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Drug Resistance in Human Lung Adenocarcinoma (A549 Cell Line): A Comprehensive Review

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ABSTRACT

Drug resistance is one of the most critical challenges in the treatment of lung cancer, particularly non-small cell lung cancer (NSCLC). The A549 human lung adenocarcinoma cell line serves as a well-established in vitro model for investigating the molecular and cellular mechanisms underlying chemoresistance. This expanded review provides an in-depth and comprehensive analysis of drug resistance mechanisms in A549 cells, including drug efflux systems, the tumour microenvironment, hypoxia, apoptosis evasion, genetic and epigenetic modifications, signalling pathways, metabolic reprogramming, cancer stem cell dynamics, autophagy, and epithelial–mesenchymal transition (EMT). Furthermore, emerging therapeutic strategies such as nanotechnology, targeted therapy, immunotherapy, and combination regimens are discussed. The review integrates classical and recent literature to provide a detailed understanding suitable for advanced academic and research purposes.

Keywords: Lung Adenocarcinoma**,** A549 cell line, Drug resistance, Multidrug resistance (MDR), Tumour Microenvironment, Targeted therapy.

1. INTRODUCTION

Lung cancer continues to be the leading cause of cancer-related mortality globally, accounting for approximately 1.8 million deaths annually. Among all lung cancer subtypes, non-small cell lung cancer (NSCLC) represents nearly 85% of cases. Despite major advancements in early detection, targeted therapy, and immunotherapy, the overall survival rate remains low due to late diagnosis and the emergence of drug resistance.

The A549 cell line, derived from human alveolar basal epithelial cells of lung adenocarcinoma, has been extensively used as an experimental model to study tumour biology, drug response, and resistance mechanisms. These cells exhibit epithelial morphology and possess mutations and signalling characteristics representative of NSCLC, making them highly relevant for in vitro investigations.

Drug resistance in cancer can be broadly categorised into intrinsic resistance, which exists before treatment, and acquired resistance, which develops after exposure to therapeutic agents. The mechanisms underlying resistance are complex and involve multiple interconnected pathways, including drug transport, metabolism, DNA repair, apoptosis regulation, and microenvironmental influences.

2. OVERVIEW OF DRUG RESISTANCE MECHANISMS

Drug resistance in A549 cells is not a singular event but a highly dynamic and adaptive biological phenomenon that evolves through continuous interaction between tumour cells and therapeutic stress. At the cellular level, resistance emerges from a combination of genetic instability, selective pressure imposed by chemotherapeutic agents, and activation of survival pathways. These processes collectively enable cancer

cells to evade cytotoxic effects and maintain proliferative capacity even in the presence of high drug concentrations.

One of the primary mechanisms involves decreased intracellular drug accumulation, which occurs either through reduced drug uptake or enhanced efflux. This is often accompanied by alterations in membrane transport proteins and changes in lipid composition of the plasma membrane, which influence drug permeability. In parallel, cancer cells frequently exhibit increased expression of detoxifying enzymes such as glutathione S-transferases, which neutralise reactive drug intermediates.

Another critical factor is enhanced DNA repair capability. Chemotherapeutic agents such as cisplatin induce DNA damage; however, A549 cells can activate nucleotide excision repair and homologous recombination pathways to repair this damage efficiently. This reduces drug-induced cytotoxicity and contributes to survival. Furthermore, dysregulation of apoptosis allows cells to evade programmed cell death, even when significant cellular damage has occurred.

