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Review article

Inflammatory pathway interactions and cancer multidrug resistance regulation

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ABSTRACT

Multidrug resistances against chemotherapeutics are among the major challenges related to cancer treatment. Recent studies have demonstrated that different conditions may tune the expression and activity of MDR transporters. For instance, inflammation occurs through a complex cytological process and chemical reactions in the most tumor microenvironment; it can play a critical role in cancer development and is capable of altering the expression and function of MDR transporters. Cytokines, interleukins, and prostaglandins are potent inflammatory mediators that can modulate the expression of MDRs at transcriptional and post-transcriptional levels in the most human cancer cells and tissues and potentially contribute to balance bioavailability of chemotherapeutic agents. Since cancer cases are usually accompanied by inflammatory responses, glucocorticoids and NSAIDs are the primary useful combination chemotherapies in a variety of cancer treatment protocols. In addition to the anti-inflammatory activities of these agents, they exert diverse modulatory effects on MDR-mediated drug resistance via specific mechanisms. Several factors, including cell and MDR-protein types, pharmacokinetics, and pharmacogenetics, mainly influence the regulatory mechanisms. Uncovering the networks between inflammation and multidrug resistance will be clinically helpful in the treatment of malignant cancers and decreasing the cancer mortality rates.

1. Introduction to drug resistance

Intrinsic or acquired drug resistance is an important limitation on the effectiveness of chemotherapy. Researchers believe that there is an association between developing drug resistance in cancer and altered expression of a large number of genes in cellular transport, metabolism, mitogenic, and survival pathways [1].

Fig. 1 has outlined the main mechanisms involved in cancer drug resistance. The following mechanisms are proved to be common in cancer drug resistance: overexpression of transmembrane glycoprotein pumps, expression changes of drug targets such as dihydrofolate reductase, thymidylate synthase, and topoisomerases I and II [2], new balances in metabolic enzymes level and activity particularly of glutathione-S transferases (GST) [3] and superoxide dismutases [4], increased repair or cellular tolerance to drug-induced damage via alterations of apoptotic involving genes and proteins especially p53 and Bcl-2 [5]. These phenomena may occur independently or could be combined to confer resistance against structurally and functionally diverse cytotoxic agents [6]. Investigation of cancer drug resistance mechanisms has yielded important information about designing proper cancer chemotherapy regimens with improved therapeutic properties.

2. Multidrug resistance in cancer

Multidrug resistance (MDR) is the most common problematic mechanism in acquired drug resistance. MDR occurs when a cancer cell is exposed to a distinct anticancer drug and it develops cross-resistance against multiple structurally and functionally varieties of chemotherapeutic agents [7]. The transporters involved in multidrug resistance mainly belong to the family of ATP binding cassette (ABC) transporters. A basic ABC-transporter structure consists of two distinct conserved domain including ATP-binding domains, also known as nucleotide-binding domains (NBDs) and the second, transmembrane domains (TMDs), also known as membrane-spanning domain (MSDs) [8]. The ABC-transporters are categorized into seven subfamilies based on the sequence and unique organization of their NBDs (Table 1). The ABC

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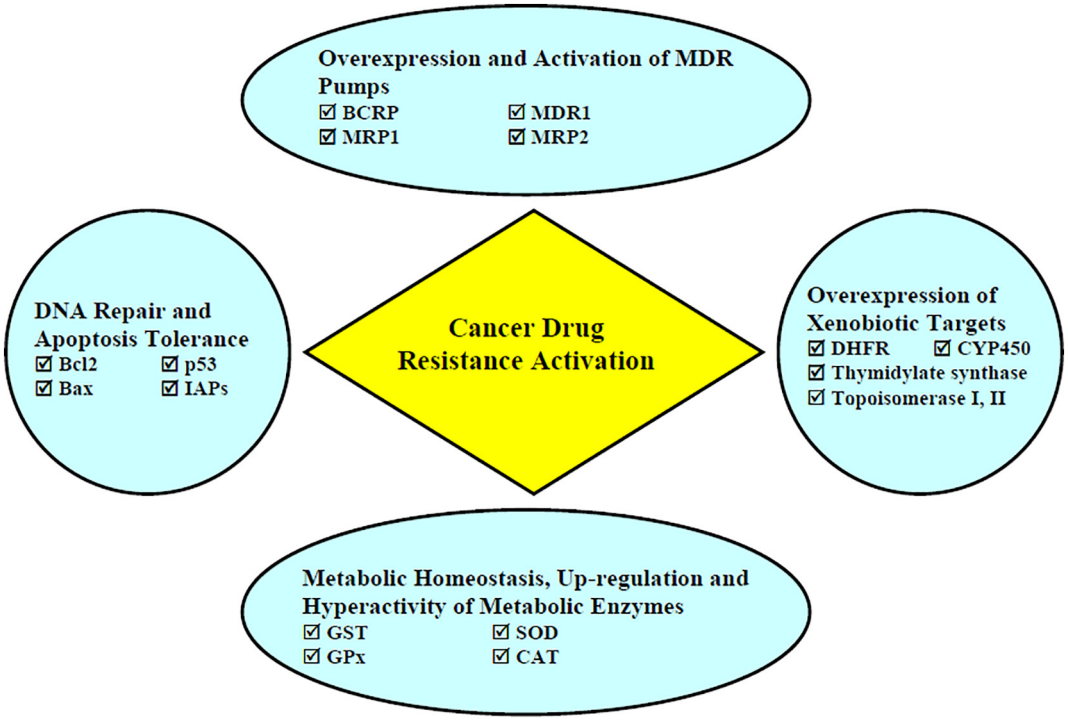

