

Title Page

**The role of ABC transporters in tissue defense and organ
regeneration**

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Running Title Page

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Non-standard abbreviations:

ABC; ATP Binding Cassette, BCRP; Breast Cancer Resistance, BSEP; bile salt export pump, CYP; cytochrome P-450, EMT; epithelial to mesenchymal transition, FAH; fumarylacetoacetate hydrolase, HSC; hematopoietic stem cell, KSL; ckit⁺/Sca-1⁺/ Lin⁻ stem cell population, *mdr1a/1b*^(-/-); MRP; multidrug resistance protein, P-glycoprotein-deficient, P-gp; P-glycoprotein, SP; side population

Abstract

ATP Binding Cassette (ABC) transporters are ATP-dependent membrane proteins predominantly expressed in excretory organs, like the liver, intestine, blood-brain barrier, blood-testes barrier, placenta and kidney. Here, they play an important role in the absorption, distribution and excretion of drugs, xenobiotics and endogenous compounds. In addition, the ABC transporters, P-glycoprotein (P-gp/*ABCB1*) and Breast Cancer Resistance Protein (BCRP/*ABCG2*), are highly expressed in a population of primitive stem cells: the Side Population (SP). SP cells were originally discovered in bone marrow by their capacity to exclude rhodamine 123 and Hoechst 33342, but extensive research revealed their presence in other non-hematopoietic tissues as well. The expression levels of BCRP and P-gp are tightly controlled and may determine the differentiation of SP cells towards other more specialized cell types. Although their exact function in these cells is still not clear, they may protect the cells by pumping out toxicants and harmful products of oxidative stress. Transplantation studies in animals revealed that bone marrow-derived SP cells contribute to organ repopulation and tissue repair after damage, e.g. in liver and heart. The role of SP cells in regeneration of damaged kidney segments is not yet clarified. This review focuses on the role of ABC transporters in tissue defense and regeneration, with specific attention to P-gp and BCRP in organ regeneration and repair.

Introduction

ATP Binding Cassette (ABC) transporters form one of the largest families of membrane transport proteins expressed in all organisms. This diverse transporter family has been extensively studied and its members play a vital role in many cellular processes. ABC transporters are responsible for multidrug resistance of cancer cells (Hyde et al., 1990), but may also be capable of transporting several substrates like metal ions, peptides, amino acids, sugars and a large number of hydrophobic compounds and metabolites across the plasma membrane as well as intracellular membranes (Dean et al., 2001).

The human ABC transporter family consists of 49 members which are divided in 7 subfamilies, from A to G, based on similarity in gene structure, order of the domains and sequence homology. Until now, 16 ABC genes have been linked to inherited diseases, like Tangier disease (*ABCA1*), Dubin Johnson syndrome (*ABCC2*), Pseudoxanthoma elasticum (*ABCC6*) and Cystic Fibrosis (*ABCC7*) (Dean, 2005). Although some ABC transporters have been studied extensively, the functions of many others are still unknown. The development of ABC transporter knockout animals has provided us with some insights into the function and characteristics of ABC transporters (Schinkel et al., 1997; Xia et al., 2007; Glaeser and Fromm, 2008).

ABC transporters have an important role in tissue defense through the excretion of toxic compounds and their metabolites (Russel et al., 2002; Szakacs et al., 2008). The expression levels of the transporters are tightly regulated, emphasizing their importance in organ protection (Leslie et al., 2005). Moreover, two ABC transporters, the Multidrug Resistance Gene 1 product (*MDR1/ABCB1*), P-glycoprotein (P-gp), and ABCG2 or Breast Cancer Resistance Protein 1 (BCRP), have been implicated in tissue regeneration. Both efflux pumps are highly expressed on side population (SP) cells, a population of primitive bone marrow-derived stem cells with long term repopulating capacities. A loss of expression leads to cell differentiation, indicating that P-gp and BCRP might determine stem cell-induced tissue remodeling through their differential expression. SP cells have been implicated in the

