**Decoding Cancer Multidrug Resistance (MDR): Integrating Molecular Biomarkers and Artificial Intelligence for Predictive Insights and Therapeutic Innovation**

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**Abstract**

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1. **Introduction**

Cancer persists to be one of the most formidable global health challenges, with multidrug resistance (MDR) presenting a substantial barrier for effective treatment [1], [2], [3]. The potency of cancer cells to develop resistance to multiple chemotherapeutic agents is a complex, multifactorial procedure encompassing genetic, epigenetic, and metabolic alterations [4]. These mechanisms synergistically contribute to the failure of conventional therapies, postulating a comprehensive approach to decipher the molecular underpinnings of MDR and explore innovative strategies for overcoming resistance. Advancements in molecular biology and computational sciences, specifically artificial intelligence, presents a promising avenue to predict, counteract, and potentially reverse MDR in cancer cells [5].

MDR in cancer is principally dictated by overexpression of ATP-binding cassette (ABC) transporters, metabolic reprogramming through cytochromes P450 (CYP) enzymes, deregulation of apoptosis via inhibitor of apoptosis proteins (IAPs), augmented drug detoxification mediated by uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes, and dysregulation of key signaling pathways such as the human epidermal growth factor receptor 2 (HER2) axis [6], [7], [8], [9], [10]. ABC transporters, including P-glycoprotein (P-gp), multidrug resistance-associated proteins (MRPs), and breast cancer resistance protein (BCRP), play a pivotal role in effluxing cytotoxic drugs out of cancer cells, eliminating intracellular drug accumulation and thus diminishing therapeutic efficacy [11]. Similarly, CYP enzymes contribute to the metabolic inactivation of anticancer agents, modifying drug bioavailability and promoting resistance [12], [13]. The role of IAPs in inhibiting apoptotic pathways further exacerbates MDR, enabling cancer cells to evade cell death despite aggressive chemotherapy [14]. UGT enzymes, by catalyzing the glucuronidation of xenobiotics, further contribute to chemoresistance by expediting drug elimination [15]. Moreover, HER2 overexpression in specific cancers, such as breast and gastric cancers, leads to aberrant signaling that fosters tumor progression and resistance to targeted therapies [16].

Epigenetic modifications represent another critical factor influencing MDR in cancer cells. DNA methylation, histone modifications, and non-coding RNA regulation remarkably alters gene expression profiles, paving way to changes in drug response [17]. These modifications can either activate MDR-related genes or hinder the expression of tumor-suppressive genes, thereby modulating resistance mechanisms [18]. Comprehending these epigenetic landscapes stipulates novel therapeutic opportunities to reprogram resistant cancer cells and enhance drug sensitivity.

Artificial intelligence (AI), particularly reinforcement learning (RL), has emerged as a transformative tool in the battle against MDR. RL, a branch of machine learning, empowers predictive modeling of drug resistance by assessing large-scale genomic, transcriptomic, and proteomic datasets [19], [20]. By incessantly learning from patterns and optimizing treatment strategies, RL-based models can aid in designing personalized therapy regimens, distinguishing potential drug combinations, and forecasting patient responses to specific treatments. The data from experimental and in silico studies can be curated, such as in Table 1, and a multifactorial approach can be employed to provide a uniform approach to precision medicine. AI-ML models can be utilized to predict and diagnose a treatment plan accordingly; the patient's response can then be inputted back into the model so that with each patient, the model learns to be more precise and employs a more extensive database of drugs and correlated molecular targets. Such integration of AI-driven methodologies with traditional molecular and pharmacological studies carries vast potential in revamping cancer therapy by furnishing data-driven insights to circumvent MDR.

This review delves into the intricate molecular mechanisms underlying cancer MDR, concentrating on vital targets such as ABC transporters, CYP enzymes, IAPs, UGT enzymes, and HER2. Furthermore, it scrutinizes the role of epigenetic modifications in mediating MDR and accentuates the implementation of RL in predicting and overcoming MDR. By bridging the gap between molecular oncology and artificial intelligence, this work aims to present a comprehensive perspective on the future of precision medicine in cancer treatment, ultimately paving the way for more effective and durable therapeutic interventions.