Fig. 1. Main mechanisms involved in cancer drug resistance.

transporters are also structurally classified as full transporters consisting of the typical two TMDs and two NBDs, or as half transporters containing only one TMD and one NBD. A half transporter becomes functionally active only if specific dimerization with another half transporter occurs. These transmembrane proteins are members of one of the largest and most ancient superfamilies present in both prokaryotes and eukaryotes and actively expel cytotoxic drugs out of the tumor cell, and lowering the therapeutic drug concentrations inside the cell. Human ABC proteins are expressed constitutively in a variety of normal cells and tissues, especially in secretory and absorptive organs, placental, and blood-tissue barriers. They show important physiological, pharmacological, and toxicological functions. Among the diverse ABC-transporters, the following members have been recognized as the most problematic groups in clinical cancer treatment: the breast cancer resistance protein (BCRP, ABCG2, MXR, or ABCP), the classical P-glycoprotein (P-gp, MDR1, or ABCB1), and the multidrug resistance-associated proteins (ABCC1, or MRPs) [9].

P-gp was primarily isolated from a multidrug resistant variant of Chinese hamster ovary cell in 1976 and ultimately subclassified to the ABCB family. P-gp is a 170-kDa membrane anchor protein and most frequently efflux bulky amphipathic and nonionic xenobiotics, such as taxanes, anthracyclines, and vinca-alkaloids. On the other hand, inhibitor agents that target P-gp function have also been extensively studied. These inhibitors may competitively (such as cyclosporine-A) or non-competitively (such as verapamil) interfere with P-gp-mediated transport and increase the intracellular accumulation of cytotoxic agents [10].

MRPs are among the ABCC family and contain 13 members. MRPs could be classified into two individual classes based on the presence of a third N-terminal MSD. The short members of the family with 12 transmembrane segments (MRP4, 5, 8, 9) have a conventional full ABC transporter structure with two NBDs and two MSDs; whereas the larger members of this family consists of 17 transmembrane segments (MRP1, 2, 3, 6, 7) possess an additional N-terminal MSD. MRPs are responsible for conferring resistance to some natural cytotoxic agents, nucleoside and nucleotide analogs. Unlike P-gp the human MRPs can transport the organic anions such as cytotoxic drugs conjugated to glutathione (GSH), sulfate, or glucuronate. Although a growing number of compounds noncompetitively inhibit these proteins, MRP substrates mostly compete reciprocally for transport. MRPs are inhibited by some compounds, such as probenecid, indomethacin, glibenclamide, plant-derived flavonoids such as genistein and quercetin, as well as designed synthetic flavonoids such as flavopiridol. Several P-gp inhibitors including the quinoline derivative MS-209 and the pipecolinate derivative VX-710 are found to cross-react with MRP1. However, most of the general MRP inhibitors have shown relatively low affinity and specificity for other transporters [11] (Table 1).

BCRP categorized in the second class of the G subfamily based on the structure and was first identified in malignant breast cancers. BCRP is a 72 kDa half transporter consisting of six transmembrane amino acid segments and is requiring dimerization to form an active transport complex. BCRP substrates have wide ranges including anthracyclines, bisantrene, camptothecin, daunorubicin, doxorubicin, epirubicin, etoposide, flavopiridol, Hoechst 33342, methotrexate, mitoxantrone, topotecan derivatives, SN-38, carcinogens, and dietary toxins. A limited number of inhibitors have been identified to circumvent BCRP-mediated drug resistance. These inhibitors include AG1478, lapatinib, erlotinib, gefitinib, imatinib, sunitinib, wortmannin, novobiocin, VX-710, LY294002, elacridar, PD98059, FTC, and Ko143 (Table 1). Some of these drugs have already been proven in clinical studies for humans and animals. There are considerable overlaps between the substrates and inhibitor spectrums of BCRP, P-gp, and MRP1, despite the structural difference between them [12,13].

3. Malignant cancers and inflammatory signals

An injury caused by physical, chemical, or biological stimulations triggers the vascular tissues to respond; this response is known as inflammation that could be classified as either acute or chronic. The acute inflammation has a rapid onset and becomes severe somewhat quickly; its manifestations usually last for only a few days. However, chronic inflammations have slow onsets that persist longer (from weeks to years). The first relationship between inflammation and cancer was suggested in 1863 when the leucocytes were discovered in neoplastic

Table 1
Classification, substrates and inhibitors of human ABC proteins involved in multidrug resistance.