regeneration of various organs, like liver (Lagasse et al., 2000), skeletal muscles (Jackson et al., 1999) and heart (Jackson et al., 2001). Several studies addressed their participation in renal regeneration, but others excluded their role (Kale et al., 2003; Poulsom et al., 2003; Duffield and Bonventre, 2005; Huls et al., 2008b). Here an overview of the role of ABC transporters in tissue defense and organ regeneration is given, with a focus on the role of P-gp and BCRP in these processes. Special attention is given to their potential in regeneration of damaged nephron segments after acute kidney injury.

ABC transporters in tissue defense

The localization of ABC transporters in organs with a barrier function and the broad substrate specificities suggest an important role in tissue defense. The efflux pumps are determinants for the absorption, distribution and excretion of drugs, xenobiotics and their metabolites (Figure 1). Entrance in the systemic circulation is prevented by the apical expression of ABC transporters in the intestine (Mao and Unadkat, 2005), like P-gp and BCRP, and the action of these transporters leads to a decreased drug concentration in the liver. The liver is the major site of xenobiotic metabolism in the body, in which enzymes, like the cytochrome P-450 (CYP) family members catalyze the oxidative metabolism of many drugs, eventually affecting both drug efficacy and drug toxicity (Schuetz et al., 1996). P-gp is able to mediate cellular efflux of CYP modulators, like rifampicine. Rifampicine induces CYP3A activity in a dose-dependent manner, thus a lower intracellular concentration results in a decreased CYP3A activity (Schuetz et al., 2000; Yasuda et al., 2002).

Drug distribution to the brain is hampered by ABC transporters like P-gp, multidrug resistance proteins 1 and 2 (MRP1/2; *ABCC1/2*), MRP4 (*ABCC4*) and BCRP in the blood-brain barrier (Kusuhara and Sugiyama, 2001; Begley, 2004; Perriere et al., 2007). Although these transporters protect the central nervous system, effective drug treatment of brain tumors, epilepsy and several mental disorders is limited (Potschka et al., 2002; Tate and Sisodiya, 2007; Gerstner and Fine, 2007; Loscher and Potschka, 2005; Fellner et al., 2002). The importance of transporters in the blood-brain barrier was emphasized in *mdr1a*^(-/-) mice,

which died from the neurotoxic action of ivermectin, a known P-gp substrate, after treatment for mite infestation (Schinkel, 1997;Schinkel et al., 1995).

ABC transporters affect, besides drug absorption and drug distribution, also the excretion of drugs into the bile or urine. In the liver, ABC transporters are responsible for the elimination of xenobiotics and their metabolites into bile (P-gp, Bile Salt Export Pump (BSEP; *ABCB6*), MRP2) or in the systemic circulation (MRP1/3). More water-soluble drugs can be excreted into urine by the kidney, where ABC transporters are localized along the apical membrane (P-gp, MRP2/4 and BCRP) of proximal tubule cells.

The defense mechanism formed by ABC transporters under physiological circumstances is directed against accumulation of potentially harmful compounds. Interestingly, in a situation of organ damage or disease, changes in the expression levels of ABC transporters have been observed, likely to compensate for the increased load of harmful products of oxidative stress formed during an insult or to compensate for the loss of efflux pumps in damaged tissues. In severe human liver disease (primary biliary cirrhosis, cell necrosis or chronic hepatitis), MRP2 is down-regulated, but P-gp, BCRP, MRP1 and MRP3 (*ABCC3*) were up-regulated, suggesting protection against the accumulation of toxic bile constituents and prevention of further liver damage (Ros et al., 2003a;Van der Borght et al., 2006). A genetic defect in *ABCC2* leads to mild hyper-bilirubinemia, called the Dubin Johnson syndrome. These patients show up-regulation of MRP3 in the liver (Corpechot et al., 2006). In this way, the body uses a compensatory mechanism to prevent (further) injury, a phenomenon also seen in other organs. In the intestine, a temporary up-regulation of P-gp was found after ischemic reperfusion damage, stimulating tissue recovery indirectly by reducing accumulation of potentially harmful substances (Omae et al., 2005). After an ischemic insult in the brain, various ABC transporters were up-regulated, among which the increase in *Bcrp* was most pronounced. This not only prevents brain penetration of harmful compounds, but might also positively affect neurogenesis (Dazert et al., 2006). In the skin, cellular cholesterol levels regulate *ABCA1* expression, which suggests that this key

