
Chrono-Adaptive Resistance Disruption (CARD): A Novel Pharmacological Framework to Address Anticancer Drug Resistance

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Abstract

Drug resistance in anticancer therapy has long remained an open problem in biomedical and pharmacological research in oncology. Nevertheless, despite numerous efforts aimed at targeting biological mechanisms at the molecular and pathway levels and testing various combination therapies, the present pharmacological approach has remained largely stagnant and insensitive to changes in circadian rhythms of tumor biology and drug resistance. However, an emerging body of preclinical and clinical data suggests that circadian rhythms play a pivotal biological role in regulating drug metabolism, cell stress, DNA repair, and adaptive resistance mechanisms. This article introduces a conceptual framework termed Chrono Adaptive Resistance Disruption (CARD), and proposes a novel pharmacological strategy aimed at using circadian biology to control anticancer drug resistance. Unlike other approaches based on chronotherapies and/or resistance management, CARD focuses on proactive disruption of resistance trajectories based on time optimal drug regimens and adaptive pharmacological interventions. It provides a biological framework, supported by various preclinical and clinical data in the biomedical and pharmacological literature. Notably, to date, this combined strategy has not been explicitly conceptualized as an integrated framework in the biomedical and pharmacological literature, underlining the potential novelty and translational relevance of CARD.

Keywords: resistance to anticancer drugs; chrono pharmacology; circadian rhythm; adaptive resistance; pharmacodynamics; chrono adaptive resistance disruption

Introduction

Anticancer pharmacotherapeutic agents such as targeted therapies, antibody-drug conjugates, immune checkpoint inhibitors, and precision-guided small molecules have revolutionized the treatment of cancer [1]. Despite all these developments, drug resistance is currently recognized as the main reason for treatment failure, tumor recurrence, tumor metastasis, and cancer-related mortality[2]. From a biomedical and pharmacological perspective, drug resistance is no longer considered a phenomenon resulting from constant genomic mutations but rather a dynamic and adaptive biological phenomenon involving time-dependent variations in intracellular signaling, pharmacokinetics, tumor metabolism, DNA repair, and phenotypic plasticity[3].

Recent advances in circadian oncology have revealed that tumor cells contain dysregulated but functioning molecular clocks involving the CLOCK, BMAL1, PER, and CRY proteins, which regulate tumor cell transcriptional oscillations controlling cell cycle, apoptosis, oxidative stress,

autophagy, immune surveillance, and xenobiotic metabolism [4]. These oscillations directly regulate drug absorption, intracellular drug exposure, drug target engagement, DNA damage accumulation, and repair kinetics [5]. Therefore, the pharmacodynamic sensitivity of tumor cells to cytotoxic, targeted, and immunotherapeutic agents may be significantly altered according to the time of day when drug administration occurs [6].

The traditional dosage forms of chemotherapy agents have been standardized and have been based on chronological time, ignoring the biological time differences in the host and cancer cells[7]. The conventional approach, based on static dosing regimens, may inadvertently allow cancer cells to be exposed during their period of relative low susceptibility, while simultaneously triggering the activation of adaptive survival pathways during the post-treatment recovery period[8]. Recent studies indicate the importance of the temporal match between the dosing regimen of chemotherapeutic agents and the circadian vulnerability period, where the lack of such temporal match contributes to the development of reversible drug-tolerant persister states, altered expression of ABC transporters, increased DNA repair, and metabolic compensation [9]. The relevance of the circadian timing system has been emphasized in the development of resistance in breast cancer and glioblastoma, where circadian disruption has been directly implicated in the development of endocrine resistance, ABCB1 transporter-mediated efflux, temozolomide tolerance, stemness maintenance, and activation of the DNA repair pathway [10, 11]. In the case of breast cancer, BMAL1/PER2 expression has been implicated in the development of altered estrogen receptor expression, leading to endocrine resistance. In the case of glioblastoma, the circadian control of DNA repair enzymes and tumor stem-cell cycling influences the efficacy of chemotherapy agents such as alkylating agents and kinase inhibitors [11].