Subfamily	Number of proteins	Names	Substrates	Inhibitors
ABCA (ABC1)	14	ABCA2	Not identified yet	U18666a
ABCB (MDR/TAP)	11	ABCB1 (P-gp)	Adriamycin, Berberine, Bisantrene, Daunorubicin, Digoxin, Doxorubicicn, Etoposide, Fexofenadine, Irinotecan, Loperamide, Mitoxantrone, Paclitaxel, Seliciclib, Topotecan, Vinblastine, Vincristine	Agosterol A, Amiodarone, Anthranilmide, Cyclosporine D, Isothiocyanates, Ms-209, NSC-38721, Progestrone PSC-833, Quiniline, Reserpine, Tariquidar Verapamil, VX-710, XR-9576
		ABCB4 (MDR2)	Digoxin, Daunorubicin, Ivermectin, Paclitaxel, Vinblastine	Cyclosporine A, Valspodar, Verapamil
		ABCB11 (BSEP, SPGP)	Pravastatin	Cyclosporine A, Paclitaxel, Reserpine, Rifamycin SV, Tamoxifen, Troglitazone, Valinomycin
ABCC (CFTR/MRP)	13	ABCC1 (MRP1)	Adefovir, Aflatoxin, Apicidin, Atrazine, Berberine, Chlorambucil, Ciprofloxacin, Citalopram, Cyclophosphamide, Daunorubicin, Difloxacin, Doxorubicin, Edatrexate, Epirubicin, Ethacrynic acid, Etoposide, FK228*, FR901228, Grepafloxacin, Hydroxyflutamide, Idarubicin, Indinavir, Irinotecan, Melphalan, Methotroxate NSC-630176, Paclitaxel, Pirarubicin, Ritonavir, Saquinavir, SN-38, Vinblastine, Vincristine, ZD1694	Agosterol A, Benzbromarone, Cyclosporine A, Euchrestaflavanone, Isothiocyanates, MK571, MS-209, NSAIDs, Quercetin, Rifampicin, Sophoraflavanone, VX-710, XR-9576
		ABCC2-6 (MRP2-6)	Acetaminophen glucuronide, Atorvastatin, Cisplatin, Doxorubicin, Etoposide Fexofenadine, 5-fluorouracil, Glutathione and glucuronide conjugates, Methotrexate, Mitoxantrone, Olmesartan Rosuvastatin, Teniposide Valsartan, Vincristine Vinblastine	Benzbromarone Cyclosporine, Delaviridine, Diphenylamine-2-carboxylate, Dipyridamol, Efavirenz, Emtricitabine, Furosemide, Indometacin, Isothiocayanates, Lamivudine, MK751, Nevirapine, Probenecid, Sulfinpyrazone, Tenofovir, Trequinsin, VX-710, XR-9576, Zaprinast
		ABCC10 (MRP7)	Cyclosporine-A, E217βG Glycolithocholate 3-sulfate, MK571, Leukotriene-C4	PD173074, Tariquidar
		ABCC11 (MRP8)	Bile acids, cAMP, cGMP, DHEA, 5-FU, LTC4, MTX, PMEA	Arylaminobenzoates diphenyl-2-carboxylate, 5-nitro-2-(3-phenylpropylamino) benzoate
		ABCC12 (MRP9)	Organic anions such as drugs conjugated to glutathione, sulfate or glucuronate	Not identified yet
ABCD (ALD)	4	Not reported in MDR yet	Long and branched-chain acyl-CoA Un-branched saturated fatty acids	Not identified yet
ABCE (OABP)	1	Not reported in MDR yet	Oligoadenylate	Not identified yet
ABCF (GCN20)	3	Not reported in MDR yet	Amino acids	Not identified yet
ABCG (WHITE)	5	ABCG2 (BCRP)	Anthracyclines, Bisantrene, Campthotecin, Daunorubicin, Doxorubicin, Epirubicin, Flavopridol, Imatinib, Irinotecan, Methotrexate, Mitoxantrone, Nucleoside analogs, Pantoprazole, Prazosin, SN-38, Statins, Topotecan	Estrone, 17ß-estradiol, Fumitremorgin C, Imatinib mesylate, Iressa, Ivermectin Ko132, Ko134, Novobiocin, Omeprazole, Ritonavir