cholesterol efflux carrier controls the maintenance of the keratinocyte barrier (Jiang et al., 2006).

Information on renal ABC transporters during injury or tissue repair is limited. After partial nephrectomy mRNA levels of P-gp were elevated, which was also found for Mrp2 (Laouari et al., 2001). Following renal damage induced by cadmium or lipopolysaccharide, increased P-gp levels were seen as well (Thevenod et al., 2000; Heemskerk et al., 2007). In addition, after the induction of ischemia-reperfusion injury in mice, expression levels of P-gp and Bcrp were up-regulated but Mrp2 levels were decreased (Huls et al., 2006). This is in contrast to experiments performed in rats, where Mrp2 levels were clearly upregulated after renal injury (Heemskerk et al., 2007; Notenboom et al., 2006).

In the mammary gland of lactating animals, expression of BCRP was highly upregulated and responsible for the active secretion of nutrients into milk, but also responsible for the excretion of toxicants and drugs, like topotecan, PhIP (2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine) and cimetidine (Jonker et al., 2005).

In SP cells, the transporters P-gp and BCRP also define the specific stem cell phenotype, possibly because the efflux pumps protect stem cells from genetic damage due to naturally occurring toxic compounds which are substrates for these transporters (Krishnamurthy et al., 2004). Expression levels are downregulated upon SP cell differentiation and hematopoietic maturation (Bunting et al., 2000; Bunting, 2002). It was suggested that BCRP expression may play a role in early stem cell self-renewal by partially blocking differentiation, and P-gp may promote differentiation and engraftment (Bunting et al., 2000). Apparently, both efflux pumps are essential in tissue remodeling by SP cells.

P-glycoprotein/ABCB1

P-glycoprotein was discovered in 1976 as an efflux pump in a colchicin-resistant cell line, and ten years later, the gene encoding for P-gp was discovered. Until now, it is the most extensively studied ABC transporter. In addition to its expression in a number of tissues with a barrier function (Figure 1), P-gp is also present in many hematopoietic cell types (Drach et

al., 1992), including CD34⁺ stem cells (Chaudhary and Roninson, 1991), c-kit⁺ stem cells (Sorrentino et al., 1995) CD56⁺ Natural Killer (NK) cells and CD8⁺ cytotoxic T cells (Neyfakh et al., 1989; Klimecki et al., 1994; Drach et al., 1992; Chaudhary and Roninson, 1991).

P-gp is capable of transporting many drugs and endogenous substrates. P-gp substrates are cationic or amphipathic in nature and mainly hydrophobic, indicating that they can diffuse passively across the membrane and penetrate tissues. Besides its ability to induce chemotherapy resistance, P-gp confers resistance to a vast array of clinically and toxicologically relevant compounds, including immunosuppressive drugs, HIV protease inhibitors and antibiotics (Bauer et al., 2005; Sarkadi et al., 2006). To overcome the problem of multidrug resistance, P-gp function is inhibited with substrates usually acting as competitive inhibitors, like verapamil and cyclosporin A (first and second generation of P-gp inhibitors), or by blocking P-gp function directly (third generation inhibitor), like elacridar (GF120918) (Breedveld et al., 2006; Hyafil et al., 1993; Dantzig et al., 1996; Pussard et al., 2007; Ejsing et al., 2006).

