Genomic and Proteomic Insights into ABC Transporter-Mediated Drug Resistance in Cancer

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Abstract: ATP-binding cassette (ABC) transporters play a key role in the development of multidrug resistance (MDR) in cancer, as they actively pump chemotherapeutic agents out of tumor cells, thereby limiting drug accumulation and efficacy Of the 48 known human ABC transporters, members such as P-glycoprotein (ABCB1), MRP1 (ABCC1) and BCRP (ABCG2) are indeed implicated in clinical drug resistance across a variety of malignancies. In this review, we will examine the most recent genomic and proteomic studies on the regulation, expression, and function of ABC transporters in cancer. Genomic studies have identified mutations, polymorphisms, and epigenetic factors that affect transporter activity and expression, thereby contributing to variability in drug response among individuals. Proteomic studies have provided detailed identification of post-translational modifications and protein–protein interactions that can affect transporter stability and trafficking. In addition, multi-omics studies have provided new insights into regulators of ABC transporters and novel therapeutic targets to reverse MDR. A thorough understanding of the molecular complexities of each ABC transporter family member is crucial for establishing predictive biomarkers and developing strategies to overcome drug resistance. This synthesis of genomic and proteomic data supports the need to consider how the variability of different ABC transporters contributes to each individual's resistance, which in turn highlights the need for personalized approaches in cancer therapy to optimize the effects while overcoming the specific mechanisms linked to ABC transporter-mediated drug resistance.

Keywords: Genomic, Proteomic, ABC Transporters, Drug Resistance, Cancer, Multidrug Resistance (MDR), Therapeutic Targets.

1. INTRODUCTION

1.1. ABC Transporters and Drug Resistance

ATP-binding cassette (ABC) transporters are one of the largest families of membrane proteins, capable of hydrolyzing ATP to transport substrates across membranes. ABC transporters have essential physiological roles, including lipid transport, antigen processing, and the clearance of toxins from cells. Their drug efflux capabilities are particularly relevant in cancer, as they play a crucial role in the multidrug resistance (MDR) phenotype observed in cancers [1]. The 48 human ABC transporter genes, some have been widely linked to drug resistance, notably P-glycoprotein (ABCB1), multidrug resistance-associated protein 1 (MRP1/ABCC1), and breast cancer resistance protein (BCRP/ABCG2). These proteins can transport a variety of anticancer drugs with diverse structures, such as doxorubicin, paclitaxel, vincristine, and topotecan. By pumping drugs out of cells, the overall level of drug within the cell is decreased, thereby increasing the level of treatment failure and cancer recurrence [2,3]. There have been several studies demonstrating that their overexpression is common is solid tumors and hematological malignancies (i.e. leukemia). All of these drug transporters contribute to the clinical difficulty in treatment and the likelihood for treatment failure [4].

1.2. Overview of Drug Resistance in Cancer

Drug resistance is a major hurdle in cancer treatment and limits the long-term success of both traditional chemotherapy and targeted therapies. Resistance can be intrinsic (pre-existing in tumor cells)

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or acquired during treatment [5]. Mechanisms of resistance can include enhanced DNA repair, cell survival by escape from apoptosis, alteration in drug metabolism, the epithelial-mesenchymal transition (EMT), and in particular, enhanced drug efflux from drug-sequestering ABC transport proteins [6]. ABC transporters are integral to intrinsic and acquired resistance, frequently occurring as a consequence of long-term drug exposure. The expression of transporters can be altered in response to changes in signaling and altered expression of transcription factors (e.g., NF-κB, p53) and microRNAs (miRNAs) that integrate environmental signals and cellular stress responses [7,8]. Therefore, inhibition of ABC transporters or its upstream regulators is a clear pharmacological opportunity for overcoming drug resistance and effectively sensitizing resistant tumors to therapy.

This (Figure **1a**) depicts how structural changes to a cellular target can lead to drug resistance. On the left, a drug (blue) binds to the target site in a drug-sensitive state, allowing the drug to exert its therapeutic effect. As depicted on the right, either mutation or conformational change of the target induces a loss of binding affinity as the drug cannot fit the changed or mutated target site. This profoundly impacts the ability for drugs to exert their effect, serving as a common mechanism for how cells develop resistance to targeted therapies.

1.3. The Value of Studying Genomics and Proteomics for Drug Resistance Research

Recent developments and breakthroughs in genomic and proteomic technologies have expanded and deepened our understanding of the underlying molecular mechanisms for ABC transporter-mediated drug resistance. Genomics studies and techniques, such as whole-exome sequencing and genome-wide association studies (GWAS), have provided insight into single nucleotide polymorphisms (SNPs), gene amplifications, and mutations in the genes of ABC transporters, all of which can have an effect on drug response [9,10] and transporter functionality. There have been associations made between polymorphisms in ABCB1 (for example, C3435T) and altered expression levels of ABCB1, which have shown differential outcomes in patients receiving both taxanes and anthracyclines [11,12].

The illustrated architecture diagram (Figure **1b**) depicts the combined multi-omics workflow used to study ABC transporter mediated drug resistance in cancer. The schematic description of the workflow begins with obtaining samples from cancer biopsies to obtain the biological source for downstream studies and analysis. DNA sequencing was performed to obtain the mutations, copy number variations and gene expression of the ABC transporter gene(s) involved. Meanwhile, we performed proteomic profiling using mass spectrometry, to quantify protein expression and post-translational modification. The data from both omics' layers are integrated as a unified dataset for ultimate interpretation. Evidence of clinical resistance markers will come from this integration, which will begin bioinformatics analysis with computation and artificial intelligence techniques to decipher relationships and correlations with genomic alterations and proteomic responses. We intend to define such resistance markers - molecular markers that contribute to drug efflux and failure of therapeutic response, for possible targets to overcome resistance. This combined multi-omics workflow will provide a systems-level description of drug resistance mechanisms, bridging molecular biology with the clinic [13,14].