tissues, by Rudolf Virchow [14]. Since then, chronic inflammation has been identified as the major etiological factor for cancer development in different studies. Some examples that have identified these associations include the link between human papilloma virus and cervical, esophagus, and larynx cancers; Helicobacter infections and gastric adenocarcinoma; hepatitis B virus and cirrhosis and hepatocellular carcinoma; schistosomiasis and bladder carcinoma, asbestos-induced inflammation and bronchogenic carcinoma or mesothelioma in human [15,16]. However, the relationship between some chronic inflammatory diseases, such as psoriasis and increased cancer risk is debated [17]. Various cells and cytokines are involved in the molecular mechanism and tuning of the inflammatory process in tumors and any cancer tissues consist of their unique innate immune cells (i.e. dendritic cells, tumor-associated macrophages (TAMs), natural killer T cells (NKT), neutrophils, mast cells, and myeloid-derived suppressor cells) and adaptive immune cells including, B-cells and T-lymphocytes [18,19]. To regulate tumor growth, these diverse cells make use of several methods to communicate with each other including cell-cell direct contact or by cytokine-mediated signaling. It can be assumed that a tumor microenvironment is a place for co-existence of antitumor immunity and tumor-promoting inflammation. The balance between them specifies the path of tumor progression [20]. Increasing evidence demonstrates that T-lymphocytes and TAMs are the most frequently immune cells existing within the tumor microenvironment. TAMs mostly contribute to tumor growth, angiogenesis, invasion, and metastasis [21–23]. It is worth noting that T cells have both tumor-suppressive (T helper-1) and tumor-promoting (T regulatory) effects; this is due to the production of both immunosuppressive and proinflammatory cytokines. In addition to the immunosuppressive cytokines, cytotoxic cells (like cytotoxic T lymphocytes) also trim the antitumorigenic activity of T lymphocytes (Fig. 2) [24]. NKT cells are the only cells that lack protumorigenic roles [25,26].

Different tumor development stages, including initiation, promotion, malignant conversion, invasion, and metastasis can contribute to the progression of inflammation. Inflammatory microenvironments may induce mutations, epimutations in DNA, and genomic instability that lead to tumor initiation. This condition is believed to lead to the production of reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI), which can trigger DNA damage and genomic instability. For example, mutations and inactivation of p53 or repression of mismatch repair enzymes presumably caused by direct oxidative damage, suggest that chronic inflammation causes genomic changes. Up-regulation of activation-induced cytidine deaminase (AID, a potent mutator) in tumor environment introduces mutations in critical proto-oncogenes including p53, c-Myc, and Bcl-6. Inflammation dependent mutations may occur through nonhomologous recombination and NF-κB-mediate inactivation of p53-dependent genome surveillance [27,28]. Epigenetic mechanisms including, histone modifications, DNA methylation, and microRNA-based silencing play key roles in inactivation of tumor suppressors, like INK4a and antigen-presenting cells that accompany tumor initiation. Production of growth factors and cytokines during inflammation also provide a complex mutagen-signaling environment that enhances cancer stem cell selection and growth [15,29].

Inflammation may also promote proliferation and survival of premalignant cells. Tumor-promoting cytokines normally are secreted by immune or inflammatory cells. These messengers activate transcription factors, particularly NF-κB, STAT3, and activator protein 1 (AP-1) in susceptible cells to up-regulate survival genes and activate cell division and growth to colonize malignant cells. Inflammation can also accelerate the growth of new capillary blood vessels to provide the blood, which is necessary for the subsequent growth phases. Activated transcription factors like AP-1, NF-κB, and STAT3 directly regulate proangiogenic genes such as CXCL1, CXCL8, hypoxia-inducible factor 1 alpha (HIF1a), IL-8, and VEGF in TAMs and other responsible hematopoietic cells (Fig. 2) [30,31].

Cytokines are a broad category of soluble proteins that play critical roles in different stages of immunity and inflammation as signaling messengers. Cytokines are classified according to the original cell sources and their function into chemokines, colony-stimulating factors, interferons, interleukins, lymphokines, and monokines. Regardless of cellular sources, cytokines can either stimulate or inhibit tumor progression [32]. Some inflammatory cytokines like IL-12, IFNγ, and TRAIL demonstrated antitumor immunity; while, TNF-α, EGFR ligands, and TGF-β have been reported to stimulate cancer cell growth and survival. FasL, granzyme B, perforin, and TRAIL are among the direct signaling cytotoxicity of NK cells and cytotoxic T lymphocytes (CTLs) toward cancer cells. T helper cells have considerable enhancing effects on cytotoxic immunity via the production of IFNγ and in some instances IL-17A. Dendritic cells and macrophages prime NK and T lymphocyte-mediated responses to cancer cells via foreign antigen presentation and IL-12, IL-15, and IL-18 cytokine secretion. On the other hand, IL-6, IL-17, and IL-23 enhance tumor progression; it is understood that these cytokines can be stimulated if various downstream effectors, such as caspases, AP-1, NF-κB, STAT, and SMAD transcription factors are activated (Fig. 2) [33].

4. MDR-pump regulation by inflammatory mediators

Over the past decades, several investigations have confirmed the relation between inflammation mediators and activity and regulation of MDR transporters, which enhance the chemosensitivity of resistant cells toward anticancer agents. Apparently, at various molecular levels including transcriptional, post-transcriptional, translational, and/or post-translational stages, these modulations can occur. Some pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α affect MDR fluctuation more significantly. Energy is usually focused on restoring homeostasis during an inflammatory response. Thus, any other processes may have less importance. Consequently, drug transporters may not be manufactured temporarily [34,35].