The development of P-gp-deficient mice, the *Mdr1a/1b*^(-/-) mice, contributed to the identification of more specific substrates. Rodents have two genes encoding for the efflux pump, *Mdr1a* and *Mdr1b*. At first sight, no obvious phenotype was discovered in these mice except for a larger susceptibility to drug toxicity due to accumulation in the brain or liver (Schinkel, 1997). However, after careful characterization altered gastrointestinal and renal phenotypes were discovered. Under specific pathogen-free conditions, *Mdr1a*-deficient (*Mdr1a*^(-/-)) mice developed spontaneous colitis and signs of severe chronic inflammation of the gut, probably caused by abnormalities in the epithelial lining of the gut (Resta-Lenert et al., 2005). We recently showed that the double knockout (*Mdr1a/1b*^(-/-)) mice have disturbed renal tubular function caused by decreased intracellular ATP levels and impaired mitochondrial morphology (Huls et al., 2007). The generalized proximal tubular dysfunction demonstrates striking similarities with renal Fanconi syndrome, as tubular reabsorption of amino acids and low molecular weight proteins were decreased. These findings emphasize the importance of the efflux pump for intestinal and renal tubular function.

In addition to its protective function, P-gp has also been implicated in resistance to apoptosis. Several mechanisms have been described that could explain this event. First, P-gp might inhibit Fas-induced caspase-3 activation possibly by inhibiting caspase 8 activation. ATP binding and/or hydrolysis are required for its caspase inhibitory effects, because mutations in the ATP binding regions abolished P-gp-mediated Fas resistance (Ruefli et al., 2002). Secondly, P-gp may affect ceramide-induced apoptosis. Ceramide mediates cell death, but is intracellularly converted into the non-toxic glucosylceramide. By mediating the translocation of glucosylceramide from the cytosolic to the luminal face of the Golgi, P-gp influences ceramide metabolism and, indirectly, causes apoptosis resistance (Pallis et al., 2002;Turzanski et al., 2005). After injury, apoptosis contributes to tissue remodeling and elimination of redundant or damaged cells and by stimulation of this pathway, P-gp may affect the regeneration process in damaged tissue.

Breast Cancer Resistance Protein 1/ABCG2

Breast Cancer Resistance Protein (BCRP) was first cloned by Doyle et al. (1998) in the drug resistant breast cancer cell line (MCF-7). BCRP is a half-transporter with a size of 72 kDa, and, like other ABC half-transporters, BCRP probably functions as a homodimer. Whether it may also function as a heterodimer with other ABCG subfamily members is unclear (van Herwaarden and Schinkel, 2006). BCRP expression overlaps largely with P-gp, as the protein can be found in tissues like the placenta, prostate, small intestine, brain, colon, liver and ovary (Doyle et al., 1998). We recently discovered BCRP in human kidney as well, where the protein is localized to the apical membrane of the proximal tubules (Huls et al., 2008a). In addition, BCRP was identified in the mammary gland of humans, cows and mice.

BCRP transports a wide range of substrates including large molecules, uncharged or compounds with an amphiphilic character. There is considerable overlap in anticancer drug substrate specificity between BCRP and P-gp, but there are also several differences in the substrate specificities of both transporters (Litman et al., 2000). Like P-gp, the efflux pump does not require glutathione (Krishnamurthy and Schuetz, 2006), but in contrast to P-gp,

