Reversing multidrug-resistance of cancer stem cells by natural agents

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Abstract

Cancer stem cells (CSCs) are a subpopulation of malignant cells with the capacity of self-renewal, differentiation, metastasis and tumorigenesis. It is believed that CSCs are also responsible for failure of chemotherapy in various tumor types, since they become resistant to a wide range of anti-cancer drugs. Inappropriate drug delivery, due to overexpression of efflux pumps, is one of the main factors contributing multidrug-resistance (MDR) of CSCs. To achieve more effective therapeutic strategies, significant effort has been made to identify natural agents that specifically target MDR in CSCs. For instance, a number of flavonoids have shown to be MDR reversal agents by inhibiting P-glycoproteins (P-gp), including baicalein, quercetin, phloretin , silymarin and icaritin that enhance the cytotoxicity of other chemotherapeutics. Sesquiterpenes, such as mogoltacin, conferone, auraptene, celafolin and celorbicol ester, are another group of natural derivatives that reverse MDR through inhibition of P-gp and other transports like MRPs and ABCG2. Curcumin, a well-known polyphenol natural product, prevents P-gp activity, and very interestingly, demethoxycurcumin and bisdemethoxycurcumin down regulate the expression of MDR1, which encodes P-gp. Beside exploring new natural compounds, current chemotherapeutics have also been developed to directly inhibit the activity of P-gp and MRPs in cancer cells. For example, vinblastine and azidopine bound to the transport sites of P-gp, while amoxapene and ioxapine non-competitively bound at the allosteric sites of P-gp, all leading to the intracellular accumulation of its substrates.

Keywords: Cell and Cancer, Cancer Stem Cells, Stem Cells and Cancer, Drugs and Cancer, Chemotherapy

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