There is a negative correlation between P-gp and BCRP transcription and translation with a significant reduction of the *IL-1b* and *IL-6* transcript levels during active inflammation in the colonic epithelium in people suffering from ulcerative colitis. The Experimental models of intestinal inflammation in rats suppress the expression and activity of intestinal MDR1 and MRP2. A decreased MRP2 level was also observed in the intestine of rat treated with LPS and in several other models of inflammation, such as chronic renal failure and cholestasis. Scientists firmly believe that there is a reduction in the expression and activity of several efflux transporters such as MRP2, MRP3, and MRP4 during inflammatory processes in the intestine. Reduced BCRP expression was also observed in the duodenum during obstructive cholestasis [36,37]. Some studies have reported the elevated blood concentrations of the P-gp substrates like cyclosporine and tacrolimus in pediatric patients during diarrhea episodes. MDR1 expression in the inflamed intestinal epithelium was also decreased by inflammatory cytokines in patients with various gastrointestinal inflammatory disorders. Intestinal inflammation was developed spontaneously in IL-10–deficient mice which are reported to decrease P-gp function and expression all along the intestine. Jejunum expression of MDR1a and MDR1b was reported to be down-regulated in the endotoxin-treated rats. Moreover, dextran sodium sulfate-induced colitis and chronic renal failures represent a dramatic reduction of MDR1 protein expression and activity in rats [38].

Some papers have introduced IFN-γ, IL-2, and TNF-α to chemosensitize different human and mice carcinoma cells by down-regulation *MDR1* gene. Furthermore, reduced P-gp activity was observed in Caco-2 (human colorectal adenocarcinoma) cells treated with plasma from renal failure rats containing increased levels of pro-inflammatory cytokines such as TNF-α and IL-6. A reduction in hepatic expression and activity of P-gp was caused by turpentine-induced acute phase response (APR) in rats because of *MDR1a* and *MDR1b* gene suppression.