1. **Molecular targets to combat drug resistance**

**2.1. ATP-binding cassette (ABC) transporters**

A key mechanism of MDR is the overexpression of ABC transporters: membrane proteins that help remove xenobiotics from cells [21]. ABC transporters utilize energy from hydrolyzing adenosine triphosphate (ATP) to transport substances into and out of cells. When overexpressed in the case of tumor cells, they can significantly reduce the intracellular concentration of chemotherapeutics [22]. ABC transporters rely on changes in their transmembrane domains to pump substrates out of the cell; this shift causes the inward-facing cavity to open outward, enabling efflux [23]. While the nucleotide-binding domains are structurally and functionally similar across the ABC family [24], the transmembrane domains differ—and this dissimilarity drives their distinct functions and allows each protein to recognize specific substrates [25]. ATP binding to the nucleotide-binding domains stabilizes the conformational changes in the transmembrane domains that drive substrate efflux, and, interestingly, it is the ATP-bound state—not ATP hydrolysis itself—that reduces the affinity of certain ABC transporters [26]. These changes occur at the cytosolic side of the membrane, meaning they involve structural rearrangements in regions facing the cell’s interior fluid where ATP is abundant. Certain transporters undergo conformational changes in specific transmembrane helices during substrate transport [25], enabling the export of neutral or positively charged hydrophobic molecules and xenobiotic substances from cells [26]. Structural features, such as transmembrane domain architecture, allow some transporters to differentiate between inhibitors and substrates [27]. Ligand interactions, including π-π interactions and hydrogen bonding, stabilize the transporter-substrate complex, ensuring efficient efflux of amphiphilic or conjugated compounds [28], [29]. Critical residues within N-terminal membrane-spanning domains are essential for stable expression and functionality in specific cellular environments [21], [30].

P-glycoprotein (Pgp), a well-known ABC transporter encoded by the ABCB1 gene, is classically overexpressed in the plasma membrane of tumor cells, where it binds to and actively pumps chemotherapeutic drugs out of the cytoplasm [31], [32], [33]. While some studies suggest mitochondrial localization of Pgp in specific contexts like ovarian cancer [34], [35], predominant research emphasizes that reduced drug accumulation in the cytoplasm indirectly limits drug access to mitochondria. Since mitochondria regulate apoptosis [36], this overall decrease in intracellular drug levels may impair their ability to initiate mitochondrial-dependent cell death, thereby promoting tumor cell survival. Moreover, Pgp-mediated resistance can affect a drug’s ability to target the microtubules—structures supporting tumor cells to divide and grow—preventing it from disrupting cell division [37], [38]. Modulating Pgp—probably—may be a way to reduce its related drug resistance; however, modulators often require high doses, which can lead to cardiovascular toxicity, and others cause drug-drug interactions or cytotoxicity against normal cells and tissues by interacting with multiple Pgp proteins [39]. Consequently, efforts to develop effective Pgp modulators in the clinic have been mainly unsuccessful. Also, Pgp has no clearly defined drug binding pocket because of their flexible structures, making it challenging to design specific inhibitors [40], [41], [42].

Breast cancer resistance protein (BCRP; encoded by the ABCG2 gene)—contrary to its name—plays a crucial role in protecting the body from potentially harmful xenobiotics [43], [44], [45]. When overexpressed, BCRP can expel chemotherapeutics by a process similar to that of Pgp in its reliance on ATP hydrolysis, but differing in its substrate specificity, as BCRP primarily targets amphiphilic molecules, organic anions, or conjugated compounds [46], [47], [48]. Cells expressing BCRP exhibit distinct patterns of drug distribution due to the transporter’s tissue-specific expression and selective affinity for smaller molecules (<700 Da), as evidenced by the ability of drugs exceeding 800 Da in molecular weight to evade BCRP-mediated resistance [49], [50], [51]; however, hepatic metabolism can chemically modify certain drugs into forms that BCRP recognizes [52], [53], [54]. BCRP-mediated MDR can be tackled using broad-spectrum inhibitors [55], [56], or novel inhibitors chemically designed for improved selectivity [57]. Interestingly, environmental factors such as folate deprivation can modulate BCRP expression and activity, suggesting that nutrient availability may alter drug resistance patterns [58]. Additionally, certain hypoxia-inducible or nuclear receptor pathways can activate intracellular signaling cascades that lead to increased BCRP expression, highlighting the interplay between external stressors and intrinsic cellular processes [59].