In a complementary manner, proteomic profiling has made it possible for researchers to characterize transporter expression at the protein level, and post

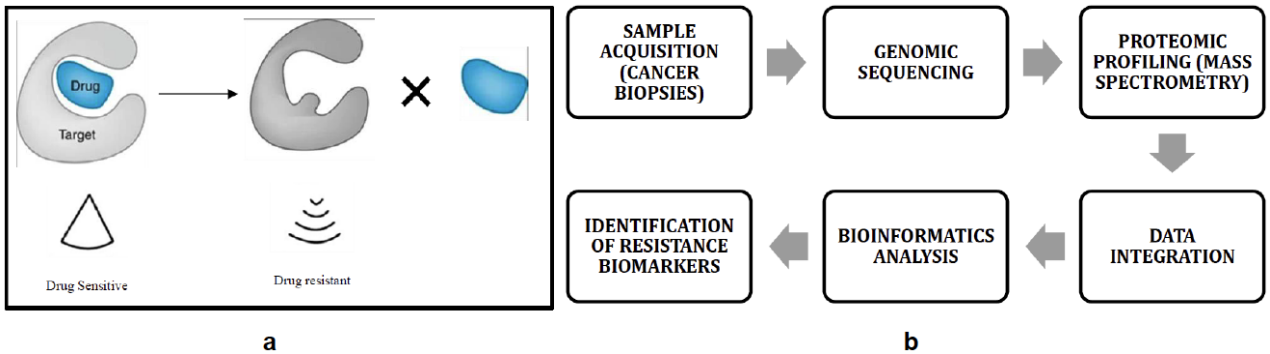

Figure 1: a: Mechanism of Drug Resistance through Target Mutation. **b:** Integrated Genomic and Proteomic Workflow for Drug Resistance Analysis.

translational modifications (by differential phosphorylation and ubiquitination) that could effect stability and localization of transporters [15]. In turn, proteomics can also provide direction in identifying protein–protein interactions that control ABC transporter function which could be important for either modulating this functionality or drug development. Finally, researchers can draw upon multiple-tailored approaches that might contain transcriptomic, proteomic, and metabolomic studies that allow for a more integrated systems-level understanding of the resistance mechanism itself. Together these approaches can lead to biomarker development that identifies early onset of drug resistance and personalized therapy [16]. Ultimately, studies into the genomics and proteomics of ABC transporters are ultimately important for not only a proper understanding of MDR, but also for devising next-generation inhibitors, combination therapies, and predictive models of drug responsiveness. Resistance continues to threaten cancer therapies, and therefore, any potential molecular clues will provide us with more hope in circumventing resistance and providing patients with more favorable outcomes.

This review paper is divided into six main sections. After the introduction, Section II provides an in-depth overview of ATP-binding cassette (ABC) transporters and their mechanisms and implications for mediating resistance in cancer. Section III investigates the genomic context of ABC transporters, with emphasis on mutations and variants contributing to resistance mechanisms. Section IV discusses proteomic considerations, including insights regarding expression levels of proteins, functional activity evaluations, and analyses of transporter proteins. The clinical significance of the genomic and proteomic evidence and the implication of upcoming strategies to overcome drug resistance and the importance of personalized medicine is covered in Section V. Review paper conclusions and directions for future research aimed improving future outcomes for cancer treatment is discussed in Section VI. Overall, this organization facilitates a discussion of how multi-omic insights obtained from ABC transporters will inform and transform therapeutic approaches to combat drug resistance.

2. ABC TRANSPORTERS IN DRUG RESISTANCE

2.1. ABC Transporters and Their Structure: Overview

ATP-binding cassette (ABC) transporters are a family of transmembrane proteins that are fundamental in the efflux of a broad range of endogenous and exogenous substrates (e.g., anticancer agents). ABC transporters are characterized structurally by two conserved nucleotide-binding domains (NBDs) that hydrolyze ATP and two transmembrane domains (TMDs) that forms the substrate translocation pathway [17]. In the human genome, ABC transporters have 48 genes and can be organized into seven subfamilies (ABCA–ABCG), based on sequence homology and organization of the domain [18]. Clinically relevant members include ABCB1 (P-glycoprotein), ABCC1 (MRP1), and ABCG2 (BCRP). These transporters are expressed at a number of physiological barriers including intestinal epithelium, blood–brain barrier, and placenta, which serves as a protective mechanism against xenobiotics [19]. However, in cancer, overexpression of these transporters worsens therapeutic efficacy, through decreasing intracellular concentrations of high energy substrates [20]. The structural biology of ABC transporters highlights their substrate specificity and is useful in the rational drug design of inhibitors [21].

2.2. Ways that ABC Transporters Mediate Drug Resistance

ABC transporters chiefly mediate multidrug resistance (MDR) by promoting ATP-dependent drug efflux. Within cancer cells, ABC transporters diminish the intracellular levels of numerous structurally dissimilar anticancer drugs, for example anthracyclines, taxanes, vinca alkaloids, and tyrosine kinase inhibitors (TKIs) [22]. The outcome of the action of ABC transporters is reduced levels of drug at the action site, thereby decreasing the cytotoxic response to the target, cancer cell. In addition, ABC transporters can affect resistance based on effects on cancer stem cell (CSC) phenotype(s), which in turn influence tumor initiation, metastasis, and recurrence. For example, it has been shown that ABCG2 is frequently expressed in both hematopoietic and solid tumor CSC populations and is associated with drug resistance to specfic drugs including mitoxantrone and topotecan [23]. Interaction of ABC transporters with apoptosis-associated proteins including Bcl-2 and p53 further complicate our developing understanding of their effect on treatment [24,25]. Furthermore, the transporter expressions themselves may be impacted by tumor hypoxia, epigenetic alterations, and microRNAs. For example, hypoxia-inducible factor 1-alpha (HIF-1α) has been shown to compel ABCB1 and ABCG2 experssion under hypoxic conditions and promote multidrug resistance in solid tumors such as glioblastoma and breast cancer varieties [26]. Both methylation and

histone modifications of transporter genes may silence and/or activate expression resulting in altered drug sensitivities in different patient populations [27,28].