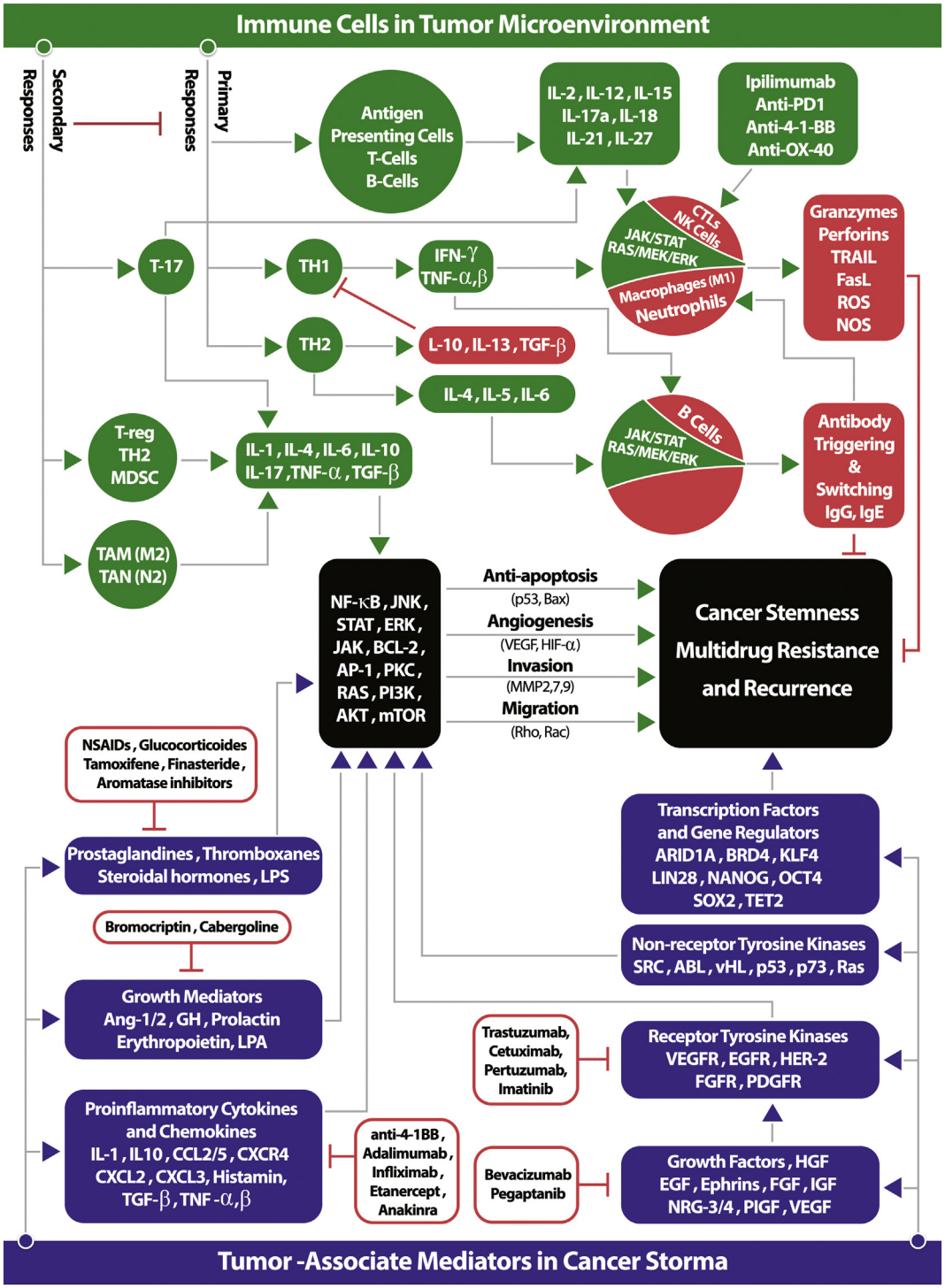

Fig. 2. Inflammatory immune cells and cancer microenvironment interactions with multidrug-resistant tumors.

Significant reductions of P-gp and MRP2 expression were also observed in endotoxin-induced inflammation in rodent livers [39,40].

In fact, studies conducted on pro-inflammatory cytokines have shown that the expression of MDR1 was suppressed by the administration of IL-6 in primary rat hepatocytes and mice in vivo suggesting the involvement of IL-6 in the inflammation-mediated decrease of P-gp expression [33]. Besides, some studies have reported the contributing role of TNF-α in endotoxin-induced decrements of mice hepatic P-gp expression [39]. P-gp activity and the transcript amounts were reduced in IL-1β- or IL-6-treated human hepatoma cells [41]. It is believed that Endotoxin-induced systemic inflammation in near-term pregnancy leads to an imposed dose-dependent elimination of several mice placental genes, including *MDR1a* [42].

Intracranial accumulation of doxorubicin is caused by decreased P-gp protein expression in the brains of endotoxin-treated mice. The administration of intraperitoneal or intracranial LPS leads to the production of respective systemic or CNS inflamed rat models. They trigger marked decreases in *MDR1a* transcripts in the CNS and consequently increased P-gp fluorescent substrates, including cyclosporine-A, digoxin, and 99mTc-sestamibi in the brain. Treating rat astrocyte primary cells with gp120 antigen (an envelope glycoprotein for HIV-1) generates an intense inflammatory response in vitro; this would cause a

decreased P-gp expression and increased accumulation of P-gp substrates. It was reported that the renal expression of MDR1a and MDR1b was reduced by endotoxin administration; it also reduces fluorescent rhodamine-123 excretion from rat kidneys dramatically [43,44].

It is believed that the regulation of BCRP and MRP is similar to that of P-gp in the most cells. A decreased BCRP and MRP expression can be mediated by inflammatory conditions which alter the distribution of their substrates. Dramatic reductions in the hepatic MRP2 translation and pump activity have been reported in metabolic cholestasis models (like endotoxemia) by numerous research groups conducted over the past decade. It was reported that significant decreased *MRP2* expression during inflammation was mediated by IL-6 in IL-6-knockout mice and interleukin-6-treated wild-type mice [45]. Some studies have reported that *MRP2* mRNA decreased in LPS-treated rat liver slices significantly [46]. According to recent studies, decreased amount of *BCRP* mRNA was also observed in the livers of endotoxin-treated rats [35]. P-gp and BCRP transcription and translation were decreased approximately 40–50% by IL-1b and TNF-α treatment of primary placental trophoblasts. However, no significant effects were caused by IL-6 on the transporter mRNA and proteins [47]. According to some other studies, lipopolysaccharide leads to a decreased BCRP expression level in placentas of rats. Some studies reported that the expression of BCRP and activity in the human brain microvascular endothelial cell line, hCMEC/D3, at long term incubation with high doses of TNF-α decreased significantly [48,49].

Although the previously mentioned researches are not all supporting documents that have been accomplished yet, there exist diverging reports that proinflammatory cytokines do not change or even increase the MDR protein [33]. Previously IL-6, IL-1b, and TNF-α was reported as significant BCRP transcription, translation, and activity inducer in MCF-7 cells [50], but few studies showed that BCRP was not regulated by proinflammatory cytokines in resistant BCRP-overexpressing gastric and cervical cancer cell lines [51]. It has also been shown that increased amounts of *MDR1* mRNA in treated cells by IL-1β and IL-6 [33]. P-gp transcript and protein levels increased following the treatment of Caco-2 cells by IFN-γ, but the activity remained unchanged which could be associated with the unsatisfactory localization of P-gp in the apical membrane following the treatment [52].

According to various studies, TNF-α also has divers effects on the expression and action of MDR [53]. Several researched showed an elevated P-gp expression level in the blood-brain barrier after TNF-α treatment; however, BCRP protein level remained unchanged after the same condition in freshly isolated rat brain capillaries [54]. Some researchers have reported that the expression of MDR1b was induced significantly in primary rat hepatocytes cultured in the presence of TNF-α. However, a three-fold release of TNF-α was observed in sulfasalazine-resistant human T cells (CEM/SSZ) and simultaneously marked induction of BCRP compared with parental CEM cells. Exogenous TNF-α was proved to be associated with increased *MRP1* transcript levels in HCT116 colon carcinoma; while MRP overexpressing cells was not affected by TNF-α [55].

