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REVIEW ARTICLE

Multiple resistance to carcinogens and xenobiotics: P-glycoproteins as universal detoxifiers

Thomas Efferth[1] · **Manfred Volm**[2]

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Abstract The detoxification of toxic substances is of general relevance in all biological systems. The plethora of exogenous xenobiotic compounds and endogenous toxic metabolic products explains the evolutionary pressure of all organisms to develop molecular mechanisms to detoxify and excrete harmful substances from the body. P-glycoprotein and other members of the ATP-binding cassette (ABC) transporter family extrude innumerous chemical compounds out of cells. Their specific expression in diverse biological contexts cause different phenotypes: (1) multidrug resistance (MDR) and thus failure of cancer chemotherapy, (2) avoidance of accumulation of carcinogens and prevention of carcinogenesis in healthy tissues, (3) absorption, distribution, metabolization and excretion (ADME) of pharmacological drugs in human patients, (4) protection from environmental toxins in aquatic organisms (multixenobiotic resistance, MXR). Hence ABC-transporters may have opposing effects for organismic health reaching from harmful in MDR of tumors to beneficial for maintenance of health in MXR. While their inhibition by specific inhibitors may improve treatment success in oncology and avoid carcinogenesis, blocking of ABC-transporter-driven efflux by environmental pollutants leads to ecotoxicological consequences in marine biotopes. Poisoned seafood may enter the food-chain and cause intoxications in human beings. As exemplified with ABC-transporters, joining forces in interdisciplinary research may, therefore, be a wise strategy to fight problems in human medicine and environmental sciences.

Keywords ABC-transporter · Cancer · Carcinogenesis ecotoxicology · Multi-drug resistance · Multi-xenobiotic resistance

Abbreviations

ABC	ATP-binding cassette
ADME	Absorption, distribution, metabolization and excretion
BCRP	Breast cancer resistance protein
cMoAT	Canalicular multispecific organic anion transporter
CYP	Cytochrome P450 monooxygenase
EGFR	Epidermal growth factor receptor
MDR	Multidrug resistance
mdr1	Rodent multidrug resistance gene 1
MDR1	Human multidrug resistance gene 1
MRP	Multidrug-resistance-related protein
MXR	Multi-xenobiotic resistance
P-gp	P-glycoprotein
NSCLC	Non-small cell lung cancer
TAP	Transporter associated with antigen processing

Introduction: role of P-glycoprotein for multidrug resistance of cancer

The existence of a plethora of exogenous xenobiotics in nature, as well as endogenous toxic metabolic products necessitates that all organisms on this globe possess molecular and cellular mechanisms to detoxify and excrete harmful substances. The detoxification functions

✉ Thomas Efferth
efferth@uni-mainz.de

Manfred Volm
m.volm@gmx.de

[1] Department of Pharmaceutical Biology, Johannes Gutenberg University, Mainz, Germany

[2] University of Heidelberg, Heidelberg, Germany

allow the survival even under adverse environmental conditions. This is a fundamental biological principle from unicellular to complex organisms such as mammals and human beings.

For this reason, the question can be addressed, whether or not evolutionary conserved detoxification mechanisms may exist, which are capable to recognize and extrude a wide variety of structurally and functionally different toxic compounds. Since organisms cannot predict to which toxins and how often they will be exposed during their life time, such mechanisms have to fulfill very broad detoxifying functions to reliably protect mechanisms from the detrimental effects of toxic substances.

A well-known transport protein with a very broad substrate specificity is an efflux pump termed P-glycoprotein, whose encoding gene has been first cloned in multidrug-resistant tumor cells in 1986 (Roninson et al. 1986). Soon after its identification, it turned out that P-glycoprotein and the *MDR1* gene belong to the human gene family of ATP-binding cassette (ABC) transporters, which consist of 49 gene members. ABC-transporters can be found throughout most—if not all—organisms from bacteria to humans and plants. The broad distribution of ABC-type pumps allows the speculation they may serve as universal detoxifiers in nature.

P-glycoprotein acts as an ATP-consuming transporter that extrudes a large multitude of diverse chemicals out of cells. The range of chemicals reaches from cytotoxic anticancer drugs (conferring multidrug resistance of tumors), to other pharmacological drugs in normal tissues in the body and also xenobiotics (mediating protection from toxic insults). This implies that one and the same biological principle, i.e. transport of chemical compounds, can lead to very different phenotypes:

1. P-glycoprotein expels numerous anticancer drugs in tumors, leading to pleiotropic or multidrug resistance (MDR), which ultimately causes failure of chemotherapy and death of tumor patients.
2. P-glycoprotein-expressing normal organs avoid the accumulation of harmful, carcinogenic compounds and thereby prevent carcinogenesis.
3. P-glycoprotein-expressing normal organs (e.g. gastrointestinal tract, kidney, liver, blood brain barrier, blood placenta-barrier etc.) are important for absorption, distribution, metabolization and excretion (ADME) of pharmacological drugs and hence for their therapeutic activity.
4. P-glycoprotein protects aquatic organisms from environmental toxins solved in water. This phenomenon has been termed multi-xenobiotic resistance (MXR) in analogy to MDR.

In the present review, we compiled facts and evidences from the literature to prove the hypothesis that P-glycoprotein and related ABC-transporters may act as universal detoxifiers in nature. Furthermore, this review addresses the implications of P-glycoprotein in different aspects of human health either by a direct action on the human being or indirectly, through its action in organisms used in human nutrition.

Multidrug resistance of tumors

The development of resistance to anticancer drugs has dogged clinical oncology since the very early days of chemotherapy. A surprising observation was that over the decades until today it was not possible to develop drugs without appearance of resistance phenomena in tumors. The development of combination therapy improved the situation compared to monotherapy, but sustainable treatment success leading to reliable cure of patients could also not be reached (Shapiro 1955; Frei et al. 1958; DeVita et al. 1970). Resistant tumor cells can acquire cross-resistance to a wide range of compounds that have no obvious structural or functional similarities, e.g., natural product derived drugs such as alkaloids (colchicine, vinblastine, vincristine), anthracyclines (doxorubicin, daunorubicin), taxanes (paclitaxel, docetaxel), or epipodophyllotoxins (etoposide, teniposide), as well as synthetic drugs such as tyrosine kinase inhibitors (imatinib, vemurafenib, ceritinib) (Biedler et al.1983; Riordan and Ling 1985; Efferth 2001; Gillet et al. 2007; Wu and Ambudkar 2014; Zeino et al. 2014; Katayama et al. 2015; Zheng et al. 2015). This phenomenon has been designated as MDR.

MDR of cancer cells is associated with decreased net cellular drug concentrations and has been attributed to alterations in the plasma membrane (Danø 1973; Juliano and Ling 1976; Skovsgaard 1978). A drug efflux pump termed P-glycoprotein (P for permeability) has been unraveled as underlying mechanism (Juliano and Ling 1976; Riordan and Ling 1979). P-glycoprotein was the first member of the ATP-binding cassette (ABC) transporter family identified in cancer. Its discovery enormously stimulated cancer research in subsequent years and numerous in vitro cell lines were characterized to overexpress P-glycoprotein and *MDR1* mRNA as well to carry amplified copy numbers of the *MDR1* genes in their genomes (Roninson et al. 1986; Shen et al. 1986; Watson et al. 2007). P-glycoprotein consists of 1258 amino acids, which are organized as two duplicated halves. It spans the cell membrane with 12 transmembrane segments and two intracellular ATP-binding domains. Drug molecules bind to intracellular binding domains at P-glycoprotein, which changes conformation by an energy-driven process (i.e. ATP cleavage) and

flips drugs to the extracellular space (Higgins and Gottesman 1992). In addition to P-glycoprotein, about one dozen other ABC transporters have been also suggested to transport anticancer drugs.

The development of resistance during repeated treatments with anticancer drugs has been termed acquired or secondary drug resistance. However, resistance can also occur in untreated tumors. This form of resistance is characterized by unresponsiveness to anticancer drugs, even if tumors have never been challenged with chemotherapy. This form is termed inherent or primary resistance. Clinically, both forms lead to the failure of chemotherapy and the question arises, whether P-glycoprotein/*MDR1* is the responsible mechanism for inherent and acquired drug resistance.

In a previous meta-analysis, a total number of 6.248 tumors were investigated for their P-glycoprotein and *MDR1* mRNA expression as well as *MDR1* gene amplification (Efferth and Osieka 1993). Therefore, we evaluated, whether the expression of P-glycoprotein/*MDR1* in human tumors was higher after chemotherapy as compared to untreated tumors before chemotherapy. Indeed, the results of the meta-analysis showed that the mRNA and protein expression levels considerably increased after chemotherapy (Efferth and Osieka 1993). This indicates that P-glycoprotein/*MDR1* plays a role for acquired or secondary drug resistance in the clinical setting. By contrast, *MDR1* gene amplification was a very rare event in clinical tumor samples and did not speak for its importance for acquired MDR in the clinic. In tumors with inherent drug resistance, overexpression of *MDR1* mRNA and P-glycoprotein expression frequently occurred as well. In conclusion, these results on a large number of clinical tumors indicated that *MDR1* mRNA and protein expression, but not gene amplification may account for both acquired and inherent MDR in the clinic.

Induction of P-glycoprotein expression

To fulfill its protective functions, P-glycoprotein can be constitutively expressed in organs, which are frequently in contact with toxins. On the other hand, P-glycoprotein expression may be induced in tissues with low expression after exposure to harmful substances. Early indications for P-gp induction trace back to the 1980s and 1990s.

The expression of ABC transporters proteins may be induced within a few hours in response to toxic insults. Gekeler et al. (1988) showed that the expression of P-glycoprotein is inducible in a short time by actinomycin D. The level of *MDR1* mRNA increased 2.5-fold within 72 h after actinomycin D was added. Chin et al. (1990a, b) reported that cells derived from human kidney carcinoma responded to heat shock and sodium arsenite exposure with an increased expression of *mdr1* mRNA within 8 h. After heat shock or sodium arsenite treatment, increased resistance of cells to vinblastine was observed. These results are in accordance with earlier data from Li and Hahn (1978), who reported that exposure to ethanol rendered cells more resistant to subsequent exposure of heat or doxorubicin. Carr et al. (1987) also found that ethanol induced drug resistance.