Table 1: Major Mechanisms of Drug Resistance in A549 Cells

Mechanism	Key Features	Molecular Components	Impact on Therapy
Drug Efflux	Active drug export	ABCB1, ABCG2, MRP1	Decreased intracellular drug concentration
Apoptosis Evasion	Inhibition of cell death	Bcl-2, Bax, Caspases	Reduced chemotherapy-induced cytotoxicity
Hypoxia	Low oxygen environment	HIF-1α, VEGF	Increased survival and resistance
Genetic/Epigenetic Changes	Gene regulation alterations	lncRNA, miRNA, DNA methylation	Altered drug sensitivity
EMT	Phenotypic transition	E-cadherin, N-cadherin	Increased invasion and resistance
Autophagy	Cellular recycling	LC3, Beclin-1, mTOR	Survival under stress
Cancer Stem Cells	Self-renewal	SOX2, OCT4, CD133	Tumour recurrence and resistance

Recent integrative studies suggest that these mechanisms are interconnected through signalling networks such as PI3K/AKT and NF-κB, forming a robust resistance phenotype that is difficult to reverse (Da Silva et al., 2026).

3. DRUG EFFLUX TRANSPORTERS AND MULTIDRUG RESISTANCE

ATP-binding cassette (ABC) transporters represent one of the most extensively studied mechanisms of multidrug resistance in A549 cells. These transmembrane proteins utilise ATP hydrolysis to actively transport

a wide range of substrates, including chemotherapeutic agents, out of cancer cells. This reduces intracellular drug concentration below therapeutic thresholds, thereby diminishing efficacy.

Among the ABC transporter family, P-glycoprotein (ABCB1), multidrug resistance-associated protein 1 (MRP1/ABCC1), and breast cancer resistance protein (ABCG2) are particularly relevant. Their overexpression has been consistently associated with resistance to drugs such as cisplatin, doxorubicin, and paclitaxel. Mechanistically, these transporters exhibit broad substrate specificity, allowing cancer cells to develop cross-resistance to structurally unrelated drugs.

At the molecular level, the regulation of ABC transporters is complex and involves transcription factors such as NF-κB and HIF-1α, epigenetic modifications, and post-transcriptional control by microRNAs and long non-coding RNAs. For example, hypoxic conditions can induce ABCG2 expression through HIF-1α activation, linking microenvironmental stress to efflux-mediated resistance.

Recent studies have expanded our understanding by demonstrating that transporter expression is not static but dynamically regulated in response to drug exposure. Adaptive upregulation of ABCC5 and ABCG2 in A549 cells has been reported following repeated chemotherapy cycles, highlighting the importance of treatment-induced selection pressure (Pan et al., 2024; Yücer et al., 2025).

Therapeutically, efforts to inhibit ABC transporters have shown mixed success. While first-generation inhibitors lacked specificity and caused toxicity, newer strategies focus on indirect modulation through signalling pathway inhibition and nanocarrier-based drug delivery systems (Pandey et al., 2025).

4. TUMOR MICROENVIRONMENT AND HYPOXIA

The tumour microenvironment (TME) plays a critical role in shaping drug response and resistance in A549 cells. It consists of a complex network of stromal cells, immune cells, extracellular matrix components, and soluble factors that collectively influence tumour behaviour. Among these factors, hypoxia is one of the most significant contributors to chemoresistance.

Hypoxia arises due to inadequate vascularisation within rapidly growing tumours, leading to reduced oxygen availability. Under these conditions, hypoxia-inducible factor-1α (HIF-1α) becomes stabilised and translocates to the nucleus, where it regulates the expression of genes involved in angiogenesis, metabolism, and survival. In A549 cells, HIF-1α activation has been shown to increase glycolytic flux, reduce mitochondrial respiration, and promote resistance to apoptosis.

Moreover, hypoxia induces the expression of drug efflux transporters such as ABCG2, thereby linking microenvironmental stress to molecular resistance mechanisms. It also enhances the maintenance of cancer stem cell-like properties, which are inherently resistant to chemotherapy.

Environmental stressors such as cigarette smoke further exacerbate resistance by inducing oxidative stress and activating detoxification pathways. Recent studies have shown that exposure to cigarette smoke leads to increased ABCG2 expression and reduced protein aggregation, enabling A549 cells to survive toxic insults (Ajenu et al., 2024).