While chronotherapy has traditionally been based on the administration of chemotherapy agents during the time of day when the tumor is most susceptible, based on the principle of minimizing toxicity, the current literature does not reflect the development of a unifying pharmacological approach for the exploitation of the biological timing differences for the disruption of the development of resistance using the principles of chronotherapy [12]. In order to bridge this gap, we have developed the concept of Chrono-Adaptive Resistance Disruption (CARD), based on the development of the concept of circadian vulnerability mapping, adaptive resistance surveillance, and chrono-sequential therapeutic interventions[13]. CARD introduces the concept of time as a variable in the development of the pharmacological approach for the disruption of the development of chemotherapy agent resistance, based on the principle of interrupting the development of resistance during the reversible period of early adaptive states, unlike conventional approaches to the management of chemotherapy agent resistance, where the

approach has been largely based on the conventional paradigm of therapeutic failure[14]. This opinion aims to establish the biological rationale, pharmacological mechanisms, relevance, and clinical implications for the development of CARD **(See Figure 1)**, the novel approach for the disruption of chemotherapy agent resistance.

Figure 1: Chrono-Adaptive Resistance Disruption (CARD)

2. Pharmacological Mechanisms Underlying Anticancer Drug Resistance

2.1 Target-Based and Pathway

Resistant cells can arise owing to intrinsic changes in the targets themselves, activation of the compensatory signalling pathways, and reprogramming of feedback circuits [18]. Point mutations in the kinase areas, over-expression of the target, and approaches that circumvent downstream signaling reduce the drug efficacy based on its pharmacodynamic profile [19]. Taking into account the aspect of chronopharmacology, the function status of the signalling pathways does not stay constant; in fact, it follows circadian patterns, meaning that the efficiency of drug-target interactions becomes time-dependent [20].

2.2 Drug Transport, Metabolism, and Circadian Regulation

The transportation of the drug, the metabolism of the drug, and circadian rhythm regulation all contribute significantly to anticancer therapy resistance. The first one is associated with changes

in transport pathways through cancer cell membranes **[18]**. It concerns the up-regulation of the membrane transport proteins responsible for the active efflux of anticancer agents from tumor cells and their subsequent elimination. Such efflux pumps include P-glycoprotein (P-gp), Multidrug resistance-associated proteins (MRPs), etc. Increased expression levels of ABC transporters have been reported to be associated with multidrug resistance to several cancers **[19]**. The second one relates to the enhanced activities of different enzymes involved in the transformation of anticancer agents in the bodies. In particular, this may concern an elevated expression and activity level of cytochrome P450 enzymes (CYP450 family). As a result, increased metabolism leads to the increased destruction of the drug molecule into inactive compounds**[20]**. Furthermore, variations in Phase II metabolic enzymes can help increase the efficiency of detoxification and, consequently, the protection of tumor cells from the harmful effects of the medication. As far as circadian rhythm regulation is concerned, it should be mentioned that the circadian clock affects the daily rhythms of genes' expression concerning the drug transportation, metabolism, and repair**[21]**. Disturbance in circadian rhythm regulation could lead to improper functioning of drug transportation and metabolism pathways resulting in drug inefficiency. Understanding the importance of chronobiology for pharmacokinetics and pharmacodynamics has led to the idea of chronotherapy, i.e., delivering the drug to a patient according to certain rhythms.**[22]**

2.3 Adaptive Drug Tolerance and Pharmacological Plasticity

Adaptive drug tolerance is a state of transient and reversible survival of cancer cells to high and lethal concentrations of drugs without the acquisition of permanent mutations for drug resistance[23]. This state is mechanistically defined by chromatin remodeling, epigenetic plasticity, metabolic downshifting, oxidative stress buffering, activation of autophagy, and unfolded protein response signaling [24]. Drug-tolerant persister cells represent the ideal therapeutic interception target for cancer treatment. In breast cancer, the development of adaptive resistance to endocrine and CDK4/6 inhibitors is mediated by alterations in the circadian rhythm of the estrogen receptor, PER2 downregulation, and rhythmic changes in the expression of ABC transporters [25]. In the context of glioblastoma, the circadian rhythm of DNA repair enzymes such as MGMT and mismatch repair has the potential to impact temozolomide sensitivity [26]. Circadian variation in the proliferation and stress adaptation of tumor stem-like cells creates a pharmacologically exploitable temporal window of vulnerability [27]. CARD targets the temporal adaptive state of cancer cells before the establishment of permanent and clonal drug resistance.

