



The development of multidrug resistance in cancer cells: the potential of ABC transporter-targeted therapy to overcome inefficiency of treatment

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Conventional chemotherapy has been widely used as a first-line treatment for cancer patients. On the one hand, these drugs are efficient against all types of cancer because of their non-selective biodistribution; on the other hand, their usage is limited by side effects (Janmaat *et al.* 2017; Kim and Khang 2020). Chemoresistance, as a result of increasing DNA repair or overexpression of ATP-binding cassette (ABC) transporters, constitutes another obstacle (Kim and Khang 2020).

ABC proteins constitute a highly conserved and ubiquitous family of proteins. Forty-eight genes and one pseudogene encoding these proteins have been classified into seven subfamilies (A–G) according to their sequence and structure similarity (Gomez-Zepeda *et al.* 2020). ABC transporters utilize energy derived from ATP hydrolysis to transport molecules across the plasma membrane against their gradient. Expression of ABC transporters has been detected in sundry tissues, especially relevant to biological barriers; these proteins are responsible for absorption, distribution and elimination of the drug (Adamska and Falasca 2018; Bloise *et al.* 2016). The overexpression of genes encoding

ABC transporters has been observed in many types of cancer and is related to the presence of multidrug resistance (MDR) (Adamska and Falasca 2018; Fultang *et al.* 2020).

MDR is the process of resistance to a broad spectrum of structurally diverse compounds and is a major cause for the inefficiency of chemotherapy (Adamska and Falasca 2018). ABC transporters, as potent efflux pumps, remove drugs from cancer cells and thereby reduce the drug's effect. Therefore, accumulation of anticancer substrate is limited by ABC transporter activity (Dantzig *et al.* 2018; Goldstein 1995). Studies on a bat-derived cell line have shown that knockdown of the ABCB1 gene or culture with verapamil, an ABCB1 inhibitor, significantly decreases cell viability. These results suggest that higher expression of the ABCB1 gene is connected with excessive drug efflux (Koh *et al.* 2019); ABCB1 overexpression makes treatment failure three times more likely (Choi and Yu 2014; Trock *et al.* 1997). Overexpression of ABC transporters has also been reported in cancer stem cells (CSCs) that occur in cancers with enhanced tumorigenic potential and MDR (Begicevic and Falasca 2017).

Therefore, exploring the genes encoding ABC proteins could contribute to solving the problems of chemotherapy failure (Kim and Khang 2020).

Inhibitors of ABC transporters, such as PSC-833, GF120918, verapamil or tyrosine kinase inhibitors, might modulate the activity of these proteins and promote the intracellular accumulation of drugs (Wu and Fu 2018). At the same time, there is no successful and safe agent to counteract MDR via inhibiting the activity of ABC transporters, and there is a lack of knowledge about the particular molecules that make up their substrates. Gaining an insight into the specific substrates transported by these proteins might throw light on the role played by ABC transporters in CSC function and the occurrence of MDR. This in turn may lead to the development of novel strategies (Begicevic and Falasca 2017).

When MDR occurs more frequently, using chemotherapy alone becomes useless and inefficient. Thus, exploring ABC protein activity and the development of ABC transporter-targeted therapy has considerable potential to reverse chemoresistance and the ineffectiveness of cancer therapies.

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