We analyzed the expression of P-glycoprotein to diverse acute cytotoxic insults. Murine NIH3T3 cells were exposed to doxorubicin, ethanol and caffeine. The cells were harvested 1 to 96 h after exposure and analyzed (Fig. 1). One hour after doxorubicin exposure, P-glycoprotein was moderately increased, from 6 to 24 h strong increases were observed, and at 36–96 h the expression declined to control levels again (Volm et al. 1995a, b). P-glycoprotein expression can occur in tumor cell lines without amplification of the MDR1 gene and even without over expression of MDR1 mRNA (Hill et al. 1990). Post-translational mechanisms are known to degrade P-glycoprotein in long-term drug-selected cells with a half-life time of 17 h (McClean and Hill 1993). It can be speculated that a comparable mechanism also accounted for the decrease of P-glycoprotein expression in short-term drug-treated cells. In cells treated with ethanol or caffeine, P-glycoprotein was moderately increased from 12 to 36 h. To estimate whether the increase of P-glycoprotein expression was accompanied by drug resistance and consequently by decreased drug accumulation, we determined rhodamine 123 accumulation 24 h after exposure to doxorubicin, ethanol or caffeine. Pretreated cells indeed accumulated rhodamine 123 to a lesser extent than untreated cells. Thus, reduced rhodamine 123 accumulation was a consequence of increased P-glycoprotein expression. In addition, we analyzed P-glycoprotein expression in a panel of rodent cell lines to examine, whether P-glycoprotein induction represents a general phenomenon. We found that 5 out 7 cell lines revealed increased P-glycoprotein expression upon exposure to doxorubicin, ethanol or caffeine (Volm et al. 1995a).

Furthermore, we analyzed P-glycoprotein expression in vivo after treatment of mice bearing L1210 leukemia ascites cells with doxorubicin (0.5 mg/kg body weight). The expression of P-glycoprotein was markedly increased already after 30 min and reached a maximum at 24 h after treatment. Thereafter, P-glycoprotein expression decreased again, and almost all cells were negative 96 h after treatment. A slight increase of drug resistance was determined 24 h after treatment (Volm et al. 1991a, b, c).

After these and other initial reports on P-glycoprotein upon short-term exposure to cytotoxic and xenobiotic drugs it turned out during the subsequent years that a wide variety of environmental insults are able to induce P-glycoprotein

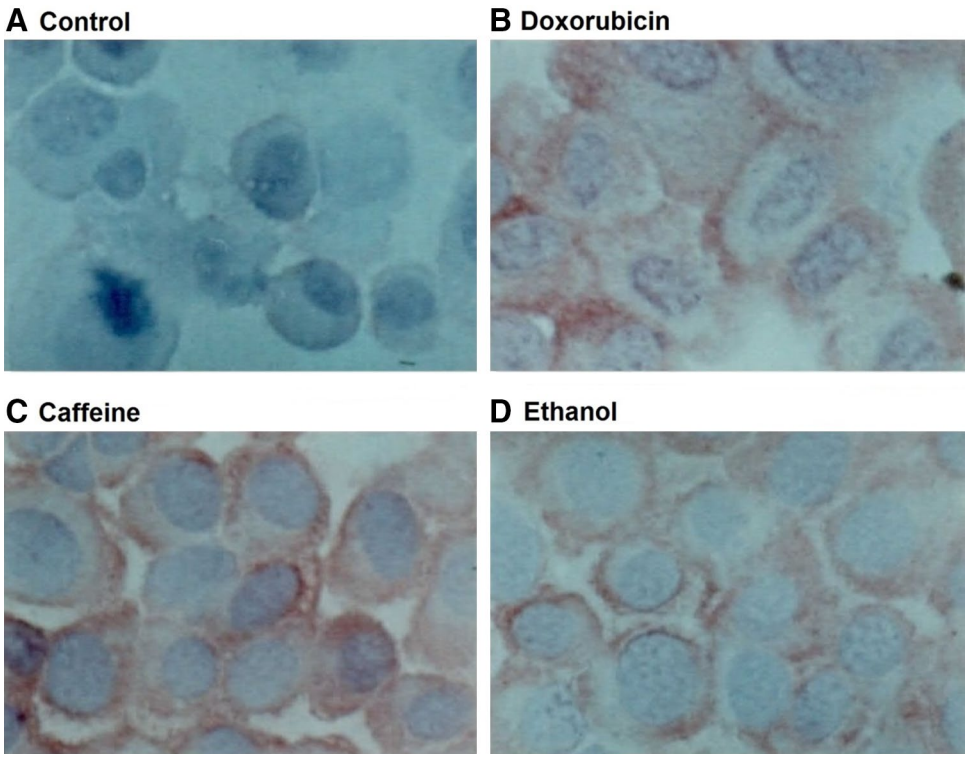


Fig. 1 Expression of P-glycoprotein in murine NIH-3T3 cells after exposure for 24 h to doxorubicin, ethanol and caffeine. Taken from Volm et al. (1995a, b)

expression leading to a stable MDR phenotype (Zhou 2008; Silva et al. 2015). The wide range of P-glycoprotein-inducing stimuli include not only direct transport substrates of this efflux pump such as chemotherapeutic drugs, but also many other stimuli:

- Mediators of inflammatory processes, e.g. lipopolysaccharide, interleukin (IL)1, IL6, tumor necrosis factor α (Akira and Kishimoto 1992; Sukhai and Piquette-Miller 2000).
- Ionizing radiation (Hill et al. 1994; Callaghan et al. 2008; Mattern et al. 1991).
- UV radiation (Ohga et al. 1998).
- Environmental herbicides, e.g. the herbicide and P-glycoprotein substrate paraquat (Dinis-Oliveira et al. 2006; Silva et al. 2011a).

The involvement of P-glycoprotein in the detoxification of environmental toxins led to the concept of intentional drug-driven expression of P-glycoprotein as antidotal pathway to prevent the detrimental effects of accidental intoxications by harmful substances (Silva et al. 2011a).

On the other hand, P-glycoprotein induction may also cause unwanted adverse events during drug therapy. Preparations of St. John's Wort (*Hypericum perforatum*) are frequently used as antidepressant herbal over-the-counter products without prescription or knowledge of the physicians. If St. John's Wort preparations are taken together with standard drugs (e.g. anticancer drugs, immunosuppressives etc.), dangerous drug interactions may take place leading to reduced drug plasma levels. The reason is that St. John's Wort causes increased metabolization of drugs in the liver. Hypericin as chemical constituent induces phase I CYP enzymes and phase III transporters such as P-glycoprotein in the liver. Due to these inductive effects, standard drugs are more rapidly metabolized and eliminated from the body, which ultimately leads to reduced and insufficient therapeutic effects (Kober et al. 2008).

In conclusion, the induction of P-glycoprotein may serve as protective mechanism to avoid cellular damage. The question arises, what would happen, if this protective mechanism fails. As a consequence, acute toxicity and death may occur on the one hand and tumor development and growth on the other hand. Hence, P-glycoprotein may be involved in resistance to carcinogenic processes.

Expression of ABC-transporters in normal organs and tissues

ABC-transporters cannot only be found in tumors as efflux pumps for anticancer drugs. They are also widely distributed in normal organs, where they transport a vast array of diverse substrates as part of the normal physiological processes in our body. To provide an overview of the human ABC transporter family, we selected 12 out of 49 efflux

pumps, which are known transporters of xenobiotics and which are related to MDR phenotypes (Gillet et al. 2007). We mined the GeneCards Database (http://www.genecards.org). Then, we subjected the protein expression data deposited in this database to hierarchical cluster analysis to see whether or not ABC-transporters are predominately expressed in certain organs in a coordinated fashion. Since ABC transporters may transport different kinds of compounds in different organs, we organized the normal tissues according to their main physiological functions (blood and immune, nervous, musculoskeletal, internal, secretory, reproductive). As shown in Fig. 2, a total of 69 normal tissues have been analyzed. *ABCC1* (*MRP1*), *ABCC4* (*MRP4*) and *ABCB1* (*MDR1, P-glycoprotein*) were the most frequent transporters expressed in normal tissues ($n=32$, $n=23$, and $n=22$, respectively). Liver was the organ, where most of the ABC transporters investigated were expressed. Seven out of 12 ABC-transporters were detected (*ABCA2, ABCB1, ABCB5, ABCC2, ABCC3, ABCC6, ABCC10*). Although close co-expression profiles for certain organs were not observed, some trends were visible in organs, where more ABC transporters were expressed than in others.

ABCB1, ABCC1 and *ABCC4* were frequently found in hematopoietic cells and organs (e.g. lymph node, tonsil, CD4-positive T-cells, CD8-positive T-cells, NK-cells, B-cells), indicating that these ABC transporters contribute to specific functions of the immune system. It is well-known that the ABC-transporter genes *TAP1* and *TAP2* (*ABCB2* and *ABCB3*) are involved in immunological processes such as antigen processing and presentation. To induce T-cell response, immunogenic proteins are intracellularly degraded to peptides, which are loaded onto the major histocompatibility complex I (MHC I), and *TAP* genes contribute to the assembly of the peptide-loading complex (Eggensperger and Tampe 2015). Remarkably, several other ABC-transporters were also expressed in immune cells. There are experimental data showing that they may be involved in the secretion of cytokines, growth factors, and cytotoxic agent (Efferth 2003). Dendritic cells are triggered by MRP1-mediated leukotriene C4 efflux (Randolph 2001). Hence, ABC transporters may control the accumulation of signal peptides regulating dendritic cell migration. Furthermore, P-glycoprotein expression is frequently correlated with enhanced susceptibility to lymphokine-activated killer cell activity (Savas et al. 1992). P-glycoprotein is expressed in resting and activated lymphocytes in autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, thrombocytopenic purpurea). These lymphocytes are resistant to drug treatment because of P-glycoprotein-mediated drug efflux (Tsujimura and Tanaka 2012; Richaud-Patin et al. 2004).

