The Multidrug Transporter Patched: A New Therapeutic Target for Cancer Therapy

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Short Communication

Despite the major progresses in biomedical research and the development of novel therapeutic strategies, cancer is still among the dominant causes of death worldwide. One of the crucial challenges in the clinical management of cancer is primary (intrinsic) and secondary (acquired) resistance to both conventional and targeted chemotherapeutics. Multidrug resistance (MDR) has been intensively studied, and one of the most prominent mechanisms underlying MDR is over expression of members of the family of ATP-binding cassette (ABC) transporters [1,2]. These transporters use energy derived from the hydrolysis of ATP to transport a wide range of substrates (endogenous toxicants and xenobiotics but also chemotherapeutic agents) across biological membranes against a concentration gradient. Since the discovery that the over expression of ABC transporters in cancer cells can mediate resistance to anti-cancer drugs, research has been directed towards developing compounds that inhibit the efflux activity of ABC transporters and increase classical chemotherapy efficacy. However, to date, the Food and Drug Administration (FDA) has not approved the use of any ABC transporter inhibitor due to toxicity issues [3,4].

It has long been postulated that the multidrug efflux transporter P-glycoprotein (P-gp/ABCB1/MDR1) mediates the main mechanism of resistance within cancer cells [5]; however, we recently showed that the Hedgehog (Hh) receptor Patched, which is over expressed in many recurrent and metastatic cancers, pumps chemotherapeutic agents such as doxorubicin (dxr) out of cancer cells thereby also contributing to chemotherapy resistance [6]. Patched is not an ABC transporters. Indeed, we showed that Patched uses the proton motive force to efflux drugs similarly to the bacterial efflux pumps from the RND family [6]. This may seem surprising in mammalian cells; however, the alteration of energy metabolism that occurs in hypoxic conditions in cancer cells has been shown to lead to lactate accumulation and intracellular acidification [7-9]. Accordingly, rapidly dividing cancer cells produce and release large amounts of protons into the extracellular compartment due to enhanced glucose utilization. This pattern of acidic extracellular environment and the alkaline cytosol is considered a hallmark of malignant cancers and is referred to as a “reversed pH gradient” [10]. Therefore, in cancer cells, Patched can function as an efflux pump using the proton gradient. This makes Patched a particularly relevant therapeutic target for cancers expressing Patched such as lung, breast, prostate, ovary, colon, brain, adenocortical carcinoma, melanoma [11-13] and myeloid leukemia [14,15] (see the Human Protein Atlas website http://www.proteinatlas.org/ENSG00000185920-PTCH1/cancer), and Patched drug efflux inhibitors potentially represent much more cancer specific and less toxic therapeutics than ABC transporters antagonists.

We developed screening tests to identify molecules able to inhibit the drug efflux activity of Patched [16]. Based on this screen, we identified several molecules able to inhibit Patched drug efflux activity and to enhance chemotherapy efficiency on different cancer cell lines which endogenously over express Patched (ongoing studies). One of these molecules is a natural compound purified from a marine sponge [17].

References

B member 1 (ABCB1) and subfamily C member 10 (ABCC10) are not primary resistance factors for cabazitaxel. Chin. J. Cancer. 2015;34:115-20.