Although decreased *MRP2* levels were observed in the inflammation, various studies reported that the inductions in the hepatic *MRP1* and *MRP3* levels of lipopolysaccharide-treated animals were done in compensation. It could be suggested that the expression of these transporters in human tissues are induced by Cytokine as well. For instance, MRP1 and MRP3 expression and activity levels in human cell lines were induced following treatment by IL-6. It worth noting that differential regulation of transporters was observed by incubation of rat or human liver slices with LPS. One day after LPS treatment, the *MRP2* transcript levels in rats decreased, but the amount of the same transporter remained unchanged in humans [56]. On the other hand, a three-fold elevation was observed in the glomerular filtration of doxorubicin in treated mice following the endotoxin-induced changes in P-gp expression and MDR1 up-regulation following non-cytotoxic treatment concentrations of the LPS [40].

5. Cyclooxygenase and multidrug resistance

Prostaglandins (PGs) are inflammatory mediators and play crucial roles in the generation of inflammatory responses. These lipids are derived from arachidonic acid and their synthesis in vivo is significantly elevated in inflamed organs by the activation of cyclooxygenase (COX) isoenzymes. To date, three isoforms of the COX enzyme have been identified. COX-1 is constitutively expressed in wide ranges of normal tissues and is considered as a housekeeping enzyme; it is believed to participate in physiological homeostasis. In contrast, COX-2 isoenzyme is trace or undetectable in most normal tissues (except in the kidney and importantly in the central nervous system) but is induced in the response of inflammatory signals and mitogenic factors. Therefore, it is assumed that COX-2 plays an important role in pathophysiological processes. COX-3 is abundant in cerebral cortex and heart and is a splice variant of COX-1 [57,58].

COX is a membrane-bound bifunctional enzyme that converts arachidonic acid to PGG2 by cyclooxygenation and then reduces PGG2 to unstable intermediate PGH2 by peroxidation. PGH2 is an intermediate substrate for the biosynthesis of other prostaglandins and thromboxanes. PGE2 and prostacyclin (PGI2) are the most important products in cyclooxygenation process during inflammation and COX-2 is considered responsible for these pathophysiological processes. Prostaglandins stimulate cancer cell proliferation, promote angiogenesis, inhibit apoptosis, and increase metastatic potentials. COX-2 levels are reported to be up-regulated in lung, breast, esophageal, bladder, prostate, colon, gastric, pancreatic head, and neck cancers [59,60].

If transcription activation and mRNA stability occur at the same time, overexpression of COX-2 is inevitable. COX-2 overexpression has been reported for a wide variety of stimuli including; in the response of pre-inflammatory cytokines (like IL-1β, NF-IL6, TNF-α, NF-κB, and AP-1), growth factors (like EGF), oncogenes (like HER-2/neu), nuclear factor of activated T cells (NFAT), viral infection (polyomavirus enhancer activator 3 (PEA3)), bacterial lipopolysaccharide, tumor simulator molecules (like phorbol esters, bile acids, vasoactive peptides, endothelin-1, ceramides, and methanandamide). It was also shown explicitly that determining COX-2 levels in neoplastic tissues is affected by posttranscriptional regulation. A series of AU-rich elements (ARE) exist in 3′-UTR of COX-2 transcripts that influence the messenger stability largely. It is worth noting that COX-2 mRNA can be stabilized and up-regulated by oncogenes, cytokines, growth factors, tumor promoters, ERK1/2, and p38. COX-2 expression may also be regulated by factors influencing the rate of protein synthesis and degradation (Figs. 2 and 3) [61].

There are many enhancer factors for COX-2 transcription, but data on negative modulators is scarce. Some researchers have illustrated that transcriptional inhibition is caused by the association of some elements with 3′-UTR of the COX-2 mRNA. To bind to the box and markedly represses COX-2 transcription, wild-type p53 competes with TATA-binding protein. Hypermethylation of specific promoter regions is an epigenetic mechanism for down-regulation of COX-2 in cancers [62]. Several anti-inflammatory cytokines, including IL-4, IL-10, and TGF-b, and steroidal and non-steroidal anti-inflammatory agents may interfere with COX-2 bioactivity and inhibit its expression. Finally, antisense miRNA technologies and some UTR-binding proteins were shown to increase *COX-2* transcript decay and translational inhibition [63].