3. Circadian Biology in Biomedical and Pharmacological Contexts

The disruption of the circadian rhythm plays an important role in developing resistance to anticancer drugs for various cancers. For instance, in breast cancer, BMAL1 and PER2 affect

the hormonal signaling and drug transport processes, where resistance develops due to the ABCB1-mediated drug efflux mechanism and endocrine escape, making it difficult to achieve the maximum benefits of using drugs like tamoxifen and doxorubicin, while the need for a proper sequencing of endocrine therapies cannot be overemphasized**[28]**. In glioblastoma, the CLOCK and CRY genes regulate the DNA repair process, and temozolomide resistance is due to the increased activity of MGMT-mediated DNA repair, making it necessary to focus on the timing of DNA repair during chemotherapy**[29]**. In colorectal cancer, PER1 expression influences the ability of resistance development via apoptosis escape, limiting the cytotoxicity of oxaliplatin; hence, the need to adopt drug infusion at specific times. Likewise, in lung cancer, the disruption of BMAL1 affects EGFR adaptation bypassing, limiting the efficacy of tyrosine kinase inhibitors (TKIs)**[30]** (Table 1).

Cancer Type	Circadian Target	Resistance Mechanism	Drug Class	CARD Relevance
Breast Cancer	BMAL1/PER2	ABCB1 efflux, endocrine escape	Tamoxifen, doxorubicin	endocrine sequencing
Glioblastoma	CLOCK/CRY	MGMT-mediated DNA repair	Temozolomide	DNA repair vulnerability targeting
Colorectal Cancer	PER1	apoptosis escape	Oxaliplatin	chrono-modulated infusion
Lung Cancer	BMAL1	EGFR adaptive bypass	TKIs	Timed kinase inhibition

Table 1. Recent literature linking circadian rhythm with cancer drug resistance mechanisms

3.1 Chrono-Adaptive Resistance Disruption (CARD)- A Novel Pharmacological Strategy

3.1.1 Definition & Conceptual Innovation

Chrono-Adaptive Resistance Disruption can therefore be defined as “a pharmacologically driven, time-dependent process that attempts to synchronize the administration of antitumor agents with the circadian rhythm of vulnerabilities in tumors while disrupting adaptive resistance mechanisms in a dynamic manner [31].” It is the principle behind CARD that differentiates it

from other treatments because instead of working with post-clinical failure, it targets resistance prevention.

4. Methodological Framework for CARD in Biomedical and Pharmacology Research

4.1 Temporal Pharmacodynamics Profile

CARD is preceded by a thorough assessment of the drug response profiles with respect to time. Pharmacodynamic probes for target inhibition, DNA damage accumulation, and apoptosis can help to determine the resistance profiles in the tumor. This is a departure from the conventional approaches on dose response, which are carried out on arbitrary points in time.

4.2 Adaptive Resistance Monitoring and Pharmacological Interception

The longitudinal tracking of molecular and pharmacological resistance phenotypes, such as circulating tumor DNA, transcriptional stress profiles, and metabolic signatures, allows early recognition of an adaptive resistance course. CARD offers a pre-emptive pharmacological treatment, the optimization of which with regards to timing or sequences prior to stable resistance emergence has yet to be standardized in biomedical pharmacology (see Figure 2).