In addition to hypoxia, the extracellular matrix (ECM) contributes to resistance by acting as a physical barrier to drug penetration and by activating integrin-mediated signalling pathways that promote survival. Collectively, these factors create a protective niche that shields cancer cells from therapeutic agents.

5. APOPTOSIS EVASION

Apoptosis, or programmed cell death, is a fundamental mechanism through which chemotherapeutic agents exert their cytotoxic effects. However, A549 cells often acquire resistance by disrupting apoptotic signalling pathways, thereby allowing survival despite extensive cellular damage.

The intrinsic (mitochondrial) pathway of apoptosis is tightly regulated by the Bcl-2 family of proteins, which includes both pro-apoptotic (Bax, Bak) and anti-apoptotic (Bcl-2, Bcl-xL) members. In resistant A549 cells, there is often an imbalance favouring anti-apoptotic proteins, leading to inhibition of mitochondrial outer membrane permeabilisation and prevention of cytochrome c release.

Additionally, caspases, which are the executioners of apoptosis, are frequently inactivated or downregulated. This further impairs the ability of chemotherapeutic agents to induce cell death. The extrinsic pathway, mediated by death receptors such as Fas and TRAIL receptors, may also be suppressed through reduced receptor expression or downstream signalling defects.

Another important factor is the role of survival signalling pathways such as PI3K/AKT and NF-κB, which promote the transcription of anti-apoptotic genes and inhibit pro-apoptotic factors. Crosstalk between these pathways and apoptotic machinery creates a robust survival network that is difficult to disrupt.

Targeting apoptosis resistance remains a key therapeutic strategy, with approaches focusing on BH3 mimetics, caspase activation, and inhibition of survival pathways.

6. GENETIC AND EPIGENETIC ALTERATIONS

Genetic and epigenetic alterations are central to the development and maintenance of drug resistance in A549 cells. Genetic mutations may affect oncogenes, tumour suppressor genes, and genes encoding drug targets, leading to reduced drug sensitivity. For example, mutations that alter drug-binding sites can render chemotherapeutic agents ineffective.

Epigenetic modifications, including DNA methylation, histone modification, and chromatin remodelling, regulate gene expression without altering the DNA sequence. These changes can silence tumour suppressor genes or activate resistance-associated genes. Importantly, epigenetic alterations are reversible, making them attractive therapeutic targets.

Recent research has highlighted the role of non-coding RNAs, particularly long non-coding RNAs (lncRNAs) and microRNAs, in regulating drug resistance. These molecules modulate gene expression at the transcriptional and post-transcriptional levels, influencing pathways such as drug transport, apoptosis, and metabolism (Li et al., 2024).

For instance, certain lncRNAs have been shown to upregulate ABC transporters or activate PI3K/AKT signalling, thereby promoting resistance. Conversely, tumour-suppressive microRNAs may be downregulated, leading to unchecked expression of resistance-related genes.

7. SIGNALING PATHWAYS IN DRUG RESISTANCE

Cell signalling pathways play a pivotal role in coordinating the cellular response to chemotherapeutic stress. In A549 cells, several key pathways are consistently implicated in drug resistance, including PI3K/AKT, MAPK/ERK, and NF-κB.

The PI3K/AKT pathway is one of the most critical survival pathways in cancer. Activation of PI3K leads to phosphorylation and activation of AKT, which promotes cell survival by inhibiting apoptotic processes and

enhancing protein synthesis. In resistant A549 cells, this pathway is often constitutively active, contributing to reduced sensitivity to chemotherapy.

The MAPK/ERK pathway regulates cell proliferation and differentiation. Aberrant activation of this pathway can lead to uncontrolled growth and resistance to anti-proliferative drugs. Similarly, NF-κB is a transcription factor that regulates genes involved in inflammation, survival, and immunity. Its activation promotes the expression of anti-apoptotic proteins and drug efflux transporters.