2.3. Significance of Understanding Mechanisms of the ABC Transporters for Therapeutic Options

Understanding ABC transporter biology is vital to improving therapeutic effectiveness in cancer. Despite multiple attempts to pharmacologically inhibit ABC transporters, only limited progress has been made in the clinic. First-generation inhibitors, like verapamil and cyclosporine A, were highly non-specific and had unacceptable toxicity, while second- and third-generation inhibitors, tariquidar and elacridar, demonstrated non-target effects and pharmacokinetic concerns in clinical trials which limited their efficacy [29]. However, the understanding of transporter function, enabled advances in pre-treatment assessment of patients to better expose specific altered biological processes related to drug response for personalized therapy. For instance, ABCB1 polymorphisms like C3435T, G2677T/A are associated with drug disposition and drug response mutations observed in patients with colorectal and breast cancers receiving treatment with irinotecan and docetaxel [11,30]. Secondly, expression levels of ABC transporters can also be utilized as prognostic or predictive markers. A high expression of ABCG2 was associated with poor progression-free survival of patients diagnosed with acute myeloid leukemia or non-small cell lung cancer [31,32]. In addition, functional imaging and associated liquid biopsy approaches to evaluate alterations in ABC transporter activity may provide translational data to monitor treatment in real-time [33]. In summary, it is vital to understand the molecular mechanisms and regulatory networks of ABC transporters for understanding drug resistance. Once we put this mechanistic understanding together with new delivery technologies, transporter inhibitors, and immune modulation, we may be able to improve the clinical efficacy of anticancer treatments [34]. ATP-binding cassette (ABC) transporter genotype gene mutation including ABCB1, ABCC1, and ABG2 is a significant contributor to drug resistance in cancer. These mutations may be somatic or germline mutations and in either case may increase the activity of transporters or change their substrate selectivity resulting in overexpression of transporters in chemotherapy-resistant tumors [35]. Nucleotide-binding domains (NBDs) mutations may affect ATP hydrolysis, which inhibits efficient expulsion of drugs, whereas mutations in the transmembrane domains (TMDs) can expand the substrate specificity and allow the expulsion of different drugs. Moreover, gene metabolism can be increased by mutations in the noncoding region to increase efflux capacity without affecting transporter structure. These mutations enable the cancer cells to evolve to chemotherapy, forming resistant generations [36]. Whole-genome sequencing (WGS), whole-exome sequencing (WES), RNA sequencing (RNA-seq), and single-cell sequencing are the recent developments in genomic technologies that made it possible to detect rare mutations and provide insights into the unusual events in transcription and splices, which influence transporter activity. CRISPR-Cas9-based functional genomic screens can also be used to verify the contribution of a given mutation to drug resistance, which is useful in determining the contribution of these changes to cancer development and resistance to cancer therapy [37, 38].

2.4. Research Gap

Studies concerning the ABC transporters and drug resistance in cancer have multiple gaps that have impeded the efforts of overcoming multidrug resistance (MDR). Although the role of ABC transporters in drug efflux is understood, the mechanisms underlying the association between these transporters and cancer stem cells (CSCs), tumor recurrence, and metastasis remain to be established. ABC transporter non-toxic, specific inhibitors have not been established, and additional research is needed to learn more about the regulation networks and epigenetic changes of transporters involved in their expression. Besides, additional data on post-translational changes and the impact of tumor microenvironment on the activity of transporters could be received. Personalized medicine and biomarker discovery, Clomics and proteomics remain to be used in clinical practice as well, and the combination of multi-omics to explain MDR in cancer remains to be researched partially. Furthermore, the transfer of such outcomes into clinical practice, including non-invasive monitoring methods and effective combinations of treatment methods is a critical area of study. These gaps will be solved to aid in the implementation of more effective measures to counteract drug resistance and improve patient outcomes.

3. GENOMIC INSIGHTS INTO ABC TRANSPORTER-MEDIATED DRUG RESISTANCE

3.1. Genetic Mutations in ABC Transporter Genes Leading Mous in Discussing Drug-Resistant Cancers

Genetic alteration of the ABC transporter genes would be able to play role in the development of drug

resistance which is mostly a reaction to the increased transporter activity or in a few cases, there would be no reaction and thus exhibit drug-resistant traits. Mutations at the somatic and germline level have been reported in common ABC transporters (including ABCB1, ABCC1, ABCG2), and such have been demonstrated to be frequently over-expressed in chemotherapy-resistant tumors. A mutation in the NBDs may inhibit the ATP binding or hydrolysis to generate energy and thus drug excretion. In certain cases, however, mutating the TMDs can also show alternative specificity of substrates and permit drug efflux of other chemotherapeutics. Mutations may also occur in noncoding regions, e.g. promoters or other cis-regulatory transcriptional control elements and may cumulatively contribute to the amysegregar of higher gene expression (needed to be expressed with the ABC transporter) in a genome, thereby preventing any reproachable changes to the protein structure of the gene in question. It is logically needed that multiple genomic anomalies are integrated to accommodate adaptation in drug-induced resistance including drug-induced resistance characterized by the acquisition of chemosimultaneous resistance amplification that subsequently becomes a fundamental force in cell survival and fitness to unfold into a clonal response to the initial selective pressure.