BCRP is able to transport phase two metabolites, like sulfated compounds (Suzuki et al., 2003;Ebert et al., 2005;Ebert et al., 2007;Zamek-Gliszczynski et al., 2006). The substrate specificity of BCRP is clearly distinct from other G-subfamily members, like ABCG1, ABCG5 and ABCG8, which were all identified as cholesterol transporters, although cholesterol itself may affect its activity (Storch et al., 2007). Several of the substrates transported by BCRP were discovered using BCRP-deficient mice (*Bcrp1*^{-/-} mice) (Jonker et al., 2002;Jonker et al., 2005). These mice showed lethal phototoxicity when subjected to alfalfa containing diet due to pheophorbide A retention, indicating that BCRP may excrete porphyrins. In addition, it has been reported that BCRP transports estradiol, estrone-3-sulfate and dehydroepiandrosterone sulfate, and recently, also transport of other androgens and phytoestrogens were found (Janvilisri et al., 2003;Huss et al., 2005;Enokizono et al., 2007). Furthermore, BCRP expression appeared to be sex-specific (Merino et al., 2005) and may be highly influenced by sex steroids (Wang et al., 2006). These findings suggest a role for BCRP in steroid metabolism.

Role of P-gp and BCRP in stem cells

In 1991, Chaudhari and Robinson (1991) discovered the expression of P-gp on CD34⁺ hematopoietic cells. Ten years later, expression and functional activity of BCRP in these cells was identified (Zhou et al., 2001). These transporters are responsible for the SP phenotype, characterized by its low retention of rhodamine 123, transported by P-gp or BCRP (Litman et al., 2000;Honjo et al., 2001), and Hoechst 33342, transported by BCRP in the cells. Although mRNA of other ABC transporters, like ABCG1, ABCA1, MRP1, ABCD4 and ABCB2, was also detected in these cells, they seem not responsible for the 'SP' phenotype (Jonge-Peeters et al., 2007). SP cells are highly enriched for hematopoietic stem cell (HSC) activity and represent approximately 0.05% of the adult nucleated bone marrow cells in mice (Goodell et al., 1996). Approximately 70% of the classic stem cell population KSL (*ckit*⁺/*Sca-1*⁻/*Lin*⁻), known for its repopulation capacities, also has the SP phenotype (Bunting, 2002).

In recent years, it has become clear that the SP population not only resides within the bone marrow, but also in other non-hematopoietical organs, like spleen tissue, umbilical cord blood, brain, kidney, heart, intestine, skin and lungs (Asakura and Rudnicki, 2002; Larderet et al., 2006; Yano et al., 2005). In these organs, they appear to have the ability to differentiate into many cell types following reintroduction in vivo, including skeletal and cardiac muscle, neurons and epithelial cells like hepatocytes (Mezey et al., 2000; Lagasse et al., 2000; Krause et al., 2001; Jackson et al., 2001; Ferrari et al., 1998; Alison et al., 2000), but also in hematopoietic cells in lethally irradiated mice (Taniguchi et al., 1996; Jackson et al., 1999). This multipotent differentiation capacity of HSCs suggests that these cells contribute significantly to tissue remodeling. This was, for example, shown in mice suffering from tyrosinemia type I due to genetic fumarylacetoacetate hydrolase (FAH) deficiency, where bone marrow transplantation resulted in a restoration in FAH activity in the liver (Lagasse et al., 2000). P-gp is expressed in the hepatobiliary membrane and upregulated after hepatic damage in resident liver progenitor cells, also designated as oval cells (Ros et al., 2003a). After partial hepatectomy, the amount of oval cells increased and the subsequent liver tissue remodeling correlated with the observed expression of BCRP (Shimano et al., 2003). Furthermore, during end-stage primary biliary cirrhosis, increased expression of BCRP was also found in endothelial cells, indicating that SP cells in the isolate may not only correspond to oval cells but also to endothelial cells (Van der Borght et al., 2006). Apparently, the transporters protect these cells against toxic bile constituents and oxidative stress, and in this way, progenitor cells are able to initiate liver repair. A similar phenomenon was described for SP cells in the heart. During early cardiac development, BCRP expressing cells were observed, but the appearance of these cells decreased upon maturation (Martin et al., 2004). However, a small population of cells exhibiting the SP phenotype remains in the heart and these cells are capable of proliferation and differentiation, and likely also responsible for repair and regeneration of heart tissue after damage. Moreover, cardiac SP cells were able to regenerate the myocardium after cold-induced transplantation injury (Oyama et al., 2007). This phenomenon was also seen in the ischemic kidney, where bone marrow-derived cells

contributed to kidney remodeling after inducing renal ischemia (Kale et al., 2003;Gupta et al., 2002;Lin et al., 2003).