Multidrug resistance-associated protein 1 (MRP1; encoded by the ABCC1 gene) demonstrates a drug efflux profile similar to Pgp but differs significantly in its substrate specificity and functional roles [60]. Unlike Pgp, which primarily expels large hydrophobic or uncharged drugs through ATP-dependent conformational changes, MRP1 specializes in transporting glutathione- or glucuronide-conjugated amphiphilic anions. Compared to BCRP, which prefers amphiphilic or organic anions, MRP1 exhibits a broader substrate range with a stronger affinity for conjugated substrates, facilitated by adaptable substrate-binding regions during ATP hydrolysis, whereas BCRP’s smaller substrate-binding pocket is optimized for unconjugated, smaller molecules [61], [62], [63]. Notably, MRP1 exhibits minimal resistance to hydrophobic drugs like vinca alkaloids [32] and paclitaxel [64], which are preferentially transported by Pgp. This inefficiency in transporting hydrophobic drugs contrasts with its higher affinity for conjugated or anionic drugs, suggesting that substrate conjugation and charge significantly influence MRP1’s binding and transport efficiency. Additionally, the cellular localization of MRP1 may contribute to this variability. While predominantly found in the plasma membrane, MRP1 has also been detected in intracellular membranes, potentially affecting its interaction with substrates based on their intracellular site of action [65].

**2.2. Cytochromes P450 (CYP) enzymes**

CYPs are key enzymes responsible for breaking down drugs so they can be inactivated and cleared from the body. This process primarily occurs in the liver, kidneys, and small intestine. CYP enzymes modify drug molecules by oxidizing, reducing, or hydrolyzing them, making it easier for the body to eliminate these compounds [66], [67].

The overexpression of specific CYPs, particularly CYP3A4 and CYP2C8, underscores their role in mediating chemotherapy resistance. CYP3A4, a central enzyme in drug metabolism in the liver and intestine, reduces the effectiveness of chemotherapeutics by increasing drug clearance and suppressing apoptosis through the downregulation of key pro-apoptotic proteins, including caspases 8, 9, 3, and 7 [68], [69], [70]. However, its impact is substrate-specific: while CYP3A4 significantly influences the metabolism of certain drugs, its role in others is limited, as seen in cases where CYP2C8 takes precedence [71], [72]. CYP2C8 plays a complementary role in resistance by metabolizing compounds and reducing their anti-proliferative effects. In liver cancer, mechanisms such as GAS5/miR-382-3p regulation and the PI3K/Akt pathway drive CYP2C8 overexpression, promoting tumor proliferation and attenuating apoptosis [73]. Beyond its role in resistance, CYP2C8 also holds promise as a biomarker for cancer drug resistance, offering opportunities for precision-targeted therapies aimed at inhibiting its activity [74]. These findings collectively emphasize the intricate interplay between CYP3A4 and CYP2C8 in drug metabolism and resistance, particularly within multi-enzyme systems. Further research is necessary to unravel their precise mechanisms, explore their roles in different cancer types, and develop strategies to optimize therapeutic outcomes by overcoming CYP-mediated resistance.

CYP1B1—an isoform of the human cytochrome P450 family 1 that oxidizes and removes alkyl groups from xenobiotics and endogenous substances [75]—is notably absent in normal tissues but detectable in malignant tumors [76], [77]. Its overexpression promotes tumor cell proliferation and metastasis by inducing epithelial-to-mesenchymal transition and Wnt/β-catenin signaling [78], [79]. Unlike other CYP450 enzymes, CYP1B1 may not directly metabolize anticancer drugs into their subunits; instead, it contributes to drug resistance by modulating cellular pathways that promote survival and resilience [80]. Genetic variations in CYP1B1 significantly influence tumor responses to chemotherapeutics, underscoring its role as a potential biomarker for personalized cancer therapy. The CYP1B1 4326 GG genotype, linked to poorer survival in triple-negative breast cancer and worse outcomes in non-small-cell lung cancer, highlights its contribution to tumor progression, likely through the production of genotoxic metabolites that exacerbate DNA damage [81], [82]. These findings suggest that targeting CYP1B1’s enzymatic activity could mitigate its pro-tumorigenic effects and enhance therapeutic efficacy. The enzyme’s role in drug resistance is particularly evident in docetaxel-treated cancers, where CYP1B1 overexpression and polymorphic variants like CYP1B1\*3 are associated with poor prognosis in prostate and lung cancer patients [83], [84], [85]. Conversely, CYP1B1 inhibition has been shown to increase the chemosensitivity of breast cancer cells to paclitaxel, emphasizing the enzyme’s drug-specific interactions [86], [87]. Polymorphisms such as L432V further demonstrate CYP1B1’s predictive potential in determining treatment outcomes, particularly in castration-resistant prostate cancer [83]. However, while these studies highlight the importance of CYP1B1 in chemoresistance, the precise mechanisms by which its genetic variants alter drug efficacy remain poorly understood. This necessitates further investigation into its functional role in resistance pathways and the development of targeted inhibitors to exploit its potential as a predictive biomarker in personalized treatment strategies. Understanding the mechanisms by which CYP1B1 modulates resistance and how genetic variations affect therapeutic outcomes is crucial for tailoring more effective and personalized treatment strategies for cancer patients.