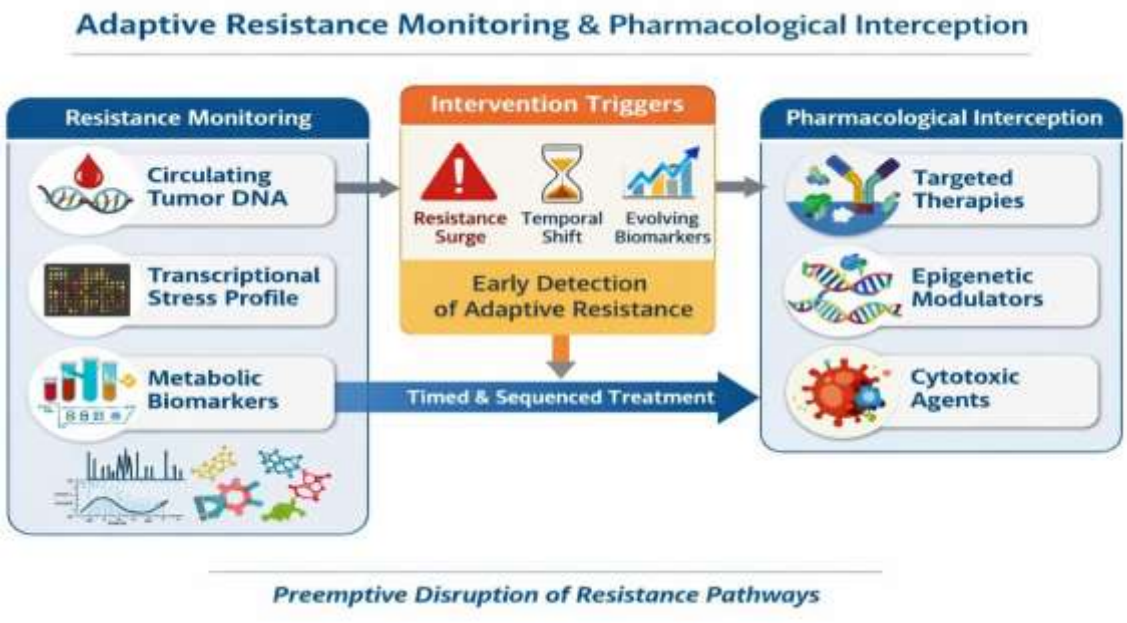

Figure 2: Adaptive Resistance Monitoring and Pharmacological Interception

4.3 Chrono-Sequential Drug

Instead of constant treatment, CARD uses chrono-sequential drug delivery, where various pharmacologic classes of drugs are released at distinct circadian times that are maximally suited to each drug's class and action. Cytotoxins, targeted therapies, and epigenetic modifiers are the precisely synchronized to disrupt resistance circuits. This approach is unprecedented among modern pharmacologic therapies.

4.4 Systems Pharmacology and Predictive Modeling

CARD merges system pharmacology models with machine learning techniques, which allow the prediction of the evolution of drug resistance depending on the temporal conditions. The approach considers time a fundamental parameter of pharmacology, which can be used for predictive purposes to optimize drug administration regimens.

5. Clinical and Translational implications of the CARD system.

The CARD system is highly compatible with the goals of biomedical and pharmacology research, covering the linkage between molecular mechanisms, drug actions, and clinical application. The implementation of CARD may help, amongst others, develop adaptive clinical trials, chronopharmacological schedules, and resistance-informed treatment guidelines. Emerging paradigms, especially within digital monitoring of healthcare and non- invasive marker analysis, provide added credence to the CARD-based treatment system.

6.Conclusion:

Chrono-Adaptive Resistance Disruption (CARD) represents a new pharmacological paradigm in which cancer drug resistance is viewed as a time-dependent and programmable process rather than an unavoidable end-stage response to long-term chemotherapy. By incorporating the principles of circadian biology, temporal pharmacodynamics, adaptive monitoring of cancer drug resistance, and systems pharmacology, the CARD model represents a new therapeutic paradigm in which the prevention of cancer drug resistance is the new goal of cancer chemotherapy. The new evidence from breast cancer and glioblastoma models lends strong support to the plausibility of the hypothesis. The integration of literature-supported circadian-based cancer drug resistance pathways and the emerging clinical evidence of chronotherapy also lends support to the plausibility of the hypothesis. While the new evidence is needed to support the hypothesis, the CARD model represents a strong new paradigm for the future development of new clinical trials of cancer chemotherapy.

List of abbreviation

CARD - Chrono-Adaptive Resistance Disruption
ABC - ATP-Binding Cassette
ABCB1 – ATP-Binding Cassette Subfamily B Member 1
ABCC1 – ATP-binding Cassette Subfamily C Member 1
ABCG2 - ATP-Binding Cassette Subfamily G Member 2
CYP450 – Cytochrome P450 Enzymes
UGT – Uridine Diphosphate Glucose
PK – Pharmacokinetics
PD - Pharmacodynamics
IC50 - Half Maximal Inhibitory Concentration
EC50 - Half Maximal Effective Concentration
MTD - Maximum Tolerated Dose
ROS - Reactive Oxygen Species
DNA - Deoxyribo Nucleic Acid
RNA - Ribonucleic Acid
mRNA - Messenger Ribonucleic Acid

Author contributions

Conceptualization: SSS**; Data curation:** SSR; **Methodology:** SSR; **Investigation:** AMM; **Supervision:** BS; **Validation:** BS; **Writing – original draft:** SSS, **Visualization:** SSS, AMM. All authors have read and agreed to the published version of the manuscript.

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