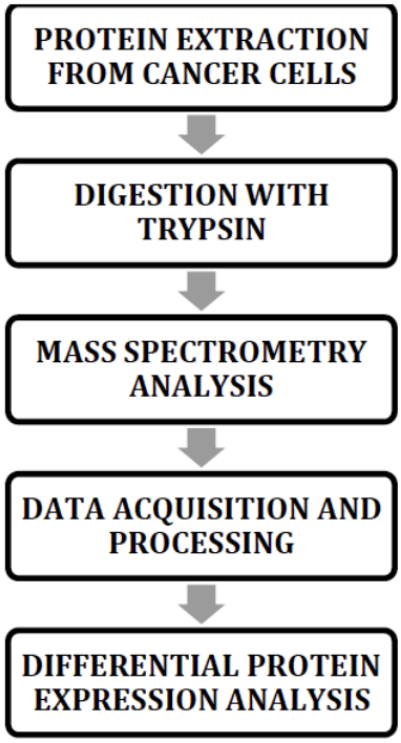

Figure 2: Proteomics Analysis Workflow.

This illustration (Figure **2**) demonstrates the sequential flow analysis used for proteomic analysis in cancer analysis. The first step is the protein extraction from cancer cells, followed by full sonication, and digestion with trypsin, which converts the proteins into peptides. The peptides are analyzed using mass spectrometry, which will produce complex spectral data. The next step is data acquisition and analysis, where a collection of raw spectral data can be analyzed into useful peptide and protein information. Lastly, a differential protein expression analysis can be preformed, that will identify changes in protein levels with respect to the two different conditions, allowing for insights into cancer-related molecular changes.

3.2. Examining Genomic Approaches to Examine Drug Resistance

With the advances in genomic technology, it is now possible to definitively identify mutations and expression patterns in ABC transporters. We can use whole-genome sequencing (WGS) and whole-exome sequencing (WES) to quantify structural variants, point mutations, and gene duplications in drug-resistant cancer. This has application with rare mutations, which conventionally would not be picked up in the assays. RNA sequencing (RNA-seq) will provide insights into the atypical transcriptional activity and aberrant splicing events, which directly impact the function of ABC transporters. For example, differential expression of splice variants of ABCG2 would result in transporter versions with not only a modified cellular location but also differing substrate affinities. Single-cell sequencing is being used to understand intra-tumoral heterogeneity and discover potentially resistant subpopulations with their own unique mutated and variant ABC profile. Functional genomic screens based on CRISPR-Cas9 are also being used with considerable promise to validate "real-world" impacts of specific mutations. In these experiments, previously mutated ABC genes are knocked in or knocked out in cancer cell lines to provide first-hand empirical evidence of whether the mutation affects multidrug resistance and to what extent it affects efflux function, as well as to contribute to the functional annotation of their genomic sequences.

3.3. Discussion on the Effect of Genomic Alterations on ABC Transporter Function

The functional consequences of genomic alterations on ABC transporters are many. Gain-of-function mutations can increase drug efflux activity, while loss-of-function mutations can lead to inactive transporters that make cells more sensitive to the effects of chemotherapy. Other polymorphisms affect post-

translational modifications and trafficking, which can result in proteins being incorrectly localized and possibly being expressed, but do not confer any drug resistance. To evaluate the systematic impact of these alterations, we propose a Mutation–Function–Resistance (MFR) Model. In this mathematical model we quantify the relationship between mutation severity, efflux efficiency, and drug survival:

Let:

M = mutation impact score (0 to 1, with 1 = high functional impact)

E = efflux efficiency

= intracellular drug concentration

S = drug survival index (inverse of drug-induced cytotoxicity)

α = cytotoxic coefficient of the drug

$D0$ = extracellular drug concentration

Emax = maximum efflux capacity and activity of a wild-type transporter

We model efflux efficiency as:

$$E = E_{max} \cdot (1 - M) \ (1)$$

And intracellular drug level as:

$$D_{in} = \frac{D_0}{1 + E} \ (2)$$

Finally, drug survival index is defined as:

$$S = \frac{1}{1 + \alpha D_{in}} = \frac{1}{1 + \alpha \cdot \frac{D_0}{1 + E_{max} \cdot (1 - M)}} \ (3)$$

This model provides predictions about how individual mutations have effects on drug resistance. A truncating mutation such that $M = 1$ means zero efflux ($E = 0$), leading to maximal intracellular drug accumulation. This leads to a low survival index, suggesting drug sensitivity. A mutation associated with $M = 0$ implies full efflux capacity; therefore, the account is related to resistance. This quantitative model will support the aims of precision oncology because it incorporates individual genomic mutation profiles in the decision-making process with respect to treatment. This will enable clinicians to estimate the degree of resistance associated with mutations and assist with individualized therapeutic regimens.

4. PROTEOMIC INSIGHTS INTO ABC TRANSPORTER-MEDIATED DRUG RESISTANCE

4.1. Assessment of Protein Expression Levels of ABC Transporters in Drug-Resistant Cancer Cells

In drug-resistant cancers, there is high expression of ATP-binding cassette (ABC) transporter proteins, notably P-glycoprotein (ABCB1), MRP1 (ABCC1), and BCRP (ABCG2) used by cells to eliminate chemotherapeutic agents by reducing the intracellular concentrations of these drugs. All of these proteins work on the plasma membrane, actively effluxing a wide array of drugs out of cancer cells to diminish drug activity. Proteomic profiling has shown a characteristic presence of ABC transporters at the protein level in resistant cancer phenotype, often associated with no significant mRNA upregulation indicating a role for translational and post-translational regulation. Beyond this, we see the critical need to assess protein abundance rather than use transcriptomic data alone. If we want to estimate resistance at the level of transporter expression it is plausible to provide a Drug Resistance Expression Index (DREI),

