Biomedicine & Pharmacotherapy 105 (2018) 53–65

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Drug metabolizing enzymes and their inhibitors' role in cancer resistance

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ARTICLE INFO

Keywords:
Cancer
Resistance
Drug metabolizing enzymes
UGTs
GSTs
DPDs
TPMTs

ABSTRACT

Despite continuous research on chemotherapeutic agents, different mechanisms of resistance have become a major pitfall in cancer chemotherapy. Although, exhaustive efforts are being made by several researchers to target resistance against chemotherapeutic agents, there is another class of resistance mechanism which is almost carrying on unattended. This class of resistance includes pharmacokinetics resistance such as efflux by ABC transporters and drug metabolizing enzymes. ABC transporters are the membrane bound proteins which are responsible for the movement of substrates through the cell membrane. Drug metabolizing enzymes are an integral part of phase-II metabolism that helps in the detoxification of exogenous, endogenous and xenobiotics substrates. These include uridine diphospho-glucuronosyltransferases (UGTs), glutathione-S-transferases (GSTs), dihydropyrimidine dehydrogenases (DPDs) and thiopurine methyltransferases (TPMTs). These enzymes may affect the role of drugs in both positive as well negative manner, depending upon the type of tissue and cells present and when present in tumors, can result in drug resistance. However, the underlying mechanism of resistance by drug metabolizing enzymes is still not clear. Here, we have tried to cover various aspects of these enzymes in relation to anticancer drugs.

1. Introduction

Currently cancer is one of the very few diseases on which exhaustive industrial as well as academic research is being conducted [1]. The basic reason for this immense focus is the dreadful nature of cancer, which involves uncontrolled proliferation of cells and has the potential to invade in different regions of the physiological system [2]. In 1990's, the main attention was given to the development of chemotherapeutic agents which could be utilized as the first line of therapy against cancer, but later on, after FDA approved many small heterocycles for the management of cancer, the research direction shifted towards developing agents which could overcome the various mechanisms of resistance reported against previously approved anti-cancer agents [3]. There are several ways by which cancerous cells can acquire resistance to cytotoxic drugs [4]. Some major mechanism of resistance against chemotherapeutic agents in cancer include primary and secondary acquired mutations [5], cross talk signaling of kinases, drug inactivation, altered cell cycle regulation and check points, blocking apoptosis, cancer stem cells, epigenetic alterations such as DNA methylation, histone modification or metabolic abnormality *etc* [6] (Fig. 1). Amongst them, researchers, since long, have majorly studied pharmacodynamic mechanisms of resistance such as, single point mutations [7] and cross signaling of kinases [8], and less focus has been laid on the pharmacokinetics mechanisms of resistance such as efflux pumps and drug metabolizing enzymes [9]. Pharmacokinetic resistance mechanisms majorly include alterations in the efflux pumps such as ATP-binding cassette (ABC) transporters such as P-glycoprotein (ABCB1), multidrug resistance associated protein 1 (ABCC1) [10,11], drug inactivation or drug elimination from the cell using drug metabolizing enzymes. The ABC transporters regulate the influx and efflux of drugs, which is an important step for the desired pharmacological action of the drug. In tumor cells, P-glycoproteins (P-gps), a drug-efflux pump coded with ABCB1, develop resistance by actively expelling chemotherapeutic agents from the tumor cells. It also hampers the oral uptake of anticancer drugs. As suggested by literature, paclitaxel, a drug used as a first line therapy against breast and lung cancer, showed increase in absorption in a P-gps-knockout (6-times higher AUC) mice when compared to wild-type mice. Further, it has been observed that administration of P-gps inhibitors in murine models enhance the oral bioavailability of paclitaxel. Above findings point out at the fact that deviation and polymorphism in P-gps activity can lead to alteration in the pharmacokinetics of drugs [12].

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https://doi.org/10.1016/j.biopha.2018.05.117
Received 18 March 2018; Received in revised form 21 May 2018; Accepted 23 May 2018