Among the tissues of the nervous and musculoskeletal systems, the retina of the eye expressed 5 out of 12 transporters investigated (ABCA2, ABCA3, ABCC1, ABCC3, ABCC5) (Fig. 2). P-glycoprotein and BCRP are expressed in intra-retinal vessels, and MRP1 and MRP4 can be found at the retinal pigment epithelium of blood-basal cell membranes, indicating differential abilities of ABC-transporters to restrict compound distribution across the blood-retina barrier (Chapy et al. 2016). In addition to these proteins, another ABC-transporter is also expressed in the eye, ABCA2 (ABCR). It is, however, not mentioned in Fig. 2, because our analysis was restricted to transporters of xenobiotic compounds. By contrast, ABCA2/ABCR transports complexes of retinal aldehyde and phosphatidyl ethanolamine in the retina (Borst et al. 2000). Mutations in this transporter contribute to Stargardt's macular dystrophy (Efferth 2001). The fact that not only ABCA2/ABCR but also several other ABC-transporters are expressed in the retina (Fig. 2) indicates that ABC-transporter-mediated translocations of substances other than retinols may also play a role in the retina.

The detoxification of xenobiotic compounds taken up by food or breath in internal organs plays an eminent role in the human body. The expression of numerous ABC-transporters in the liver has already been mentioned above. The liver represents a primary organ for the detoxification of harmful, exogenous compounds. ABC-transporters play a crucial role to fulfill this task.

The kidneys are also important detoxifiers, and they also express several ABC-transporters. The same is true for several other organs of the gastrointestinal and respiratory tracts. In addition to detoxify xenobiotics, ABC-transporters are involved in secretory functions of glands. Prostate, pancreas, and placenta and others are internal organs expressing several ABC-transporters (Fig. 2).

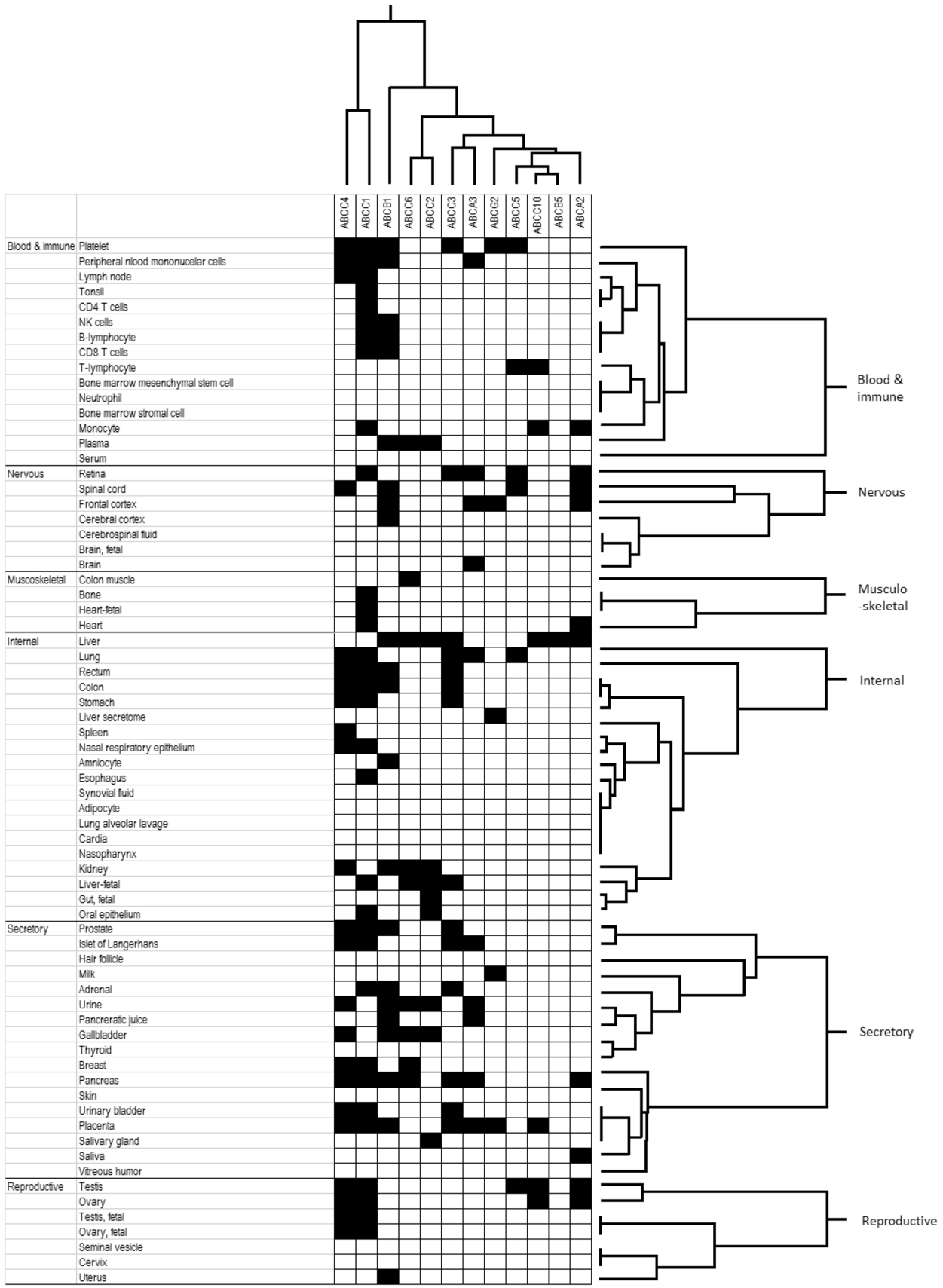
The transport of hormones represents one of the central tasks of reproductive organs. Testis and ovary expressed 5 and 4 ABC-transporters, respectively (Fig. 2).

Quite similar to the expression of ABC-transporters in human organs, their expression can also be found in most—if not all—animal tissues, which can be taken as a clue for their detoxification function all over the animal kingdom (Borst and Schinkel 1997; Jones and George 2005; O'Donnell 2009; Myllynen et al. 2010; Merola and Eubig 2012; Greenberg 2013; Ferreira et al. 2014a, b; Mealey and Fidel 2015). As an example, Fig. 3 depicts the P-glycoprotein in normal organs of the rat (Volm et al. 1990a, b, c).

Role of P-glycoprotein for resistance towards carcinogenic compounds

P-glycoprotein induction and development of resistance to carcinogens during hepatocarcinogenesis

The liver is a preferential model to study the role of ABC-transporters in carcinogenesis, because the metabolization


ABCC4
ABCC1
ABCB1
ABCC6
ABCC2
ABCC3
ABCA3
ABCG2
ABCC5
ABCC10
ABCB5
ABCA2
Blood & immune
Platelet
Peripheral blood mononuclear cells
Lymph node
Tonsil
CD4 T cells
NK cells
B-lymphocyte
CD8 T cells
T-lymphocyte
Bone marrow mesenchymal stem cell
Neutrophil
Bone marrow stromal cell
Monocyte
Plasma
Serum
Nervous
Retina
Spinal cord
Frontal cortex
Cerebral cortex
Cerebrospinal fluid
Brain, fetal
Brain
Musculo -skeletal
Muscoskeletal
Colon muscle
Bone
Heart-fetal
Heart
Internal
Liver
Lung
Rectum
Colon
Stomach
Liver secretome
Spleen
Nasal respiratory epithelium
Amniocyte
Esophagus
Synovial fluid
Adipocyte
Lung alveolar lavage
Cardia
Nasopharynx
Kidney
Liver-fetal
Gut, fetal
Oral epithelium
Secretory
Prostate
Islet of Langerhans
Hair follicle
Milk
Adrenal
Urine
Pancreratic juice
Gallbladder
Thyroid
Breast
Pancreas
Skin
Urinary bladder
Placenta
Salivary gland
Saliva
Vitreous humor
Reproductive
Testis
Ovary
Testis, fetal
Ovary, fetal
Seminal vesicle
Cervix
Uterus

◂**Fig. 2** Expression of 12 ABC transporters in normal tissues and organs. The protein expression values have been deposited in the GeneCards Database (http://www.genecards.org). These data have been subjected to hierarchical cluster analysis (WARD method) and illustrated as cluster image map

of xenobiotic compounds takes mainly in the liver. Coordinated mechanisms to detoxify harmful substances can either be specific or non-specific in nature. In the context of P-glycoprotein, its expression was induced by compounds that are specifically transported by this efflux transporter. On the other hand, P-glycoprotein expression was also upregulated upon exposure to unspecific stimuli, e.g. chemical substances that are not substrates of P-glycoprotein (e.g. ethanol, Volm et al. 1995a). The multitude of noxes, which induced hepatic P-glycoprotein expression, point to the impressive capability to cope with toxic insults taken up by the organism from the environment.

An association between resistance to chemical carcinogens and cancer development was first recognized by Haddow (1938a, b). He hypothesized that pre-neoplastic and neoplastic cells need to be resistant to such cytotoxic compounds. Otherwise they cannot grow. Hence, resistance can be understood as precondition for carcinogenesis.

The development of hepatocellular carcinoma is frequently preceded by the appearance of pre-neoplastic lesions. Four decades later, Farber et al. (1976) suggested, that liver carcinogenesis may lead to the early selection of carcinogen-resistant cells. Premalignant hyperplastic liver nodules were induced by 2-acetylaminofluorene or ethionine. Indeed, these hyperplastic nodules were resistant to other hepatotoxins, e.g. carbon tetrachloride and dimethylnitrosamine.

Subsequent investigations revealed that hyperplastic liver nodules were resistant to a wide variety of carcinogenic natural products (*e.g.* aflatoxins, pyrrolizidine alkaloids, isosafrol, *etc*.) as well as synthetic anthropogenic toxins (e.g. carbon tetrachloride, 2-acetylaminofluorene, *N*-hydroxy-2-acetylaminofluorene, dimethylnitrosamine, 7,12-dimethylbenz(a)anthrazene 2,3,7,8-tetra-chlorodibenzo-p-dioxin, phenothiazine etc. (Carr et al. 1987; Burt and Thorgeirrson 1988; Gottesmann 1988).