Phosphorylation, glycosylation, ubiquitination and acetylation are examples of post-translational modifications (PTMs) that regulate the stability, localization and activity of the ABC transporters, rather than only their levels in the cell. An example of this is phosphorylation of ABCB1 at certain locations can increase the ATPase activity and the efflux of drugs and ubiquitination can cause the transporter to be degraded, decreasing its expression to the surface. Besides, protein-protein interactions (PPIs) to cytoskeleton, kinases or scaffolding proteins can influence the trafficking and localization of the transporter. Suboptimal PTMs or PPIs in cancer cells may enable transporters to be active in the presence of therapeutic pressure, which makes them drug-resistant. Interestingly, the increase in drug efflux normally correlates with the increase in expression of ABCB1; however, the functional transport efficiency (FTE) may reduce with the increase in the level of expression, which may be associated with saturation or dysfunction of the transport mechanisms. It is important to note that the transporter expression and activity should be evaluated in order to understand the drug resistance mechanisms in a better way as opposed to using expression alone.

This figure (Figure **3**) shows respective protein expression for three major ABC transporters (ABCB1 (P-gp), ABCC1 (MRP1), ABCG2 (BCRP)) in drug-

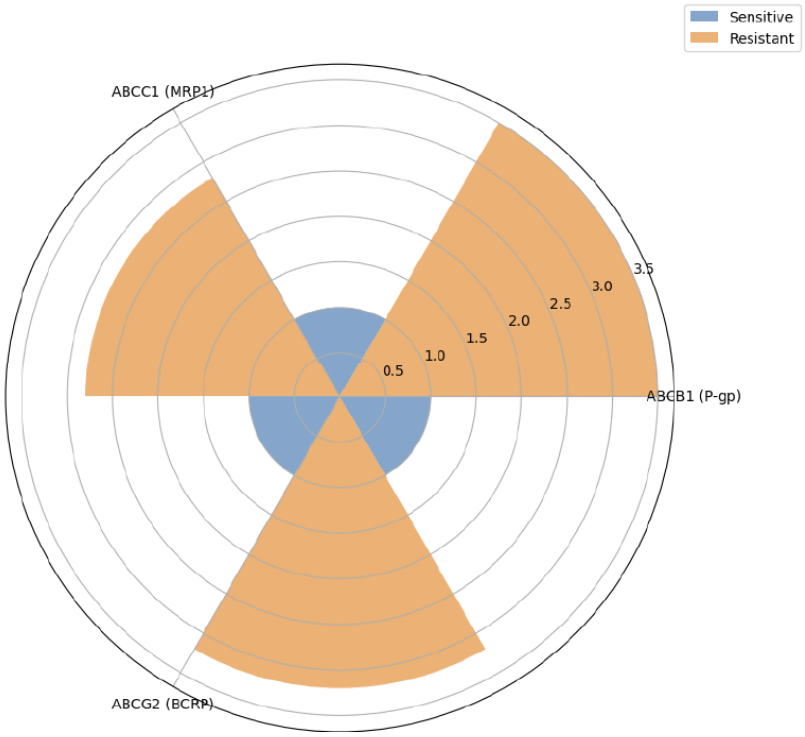

Figure 3: ABC Transporter Expression in Sensitive vs Resistant Cancer Cells.

sensitive and drug-resistant cancer cell lines. As illustrated, resistant cells have much greater expression levels of all three transporters in comparison to sensitive cells. For example, ABCB1 expression is more than three times higher in resistant cells. This is clinically relevant because increased levels of ABC protein enable greater function of drug efflux transporters, thus decreasing the concentration of drug in the cell and promoting chemoresistance. Hence, these data provide strong evidence that obtaining protein level expression and not just mRNA, will provide better predictions for clinical outcomes.

4.2. Applications of Proteomics in Drug Resistance Mechanisms

Proteomics based on high-resolution mass spectrometry (MS) is a powerful methods for characterizing not just protein abundance per se, but also protein alterations in cancer. Label-free quantification (LFQ), isobaric tag for relative and absolute quantification (iTRAQ), and stable isotope labeling by amino acids in cell culture (SILAC) permit detailed proteomic profiles of ABC transporter expression from sensitive (drug-sensitive) and resistant (drug-resistant) phenotypes. Mass spectrometry has confirmed overexpression of ABC in drug-resistant cell lines but it has also discovered others, novel proteins that are associated with resistance to anti-cancer agent treatment that may interact with or modulate the ABC transporters. Targeted proteomics, including multiple reaction monitoring (MRM), can be used to accurately quantify low-abundance transporters that can provide understanding of their contributions to resistance as well. To assess the discriminatory capacity of transporter expression as a resistance biomarker, a Receiver Operating Characteristic (ROC) analysis tool can be employed. The area under the ROC curve (AUC) quantifies the predictive power of a protein:

$$AUC_{ROC} = \int_0^1 TPR(FPR)dFPR \quad (5)$$

Where TPR is the true positive rate and FPR is the false positive rate. An AUC > 0.8 indicates the transporter possesses strong discrimination ability in detecting resistant phenotypes.

The Receiver Operating Characteristic (ROC) curve (Figure **4**) evaluates the diagnostic ability of ABCB1 protein expression to differentiate drug-resistant from drug-sensitive cancer cell lines. This ROC curve illustrates a strong diagnostic performance with the area under the curve (AUC) of almost 0.93 indicating high specificity and sensitivity. The AUC suggests that ABCB1 expression could potentially be utilized as a predictive resistance status biomarker. Furthermore, the steep rise and plateau toward the top-left corner of the curve strongly indicates that the higher level of ABCB1 expression correlates to "resistance" offering a

valuable biomarker in clinical use for stratification of patients based on predicted treatment response.