In addition to P-gp and BCRP, other ABC transporters may be involved in differentiation and regeneration processes. In human liver disease, expression levels of MRP1 and MRP3 were markedly increased, which was also seen in a comparable model conducted in rats (Ros et al., 2003a;Ros et al., 2003b). Additionally, in human keratinocytes, the differentiation of epidermal cells is characterized by the RNA upregulation of several ABC transporters, like MRP1, MRP3, MRP4, ABCG1 and especially ABCA7 (Kielar et al., 2003). It was suggested that ABCB1 and ABCG1 mediate the transport of phospholipids and the translocation of cholesterol. ABCA7 may have a dual role by keeping the lamellar body lipid homeostasis and in promoting the expansion of the cellular ceramide pool. This might direct the cells to execute essential programs, like cell cycle arrest, differentiation and apoptosis (Kielar et al., 2003). Although knowledge of the role of ABC transporters in organ repair and tissue regeneration increases, it is still limited and more research needs to be done to gain insight in these processes. It seems that P-gp and BCRP may be dominant transporters involved in tissue repair. Their specific function and mechanism are not yet understood, but their variable and controlled expression levels in SP cells and also in other cells, including renal epithelial cells, suggests an important function in regeneration.

Role of P-gp and BCRP in renal regeneration

The kidney has the capacity to regenerate almost completely after renal injury and stem cells either residing in the kidney and/or derived from bone marrow may take part in this process. In addition to HSCs and mesenchymal stem cells (Lin et al., 2003;Kale et al., 2003;Morigi et al., 2004), differentiated epithelial cells within the kidney have been implicated in renal remodeling. After renal injury, epithelial cells may acquire mesenchymal characteristics before proliferation thereby contributing to basement membrane repair (Sun et al., 2000;Poulsom et al., 2003). It was suggested that this is the most important mechanism of renal regeneration (Duffield 2005).This process, depicted in Figure 2, is called epithelial to

mesenchymal transition (EMT) and is known to be influenced by different cytokines and growth factors, influencing signal transduction pathways (Li et al., 2003).

The importance of P-gp and BCRP as xenobiotic efflux pumps, their apical localization in the kidney (Huls et al., 2008a; Huls et al., 2007; Pavelic et al., 1993) and their increased expression after ischemia-reperfusion injury in mice (Huls et al., 2006), suggest that absence of either transporter might lead to an increased sensitivity to injury. However, to our surprise we found the opposite in studies performed with P-gp- and Bcrp-deficient mice. Both mice appeared to be resistant to ischemia-reperfusion with no signs of renal injury, suggesting that the absence of both transporters is an advantage for renal repair (Huls et al., 2007; Huls et al., unpublished). After bone marrow transplantation from P-gp- or Bcrp-deficient mice into wild type mice, also protection against ischemic injury was observed (Huls et al., unpublished). This is in line with the hypothesis that bone marrow-derived cells differentiate into renal tubular cells and that P-gp and Bcrp are key players in this process (Huls et al., 2008b). The exact mechanism through which P-gp or Bcrp deficient bone marrow cells prevent renal damage is not fully clear. The decreased amount of dead cells after an apoptotic stimulus (H_2O_2) to bone marrow cells derived from P-gp-deficient mice indicates that these cells are less sensitive to apoptosis (Huls et al., 2007). The amount of apoptotic cells is a major determinant for the extent of renal damage after acute kidney injury, causing obstruction of the tubular lumen leading to a decrease in renal function (Kribben et al., 1999). Evidently, more research is needed to define the role of P-gp and Bcrp in renal protection.