Table 2: Key Signalling Pathways Involved in Drug Resistance

Pathway	Function	Role in Resistance	Targeted Therapy
PI3K/AKT	Cell survival	Inhibits apoptosis	AKT inhibitors
MAPK/ERK	Cell proliferation	Promotes growth	MEK inhibitors
NF-κB	Inflammation & survival	Upregulates anti-apoptotic genes	NF-κB inhibitors
HIF-1α	Hypoxia response	Induces resistance genes	HIF inhibitors
Wnt/β-catenin	Stem cell regulation	Maintains CSCs	Wnt inhibitors

Importantly, these pathways do not function in isolation. Extensive crosstalk exists between them, creating a complex signalling network that enhances cellular adaptability. Recent studies emphasise that resistance is driven by integrated processes involving multiple pathways rather than a single dominant mechanism (da Silva et al., 2026).

8. AUTOPHAGY AND DRUG RESISTANCE

Autophagy is a highly conserved intracellular degradation process that enables cells to recycle damaged organelles and macromolecules under stress conditions. In the context of cancer, autophagy plays a dual role, acting either as a tumour suppressor in early stages or as a survival mechanism in established tumours. In A549 lung adenocarcinoma cells, autophagy is predominantly associated with chemoresistance, particularly under conditions of nutrient deprivation, hypoxia, and exposure to cytotoxic drugs.

Mechanistically, autophagy involves the formation of double-membrane vesicles known as autophagosomes, which engulf cellular components and subsequently fuse with lysosomes for degradation. Key regulatory proteins include Beclin-1, LC3, ATG family proteins, and mTOR. In resistant A549 cells, activation of autophagy is often mediated through inhibition of the mTOR pathway, which normally acts as a negative regulator of autophagy.

Chemotherapeutic agents such as cisplatin and paclitaxel have been shown to induce autophagy in A549 cells as a protective response. This allows cancer cells to survive drug-induced stress by maintaining cellular homeostasis and preventing apoptosis. Furthermore, crosstalk between autophagy and apoptosis pathways adds a layer of complexity. For instance, Beclin-1 interacts with Bcl-2 family proteins, linking autophagic regulation to apoptotic signalling.

Recent studies suggest that inhibition of autophagy using pharmacological agents such as chloroquine can sensitise A549 cells to chemotherapy, highlighting its potential as a therapeutic target. However, the context-dependent nature of autophagy necessitates careful evaluation when designing treatment strategies.

9. EPITHELIAL–MESENCHYMAL TRANSITION (EMT)

Epithelial–mesenchymal transition (EMT) is a biological process in which epithelial cells lose their polarity and cell–cell adhesion properties and acquire mesenchymal characteristics, including enhanced motility and invasiveness. EMT is a critical contributor to cancer progression, metastasis, and drug resistance in A549 cells.

During EMT, there is downregulation of epithelial markers such as E-cadherin and upregulation of mesenchymal markers, including N-cadherin, vimentin, and fibronectin. This phenotypic shift is regulated by transcription factors such as Snail, Slug, Twist, and ZEB1/2, which repress epithelial gene expression and activate mesenchymal programs.

In A549 cells, EMT is often induced by external stimuli such as transforming growth factor-beta (TGF-β), hypoxia, and inflammatory cytokines. Activation of EMT not only enhances migratory and invasive capabilities but also confers resistance to chemotherapy and targeted therapies. This is partly due to increased expression of drug efflux transporters and activation of survival pathways such as PI3K/AKT and NF-κB.

10. CANCER STEM CELLS

Cancer stem cells (CSCs) represent a small but highly significant subpopulation of tumour cells characterised by their ability to self-renew, differentiate, and initiate tumour formation. In A549 lung cancer cells, CSCs are strongly implicated in drug resistance, metastasis, and disease relapse.

CSCs exhibit several defining features that contribute to their resistance phenotype. These include high expression of drug efflux transporters, enhanced DNA repair mechanisms, resistance to apoptosis, and the ability to remain in a quiescent state. Markers commonly associated with CSCs in A549 cells include SOX2, OCT4, Nanog, and CD133.