Figure **5** shows the Drug Resistance Expression Index (DREI) for ABCB1 across different tumor types, showing variation in ABCB1 overexpression that is cancer specific. Among the tumors analyzed, ovarian cancer has the highest DREI at 4.5, indicating the relative overexpression of ABCB1 protein in resistant samples. Pancreatic and lung cancer also have higher DREI, indicating strong proteomic basis for resistance. These findings illustrate the heterogeneity of ABC

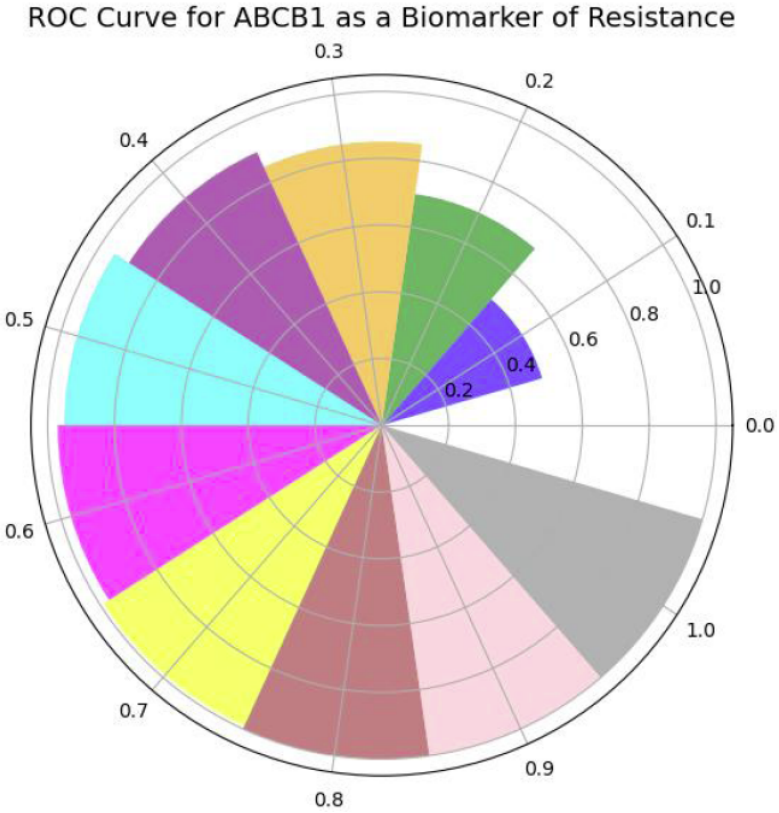

Figure 4: ROC Curve for ABCB1 as a Biomarker of Resistance.

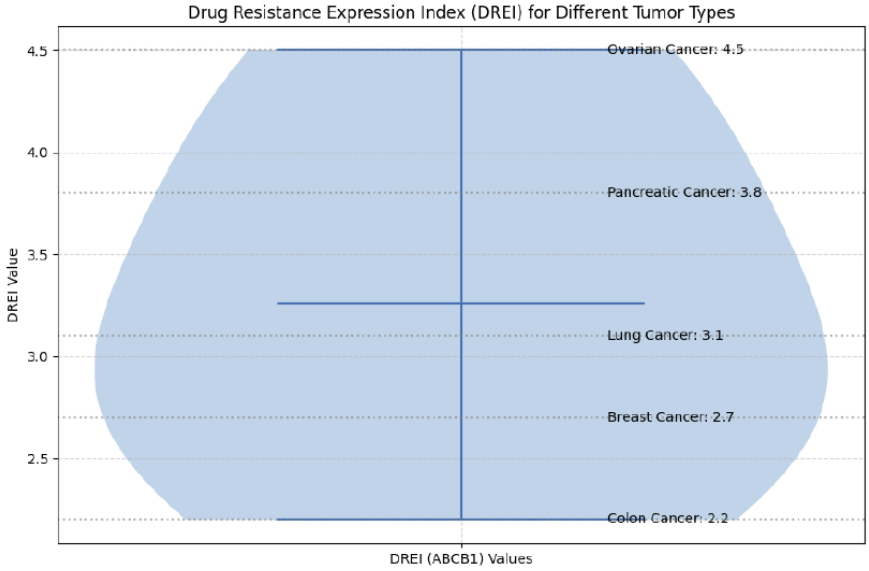

Figure 5: Drug Resistance Expression Index (DREI) for Different Tumor Types.

transporters in cancer types and the need for personalized, tumor-specific, resistance profiling for treatment considerations.

4.3. Studying Protein Interactions and Post-Translational Modifications is important for ABC Transporter Function

Phosphorylation, glycosylation, ubiquitination and acetylation are examples of post-translational modifications (PTMs) that regulate the stability, localization and activity of the ABC transporters, rather than only their levels in the cell. An example of this is phosphorylation of ABCB1 at certain locations can increase the ATPase activity and the efflux of drugs and ubiquitination can cause the transporter to be degraded, decreasing its expression to the surface.

Besides, protein-protein interactions (PPIs) to cytoskeleton, kinases or scaffolding proteins can influence the trafficking and localization of the transporter. Suboptimal PTMs or PPIs in cancer cells may enable transporters to be active in the presence of therapeutic pressure, which makes them drug-resistant. In Figure **6** Interestingly, the increase in drug efflux normally correlates with the increase in expression of ABCB1; however, the functional transport efficiency (FTE) may reduce with the increase in the level of expression, which may be associated with saturation or dysfunction of the transport mechanisms.