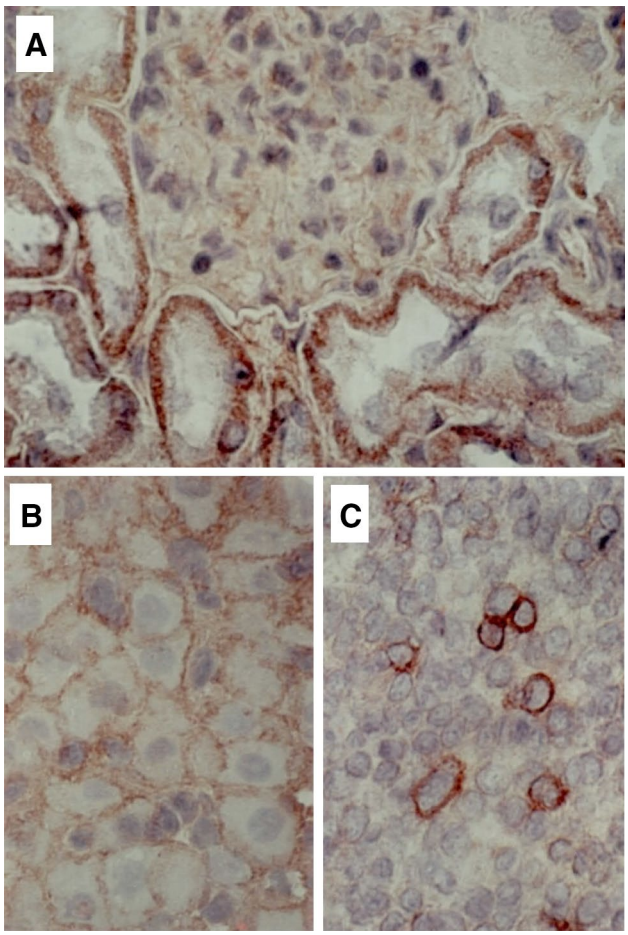


Fig. 3 Expression of P-glycoprotein in normal tissues of the rat. **a** Kidney, **b** pancreas, **c** lymph node. Taken from: Volm et al. (1990c)

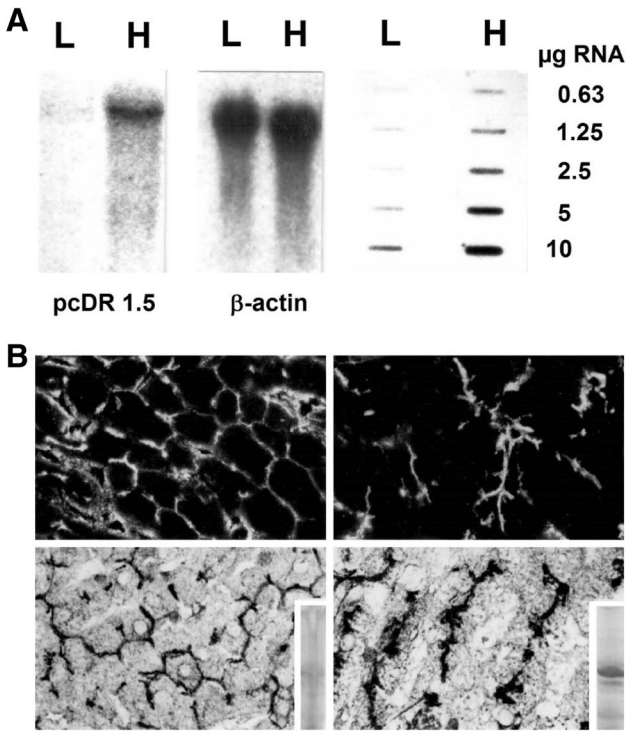


Fig. 4 Expression of *MDR1* and ß-actin mRNA in normal liver (L) and hepatocellular carcinoma (H). **a** Slot blot and Northern blot analyses were performed by using a MDR1-specific cDNA probe. Hybridization with a ß-actin cDNA served as loading control. **b** Detection of P-glycoprotein using immunofluorescence (*top*) and immunohistochemistry (*bottom*). *Left* normal liver; *right* hepatocellular carcinoma; inserts: Western blots. An increased band at 170 kD was detected in hepatocellular carcinoma. Taken from Volm et al. (1990a)

Table 1 Involvement of ABC-transporters in hepatocarcinogenesis in experimental models

Treatment	Effect	References
Partial hepatectomy	Increased *mdr* mRNA expression in pre-neoplastic and neoplastic lesions in rats	Thorgeirsson et al. (1987)
2-Acetylaminofluorene	Increased *mdr* expression in regenerating rat liver, hyperplastic nodules and hepatomas	Fairchild et al. (1987)
N-nitrosomorpholine	Increased *mdr* mRNA and P-gp expression in hepatocellular carcinoma compared to normal liver	Volm et al. (1990a)
Partial hepatectomy, chemotherapeutic drugs	Increased *mdr* mRNA expression after partial hepatectomy in rat liver	Chin et al. (1990a, b)
Partial hepatectomy	Increased *mdr* mRNA expression due to post-transcriptional mRNA stabilization	Marino et al. (1990)
2-Acetylaminofluorene, 3-methylcholandrene	2-Acetylaminofluorene or 3-methylcholandrene but not 2,3,7,8-tetrachlorodibenzo-P-dioxin induced *mdr* expression; *mdr* expression is not mediated by the Ah receptor	Gant et al. (1991)
Partial hepatectomy	Increased *mdr2* and *mdr3*, but not *mdr1* mRNA expression in C3H/HeN and B6C3/F1 mice strains	Teeter et al. (1991)
Solt-Faber protocol	Increased *mdr* mRNA and P-gp expression in hyperplastic nodules and carcinomas	Nakatsukasa et al. (1992)
2-Acetylaminofluorene, 3-methylcholandrene	Increased *mdr1* expression in primary rat hepatocytes, mouse HePa1, human HepG2, and rat H4-II-E cell lines	Gant et al. (1992)
N-methyl-*N*'-nitro-*N*-nitrosoguanidine	Rat liver epithelial cells did not show a correlation between degree of doxorubicin resistance and *mdr* gene expression upon transformation	Woo et al. (1992)
Hepatitis B virus large envelope polypeptide	Transgenic mice did not show consistent *mdr1* and *mdr2* activation during hepatocarcinogenesis. However, *mdr3* was increased. Role of *mdr3* for viral carcinogenesis	Kuo et al. (1992)
2-Acetylaminofluorene	Increased *mdr* mRNA and P-gp expression in liver; decreased biliary excretion of vinblastine, which was antagonized by the P-gp inhibitor verapamil	Schrenk et al. (1993)
In vitro cultivation	Increased P-gp expression in primary rat hepatocytes during primary culture as adaptation to unfamiliar environment. Cycloheximide also increased P-gp expression	Fardel et al. (1993)
2-Acetylaminofluorene, partial hepatectomy	2-Acetyaminofluorene increased *mdr1a* expression in pre-neoplastic lesions in rats; partial hepatectomy increased both, *mdr1a* and *mdr1b* mRNA expression	Teeter et al. (1993)
Dexamethasone, 3-methylcholandrene	Expression of *mdr1* mRNA and P-gp and rhodamine 123 efflux increased upon treatment with dexamethasone or 3-methylcholandrene in primary rat hepatocytes	Chieli et al. (1994)
2-Acetylaminofluorene	The CYP1A inhibitor a-naphthoflavone inhibited metabolic conversion of 2-acetyaminofluorene and *mdr1* gene expression in primary rat hepatocytes	Schrenk et al. (1994)
In vitro cultivation	Primary rat hepatocytes increased class II P-gp expression as a function of the time in culture due to increased mRNA stability	Lee et al. (1995)
Hepatocellular carcinoma, ademomatous hyperplasia	Increased P-gp expression in hyperplasia of livers with cirrhosis. Carcinomas expressed more P-gp than normal liver tissue, but less than hyperplasia	Nagasue et al. (1995)
2-Acetaminofluorene	2-Acetylaminofluorene increased *mdr1b*, but not *mdr2* mRNA expression in livers of Fischer, Wistar, and Sprague–Dawley rats	Hill et al. (1996)
2-Acetylaminofluorene	Primary rat hepatocytes overexpressed *mdr1* mRNA, but not *mdr2* or *mdr3* mRNA upon exposure to 2-acetylaminofluorene and showed reduced doxorubicin accumulation. Primary human hepatocytes did not change *MDR1* or *MDR2* expression or doxorubicin accumulation upon exposure to 2-acetylaminofluorene	Lecureur et al. (1996)
2-Acetylaminofluorene, cisplatin, cycloheximide	Increased *cmrp* expression in rat hepatocytes	Kauffmann et al. (1997)

Table 1 (continued)

Treatment	Effect	References
Liver tumors	Primary rat hepatocytes and liver tumors overexpressed P-gp classes I and II. Stable mRNA overexpression in tumors, but not normal livers	Lee et al. (1998)
H_2O_2	Increased *mdr1b* mRNA and P-gp expression in primary rat hepatocytes. Catalase inhibitors and antioxidants reduced intrinsic *mdr1b* and P-gp expression	Ziemann et al. (1999)
Diethylnitrosamine	Increased *MRP* mRNA expression in hepatocellular carcinomas compared to normal liver, but not canalicular multispecific organic anion transporter *(cMOAT)*	Payen et al. (1999)
Partial hepatectomy	Slightly increased *mdr1a* and *mrp1* mRNA expression; strongly increased *mdr1b* expression; slightly decreased *mrp2* expression	Vos et al. (1999)
Carbon tetrachloride	No change in *mrp2* mRNA expression	Geier et al. (2002)
Diethylnitrosamine, cisplatin, epirubicin	Increased P-gp expression in hyperplastic nodules and hepatocellular carcinomas of rats	Takeuchi et al. (2002)
1,2-Dimethylhydrazine	The P-gp inhibitor PSC-833 reduced incidence, multiplicity and burden of hepatocellular carcinoma	Kankesan et al. (2003)
2-Acetylaminofluorene plus partial hepatectomy	Increased *mdr1b, mrp1* and *mrp3* mRNA and Mrp1 and Mrp3 protein expression in periportal hepatocytes	Ros et al. (2003)
2-Acetylaminofluorene plus partial hepatectomy	Increased *abcg2/bcrp* mRNA expression	Shimano et al. (2003)
Partial hepatectomy	Decreased Mrp2 and Mrp3 protein expression and increased hyperbilirubinemia	Chang et al. (2004)
Partial hepatectomy	Increased *mrp3* mRNA and Mrp3 protein expression	Csanaky et al. (2009)
Partial hepatectomy	Increased Mrp4 protein expression and high blood bile acid levels	Miura et al. (2011)
Thioacetamide	*mrp2* mRNA expression in cirrhotic livers of thiacetamide treated mice was higher than in hyperplastic nodules and carcinomas	Tsuda et al. (2011)
Partial hepatectomy	Downregulation of *mrp2* in rat liver	Kimura et al. (2012)

The concentrations of these compounds were lower in resistant compared to normal hepatocytes (Spewiak-Rinaudo and Farber 1986) and the expression of P-glycoprotein and *mdr1* mRNA was upregulated during chemical hepatocarcinogenesis in rat models (Thorgeirrson et al. 1987; Fairchild et al. 1987).