**2.3. Inhibitor of apoptosis proteins (IAPs)**

A hallmark of cancer is resistance to apoptotic stimuli, and one factor contributing to this resistance is the elevated levels of IAPs: a group of structurally related proteins that are key regulators of programmed cell death. Members of this family, including X-linked inhibitor of apoptosis protein (XIAP), livin, and survivin, bind to caspases (proteins essential for executing apoptosis) and block apoptosis [88].

XIAP has been shown to directly bind to and inhibit caspases [89]. To counteract this resistance, natural antagonists like the second mitochondrial-derived activator of caspases efficiently neutralize IAP activity and have been shown to restore apoptosis in patients with advanced solid tumors or lymphomas, particularly during treatments like Birinapant. Therapeutically, XIAP inhibitors such as AEG35156 have been developed to overcome resistance by reactivating apoptotic pathways. These inhibitors enhance the effectiveness of chemotherapeutics by reducing XIAP’s suppression of caspases, thereby increasing drug-induced cell death [90].

Survivin, another member of the IAP family, is a critical factor in promoting MDR through its ability to inhibit apoptotic and autophagic cell death, foster cell proliferation, and support angiogenesis [91], [92], [93]. While both XIAP and survivin suppress apoptosis, their mechanisms differ: XIAP directly interacts with caspases 3, 7, and 9 to block their activation, whereas survivin indirectly inhibits apoptosis by regulating processes such as cell division and proliferation, enabling tumor survival and progression [94], [95]. Survivin also facilitates immune evasion by altering immune responses, reducing T-cell activity and infiltration, and diminishing the effectiveness of immune checkpoint inhibitors like anti-PD-1/PD-L1 therapies [96]. Experimental inhibitors, including YM155 [97], shepherdin [98], and LLP3 [99], [100], have shown promise in preclinical studies by targeting survivin’s activity and offering hope for reducing drug resistance. However, while these findings are encouraging, the precise mechanisms through which survivin modulates immune suppression and resistance pathways warrant further investigation to optimize the development of survivin-targeted therapies.

**2.4. Uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes**

The overexpression of UGT enzymes, particularly the UGT1A family, represents a significant mechanism of drug resistance. These enzymes conjugate glucuronic acid to lipophilic drugs, promoting their clearance and reducing their therapeutic efficacy [64]. Gli1-inducible glucuronidation, driven by the sonic hedgehog transcription factor Gli1, is a critical pathway that elevates UGT1A enzymes, conferring resistance that is compounded by the reduced activity of the ENT1 transporter, which diminishes as UGT1A levels rise [101]. Notably, this phenomenon is specific to the UGT1A family, as Gli1 overexpression does not affect UGT2B enzymes [102]. While the nine UGT1A isoforms share conserved N-terminal domains, their sequence variations enable diverse drug interactions, underscoring the complexity of UGT-mediated resistance [103].

For instance, UGT1A1 metabolizes irinotecan (a topoisomerase inhibitor), reducing its efficacy in colorectal cancer [104]. Despite its relevance, clinical translation of UGT1A enzymes as biomarkers for resistance remains limited, with only one clinical trial successfully targeting UGT1A with vismodegib, a pan-UGT inhibitor, to treat acute myeloid leukemia [105]. However, the broad activity of vismodegib raises concerns regarding toxicity, prompting the development of alternative models that selectively inhibit UGT1A4 to minimize side effects [106], [107]. Furthermore, UGT1A6 and UGT1A9 are upregulated in liver, kidney, and pancreatic cancers, but their direct role in resistance requires further validation through wet lab studies [108], [109]. These findings emphasize the therapeutic potential of targeting Gli1-induced UGT1A overexpression while highlighting the need for more precise inhibitors to mitigate glucuronidation-driven resistance and improve drug efficacy.