The tumour microenvironment plays a crucial role in maintaining CSC populations by providing a supportive niche through hypoxia, cytokines, and extracellular matrix interactions. Hypoxia, in particular, promotes stemness through HIF-1α-mediated signalling.

Importantly, CSCs are not static but can arise from non-stem cancer cells through processes such as EMT, highlighting the plasticity of tumour cell populations. This dynamic interconversion complicates therapeutic targeting.

Recent research focuses on targeting CSC-specific pathways, such as Wnt/β-catenin, Notch, and Hedgehog signalling, to eliminate this resistant population and improve treatment outcomes.

11. METABOLIC REPROGRAMMING

Metabolic reprogramming is a hallmark of cancer that enables tumour cells to meet the increased energy and biosynthetic demands of rapid proliferation. In A549 cells, metabolic alterations play a crucial role in drug resistance.

One of the most well-known metabolic changes is the Warburg effect, where cancer cells preferentially utilise glycolysis for energy production even in the presence of oxygen. This results in increased glucose uptake and lactate production, which can acidify the tumour microenvironment and reduce drug efficacy.

In addition to glycolysis, mitochondrial function is also altered in resistant cells. Changes in mitochondrial dynamics, including fission and fusion processes, can influence apoptosis and energy production. Furthermore, increased antioxidant capacity, mediated by glutathione and related enzymes, helps neutralise reactive oxygen species generated by chemotherapy.

Metabolic flexibility allows A549 cells to switch between different energy sources, such as glucose, glutamine, and fatty acids, depending on environmental conditions. This adaptability enhances survival under therapeutic stress.

Targeting metabolic pathways is an emerging strategy for overcoming drug resistance, with approaches focusing on glycolysis inhibitors, mitochondrial disruptors, and redox modulators.

12. THERAPEUTIC STRATEGIES TO OVERCOME DRUG RESISTANCE

i.Nanotechnology-Based Therapies

Nanotechnology has emerged as a promising approach to overcome drug resistance by improving drug delivery, enhancing targeting, and reducing systemic toxicity. In A549 cells, nanoparticle-based systems have demonstrated significant potential in reversing chemoresistance.

Nanocarriers such as liposomes, polymeric nanoparticles, dendrimers, and metallic nanoparticles can encapsulate chemotherapeutic agents and deliver them directly to tumour cells. This targeted delivery increases intracellular drug concentration and reduces the impact of efflux transporters.

Advanced systems, including membrane-fusion nanoparticles, have been shown to bypass traditional uptake mechanisms and directly deliver drugs into the cytoplasm. These systems can also be functionalized with ligands that target specific receptors on cancer cells, further enhancing specificity.

In addition to drug delivery, nanoparticles can be used for combination therapy by co-delivering multiple agents, such as chemotherapeutics and gene-silencing molecules. This allows simultaneous targeting of multiple resistance mechanisms.

Despite promising preclinical results, challenges remain in translating nanotechnology-based therapies to clinical practice, including issues related to biocompatibility, stability, and large-scale production.

ii.Combination Therapy

Combination therapy is widely regarded as one of the most effective strategies for overcoming drug resistance in cancer. By targeting multiple pathways simultaneously, combination regimens reduce the likelihood of resistance development and improve therapeutic efficacy.

In A549 cells, combination approaches often involve the use of chemotherapeutic agents alongside targeted therapies, such as tyrosine kinase inhibitors or pathway-specific inhibitors. For example, combining cisplatin with PI3K/AKT inhibitors has been shown to enhance apoptosis and reduce resistance.

Another approach involves combining chemotherapy with inhibitors of drug efflux transporters, thereby increasing intracellular drug accumulation. Additionally, combining autophagy inhibitors with chemotherapy can prevent cancer cells from using autophagy as a survival mechanism.