As shown in rat liver by stop experiments with *N*-nitrosomorpholine, specific carcinogen-induced alteration of hepatocytes can be separated from non-specific, toxic cellular changes that are fully reversible after withdrawal of the carcinogen (Bannasch and Schacht 1968). Therefore, we administered *N*-nitrosomorpholine for 7 weeks to rats. The resulting tumors were investigated 80 weeks after withdrawal of the carcinogen for their P-glycoprotein expression. We found markedly higher *mdr1* mRNA levels in hepatocellular carcinomas as compared with normal livers of control animals (Fig. 4, Volm et al. 1990a). In normal livers, P-glycoprotein was localized in a polarized fashion at the bile canalicular plasma membrane of hepatocytes. In hepatocellular carcinoma, P-glycoprotein was found at increased amounts compared to normal liver of untreated control animals (Volm et al. 1990a). The increased P-glycoprotein and *mdr1* mRNA expression in hepatocellular carcinomas compared to normal livers of control animals may explain resistance to carcinogens during hepatocarcinogenesis.

In the Solt–Faber model of hepatocarcinogenesis, the application of a carcinogenic compound was followed by partial hepatectomy (Solt and Farber 1976). The sequence of carcinogenic events includes the development of first pre-neoplastic and then neoplastic liver nodules followed by the occurrence of full-blown hepatocellular carcinoma. Already pre-neoplastic nodules expressed this ABC-transporter, indicating that the induction of P-glycoprotein represents an early event in hepatocarcinogenesis. Neoplastic nodules and hepatocellular carcinoma also revealed increased P-glycoprotein and *mdr1* expression (Fairchild et al. 1987; Thorgeirsson et al. 1987).

Interestingly, partial hepatectomy without concomitant application of carcinogenic compounds also provoked P-glycoprotein and *mdr1* expression (Carr and Laishes 1981; Thorgeirrson et al. 1987; Fairchild et al. 1987). This indicates that not only chemical P-glycoprotein substrates can induce its expression, but also unrelated

proliferation-inducing stimuli. There are also reports that the closely related *mdr2* and *mdr3* genes were upregulated upon xenobiotic exposure, indicating that the regulation of the three *mdr* genes occurs independently of each other. Other ABC transporters were also affected and xenobiotics induced their expression, e.g. MRP1-7 or BCRP (Ferguson and DeFlora 2005). Interestingly, transporters belonging to other gene families such as cMOAT were not upregulated.

Interestingly, these effects were specifically associated with malignancy, since normal cell replication in the fetal liver was not linked with increased *mdr1* expression (Thorgeirrson et al. 1987).

As shown in Table 1, there is a wide array of different carcinogenic compounds, which induced the expression of P-glycoprotein and mRNA of the encoding human *MDR1* or rodent *mdr1* genes in hepatocytes in vitro, as well as in mice and rats in vivo.

P-glycoprotein induction cannot only be observed in chemical carcinogenesis. Viral carcinogenesis (e.g. by hepatitis B virus; Table 1) or γ-irradiation also upregulated P-glycoprotein expression (Hill et al. 1990; Mattern et al. 1991). The mechanisms of increased expression may, however, differ, since γ-ray-induced P-glycoprotein expression took place in the absence of concomitant *MDR1* mRNA expression due to posttranslational mRNA stabilization leading to prolonged protein half-life times (McClean and Hill 1993).

In addition, the multiple step model of carcinogenesis (initiation, promotion, progression), where a persisting DNA lesion represents the initial event of tumor development, the role of chronic inflammation for carcinogenesis is also more and more accepted in the past years (Nguyen et al. 2015; Axelrad et al. 2016; Takeda et al. 2016). Liver cirrhosis as consequence of chronic liver inflammation was also associated with induction of P-glycoprotein expression (Table 1).

The fact that a plethora of stimuli ultimately lead to the induction of P-glycoprotein expression raises the question on the specificity of this cellular reaction and the causality between P-glycoprotein expression and carcinogenesis. This question has been addressed by the application of known inhibitors of P-glycoprotein efflux, i.e. verapamil and PSC-833. Indeed, tumor development was inhibited upon application of these efflux inhibitors. This indicates that there is a causal relationship between P-glycoprotein expression and tumor development, although the exact underlying mechanisms are awaiting to be explored.

Kankesan et al. (2003) explored the hypothesis that overexpression of P-glycoprotein is tightly associated with carcinogenesis. This hypothesis was based on findings that P-glycoprotein overexpression started early during carcinogenesis and that inhibition of P-glycoprotein function inhibited the development of cancer. Therefore, the authors determined the effect of PSC833, a potent inhibitor of P-glycoprotein function on experimental liver carcinogenesis. Indeed, PSC833 inhibited liver carcinogenesis induced by 1,2-dimethylhydrazine in rats.

These authors also studied the effect of PSC833 on *N*-methyl-*N*-nitrosourea induced mammary cancer in rats.

Table 2 Hepatocarcinogenesis in ABC-transporter knockout mice

Gene knockout	Effect	References
mdr1a (−/−)	Higher fractions of polyploid hepatocytes of knockout than of wild-type mice	Bao et al. (2000)
mdr2 (−/−)	No transport of phosphatidylcholine across canalicular membrane. The absence of phospholipids from bile led to inflammatory cholangitis and liver cancer	Mauad et al. (1994)
mdr2 (−/−)	No transport phosphatidylcholine across the canalicular membrane in liver by P-gp and develop inflammation and cancer	Katzenellenbogen et al. (2006, 2007)
mdr2 (−/−)	Increased hepatocarcinogenesis upon partial hepatectomy	Barash et al. (2010)
mdr2 (−/−)	Expression of hedgehog ligands. The hedgehog signaling antagonist GDC-0449 inhibited liver fibrosis and liver tumors and metastasis	Philips et al. (2011)
mdr2 (−/−)	Development of chronic cholestatic hepatitis at an early stage and hepatocellular carcinoma at a late stage. Friend virus B-type IN knockout mice developed more severe hepatitis and more tumors than C57 black 6 mice	Potikha et al. (2013)
mdr2 (−/−)	Glycation end products increased inflammation-driven formation of hepatocellular carcinoma	Pusterla et al. (2013)
mdr2 (−/−)	Increased expression of oncogenes, chromosomal instability and target genes of the E2F1 transcription factor after partial hepatectomy	Ella et al. (2014)
mdr2 (−/−)	Model of inflammation-mediated hepatocellular carcinoma. 76 hypermethylated genes in knockout mice	Stoyanov et al. (2015)
mrp 3 (−/−)	Delayed liver regeneration after partial hepatectomy	Fernandez-Barrona et al. (2012)
mdr1a/b, mrp2, bcrp	Reduced levels of the dietary carcinogen 2-amino-1-methyl-6 phenylimidazol[4,5-6]pyridine in the small intestine and biliary excretion in combination knockout mice	Vlaming et al. (2014)

PSC833 at daily dietary doses of 15 or 30 mg/body weight resulted in a dose-dependent inhibition of incidence and growth of mammary tumors. These results indicate that P-glycoprotein may causatively contribute to cancer development (Kankesan et al. 2004).

Carcinogenic resistance during hepatocarcinogenesis is not solely caused by P-glycoprotein. Multiple other mechanisms are also involved, e.g. phase I drug metabolizing enzymes (cytochrome P450 monooxygenases, aryl hydrocarbon hydroxylase), phase 2 enzymes (UDP-glucuronyle transferase, glutathione S-transferases, γ-glutamyltransferases, sulfotransferase) and others (epoxide hydrolase, DT-diaphorase, enzymes of the pentose phosphate pathway etc.) (Ivy et al. 1988). These mechanisms are remarkably similar to the xenobiotic resistance phenomenon in the Solt–Farber model of carcinogenesis.

Carcinogenesis in *mdr* knockout mice

The advent of gene knockout technologies allowed addressing specific gene functions in greater detail. *Mdr* knockout mice have been generated to investigate their role in carcinogenesis (Table 2). Mice lacking the *mdr1a* gene revealed disturbed transport of DNA-damaging xenobiotics and thereby more DNA lesions, which led to the appearance of polyploid cells and ultimately tumor formation. The *mdr2* gene is responsible for the transport of endogenous phosphatidylcholine transport. *Mdr2* knockout mice could not properly transport phosphatidylcholines, causing chronic inflammation. These mice developed cholangitis, which finally led to carcinogenesis. This process was even enhanced at simultaneous virus infection, which can be taken as another clue for the connection between ABC-transporter function and viral carcinogenesis. Mice lacking *mrp3* expression revealed a delayed regeneration after partial hepatectomy. Combined knockout of ABC-transporter genes prevented functional redundancy, i.e. the compound transport by one transporter has been taken over by another one. Combined *mdr1a/b, mrp2, bcrp* knockout mice could not efficiently transport carcinogenic compounds in the small intestine anymore and their biliary excretion was impaired.