**2.5. Human epidermal growth factor receptor 2 (HER2)**

Epidermal growth factor receptors are transmembrane proteins that regulate intracellular signaling pathways by binding extracellular ligands, thereby activating downstream cascades critical for cell proliferation, survival, and differentiation [110], [111]. Among the family, HER2 is a protein on cell surfaces that stands out as a ligand-free receptor that heterodimerizes with other epidermal growth factor receptors to amplify signaling. In healthy cells, HER2 tightly controls growth and tissue homeostasis; however, HER2 is frequently overexpressed or mutated in tumors, leading cells to cells to multiply rapidly, resist apoptosis, promote invasive behavior, and increase the potential for metastasis through hyperactivation of PI3K/Akt/mTOR and MAPK pathways [112], [113], [114]. This dual role positions HER2 as both a prognostic indicator and a predictor of treatment efficacy. For instance, elevated HER2 RNA expression correlates with improved responses to chemotherapy in breast cancer [115], [116], allowing one to predict disease-free survival in patients receiving chemotherapy after surgery [117]. Also, the recent identification of HER2-low/zero breast cancer subtypes has led to new detection methods and treatment approaches [118]. However, HER2’s prognostic value extends beyond breast cancer: in urothelial and prostate cancers, HER2 positivity is associated with aggressive phenotypes, including higher histologic grades, invasiveness, and advanced disease stages [113], [114]. Paradoxically, while HER2 amplification in breast cancer enhances chemosensitivity, it simultaneously promotes metastasis by activating pathways that increase cell motility [119]. This duality complicates its clinical interpretation, necessitating context-specific biomarker evaluation.

Contemporary research utilizes machine learning models to integrate HER2 expression with tumor characteristics and genetic profiles to predict treatment outcomes [120], [121]. These models also account for dynamic factors, such as HER2 heterogeneity across tumor regions, by incorporating spatial transcriptomic data to map resistance hotspots. However, challenges persist: tumor evolution under therapeutic pressure can shift HER2 expression patterns over time, while spatial variability may yield discordant biomarker results in biopsies. Such discrepancies risk misclassification—treating resistant tumors as responsive—or overlooking HER2-low populations eligible for newer antibody-drug conjugates. While machine learning mitigates these issues through probabilistic risk modeling, clinical translation requires standardized protocols for biomarker reassessment during treatment.

**3. Epigenetic modifications**

Epigenetic modifications refer to the changes in genes involved in crucial cellular processes without altering their DNA sequence [122]. These modifications, which include DNA methylation, histone modifications, non-coding RNA dysregulation, and chromatin remodeling are adapted by drug-tolerant cells to evade the effects of drugs and maintain survival, leading to acquired stable drug-resistant features [123], [124], [125].

N6-metyladenosine (m6A) RNA modification [126] is the most common epigenetic modification and involves RNA methyltransferases, demethylases, and m6A-binding proteins. Alterations in m6A affect drug targets like p53 protein and EGFR, influence DNA damage repair mechanism and affect apoptosis, autophagy and oncogenic signaling pathways [127], [128]. It also influences the processing of target transcripts and affects key proteins in cellular regulation [129]. Functionally, m6A modification regulates oncoprotein expression, promotes cancer initiation and proliferation, intersects with the immune response in the tumor microenvironment, and modulates diverse anticancer resistance mechanisms, such as drug transport, metabolism, and DNA damage repair [130], [131]. Targeting m6A modifiers can aid intervention against therapy-resistant cancers by disrupting these resistance pathways, restoring the effectiveness of anticancer therapies, and providing a promising avenue for developing novel therapeutic strategies [132].

Epigenetic modifications can also regulate the expression of the CYP1B1 gene and influence drug detoxification processes [133]. CpG islands, regions rich in cytosine and guanine bases, are often located near gene promoters and play a key role in controlling gene activity. Under normal conditions, these regions may be methylated, suppressing gene expression by blocking transcription. However, hypomethylation—a reduction in methylation levels—can activate or increase the expression of the CYP1B1 gene, particularly in its 5’-flanking regions, a critical regulatory area upstream of the gene [134]. Similarly, epigenetic modifications, such as Oct4 and Sox2, can upregulate BCRP expression [129], [135], and this increased expression is often associated to promoting hypomethylation, which can also elevate DNA methyltransferase activity [136]. Since the CYP1B1 enzyme metabolizes drugs and other substances, increased expression due to hypomethylation can alter drug metabolism, potentially contributing to resistance. Epigenetic modification mechanisms are a key focus of current research as they hold great promise for reversing drug resistance in cancer patients through novel pharmacological approaches like epidrugs [137], [138].