Recent strategies also explore the integration of nanotechnology and combination therapy, enabling co-delivery of multiple agents in a single platform. These approaches offer a promising avenue for overcoming complex resistance mechanisms.

iii.Immunotherapy and Resistance

Immunotherapy, particularly immune checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4 pathways, has revolutionised the treatment of lung cancer. However, resistance to immunotherapy has emerged as a significant challenge.

In A549 cells, resistance to immunotherapy can arise from several mechanisms, including reduced antigen presentation, upregulation of immune checkpoint molecules, and an immunosuppressive tumour microenvironment. Tumour cells may also secrete cytokines that inhibit immune cell activity.

Additionally, genetic and epigenetic alterations can affect the expression of immune-related genes, further contributing to resistance. The interaction between tumour cells and immune cells is highly dynamic, and changes in this interaction can significantly impact therapeutic outcomes.

Strategies to overcome immunotherapy resistance include combination therapy with chemotherapy, targeted therapy, or radiotherapy, as well as the development of novel immune-modulating agents.

Table 3: Therapeutic Strategies to Overcome Drug Resistance

Strategy	Mechanism	Example	Outcome
Combination Therapy	Targets multiple pathways	Cisplatin + AKT inhibitor	Enhanced apoptosis
Nanotechnology	Targeted drug delivery	Liposomes, nanoparticles	Increased drug uptake
Efflux Inhibition	Blocks ABC transporters	Verapamil	Improved drug retention
Autophagy Inhibition	Blocks survival mechanism	Chloroquine	Increased sensitivity
Immunotherapy	Activates the immune system	PD-1 inhibitors	Improved response

Overcoming drug resistance in A549 lung adenocarcinoma cells requires integrated therapeutic strategies targeting multiple mechanisms. Combination therapy enhances treatment efficacy by simultaneously inhibiting key survival pathways and promoting apoptosis.

Nanotechnology-based delivery systems improve drug targeting and intracellular accumulation, thereby increasing therapeutic effectiveness. Inhibition of efflux transporters enhances drug retention within cancer cells, while autophagy inhibition sensitises cells to chemotherapy by blocking survival mechanisms. Additionally, immunotherapy, particularly PD-1 inhibitors, activates the immune system to eliminate resistant tumour cells. Together, these approaches highlight the importance of multimodal and personalised strategies in improving treatment outcomes and combating chemoresistance in lung cancer.

13. FUTURE PERSPECTIVES

Future research on drug resistance in A549 cells should focus on a multidisciplinary approach that integrates molecular biology, bioinformatics, and clinical research. Advances in high-throughput technologies such as genomics, transcriptomics, and proteomics are providing new insights into the complex mechanisms of resistance.

Personalised medicine, which tailors treatment based on individual patient characteristics and tumour profiles, holds great promise for improving outcomes. Identification of predictive biomarkers will be essential for selecting appropriate therapies and monitoring treatment response.

Artificial intelligence and machine learning are also emerging as powerful tools for analysing large datasets and predicting drug responses. These technologies can help identify novel therapeutic targets and optimise treatment strategies.

Furthermore, the development of advanced drug delivery systems, including multifunctional nanoparticles and smart drug carriers, is expected to enhance the effectiveness of cancer therapy.

14. CONCLUSION

Drug resistance in A549 lung adenocarcinoma cells represents a complex and multifactorial challenge involving a wide range of molecular, cellular, and environmental factors. Mechanisms such as drug efflux, apoptosis evasion, genetic and epigenetic alterations, signalling pathway activation, autophagy, EMT, cancer stem cell dynamics, and metabolic reprogramming collectively contribute to the resistant phenotype.

Despite significant advances in understanding these mechanisms, overcoming drug resistance remains a major obstacle in lung cancer treatment. Emerging strategies, including nanotechnology-based drug delivery, combination therapy, and immunotherapy, offer promising avenues for improving therapeutic outcomes.

A comprehensive understanding of resistance mechanisms, combined with innovative therapeutic approaches and personalised medicine, will be essential for addressing this challenge and improving patient survival.

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