Table 3 Involvement of ABC-transporters in carcinogenesis in diverse tissues of experimental models

Tissue/tumor	Gene	Effect	References
Human kidney carcinoma cells	*ABCB1*	Increased *MDR1* gene expression upon treatment with heat shock, arsenite or cadmium	Chin et al. (1990a, b)
HEK293 cells	*ABCB1*	Increased P-gp/*ABCB1* expression upon treatment with perfluorononanoic acid	Rusiecka et al. (2008)
Colon Ca	*mdr1a*	The P-gp inhibitor verapamil reduced the number of polyps in Mdr1a(+/+) Apc(Min/+) mice and increased their survival time	Fujimoto et al. (2013)
Renal tumors	*ABCB1*	Wnt signaling contributed to nephrocarcinogenesis of cadmium, up-regulated ABCB1 and led to adaptation to cadmium toxicity	Thévenod and Chakraborty (2010)
Breast Ca		The P-gp inhibitor delayed tumor incidence, multiplicity and median tumor burden in rats	Kankesan et al. (2004)
HeLa cells	*ABCB1, ABCC1*	Increased ABCB1 and ABCC1 expression upon treatment with 1-hexyl-3-methyl-imidozolium cloridein	Rusiecka and Skladanowski (2011)
Primary embryonal fibroblasts	*TAP1, TAP2*	Downregulation of TAP1 and TAP2 after Ad12-mediated transformation (viral carcinogenesis)	Rotem-Yehudar et al. (1994)
MRP-transfected cells	*ABCC*	Transport of aflatoxin B1-8,9-epoxide	Loe et al. (1997)
Colon	*mdr1, mrp4*	P-glycoprotein and Mrp4 were not involved in transport of 2-amino-1-methyl-6-phenylimidazo[4,5-6]pyridine (PhIP) in rat distal colon and tumor formation	Nicken et al. (2013)
Colon	*BCRP*	Increased *BCRP* mRNA and protein expression in CaCo-2 cells upon treatment with benzo[a]pyrene conjugates in an aryl hydrocarbon receptor-dependent manner	Ebert et al. (2005)
Intestine	*mdr1a*	Increased spontaneously occurring DNA damage in small and large intestine of *mdr1a*(−/−) Apc (Min/+) mice	Mochida et al. (2003)
Murine fibroblasts	*TAP1*	Inoculation of C57BL/6 mice with TAP1-negative cells produced large and persistent tumors due to a lack of T-cell-dependent immune response	Johnsen et al. (1999)

Role of ABC-transporters for carcinogenesis in other organs and tissues

Since ABC-transport expression is not restricted to the liver, it is interesting to learn about the role of ABC-transporters for carcinogenesis in other organs and tissues. A number of investigations have been performed to elaborate the role of human *ABCB1/MDR1*, murine *mdr1*, human *ABCC1/MRP1*, murine *mrp4*, and human *ABCG2/BCRP* in cells and tissues of kidney, colon, breast, cervix etc. (Table 3). Comparable to the situation in liver, ABC-transporter expression was induced by both specific and non-specific stimuli.

P-glycoprotein inhibitors (e.g. verapamil or cyclosporin A) also inhibited carcinogenesis, which once more confirms a causative role of P-glycoprotein for tumor development (Yamada et al. 2003; Fujimoto et al. 2013). The number of polyps in $Mdr1a^{+/+}$ $Apc^{Min/+}$ mice fed with pellets containing verapamil was significantly lower than that in mice fed with verapamil-free pellets. The 1-year survival rate of verapamil-fed mice was also improved in a dose-dependent manner. Hence, inhibitors of P-glycoprotein may represent a novel class of chemopreventive agents against colorectal carcinogenesis.

Molecular mechanisms of P-glycoprotein induction during carcinogenesis

While there is a wealth of data showing that the expression of ABC-transporters is associated with carcinogenic processes, less is known about the molecular mechanisms that explain the link between both. Many carcinogenic chemicals are known to induce DNA lesions (Besaratinia and Pfeifer 2006; Ceccaroli et al. 2015). DNA damage initiates tumor development, if proto-oncogenes are activated or tumor suppressor genes are inactivated. The question arises, whether or not this initial step in carcinogenesis also activates P-glycoprotein expression. As shown in Table 4, oncogenes did not only promote the transition from normal to malignant cells, but also contributed to the activation and expression of ABC transporters.

Interestingly, Burt et al. (1988) showed that transformation of cells with *v-H-ras* or *v-raf* oncogenes also resulted in MDR to doxorubicin, vincristine and 2-acetylaminofluorence, as well as increased P-glycoprotein expression, independently of chemical exposure. The same has been reported for other oncogenes and also functionally inactivated tumor suppressors such as *raf*, YB1, AP1 (Fos/Jun), p53 and APC (Table 4).

Table 4 Genes regulating P-glycoprotein expression during carcinogenesis

Gene	Effect	References
v-H-ras, v-raf	Rat liver cells transformed with *v-H-ras* or *v-raf* revealed increased P-gp expression and were more resistant to doxorubicin, vinblastine and 2-acetylaminofluorene	Burt et al. (1988)
c-myc	Overexpression of *mdr* RNA class 2 in primary rat hepatocytes in culture and in rat liver carcinogenesis animal model and stabilization of *c-myc* mRNA expression	Lee et al. (1998)
APC, TCF4/b-catenin	Inactivation of the tumor suppressor APC leads to accumulation of cytoplasmic β-catenin and T-cell factor (TCF)/lymphoid enhancer factor transcription factors. Dominant-negative TCF4/β-catenin DLD-1 colon carcinoma cells showed that *MDR1* is a target gene of TCF4/β-catenin. *MDR1* was upregulated in adenomas and adenocarcinomas of patients with familiae adenomatous polyposis	Yamada et al. (2000)
COX-1, COX-2	Release of prostaglandins through activation of the cyclooxygenase system (COX-1, COX-2) participated in endogenous *mdr1b* regulation in primary rat hepatocytes	Ziemann et al. (2002)
COX-2, mPGES1	In *Heliobacter pylori*-positive patients, the expression of COX-2, microsomal prostaglandin E-synthase1 and P-gp was higher in the gastric mucosa than in *Heliobacter pylori*-negative patients	Nardone et al. (2004)
YB1	Increased YB1 expression after castration in the LNCaP prostate cancer model was associated with P-gp upregulation	Giménez-Bonafé et al. (2004)
Prostaglandin E receptor	Prostaglandin E receptor-dependent signaling via cAMP activated *Mdr1b* expression in primary rat hepatocytes	Ziemann et al. (2006)
YB1	*YB1*-transfectant HCT116 cells expressed more P-gp and were more vinblastine-resistant	Vaiman et al. (2007)
mutated p53	Human gastric carcinomas with p53 mutations showed high P-gp expression	Oliver et al. (2007)
Bmi-1	Coexpression of *Bmi-1* and *ABCB1* in early and well-differentiated hepatocellular carcinomas. Overexpression and suppression of Bmi-1 was followed by respective increase and decrease of *ABCB1* expression	Effendi et al. (2010)
MYC	MYC-driven tumors contain a side population expressing P-glycoprotein, effluxed Hoechst 33342 and was drug-resistant	Chow et al. (2012)

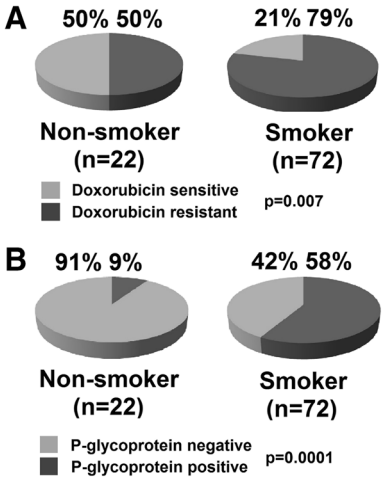


Fig. 5 Relationship of **a** drug resistance measured *in vitro* or **b** P-glycoprotein expression to smoking habits of patients with NSCLC. Taken from Volm et al. (1990b, 1991a, b)

In addition, major players in inflammatory processes reveal similar relationships, e.g. cyclooxygenases (COX1/2), as well as prostaglandin-related proteins and their encoding genes. Although the full regulatory network explaining the interplay between carcinogenesis and ABC-transporter functions remains to be elucidated, it seems to be obvious that multifactorial rather than single mechanisms are involved.

P-glycoprotein in clinical carcinogenesis

Since human lung carcinomas are predominantly caused by cigarette smoking, the question arises, whether the tumors of smokers express more P-glycoprotein and be more frequently drug-resistant than those of non-smokers. To address this question, we determined drug resistance of human non-small cell lung carcinomas (NSCLC) and compared these results with the cigarette smoking habits of the patients (Volm et al. 1990b). A total of 94 human NSCLC of previously untreated patients were analyzed for P-glycoprotein expression and for resistance to doxorubicin. We found that NSCLC of smokers were significantly more frequently resistant than tumors of non-smokers ($p = 0.007$) (Fig. 5a). Furthermore, NSCLC of smokers expressed more often P-glycoprotein than those of non-smokers ($p < 0.001$) (Fig. 5b). There was also a significant relationship between doxorubicin resistance and P-glycoprotein expression ($p < 0.0001$) (Volm et al. 1991a, b).

Table 5 Expression of ABC transporters in human tumors

Tumor type	Effect	References
Colorectal Ca	Increased expression of *ABCB1* and *ABCC1* in adenomas. In the absence of adequate mucin production, ABC transporters may protect the epithelium against environmentally induced genetic damage	Meijer et al. (1999)
Colorectal Ca	Carriers of the C3435T polymorphism in *ABCB1* developed more frequently cancer than others	Osswald et al. (2007)
Colorectal Ca	Carriers of the C3435T polymorphism in *ABCB1* had a lower tumor risk than homozygous wild-type carriers	Anderson et al. (2009)
Colorectal Ca	*ABCB*1 mRNA expression in adenomas and carcinomas higher than in normal tissue of the same individuals	Andersen et al. (2013)
Colorectal Ca	Polymorphisms in the *TAP1* gene increased tumor risk	Yamauchi et al. (2014)
Colonic cancer	ABCB1, diet, and gut microbiobes mutually interacted in colonic inflammation as early event in carcinogenesis	Andersen et al. (2015a)
Colorectal Ca, adenoma	Increased *ABCC2*, but decreased *ABCG2* expression in adenomas and carcinomas compared to normal tissues	Andersen et al. (2015b)
Gastric cancer	The C3435T polymorphism in *ABCB1* was associated with reduced tumor risk in the Japanese population	Tahara et al., 2007
Gastric cancer	Promoter methylation of *ABCB1* was higher in tumors than in non-neoplastic mucosa	Tahara et al. (2009)
Gastric cancer	P-gp was expressed fetal gastric mucosa, undetectable in adult normal mucosa, and re-expressed in chronic gastritis and gastric cancer	Rocco et al. (2012)
Liver Ca	Increased P-gp expression in hyperplasia and hepatocellular carcinomas compared to early microscopic lesions. P-gp increased during tumor progression	Bradley et a. (1992)
Cholangio-carcinoma	*MDR3*/*ABCB4* mutations were associated with cholangitis, biliary dysplasia and cholangiocarcinoma	Wendum et al. (2012)
Bladder Ca	Increased *ABCB1* mRNA expression in tumors compared to normal urothelium	Clifford et al. (1996)
Oral squamous cell carcinoma	*ABCB5* expression was significantly increased in tumors vs. normal tissues	Grimm et al. (2015)

Oncogenes may provide a mechanistic explanation for the connection between P-glycoprotein, resistance and carcinogenesis. Exposure to chemical carcinogens led to the activation of oncogenes in lung cancer patients (Volm et al. 1992; Wodrich and Volm 1993; Volm 1993). We found that lung carcinomas of smokers more frequently expressed c-FOS and c-Jun proteins than carcinomas of non-smokers ($p = 0.017$ and $p = 0.036$, respectively). Additionally, expression of the epidermal growth factor receptor (EGFR) was increased in lung carcinomas of smokers compared to non-smokers, however, without reaching statistical significance.