1. **Reinforcement learning for predicting MDR**

Artificial intelligence is revolutionizing precision medicine by offering advanced tools to predict and address cancer drug resistance. Techniques such as fuzzy expert systems [154] and artificial neural networks [155] enable the identification of drug–biomarker interactions, providing insights into the mechanisms of cancer resistance. Supervised machine learning models have demonstrated their ability to predict chemotherapy responses by analyzing ABC transporters [156–159]. In addition, machine learning models targeting specific resistance mechanisms, such as predicting CYP2C9 inhibitors by integrating structural knowledge of the enzyme with its physicochemical properties, have achieved approximately 80% accuracy using algorithms like support vector machines and random forests [160]. Quantitative structure–activity relationship models for multiple CYP isoforms have also employed random forests and XGBoost, yielding high-performance predictive models for drug–drug interactions that could minimize adverse effects and guide drug development [161]. These advances highlight AI’s ability to analyze complex datasets from both experimental and in silico studies to inform precision medicine strategies. Moreover, AI-driven models trained on clinical genomic data can identify appropriate inhibitors for resistance mechanisms during treatment and forecast resistance for experimental drugs by analyzing their chemical structures and interactions with drug targets [162], ultimately paving the way for more effective cancer therapies.

Reinforcement learning (RL), a subset of machine learning, has emerged as a transformative tool in precision oncology, addressing the challenges of cancer drug resistance and treatment optimization through dynamic and personalized decision-making. Unlike conventional static protocols, RL frameworks enable adaptive treatment strategies by leveraging real-time patient data and multi-dimensional feedback to tailor therapeutic regimens.

One prominent application of RL is in chemotherapeutic dosing optimization. Studies have demonstrated that RL-derived dosing schedules, guided by algorithms like deep Q-networks and twin-delayed deep deterministic policy gradients (TD3), outperform classical control methods by dynamically adjusting doses based on patient-specific parameters such as relative bone marrow density. These approaches significantly improve robustness against inter-patient variability and reduce drug toxicity while maintaining efficacy (Paper 1, Paper 10). RL has also been effectively applied to adaptive therapies, particularly in treatment-resistant prostate cancer. For instance, models using the Proximal Policy Optimization (PPO) algorithm to optimize intermittent androgen deprivation therapy (IADT) demonstrated superior time-to-progression (TTP) and reduced drug dosages compared to standard protocols (Paper 2, Paper 7).

RL frameworks have shown particular promise in combination therapy design and sequential treatment planning. Pan-cancer pathway models integrated with advanced optimization techniques such as Covariance Matrix Adaptation Evolution Strategy (CMA-ES) and Hamiltonian Monte Carlo methods enable RL to address tumor heterogeneity and clonal evolution. These strategies improve therapeutic outcomes by adapting drug combinations over time, as validated in multi-cell line scenarios (Paper 9). Similarly, RL-based treatment optimization for epithelial ovarian cancer employs Markov Decision Processes (MDPs) to achieve personalized and dynamic therapeutic schedules, significantly improving survival outcomes over static protocols (Paper 6).

Beyond treatment scheduling, RL's application extends to drug discovery and design. Generative frameworks such as PaccMannRL utilize transcriptomic data to condition the generation of anticancer compounds tailored to specific cancer profiles. These models optimize molecules for efficacy against cancer-specific molecular landscapes, showcasing RL's capacity to integrate systems biology with drug discovery (Paper 3). Additionally, RL has been leveraged to predict inhibitors for drug-metabolizing enzymes such as CYP2C9, combining structural knowledge with physicochemical properties. These models achieve high predictive accuracy and support the rational design of inhibitors for drug-drug interactions (Paper 4).

RL also plays a vital role in treatment pathway optimization. For instance, an RL-based approach modeled for oncology treatment trajectories demonstrated improved progression-free survival (PFS) compared to static protocols. By integrating multi-modal data, including tumor progression metrics and genetic markers, RL agents adapt therapeutic strategies to evolving patient conditions, significantly reducing treatment toxicity (Paper 8). The study highlights RL’s potential to bridge the gap between traditional protocols and personalized medicine by dynamically balancing efficacy and adverse effects.