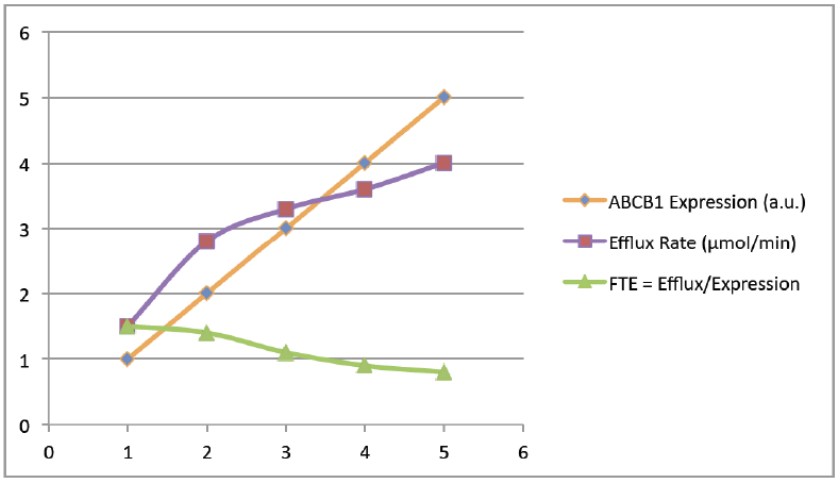

Figure 6: Functional Transport Efficiency (FTE) in Different Cell Lines.

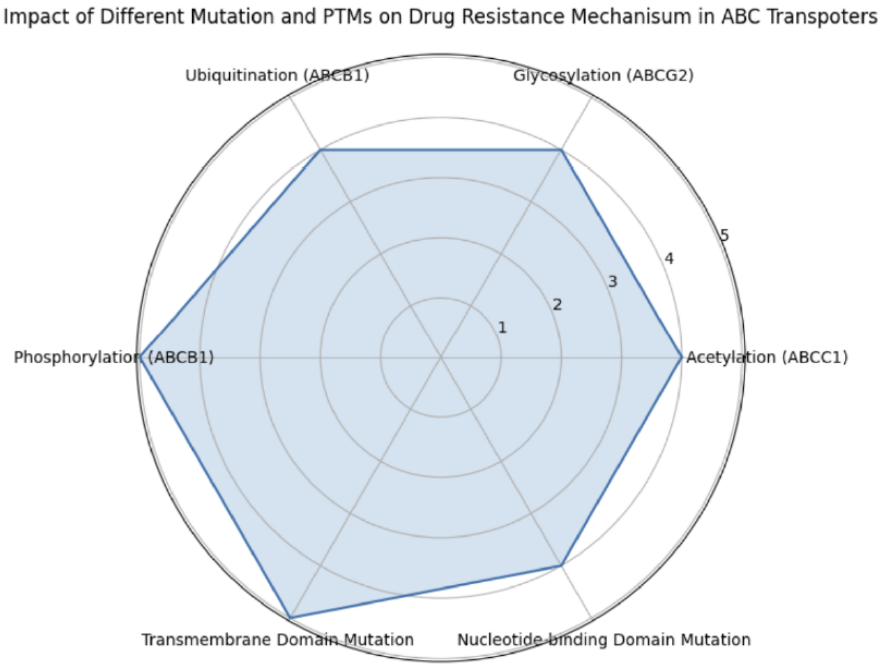

Figure 7: Impacts of Different Mutations and PTMs on Drug Resistance Mechanisms in ABC Transporters.

It is important to note that the transporter expression and activity should be evaluated in order to understand the drug resistance mechanisms in a better way as opposed to using expression alone.

4.4. Impact of Different Mutations and PTMs on Drug Resistance Mechanisms in ABC Transporters

The Figure **7** shows the comparative effects of various mutations and post-translational modifications (PTMs) on the drug resistance mechanisms in the ABC transporters with specification in major factors such as acetylation, glycosylation, ubiquitination, phosphorylation, and mutations of transmembrane and nucleotide-binding domains. The graph shows that both acetylation (ABCC1) and glycosylation (ABCG2) has a high and comparable effect on drug resistance because each modification has a significant impact on both transporter stability and localization, hence drug efflux. There is also a high impact of Phosphorylation (ABCB1), which increases ATPase activity and rate of drug efflux, yet another way of supporting resistance.

On the other hand, ubiquitination (ABCB1) though significant in controlling transporter surface expression, has a little less effect because it could lead to degradation of the transporter. The transmembrane domain and nucleotide-binding domain mutations also play a significant role in resistance, but their effect is somewhat less pronounced than that of the PTMs discussed, presumably due to the fact that they cause changes in substrate specificity or reduced ATP binding capability that may reduce the efficiency of transporter activity during drug efflux. Altogether, the graph highlights that PTMs, namely, acetylation and phosphorylation, are significant in changing the functionality of ABC transporters and block multidrug resistance in cancer.

5. DISCUSSION

The analysis must focus on some major weaknesses of the study of the ABC transporters in drug resistance. Among them are inter-omics integration issues, such as integrating genomics, proteomics, and PTMs are affected by the problem of inconsistent sample qualities, sample normalization, and complexities in computations. Another possible limitation is that of sample heterogeneity since most studies utilize cell lines or small biopsies that are not representative of clinical tumor heterogeneity and complexity. Additional problems of non-uniformity in recording of the expression and functions of ABC transporter also make it difficult to compare such studies. Also, the translational distance between the identification of biomarkers of ABC transporters and clinical practice remains unbroken since, in terms of regulatory, technical, and cost aspects, implementation is still unattainable. In order to improve the personalized medicine discussion, it is important to note that although some researchers have proposed that ABC transporter polymorphs and expression are associated with drug resistance, no companion diagnostics involving ABC transporter have been approved by the FDA. The need to stratify patients on the basis of transporter expression has been demonstrated in clinical trials, e.g. of LY3023414, but functional assays of transporter activity are required. The next step towards translating biomarker discovery into clinical practice involves assay standardization and creation of combination therapies or superior drug delivery vehicles that circumvent transporter-mediated drug efflux. Even though most of the strategies remain in the preclinical phase, they are promising advances towards more personalized cancer therapy.

6. FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS

6.1. Possible Strategies to Intervene on ABC Transporter-Mediated Drug Resistance

Overcoming ABC transporter-mediated drug resistance in cancer remains a clinical challenge, but a number of promising strategies are under evaluation. An example of this approach would be the development of ABC transporter inhibitors which aim to inhibit efflux activity to restore intracellular drug concentration. First- and second-generation inhibitors did not display as specificity or were rendered ineffective because of toxic drug–drug interactions, but newer generation third-generation inhibitors are considering this specificity to minimize off-target effects. When use together with chemotherapeutics, these inhibitors may resensitize resistant tumor cells to the chemotherapeutic. Another strategy would be to modulate or selectively target upstream regulators associated with expression of ABC transporters. Transcription factors, such as NF-κB, HIF-1α, and p53 all regulate ABCB1 and ABCG2 where inhibiting these pathways could therefore reduce ABC transporter activity, and consequently, also reduce an ABC-dependent drug resistance. Additionally, there is a growing interest in epigenetic therapies (e.g. DNA methyltransferase inhibitors, histone deacetylase inhibitors) to downregulate expression of ABC transporter genes by altering chromatin accessibility to the factors regulating transporter gene expression.

Lastly, nanoparticle-based drug delivery systems are emerging as a solution for bypassing ABC-mediated efflux by delivering drugs into the cytoplasm of tumor cells, or using encapsulation methods that shields drugs from the recognition by efflux pumps. These targeted delivery methodologies do not only maintain drug loading in tumor cells more effectively but also minimize the risk of systemic toxicity to normal tissues.

6.2. Translating Genomic and Proteomic Findings into Clinical Care

Integrating genomic and proteomic information into clinical workflows is important for progressing cancer management. Genomic profiling identifies patients with mutations or amplifications in ABC transporter genes, allowing an oncologist to know which patients may be resistant to therapy, and act accordingly. For example, patients with ABCB1 overexpression or gain-of-function mutations may benefit from treatment regimens which include transporter inhibitors or chemotherapeutics that are not substrates for these transporters. An additional level of resolution presented by proteomic data lets clinicians involve the expression and functional condition of proteins that relate to resistance, understanding that transcriptomic data can not mirror protein concentrations as result of post-transcriptional control. As an example, the levels of transporter proteins in tumor biopsies can be measured by mass-spectrometry-based assays, which would provide real-time evaluation to consider when delivering therapy. Liquid biopsy, which uses circulating tumor DNA (ctDNA) and exosomal proteins, can be used in clinical practice in the future to evaluate the status of ABC transporters in a non-invasive way during the treatment. This dynamic perspective can be used to guide the prevention of resistance at its early stages and help make necessary adjustments to the course of treatment.

6.3. The Rise of Personalized Medicine in Cancer Therapy and Potential Changes Given Genomic & Proteomic Information

The rise of personalized medicine in the area of oncology is due, in part, to an increased awareness that each tumor (primary and recurrent) is different at the genomic and proteomic levels. For instance, drug resistance mediated by transporters of the ABC superfamily is different among patients, and even within specific regions of the same tumor, as expression and function may not function the same in the different regions of that tumor. Personalized medicine allows for the targeting of treatments based on each individual's unique molecular resistance response. For instance, based on the genetic (and proteomic) resistance data, a clinician could classify a tumor to be at high risk for resistance, and take the initiative to develop a personalized plan. In this case, they may opt to use drugs that are not effluxed, change drugs to alternative combinations that pre-empt resistance (i.e. potential resistance in advance), and/or use a new inhibitor, based on the identified resistance mechanism. Depending on the limitations of the drug trial, patients could be stratified by their transporter profiles to possibly enhance therapeutic outcomes and improve on the success of the investigational agent. In conclusion, the development of precision medicine is transitioning cancer care from a single, one-size-fits-all approach to a highly malleable evidenced-based, tailored approach, based on a molecular diagnosis, which will hopefully improve patient-related outcomes, but also be more efficient in healthcare delivery processes.

7. CONCLUSION

In conclusion, genomic and proteomic studies have greatly enhanced our understanding of ABC transporter-mediated drug resistance in cancer. Genomic studies identified significant mutations, gene amplification and regulatory elements that ultimately altered the expression and function of ABC transporters such as ABCB1, ABCC1 and ABCG2. Meanwhile, proteomic studies identified the effects associated with drug resistance and modulations in protein expression levels, post-translational modifications and functional activity that could not have been predicted through genomic or gene expression analysis alone. Thus, these investigations have illustrated the complexity of drug resistance and the value of linking genomic and proteomic multi-omic approach to address the underlying struggle of multidrug cytotoxic therapy resistance. Our understanding of the ABC transporter landscape informs us on possible targeted therapies, combinations with inhibitors or other treatments in conjunction to therapeutic groups or unique attributes based upon their genomic and proteomic information. Therapeutic resistance continues to be one of the primary limitations in effective cancer treatment, and the need to investigate novel biomarkers, optimize diagnostic delivery systems and refine therapeutic interventions remains a critical need. Future work should focus on studying the real-time evolution of resistance, applying different drug delivery systems to avoid the influence of transporter activity, and

validating predictive models across varied cancer types. Overall, understanding the biology of ABC transporters in the most thorough and dynamic fashion will be essential in preventing therapeutic resistance so that improved long-term and overall outcomes can be achieved.

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