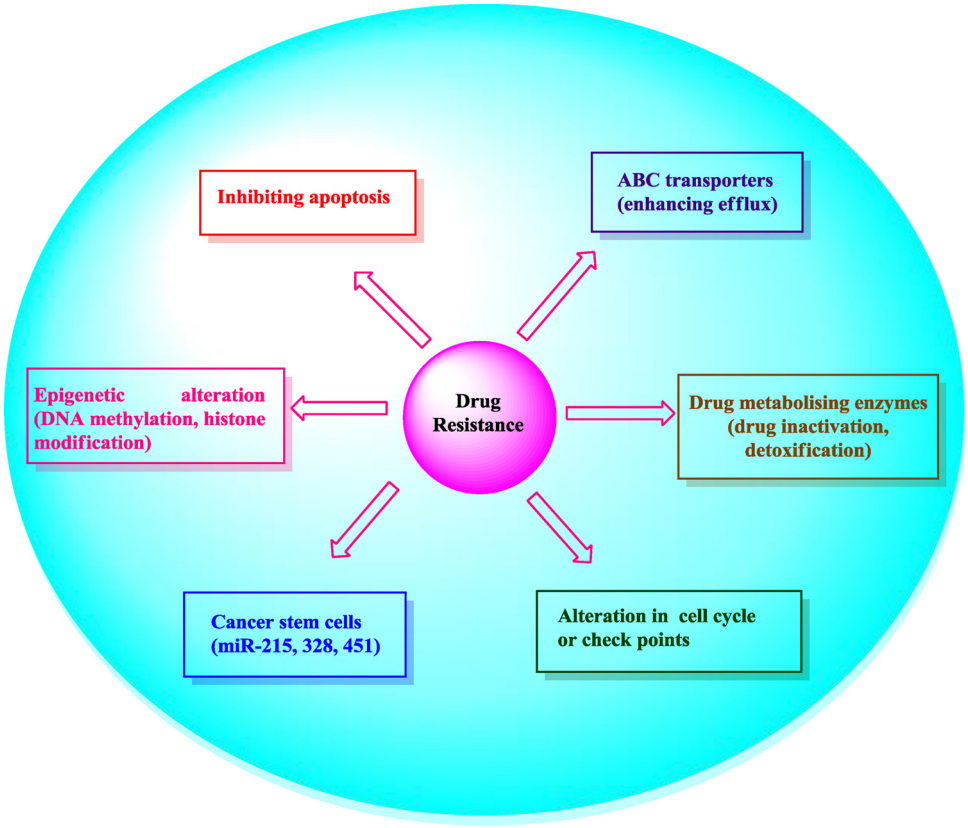

Fig. 1. Different mechanism of drug resistance.

Another important unfamiliar mechanism of resistance is the deactivation of the molecules by drug metabolizing enzymes (DMEs). DMEs regulate both the activation and deactivation process of chemotherapeutic agents. But tumoral DMEs are majorly involved in deactivation of chemotherapeutic agents, thereby imparting immunity to cancer cells. These enzymes are the major source of variation in a drug's therapeutic efficacy and toxic effects towards the specific organs and tissues. Conversely to other DMEs, tumoral DMEs negatively alter the potency and efficacy of chemotherapeutic agents. Few such tumoral DMEs includes uridine diphospho-glucuronosyltransferases (UGTs), glutathione-S-transferases (GSTs), dihydropyrimidine dehydrogenases (DPDs) and thiopurine methyltransferases (TPMTs) [13].

One of the commonly observed such example is of UGT superfamily enzymes, which catalyze glucuronidation of their substrates.

Another superfamily of detoxifying enzymes includes GST superfamily, well-known to prevent damage of biomolecules from electrophilic species. Overexpression of GSTs in tumors cells increases deactivation of chemotherapeutic agents leading to a reduction in their efficacy [14]. In general, drug deactivation of anti-cancer agents is one of the reasons of resistance acquired by anticancer drugs that requires advance exploration.

However, the clinical significance of DME in cancer chemotherapy is still not clear, thus our main focus in this review is to provide evidence towards the role and clinical implications in cancer resistance, including expression and physiological functions of drug metabolizing enzymes (other than cytochrome p450 superfamily) within the tumor cell, in order to explore them as potential drug targets.

2. Role of drug metabolizing enzymes in pharmacokinetic resistance

2.1. Uridine diphospho-glucuronosyltransferase (UGTs)

UGTs are found in the cytosol and help in the glucuronidation reaction, a chief component of phase-II metabolism. Human UGT genes, including UGT1 and UGT2, are found expressed throughout the physiological system, including organs such as breast, prostate gland, placenta, and play a vital role as metabolic defense system against pathogenic invasion. The literature suggests, in various cancer stages, downregulation of UGT1 A1 expression occurs [13]. Similarly, its expression is also inversely regulated by methylation on the promoter region of DNA. However, overexpression of tumoral UGT, UGT1 A1 has been reported to limit the function of topoisomerase I inhibitor irinotecan. Interestingly, upon suppressing UGT1 A1, function of irinotecan is restored [15]. This limitation in the therapeutic potential of anti-cancer agents in correlation with tumoral UGT1 A1 expression establishes its role in resistance [16].

Physiologically, UGTs catalyze the transfer of the glucuronyl moiety of uridine diphospho-glucuronosyltransferase to various endogeneous substates such as bilirubin, bile acids, steroids and exogenous molecules such as drugs and pollutants. The formation of glucuronide product help in the easy excretion or elimination of drug from the body as compared to substrate, as it makes the product more polar and water soluble [17]. However, the decrease in the enzyme activity in rest of the body may cause toxic consequence for drugs, as glucuronidation step is the important part of phase-II metabolism in the detoxification process. But upregulation of the same in the tumor results in failure of therapeutic outcomes of the drug.

2.1.1. Structural features of UGTs

Based on the similarity in the sequences, UGTs enzymes are