metabolism has a direct effect on the efficacy of chemotherapy. Dihydropyrimidine dehydrogenase, the most important metabolic enzyme of 5-fluorouracil, is notably elevated in lung adenocarcinoma tissues, compared with squamous cell carcinoma, indicating that squamous cell carcinoma might be more susceptible to chemotherapy using 5-FU [14]. On the other hand, the gene thymidine kinase-1 is overexpressed in squamous cell carcinoma of the lung but under-expressed in lung adenocarcinoma, and its expression impacts the possible efficacy of the novel agent TAS-102 (which requires TK-1 phosphorylation) to predict that lung adenocarcinoma may be resistant to this agent [15].

(6) Major signaling pathway imbalances that are the major drivers of chemotherapy resistance

Chemotherapy resistance is directly connected with an aberrant activation of various intracellular signaling pathways. KEAP1/NRF2 pathway, which is an important controller of cellular responses to oxidative stress and metabolic pressure, often has mutations or expression abnormalities in NSCLC (higher nuclear NRF2 expression, loss of KEAP1 expression). One of the primary mechanisms of NRF2activation is the loss of KEAP1 function resulting in nuclear translocation and sustained activation of NRF2 [16]. Also, mutations in NFE2L2 (gene encoding NRF2) are another form of activation: mutations of exon 2 of the NFE2L2 gene encoding the binding site of the NRF2 protein with KEAP1 interfere with the negative regulation of NRF2 by KEAP1, allowing NRF2 to be activated [17]. NFRI expression at high nuclear levels of NRF2 activates cascade of cytoprotective genes, which enhances cancer cell survival and proliferation. This increased cellular immune response is believed to be a significant resistance to the platinum-based chemotherapy agents [16]. It is important to note that the mechanisms that do not depend on KEAP1 loss could also contribute to NRF2 nuclear localization. To illustrate, the subcellular localization of NRF2 could be under control of phosphorylation by different protein kinases (including protein kinase C, extracellular signal-regulated kinase, Jun N-terminal kinase, and phosphatidylinositol 3-kinase) and/or the ratio of nuclear export signal and nuclear localization signal motifs within the NRF2 protein itself, without the involvement of

The TAK1-LUBAC/IKK-NF-κB signaling axis has been highly activated in lung squamous cell carcinoma and this pathway provides resistance to cisplatin chemotherapy. Lung squamous carcinoma cells have elevated NF-0 B activity, reflected by low levels of the NF-κB inhibitor protein I (I) B, elevated phosphorylation of the NF-κB subunit p65 at Ser536 (P-p65), and nuclear localization of p65 compared with lung adenocarcinoma cells. At the same time, the target genes of NF-κB (TNF and CCL2) are more basally expressed in squamous carcinoma cells of the lungs [18]. Thus, blocking this pathway (e.g., with the help of LUBAC or TAK1 inhibitors) with standard chemotherapy can be regarded as one of the possible treatment options in relation to lung squamous cell carcinoma.

(7) Involvement of tumor microenvironment and immune regulation

Drug resistance is not only due to the presence of tumor cells but also the microenvironment. KEAP1 mutations in the KEAP1-NRF2 pathway are linked with resistance to chemotherapy, radiotherapy and targeted agents. Various reports all suggest that KEAP1-mutant lung adenocarcinomas generally have an immune-cold tumor microenvironment [17, 19]. The features of this microenvironment are a decrease in immune cell infiltration, loss of T cell activity, and increased immunosuppressive signaling. The Cancer Genome Atlas data analysis

indicates that KEAP1-mutant tumors display markedly different core immune characteristics, T cell receptor repertoire diversity, helper T cell related signaling and immunomodulatory gene expression all contributing to the establishment of a local environment that is not conducive to immune cell recognition and attack [19]. This immunosuppressive condition can be viewed as one of the primary causes of inadequate response to immunotherapy in this group of patients [17]. The linkage of KEAP1 with immune resistance is also contingent on concomitant genomic changes and this indicates the clinical relevance of KEAP1-NRF2 pathway disruption in lung cancer.

