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REVIEW

P-glycoprotein inhibitors of natural origin as potential tumor chemo-sensitizers: A review

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ABSTRACT

Resistance of solid tumors to treatment is significantly attributed to pharmacokinetic reasons at both cellular and multi-cellular levels. Anticancer agent must be bio-available at the site of action in a cytotoxic concentration to exert its proposed activity. P-glycoprotein (P-gp) is a member of the ATP-dependent membrane transport proteins; it is known to pump substrates out of cells in ATP-dependent mechanism. The over-expression of P-gp in tumor cells reduces the intracellular drug concentrations, which decreases the cytotoxicity of a broad spectrum of antitumor drugs. Accordingly, P-gp inhibitors/blockers are potential enhancer for the cellular bioavailability of several clinically important anticancer drugs such as, anthracyclines, taxanes, vinca alkaloids, and podophyllotoxins. Besides several chemically synthesized P-gp inhibitors/blockers, some naturally occurring compounds and plant extracts were reported for their modulation of multidrug resistance; however, this review will focus only on major classes of naturally occurring inhibitors *viz*., flavonoids, coumarins, terpenoids, alkaloids and saponins.

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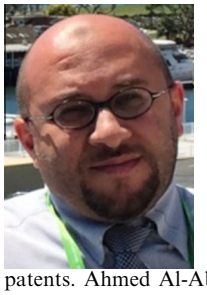

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Introduction

Definition and molecular background

Multidrug resistance (MDR) is the ability of drug resistant tumors to exhibit simultaneous resistance to a number of structurally and functionally unrelated chemotherapeutic agents.

P-glycoprotein (P-gp), the very famous MDR family member protein, was first characterized in multidrug resistant Chinese hamster ovary (CHO) cells by Ling and co-workers [1]. P-gp transports in a unidirectional fashion any xenobiotic as a substrate outward via an ATP-dependent mechanism. In tumor cells, expression of P-gp results in reduction of intracellular drug concentrations with consequent decrease in the cytotoxicity of a broad spectrum of antitumor drugs including anthracyclines (e.g. doxorubicin; DOX), vinca alkaloids (e.g. vincristine), podophyllotoxins (e.g. etoposide) and taxanes (e.g. taxol). Gene sequence analysis in different species revealed two human P-gp genes, three mouse P-gp genes and one P-gp gene in hamster cells [2]. Structure of human P-gp protein comprises 1280 amino acid in 12 transmembrane segments and one ATP-binding motif with three characteristic glycosylation sites [3].

Three different P-gp isoforms were identified (P-gp class I, II and III); only P-gp class I and III were characterized in various normal human tissues with potential role in the normal physiology of these tissues [4]. P-gp class III is expressed in liver hepatocytes; and mice lacking its expression fail biliary phopholipid secretion. P-gp is expressed as well in a wide range of epithelia with potential transport function, such as colon, small intestine, liver, pancreas, kidney, uterus and placenta. In addition, P-gp was found expressed in highly specialized capillary transport endothelia such as brain and testis [5–8].

Other MDR-related proteins were discovered within different types of malignancies [9] such as multidrug resistance related proteins (MRP's) [10,11] and breast cancer resistance protein (BCRP-1) [12–14]. Compounds inhibiting these P-gp related efflux proteins are supposed to increase the intracellular concentration of chemotherapeutic agents in similar way to inhibiting P-gp molecule itself. [15–18].

Despite the role of P-gp transporter in normal physiology; the overexpression of P-gp (and related proteins) on tumor cells results in significant decrease in the intracellular concentration of a wide range of anticancer drugs nonetheless of natural origin. Early evidence for the role of P-gp in the efflux of anticancer drugs outward and abolishing their cytotoxicity was observed before more than two decades. Purified membrane vesicles from resistant tumor cells significantly bind more radiolabeled vincristine [19,20]. P-gp showed significant role in the transport of anthracyclines in Madin–Darby canine cells as well [20]. In addition, radiolabeled colchicines transport was found to be mediated by purified P-gp particles [21].

Several molecular mechanisms have been postulated for P-gp mode of action such as increasing the intracellular pH, depolarizing plasma membrane electric potential, proton and chloride ion pumps [22,23]. The leaflet flip model of Higgins and Gottesman appears to be the most descriptive molecular explanation to the mode of P-gp action [24].

P-gp receptor modulation

The P-gp inhibitor may act as a competitive blocker via occupying the drug binding sites or as a non-competitive antagonist by binding chemosensetizer sites [25]. Example for competitive binding of two drugs on the same binding site of P-gp molecule was found for competition between radiolabeled vinblasine and azidopine on purified P-gp molecules [26]. Similarly, binding of radiolabeled vinblasine was inhibited by co-incubation with vincristine and daunorubicin [27]. On the other hand, colchicines, actinomycin-D and calcium channel blockers do not compete for vinblastine-binding site within P-gp molecules; yet inhibiting the binding of radiolabeled vinblasine or azidopine would suggest multiple binding domains on P-gp molecules [28]. ATPase activity of P-gp molecule was first