Furthermore, we investigated tumor tissues of untreated and cytostatic agent-treated patients with nephroblastoma for expression of P-glycoprotein to ascertain whether resistance proteins are changed after treatment (Volm et al. 1995b). Nephroblastoma (or Wilms' tumor) is one of the most frequent solid malignant tumors in children and generally responds well to chemotherapy. Despite of excellent therapy results, the development of resistance to anti-cancer drugs still remains a major drawback. In the course of a cooperative clinical study, tumor tissues of 31 patients with nephroblastoma were retrospectively investigated for P-glycoprotein expression. Twenty-three children with stage I-III tumors were treated with actinomycin D and vincristine for 4–8 weeks. The therapeutic strategy was pre-operative chemotherapy to increase the rate of resectable tumors. Eight children did not receive pre-operative chemotherapy. Tumor tissues were analyzed for MDR1 mRNA expression. In untreated patients, P-glycoprotein was not detected. However, in patients treated with actinomycin D and vincristine, 12 out of 23 tumors revealed increased *MDR1* expression ($p < 0.01$) (Volm et al. 1995b).

Increased expression levels of P-glycoprotein and other ABC-transporters in tumors compared to the corresponding normal tissues has been observed by numerous other authors. This has been demonstrated for the expression of *ABCB1/MDR1, ABCB2/TAP1, ABCB5, ABCC1/MRP1, ABCC2/MRP2*, and *ABCG2/BCRP* in colorectal carcinoma, gastric carcinoma, liver carcinoma, bladder carcinoma and oral squamous cell carcinoma, respectively (Table 5). The functionality of ABC-transporters is not only determined by the protein expression level, but also by the single nucleotide polymorphisms (SNPs). Subjects with SNPs in the *ABCB1/MDR1* and *ABCB2/TAP1* genes bore a higher risk for cancer than persons with wild-type genes (Table 5).

Beyond human beings: P-glycoprotein in multi-xenobiotic resistance

The expression of P-glycoprotein in normal organs raises the question about a general detoxification function of this transporter throughout evolution of life. Interestingly, P-glycoproteins and related ABC-transporters are not only present in mammals (e.g. human, mouse, rat, rabbit, pig, monkey, dog, cattle, etc.), but also in other vertebrate (e.g. fishes, reptiles) and avertebratae (worms, molluscs, insects) (Borst and Schinkel 1997; Jones and George 2005; O'Donell 2009; Myllynen et al. 2010; Merola and Eubig 2012; Greenberg 2013; Ferreira et al. 2014a, b; Mealey and Fidel 2015) and even in bacteria and yeast (Kerr et al. 2010; Prasad and Goffeau 2012; Stocker et al. 2015). In protozoa such as *Plasmodium falciparum*, P-glycoprotein plays an important role for the development of resistance against anti-malarial drugs (Ibraheem et al. 2014). A comparable role of P-glycoprotein has been recognized for resistance of bacteria towards antibiotic drugs (Zhang and Ma 2010). During evolution of life, the extrusion of toxic substances has been a crucial requirement to survive under unfavorable environmental conditions. Therefore, the detoxification functions of P-glycoprotein can be assumed to be much broader than the efflux of pharmacologically active drugs in tumor patients. Many aquatic organisms live in water highly polluted with anthropogenic or natural toxins. Water pollution is most frequently characterized by a mixture of numerous toxic compounds. It is well imaginable that the evolutionary answer to complex pollution stress was the development of broad-spectrum detoxifying transporters of the P-glycoprotein type. The detection of P-glycoproteins in aquatic organisms from highly polluted environments gave reason to coin the term multi-xenobiotic resistance (MXR) in analogy to multidrug resistance (MDR) in cancer.

The physiology, pharmacology and toxicology of several of these P-glycoproteins have been investigated in detail. It turned out that they did not only mediate resistance against a plethora of environmentally hazardous pollutions (e.g. sulfallate, dacthal, pentachlorophenol), but also to many xenobiotic compounds known to induce tumors in human beings or in experiments with animals. Examples are 2-acetylaminofluorene, benzo[a]pyrene, aminoanthracene and many others. Furthermore, the cross-resistance profiles of these P-glycoproteins also comprised classical anticancer agents such as vincristine or daunorubicin. Well-known inhibitors of drug efflux of human P-glycoprotein also inhibited toxin extrusion of P-glycoprotein of aquatic animals (e.g. verapamil, cyclosporine A, dihydropyridines, progesterone, amiodarone, quinidine, etc.) (Volm 1998; Amiri-Kordestani et al. 2012; Binkhathlan and Lavasanifar 2013). During the past years, numerous data on ABC-transporter expression in aquatic organisms illustrated the full biological dimension of this phenomenon. Both achordata (mussels and clams, sea urchins, worms, water flea) as well as chordata (fishes) upregulate ABC-transporter expression in their organs upon exposure with natural or xenobiotic anthropogenic toxins in their environment (Tables 6, 7).

Table 6 Multi-xenobiotic resistance in aquatic organisms (Achordata)

Organism	Observation	References
Mytilus californianus (Mediterranean mussel)	Induction of P-glycoprotein expression and activity upon exposure with the pesticides pentachlorophenol and chlorthal	Eufemia and Epel (2000)
Mytilus californianus (Mediterranean mussel)	Inhibition of calcein-AM efflux by PSC-833 and MK571	Luckenbach et al. (2008b)
Mytilus galloprovincialis (Mediterranean mussel), *Dreissena polymorpha* (Zebra mussel)	Induction of P-gp-type transporter and rhodamine B efflux by Diesel-2 oil water extract	Smital et al. (2003)
Mytilus galloprovincialis (Mediterranean mussel)	P-gp activity upon exposure to polychlorinated biphenyls (PCBs) and polycyclic aromatic hydrocarbons (PAHs) was not affected by seasonal variations	Bodin et al. (2004)
Mytilus galloprovincialis (Mediterranean mussel)	Fluoxetine downregulated *abcb* expression by a CAMP/PKA-regulated mechanism	Franzellitti et al. (2013)
Mytilus edulis (Baltic Sea blue mussel)	P-gp, but not MRP2 expression changed in relation to high temperature, low salinity and anerobiosis, but not low temperature	Luedeking and Koehler (2004)
Mytilus edulis (Baltic Sea blue mussel)	Benzo(a)pyrene upregulated P-gp	Prevodnik et al. (2007)
Mytilus edulis (Baltic Sea blue mussel)	Higher ABC-transporter expression, if collected from polluted harbor waters than from clean water. Calcein-AM efflux in hemocytes was inhibited by MRP-inhibitors, but not by P-gp inhibitors	Rioult et al. (2014)
Arbacia lixula (Black sea urchin), *Paracentrotus lividus*, (Purple sea urchin)	Expression of a*bcb1, abcc1,-2,-3,-5,-9* and *abcg2* homologues	Bošniak et al. (2013a)
Paracentrotus lividus (Purple sea urchin)	Induction of *abcb1* and *abcc9* gene expression in embryos by exposure to oxybenzone, mercuric chloride, and trybutiltin	Bošniak et al. (2013b)
Daphnia magra (Water flea)	Cloning of *abcb1, abcc1/3, abcc4* and *abcc5;* inhibition of rhodamine 123, rhodamine B and calcein-am was efflux by reversin 205, MK571, and cyclosporin A. Increased ABC transporter expression upon exposure to mercury, pentachlorophenol and dacthal	Campos et al. (2014)
Daphnia magna (Water flea), *Lumbriculus variegatus* (California blackworm)	Expression of *abcb1* and *abcc*. Differential inhibition of rhodamine B and calcein-AM influx by verapamil (non-specific ABC inhibitor), reversin 205(ABCB1 inhibitor) and MK571 (ABCC inhibitor)	Vehniäinen et al. (2015)
Daphnia magna (Water flea)	Penta chlorophenol resistance was associated with increased *abcb1* transcription	Jordão et al. (2016)
Dreissena polymorpha (Zebra mussel)	*abcb1* expression and vinblastine efflux was absent in eggs and increased in larvae	Faria et al. (2011)
Dreissena polymorpha (Zebra mussel)	Expression of an *abcc* homologue. Inhibition of calcein-AM efflux by MK571. Dacthal and mercury induced *abcb1* and *abcc* gene expression in larvae	Navarro et al. (2012)
Dreissena polymorpha (Zebra mussel)	Expression of *abcb1* and *abcc1*-type transporter homologues in gills. Inhibition of calcein-AM efflux by abcb1-(reversin 205, verapamil) and *abcc1*-(MK571) type specific inhibitors	Faria et al. (2016)
Anodonta anatina (Duck mussel), *Sinanodonta woodiana* (Chinese pond mussel)	*S. woodiana* as invasive species showed decreased rhodamie B accumulation compared to *A. anatina* as native species. *S. woodiana* was better adapted to unfavorable environmental conditions	Bielen et al. (2016)
Ruditapes philippinarum (Manila clam), *Scapharca subdrenata* (saltwater bivalve), *Tegillarca granosa* (Blood cockle)	Cloning of different P-gp paralogues; differential expression in gill, digestive gland, adductor muscle and manthe after exposure to the toxigenic dinoflagellatate *Prorocentrum lima*	Huang et al. (2015)
Suberitus domuncula (Sea orange sponge), *Corbicula fluminea* (Asian clam)	Amorphous aggregates ("marine snow") appear periodically, cause mats on the sea bottom and cause death of benthic metazoans. Extracts of these gel-like aggregates inhibited P-gp efflux	Müller et al. (1998)