The effect of targeted therapy can also be suppressed by an immunosuppressive microenvironment (high PD-L1) in particular. The effects of PD-L1 expression on EGFR-TKI efficacy is still a controversial issue, with only a few studies being limited and even conflicting; some even indicate that high PD-L1 expression can delay cancer progression [7-10]. So, more studies should be conducted to clarify the communication network between EGFR and PD-1/PD-L1.

3. Discussion: Predictive Biomarkers and Therapeutic Strategies

The processes of drug resistance in lung cancer have multiple dimensions such as molecular changes, microenvironment, pathological subtypes, and cancer stem cells. Biomarker screening and novel therapeutic agents can be used to obtain a more precise intervention clinically.

(1) Histology-specific predictive biomarkers

It has been demonstrated that the efficacy of GP chemotherapy (gemcitabine plus cisplatin) is closely related to platelet activation status. In a retrospective study of 169 patients with advanced or metastatic NSCLC the overall resistance rate on GP regimens was found to be 72.19% [20]. Additional analysis found that particular platelet parameters were considered significant predictors of GP resistance: in adenocarcinoma patients, an increase in the mean platelet volume was a negative predictor of GP resistance (OR=5.811); in squamous cell carcinoma patients, an increase in plateletcrit was a negative predictor of GP resistance (OR=3.517). These results indicate that high indexes of platelet activation (MPV and PCT) can be an indicator of non-response to GP regimens. Moreover, MPV and PCT turned out to be independent prognostic variables of the overall survival in the patients with NSCLC, which once again confirmed the platelet activation status as a possible prognostic biomarker [20]. These works justify the use of personalized sensitivity tests on drugs or biomarkers prior to chemotherapy to maximize the choice of initial regimen and prevent initial resistance.

Platelet parameters (MPV) are important predictors of GP resistance in adenocarcinoma but CA125 is a better predictor of GP resistance in squamous cell carcinoma. This variation is likely to indicate inherent differences in tumor biology, microenvironmental interactions and response to chemotherapeutic agents among varied pathological forms of NSCLC. Adenocarcinoma can rely more on platelet-mediated processes (such as supplying growth factors or shielding tumor cells against chemotherapy assault) to obtain resistance, whereas the development and drug-resistance of squamous cell carcinoma may be more directly linked to the amount of tumor burden or tortuous pathways exemplified by CA125 [20]. Both MPV and CA125 show a high predictive ability of adenocarcinoma and squamous carcinoma respectively, and their combinations could be used to build more effective predictive models to drive the process of clinical decision-making more precisely.

(2) Large-panel genetic-testing guiding value

Large-scale genetic testing is of great importance to identify acquired resistance mutations (including acquired EGFR mutations) and co-mutations (including EGFR with TP53) [5, 6]. It can be used to determine the direction that should be taken in subsequent treatment by utilizing the molecular profile of tumor,

especially more specific direction on how to take advantage of new agents, e.g., bispecific antibodies. In EGFR-mutant pulmonary adenosquamous carcinoma patients who have undergone several lines of treatment and subsequently developed progression, Ivonescimab, which is a bispecific antibody, has shown good results in efficacy and safety [6]. Ivonescimab is a first-in-class bispecific antibody (programmed cell death protein-1 / vascular endothelial growth factor A) that competitively interacts with PD-1 to its ligand PD-L1 to reverse PD-1/ PD-L1-mediated immunosuppression, and that also competitively interacts with VEGF-A with VEGFR2 to suppress It overcomes immune evasion and tumor vascularization by integrating both immune checkpoint blockade and anti-angiogenic effects. In the tumor microenvironment, its association with VEGF-A dimers increases affinity to PD-1, more specifically reversing immunosuppression and normalizing vases, and acting synergistically as an anti-tumor with a higher specificity. There is also an IV-based inhibitor, Ivonescimab, which minimizes the overlapping toxicity of two-drug regimens, eliminating the pharmacokinetic incompatibility and cumulative toxicity problems of conventional combinations of immunotherapy and anti-angiogenic agents. Even though Ivonescimab shows great therapeutic effects with excellent safety profiles, additional studies on its sustainability and long-term survival advantages are justified [6].