Future perspectives

It is clear that P-gp and BCRP protect cells and tissues by reducing the accumulation of harmful compounds. On the other hand, their absence leads to protection against ischemic injury in the kidney, a mechanism in which bone marrow-derived cells seem to play an important role. As incomplete recovery of the kidney after acute injury may lead to progressive loss of renal function over time, novel, effective, treatment for acute kidney injury

remains a challenge. The contribution of SP cells is probably too small to reverse renal injury and to repair renal damage and the use of the bone marrow-derived cells in the clinic will be questionable. Still, the use of bone marrow-derived stem cells holds great promise. These cells have many advantages, predominantly through the absence of immunologic reactions. Therefore, future research should be directed to increase the contribution of bone marrow-derived cells to renal regeneration, possibly by modifying the expression of P-gp or BCRP in the bone marrow. Functional knock-down of P-gp or BCRP in by specific inhibitors or by small interfering RNA (siRNA) may be a novel strategy to treat acute kidney injury. The systemic inhibition of P-gp or BCRP is probably less successful because of the resulting accumulation of potentially toxic xenobiotics and metabolic waste products, due to enhanced absorption and reduced elimination. In addition, long-term P-gp inhibition or BCRP down-regulation might also provoke renal disorders, like observed in P-gp deficiency (Huls et al 2007), or enhanced toxic susceptibility, as reported for both knockout animals (Schinkel, 1997; Jonker 2002). A selective down-regulation of the functional expression of P-gp and BCRP in bone marrow may overcome these side effects. Obviously, methods should be developed *in vitro* and in animal models *in vivo* to test this concept in renal regeneration after injury.

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Bcrp1/ABCG2 is expressed in a wide variety of stem cells and is a molecular determinant of the side-population phenotype. *Nat Med* **7**:1028-1034.

Footnotes

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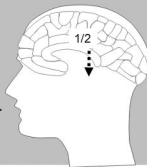
Legends for Figures

Figure 1. Tissue distribution of P-gp and BCRP. Dotted arrows indicate the direction of efflux of substrates excreted by P-gp or BCRP. Both transporters are expressed in the luminal membrane of the endothelial cells comprising the blood-brain barrier (1), where they protect the brain from toxic substrates, the choroid plexus within the brain (2), the apical membrane of epithelial cells of the mammary gland during lactation (3), the canalicular membrane of hepatocytes (4), the brush border membrane of proximal tubules (5), which mediates the excretion into the urine, the apical membrane of the intestinal epithelial cells (6), which prevents the absorption of substrates into the human body, the syncytiotrophoblasts (7) and the side population within the bone marrow (8).

Figure 2. Proposed mechanisms of renal regeneration. Differentiated tubular cells are able to regenerate the injured tissue after proliferation and spreading. Moreover, differentiated tubular cells could dedifferentiate via the process of EMT towards more primitive mesenchymal cells. Subsequently, cells migrate to the sites of injury and repair the damaged tubules. In addition, stem cells either localized within the kidney or derived from bone marrow might regenerate the damaged tissue by differentiation towards tubular cells. Upon differentiation, P-gp and BCRP are down-regulated in stem cells and transition cells.

Figure 1

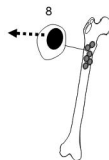
Oral intake



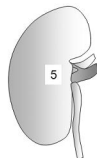
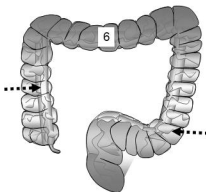
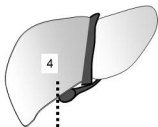
Intravenous admission



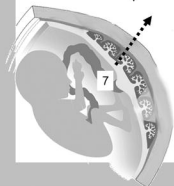
Vascular space



Breast milk



Urinary excretion



Fecal excretion



Figure 2

Epithelial to mesenchymal transition

