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Invited review

The importance of breast cancer resistance protein to the kidneys excretory function and chemotherapeutic resistance

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ABSTRACT

The relevance of membrane transporters gained momentum in recent years and it is now widely recognized that transporters are key players in drug disposition and chemoresistance. As such, the kidneys harbor a variety of drug transporters and are one of the main routes for xenobiotic excretion. The breast cancer resistance protein (BCRP/*ABCG2*) is widely accepted as a key mediator of anticancer drug resistance and is a prominent renal drug transporter. Here, we review the role of BCRP in both processes and present a multitude of variables that can influence its activity. An increasing number of renally cleared chemotherapeutics, including tyrosine kinase inhibitors, described as BCRP substrates can modulate its activity via transcription factors and cellular signaling pathways, such as the phosphoinositide 3-kinase (PI3K) pathway. In addition to pharmacological actions, genetic variations, as well as differences between species and gender can affect BCRP function, which are also discussed. Furthermore, the role of BCRP in light of cancer treatments and the implications for novel therapeutic interventions that take into account renal function are discussed.

Contents

1. Introduction

Transporters are key players in drug disposition, with active roles in excretion, drug-drug interactions and other pharmacologically relevant interactions, such as drug-nutrient or drug-toxicant interactions, thereby influencing the concentration of the drug at the target site (Konig et al., 2013). Our understanding of the role played by transporters and their contribution to physiological processes has gone beyond the classical view where these mechanisms were merely responsible for translocating substrates from the cytoplasm to extracellular compartments and *vice versa* (International Transporter et al., 2010). Xenobiotic transporters are implicated in many processes, including intestinal absorption, maintenance of blood-organ barriers – including the brain, testis and placenta, – bile secretion in the liver, as well as in renal function, where the overwhelming majority of xenobiotics and metabolic bi-products are excreted via active membrane transport (Konig, et al., 2013; Nigam, 2015).

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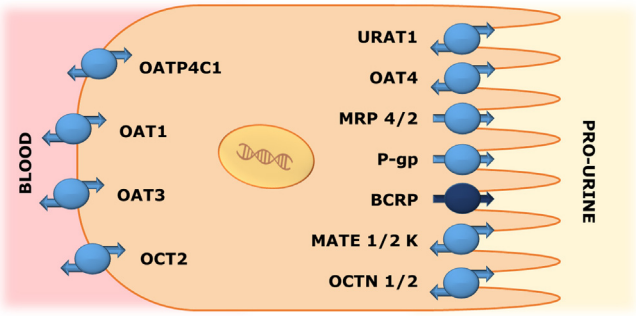

Fig. 1. Drug transporters in the proximal tubule. Influx transporters facing the blood side: organic anion transporter protein 4C1 (OATP4C1), organic anion transporter 1 and 3 (OAT1 and −3) and organic cation transporter 2 (OCT2). Efflux Transporters expressed at the apical membrane – urate anion exchanger 1 (URAT1), OAT4, multidrug resistance protein 2 and 4 (MRP2 and −4), and P-glycoprotein (P-gp). Breast cancer resistance protein (BCRP), multidrug and toxin extrusion protein 1 and 2K (MATE1 and −2K) and the organic carnitine transporter 1 and 2 (OCTN1 and −2). Solute carrier transporters (SLCs) are depicted as ⇐⇒, and ATP binding cassette (ABC) transporters as ⊂⇒.

The kidneys are responsible for a variety of key regulatory functions that are tightly associated with other physiological processes. These include regulation of physiological pH by maintaining appropriate acid-base homeostasis, generation of hormones responsible for stimulating the production of red blood cells and regulation of blood pressure by controlling the volume of body fluids. The kidneys are also responsible for nutrient reabsorption and the hallmark of renal function is their excretory role of endo- and xenobiotics from the peritubular capillaries into the pro-urine. (Masereeuw et al., 2014). The properties that enable renal transporters to mediate drug excretion are also of paramount importance in chemotherapeutic drug resistance. Although physiologically distinct, cancer drug resistance and renal excretion both rely on active (i.e. ATP-driven) membrane transport, via multidrug resistance efflux transporters of the ABC superfamily.