(3) Diagnosis and treatment of histological transformation

It is important to monitor the development of features of histological transformations and react to them at the earliest stage to modify the treatment plan. The histological transformation causes could be the presence of adenosquamous carcinoma elements, or squamous transformation due to therapy. Loss of liver kinase B1 or phosphatase and tensin homolog deletion are linked with adenosquamous carcinoma development in KRAS-mutant adenocarcinoma mouse models [21]. There are known genetic events (like LKB1 deletion) that have been proved to be linked to squamous transformation and the LKB1-deficient tumors exhibit higher rates of squamous transformation [22, 23]. It is interesting to note that LKB1 is inactivated in all human tumors that co-express TTF-1 and p63 [24]. But the mechanism of formation of adenosquamous carcinoma and the specific molecular processes of histological transformation is controversial, and further study at several different levels such as genetics, signal pathways, and CSC markers is needed to clarify the mechanism of transformation, which would lead to more effective interventions in reducing resistance due to histological transformation.

(4) Therapeutic interventions that address CSCs and proteins related to drug resistance

Various proteins and metabolic enzymes linked to drug resistance are tissue specific, and can direct optimal drug choices. As an illustration, more specific treatment regimens can be developed based on phenomena of protein co-expression (e.g., P-gp mostly co-expressed with LRP in lung squamous carcinoma) and the higher expression rate of MRP in adenocarcinoma (47%) with positive correlation to the extent of tumor differentiation [11]. The TK-1 (high in squamous carcinoma vs. low in adenocarcinoma of the lung) difference in expression can predict the possible difference in efficacy of the new agent TAS-102, the active form of which is determined by the phosphorylation of TK-1 [15].

New therapeutic methods which are dependent on CSC biomarkers have good promise, with most of them employing a mix of many biomarkers to detect and isolate CSCs in tumor tissues [12]. Inhibitors, monoclonal antibodies, bispecific antibodies, antibody-drug conjugates or aptamer-drug conjugates and CAR-T therapies are all treatment strategies that target these markers. As an illustration, one of the major contributors of multidrug resistance is the cell membrane transporter protein, ABCG2. Multidrug resistance can be reversed by using a tyrosine kinase inhibitor drug called Axitinib that can inhibit the activity of the ABCG2 transporter in CSCs. Topoisomerase I inhibitor FL118 has been identified to silence the expression of ABCG2, ALDH1A1, and Oct-4, thus enhancing sensitization of chemotherapy, and blocking CSC growth; FL118 is also active against irinotecan-, topotecan-, and cisplatin-resistant tumors which have developed resistance to ABC transporter activity [12].

4. Conclusion and Future Perspectives

The multiple factors and layers that influence chemotherapy resistance in pulmonary adenosquamous carcinoma are multi-layered complex biological processes. The mechanisms include classical drug efflux pump overexpression (MRP, LRP), the expression of drug-metabolizing enzymes (DPD, TK-1), acquired gene mutations (EGFR L858R), abnormalities of key signaling pathways (KEAP1/NRF2, NF-κB), tumor cell plasticity (CSCs, histological transformation), and tumor microenvironment rem These mechanisms show considerable variations between histological components (adenocarcinoma and squamous carcinoma) as well as they overlap with one another, forming significant obstacles to clinical management.

Future research directions are to: 1) dynamic follow-up of trends of resistance evolution by using multi-omics analysis and repeat biopsies before and after therapy; 2) develop histology-specific predictive biomarkers (including platelet parameters, CA125) to select personalized With the use of multidimensional and multi-level, comprehensive interventions, it is hoped that the clinical outcomes of patients with pulmonary adenosquamous carcinoma can eventually be improved.

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