Table 6 (continued)

Organism	Observation	References
Carbicula fluminea (Freshwater clam)	Induction of P-gp-type transporter upon cadmium and zinc exposure	Achard et al. (2004)
bivalve gills	Expression of *abcb*- and *abcc*-type transporter homologues. Inhibition of calcein-AM efflux by PSC833 and MK571	Luckenbach et al. (2008a)
Perna perna (Brown mussel)	Zinc chloride increased P-gp expression and rhodamine B efflux	Franco et al. (2006)
Unio pictorum (Freshwater painter's mussel)	P-gp-mediated rhodamine B transport in haemocytes	Zaja et al. (2006)
Eulimnogammarus cyaneus, E. verrucosus (amphipods)	Natural organic matter from Lake Baikal and carbon tetrachloride reduced rhodamine B efflux	Timofeyev et al. (2007)
Cyphoma gibbsum (Flamingo tongue snail), *Tritonia hamnerorum*(marine gastropod mollusc)	Detection of ABCB- and ABCC-type proteins and gene sequences	Whalen et al. (2010)
Corbicula fluminea (Golden freshwater clam)	Lead induced P-gp expression and decreased rhodamine B accumulation	Rocha et al. (2012)
Eisenia fetida (Red californian earth worm)	Cloning of an *abcb1* homologue; inhibition of rhodamine B and rhodamine 123 transport by several ABC transporter inhibitors	Bošnjak et al. (2014)
Perna viridis (Asian green mussel)	After exposure to the toxic dinoflagellate *Prorocentrum lima*, gills expressed ABC-transporters and showed decreased accumulation of okadaic acid (=main dinoflagellate poison)	Huang et al. (2014)
*Corbicua fluminea (*Asian clam)	Fluoxetine is a sertonin reuptake inhibitor that is widespread in aquatic environments. Fluoxetin inhibited the MXR system by downregulation of *abcb1, abcc2* and *abcg2* gene expression	Chen et al. (2015)

Role of P-glycoprotein in ecotoxicology

There were huge efforts to identify inhibitory compounds for P-glycoprotein, to develop novel treatment strategies to overcome MDR in human cancers and to improve chemotherapy outcomes in the clinic. Most of these P-glycoprotein inhibitors were from a wide range of either existing drugs from many different pharmacological classes and newly synthesized with the intention to modulate P-glycoprotein modulators. It was largely overseen in clinically oriented cancer research that there are also numerous compounds and poisons throughout nature with the ability to inhibit P-glycoprotein's drug efflux. More recently, compounds from medicinal herbs and marine organisms have been recognized as promising P-glycoprotein inhibitors with the potential to be clinically applied as MDR modulators of tumors (Molnar et al. 2010; Eichhorn and Efferth 2012; Long et al. 2016). In addition, there are also a lot of environmental toxins of either natural or anthropogenic origin capable to inhibit the efflux function of P-glycoprotein. While their pharmacological potential in clinical oncology is rather limited because of their toxicity, they inhibit P-glycoprotein in aquatic organisms. The modulation of MXR may have important implication for environmental risk assessment, because harmful compounds do not only comprise of direct toxic compounds, but also of compounds that inhibit P-glycoproteins to detoxify other toxic xenobiotics. Organisms surviving in pollutant environments require functional P-glycoproteins to detoxify poisonous noxes taken up from the environment.

Oyster gills (*C. virginica*) at highly polluted sites revealed higher P-glycoprotein expression than those from less polluted locations (Keppler and Ringwood 2001). Similar findings are reported for other organisms. Furthermore, mussels (*M. galloprovincialis*) transferred from polluted to clean locations reduced their P-glycoprotein activity (Smital and Kurelec 1998a, b). Vice versa, organisms (e.g. grass shrumps, *Palaemonetes pugi* exposed to urban and agricultural waste express high levels of P-glycoprotein (Finley et al. 1999). The induction of P-glycoprotein expression upon exposure to environmentally hazardous chemicals represents a strong clue for the detoxifying function of P-glycoprotein in these organisms. During evolution of life, P-glycoprotein seemed to provide an important survival advantage against adverse selection pressures from the environment.

If P-glycoprotein-mediated efflux processes are blocked by chemosensitizing, environmentally hazardous compounds, these organisms will die. The dimension of this problem is illustrated by the fact that there is a correlation with the degree of water pollution and the presence of P-glycoprotein chemosensitizers. The more polluted the

Table 7 Multi-xenobiotic resistance in aquatic organisms (Chordata)

Organism	Observation	References
Danio rerio (Zebrafish)	Expression of *abcb4* and *abcb5*, but not *abcb1*. Abcb4 but not Abcb5 was functionally active, transported rhodamine B, calcein-AM, vinblastine, vincristine and doxorubicin, and was inhibited by cyclosporin A, PSC833, MK571 and verapamil	Fischer et al. (2013)
Danio rerio (Zebrafish)	The pesticide methyl parathion activated its detoxification in liver. Verapamil increased liver toxicity of methylparathion. Co-exposure of both compounds increased liver expression of *abcb1* and *abcc4*	Nornberg et al. (2015)
Danio rerio (Zebrafish embryos)	Perfluorooctane sulfonate (PFOS) inhibited Abcb4	Keiter et al. (2016)
Onchorhynchus mykiss (Rainbow trout)	P-gp expression; inhibition of rhodamine 123 efflux by the P-gp inhibitor verapamil in primary epithelial cells	Shúilleabháin et al. (2005)
Onchorhynchus mykiss (Rainbow trout)	Expression of *abcb1a, abcb11, abcc1-3, abcc5, abcg2, abcb1b*, and *abcc4* in different fish cell lines	Damaré et al. (2011)
Ictalurus punctatus (*Channel catfish*)	Increased P-gp expression in liver upon exposure with vincristine, beta-naphthoflavone, benzo(a)pyrene, and 3,4,3′,4′-tetrachlorobiphenyl	Doi et al. (2001)
Fundulus heteroclitus (mummichog, killifish)	P-gp expression and efflux activity in hepatocytes upon exposure to a broad range of environmental and chemotherapeutic toxins	Albertus and Laine (2001)
Cyprimus carpio (Common carp)	Inhibition of rhodamine B accumulation in lateral muscles, liver and bile by cyclosporin A and verapamil	Smital and Sauerborn (2002)
Anoplarchus purpurescens (High cockscomb blenny)	Hepatic P-glycoprotein expression was higher in fishes exposed to crude oil or pulp mill effluents than from clean waters	Bard et al. (2002)
Scophthalmus maximus (Turbot)	Hepatocytes accumulated rhodamine B in a competitive manner with verapamil	Tutundjian et al. (2002)
Mullus barbatus (Red mullet)	Expression of *abcc*-related genes in the liver	Sauerborn et al. (2004)
Common carp, European chub, sheep, barbel, silver russian carp (cyprinid species)	Expression of Abcb1- and Abcc-type proteins in the liver of all five species	Sauerborn et al. (2010)
Chelon labrosus (Thicklip grey mullet)	Detection of *abcb1, abcb11, abcc2, abcc3, abcg2*. Perfluorooctane sulfonate induced abb1, *abcb11* and *abcg2* gene expression. Fuel oil downregulated *abcb11* and *abcc2* gene expression	de Cerio et al. (2012)
Oreochromis miloticus (Nile tilapia)	Expression of *abcb1b, abcb11, abcc1, abcc2*, and *abcg2* in embryonic and larval stages	Costa et al. (2012)
Fish hepatoma cell line	Nonionic surfactants (including alcohol polyethoxylates and polypropylene glycols as major components of contaminated freshwater sediments) inhibited P-gp-mediated efflux of calcein-AM in multidrug-resistant PLHC-1/dox cells	Zaja et al. (2013)
Dicentrarchus labrax (European seabass)	Benzo(a)pyrene increased *abcc2* transcripts and rhodamine 123 efflux in primary hepatocytes	Ferreira et al. (2014a, b)

water is, the more P-glycoprotein inhibiting toxins it contains (Smital and Kurelec 1997).

Conclusions

During evolution of life, cellular and molecular mechanisms have been developed to avoid and repair acute or chronic harm by xenobiotic toxic compounds. Successful defense by these mechanisms contribute to salutogenesis of organisms, while their failure may lead to intoxications (hepato-, nephro-, terato-, hematotoxicity, etc.) and on the long run to tumor development, neurodegenerative diseases and others. Hence, detoxification and carcinogenesis are two sides of the same coin.

The induction of P-glycoprotein expression both by specific transport substrates of this efflux pump, as well as by non-related unspecific stimuli raises the question, as to whether P-glycoprotein may be part of a broader line of defense against harmful substances. In analogy to the SOS response in bacteria, it can be imagined that an entire battery of detoxification mechanisms may be activated upon

challenge with xenobiotics. Indeed, multidrug-resistant tumor cells express not only P-glycoprotein. They also reveal specific changes in phase I (decreased cytochrome P-450 monooxygenases) and phase II drug-metabolizing enzymes (increased glutathione S-transferases and glucuronyltransferases) as first shown by Cowan et al. (1986). These resistant cells were not only resistant to classical anticancer drugs, but also to carcinogens.

These basic biological mechanisms are realized all over in the animal kingdom and ABC-transporters can even be found in bacteria and yeast. In the truest sense of the word, P-glycoproteins are universal detoxifiers in the nature. However, problems arise, if anthropogenic chemicals are introduced to the environment as waste. Although the chemical waste is partly extruded, e.g. from aquatic organisms allowing their survival in polluted waters, some of these xenobiotic substances act as inhibitors of ABC-transporters. Poisoned aquatic organisms may or may not die due to malfunctioning ABC-transporters, but at least they suffer from chemical intoxication. There is some probability that partly intoxicated aquatic organisms are harvested and used as seafood for human nutrition. Thereby, it is not difficult to imagine how easy anthropogenic environmental chemical waste would end up in the human food-chain with unforeseeable consequences for human health.

Drug resistance and carcinogenesis in cancer biology cannot be considered separately from general biological processes in nature. This means as converse argument, that results of biomedical research possibly can be transferred even disciplines of life sciences, which are distant. The detoxification of toxic substances is of general relevance in biological systems. Joining forces may, therefore, be a wise strategy to fight problems in medicine, in environmental science and elsewhere in life sciences. To our opinion, interdisciplinary research may be a superior concept.

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