RL’s adaptability is particularly evident in addressing stochastic tumor dynamics. Frameworks leveraging deep deterministic policy gradient algorithms successfully manage emergent resistance by preemptively adapting dosing schedules to evolving tumor characteristics, minimizing resistance amplification (Paper 5). These approaches showcase RL’s ability to predict and counteract resistance mechanisms in real-time.

These diverse applications highlight RL’s capacity to address critical challenges in oncology, from optimizing dosing schedules and designing combination therapies to discovering personalized drugs and adapting to evolving resistance mechanisms. Insights from these studies collectively position RL as a cornerstone of next-generation precision oncology, promising improved outcomes and a significant reduction in treatment-related toxicity.

Artificial intelligence (AI) and ML play a significant role in precision medicine by utilising techniques such as fuzzy expert systems, artificial neural networks, and machine learning, as shown in Figure 2. ML models have been previously established to predict drug-biomarker interactions for predicting cancer resistance. AI is employed in healthcare for virtual and physical applications, ranging from electronic health records to robotic-assisted surgeries and AI-generated prosthetics. As a subset of AI, machine learning enables personalised experiences by leveraging algorithms and data to make predictions supported by mathematical data points[139]. Artificial intelligence models can be trained on active clinical genomic data to not only analyse which respective inhibitor can be used based on the resistance mechanism that arises for a particular anti-cancer drug but also forecast potential resistance mechanisms that may arise for newer experimental drugs based on their chemical structures and interactions with the drug targets[140].

Conventional Hansch analysis, linear and non-linear classification algorithms, pharmacophore modelling and artificial neural networks, supervised and unsupervised, can predict ABC transporter inhibitors[141]. Previously, machine learning (ML) models have shown potential in predicting chemotherapy response based on ABC transporter expression in breast cancer, acute myeloid leukaemia, nasopharyngeal carcinoma and Hodgkin lymphoma[142], [143], [144], [145].

Recent studies have developed classification models specifically targeting the prediction of CYP2C9 inhibitors. These models integrate structural knowledge of the CYP2C9 enzyme with the physicochemical properties of potential inhibitors. Using machine learning algorithms like support vector machines and random forests, researchers achieved an accuracy of approximately 80% in predicting inhibitors from large datasets such as ChEMBL and PubChem[146]. Quantitative structure-activity relationship models using various descriptors have also been constructed for multiple CYP isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4). Techniques like random forests and XGBoost were employed to create high-performance predictive models for drug-drug interactions[147].

The data from experimental and in silico studies can be curated, such as in Table 1, and a multifactorial approach can be employed to provide a uniform approach to precision medicine. AI-ML models can be utilised to predict and diagnose a treatment plan accordingly; the patient's response can then be inputted back into the model so that with each patient, the model learns to be more precise and employs a more extensive database of drugs and correlated molecular targets.

1. **Conclusion**

The key takeaway is that the molecular mechanisms behind multidrug resistance in cancer are multifactorial and complex. Targeting only one mechanism may be insufficient to overcome chemoresistance. Gene expression profiling of patients in accordance with ABC transporters, CYP enzymes, IAPs, UGT enzymes, HER2, and epigenetic modifications can help develop more precise predictive models for chemotherapy response, as demonstrated in breast cancer patients undergoing neoadjuvant chemotherapy[148]. The staging, grading, and classification of cancer, along with tumour microenvironment characterisation and molecular characterisation, which focuses on identifying the genetic biomarkers mentioned in the paper, can be used to create personalised medicine treatments.

One of the limitations of this review is its heavy reliance on in vitro studies and the lack of extensive in vivo validation for many of the findings. Further research, particularly clinical trials, is needed to confirm the clinical significance of these biomarkers and the efficacy of targeted therapies.

Following clinical confirmation of the link between genetic biomarkers and resistance to a particular anti-cancer therapy, AI and ML models can be utilised to assess each patient for a large-scale genetic biomarker to ensure personalised treatment. ML models can predict drug-biomarker interactions and chemotherapy responses based on the expression of various resistance-related genes, including ABC transporters and CYP enzymes. These models can assist in identifying appropriate inhibitors based on the resistance mechanism and predicting potential resistance mechanisms for new drugs. Thus, a multifactorial approach that integrates clinical and molecular data, including gene expression profiling, tumour characteristics, and genetic biomarkers, is recommended to develop precise predictive models and personalised medicine treatments.

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