A myriad of factors contribute to chemoresistance, as cancers are inherently heterogeneous, and their genetic instability can facilitate the acquisition of drug resistance either to cope directly with cytotoxic drugs or to recover from their effects (Ifergan et al., 2005; Gonen and Assaraf, 2012; Ferreira et al., 2016; Li et al., 2016; Wijdeven et al., 2016; Zhitomirsky and Assaraf, 2016). Cell survival mechanisms can be hijacked, growth pathways permanently activated, or the DNA repair machinery enhanced, thereby reducing cellular sensitivity to DNA damage (Jeggo et al., 2016). Programmed cell death cascades can become altered or silenced, rendering cancer cells resistant to toxic stress. Further, metabolic processes and enzymatic activities are upregulated and adapted in order to cope with high bioenergetics demands stemming from accelerated growth (Li et al., 2016; Wijdeven et al., 2016). Chemotherapy by itself can promote or enhance drug resistance phenotypes. This phenomenon arises when cancer cells alter their homeostasis by modifying gene expression or re-routing signaling pathways as a response to drugs targeting particular cellular processes. Drugs can also exert selective pressure in the cancer microenvironment, favoring the growth of subpopulations with constitutive resistance genes or that adapt to harness such mutations (Holohan et al., 2013). This plasticity, derived from their genomic instability, is a major enabler of cancer chemoresistance.

On top of these effects, multidrug efflux pumps expel a wide spectrum of structurally and mechanistically distinct chemotherapeutic agents from tumors, hence limiting their cytotoxic potential. Given the plethora of factors contributing to cancer chemoresistance (Gonen and Assaraf, 2012; Ferreira et al., 2016; Li et al., 2016; Raz et al., 2016; Wijdeven et al., 2016; Zhitomirsky and Assaraf, 2016), multidrug efflux transporters are just a component of a fairly large array of mechanisms of chemoresistance. Nonetheless, since the original description of a multidrug resistance (MDR) protein, *P*-glycoprotein (P-gp, *ABCB1*), the body of evidence validating the role of membrane transporters in poor cancer drug response has markedly expanded (Fletcher et al., 2016). The additional depiction of P-gp in adult organs, including the kidneys, and the discovery of a myriad of other drug transporters, cemented the role of these transporter proteins in drug resistance and excretion. The breast cancer resistance protein (BCRP/ABCG2), has been increasingly implicated in the handling of renal clearance of metabolites and relevant therapeutic drugs, including many chemotherapeutic agents. In the kidneys BCRP expressed at the apical membrane along with other MDR efflux transporters, including P-gp, with great substrate promiscuity between them and consequent functional redundancy in urinary excretion. In the current review, we present the role of BCRP regarding both kidney function and cancer MDR.

2. Renal transporters and drug excretion

In the process of removing solutes from the systemic circulation, following glomerular filtration, water, nutrients and salts are reabsorbed to prevent losses, whereas xenobiotics such as drugs and environmental toxicants, as well as metabolic bi-products, endogenous wastes, must be removed from the bloodstream and concentrated in the urine. This latter process takes predominantly place at the proximal tubule epithelium (PTE), which expresses multiple membrane transporters, as well as an array of phase I and phase II metabolism enzymes. Together, these elements render PTE cells (PTEC) crucial for disposition of xenobiotics. PTEC are highly polarized and specialized cells that consist of two surfaces, one exposed to the interstitium, thus surrounded by a network of capillaries, and another exposed to the tubular lumen and covered with microvilli, forming a brush-border membrane with a large surface area (Fig. 1). This polarization of cells enables them to act as a selective barrier, where solutes, ions, drugs, metabolites and other compounds can be shuttled unidirectionally either back to the circulation or into the pre-urine. Membrane-bound carrier proteins are responsible for the selective nature of transport in PTE, by binding substrates in order to relocate them. These proteins can be divided into ion channels, solute carriers, aquaporins or efflux pumps. With regard to drug excretion, efflux pumps belonging to two families are pivotal to the process.

The Human genome organization (HUGO; http://www.genenames.org) reports a highly diverse group of membrane transport proteins that includes over 300 entries, *viz.* the solute carrier (SLC) family. A number of these carriers are expressed in the PTE, providing specificity for different classes of drugs, as well as metabolites and nutrients; these transporters are involved in both excretion and reabsorption of solutes. SLC transporters facilitate the uptake of xenobiotics from the interstitium and a range of substrates including negatively charged solutes handled by organic anion transporters 1 and 3 (OAT1, *SLC22A6* and OAT3, *SLC22A8*, respectively), as well as the organic anion transporter polypeptide 4C1 (solute carrier organic anion transporter family member 4A1; *SLCO4C1*) (Nigam et al., 2015). Alongside, the organic cation transporter 2 (OCT2; *SLC22A1*) handles positively charged solutes. The apical side of PTEC faces the lumen of the nephron and a set of transporters present at this side extrude solutes, drugs, metabolic bi-products and other compounds into the ultra-filtrate, a process which concentrates xenobiotics and metabolic waste compounds in the urine. Present at this side are the multidrug and toxin extrusion protein 1 and 2 (MATE1 (*SLC47A1*) and MATE2K