Like many inflammatory mediators, COX-2 has shown distinct effects on the MDR expression (Table 2). Growing evidence indicates that elevated *COX-2* expression is associated with the MDR proteins levels like BCRP, MDR1, MRP1, MRP2, and MRP3 and it strongly interferes with the chemotherapy outcome in cancer patients [64]. For example, immunohistochemistry analyses of human breast and ovarian cancers revealed a strong positive correlation of MDR1 and *COX-2* expression [65,66]. Overexpression of COX-2 in animal cells up-regulated the MDR1 [67]. PGE2, PGF2a, and arachidonic acid significantly induced *MDR1b* gene expression and its transport activity when added directly

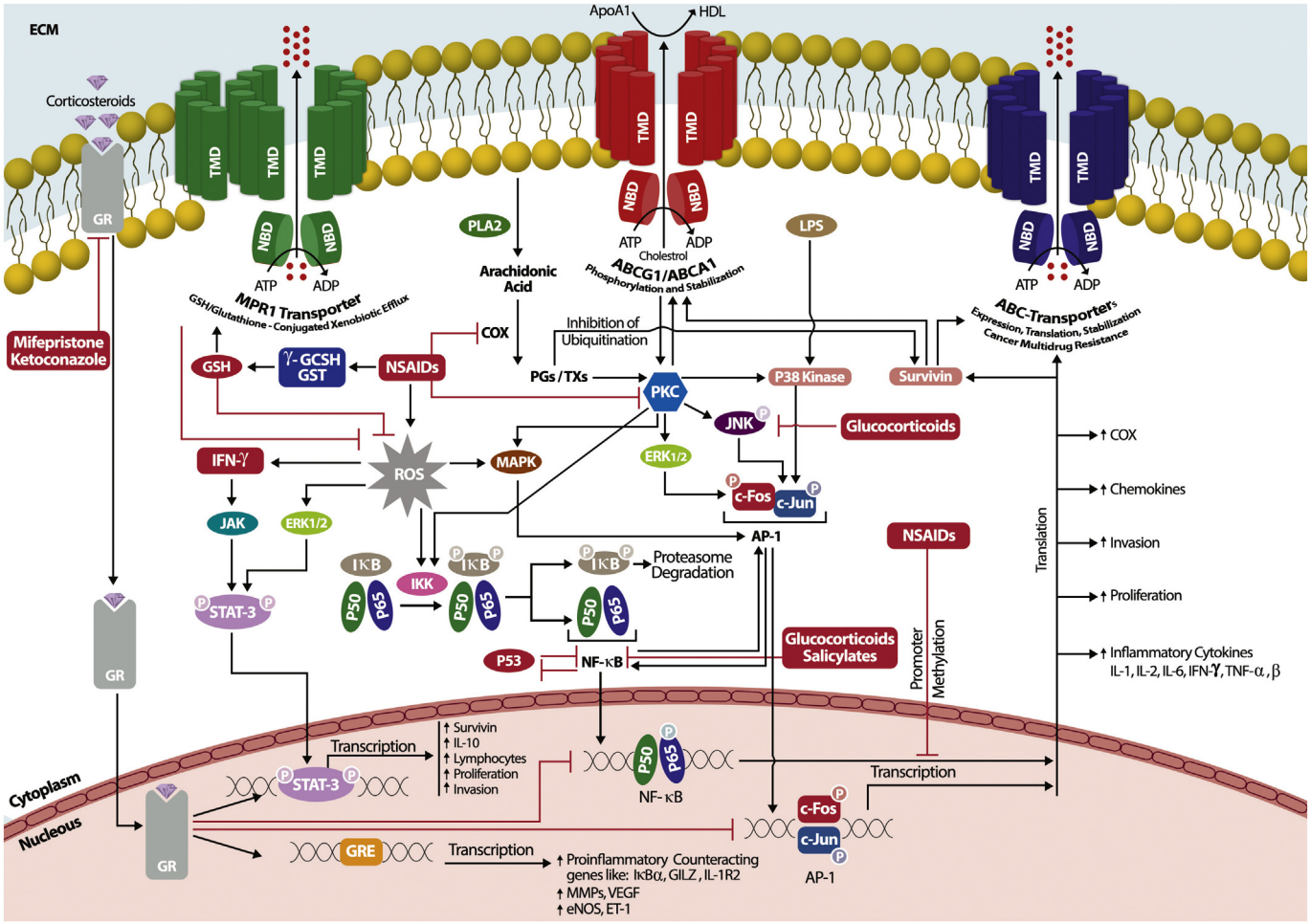

Fig. 3. Schematic representation of the glucocorticoid receptors, COX-dependent, and COX-independent proposed mechanisms of multidrug resistance regulation.

to the culture medium of primary rat hepatocytes [60,68]. COX-2 overexpression can also induce the MRP1 expression in TR-5 colon cancer cells, resulting in chemoresistance to cisplatin. TR-5 cells in this study were pretreated with the COX-2 selective inhibitor JTE-522, which restored chemosensitivity of these cells to cisplatin [69]. TPA-induced COX-2 expression could increase BCRP activity and expression in different breast cancer cells. However, some results reveal different correlations between COX-2 level and MDR expression. For example, enforced expression of COX-2 in human NCI-H460 large cell lung cancer did not enhance MRP1 and P-gp expression. A negative correlation was observed in medullary thyroid carcinoma cells between COX-2 and MRP2 expression that was quite the opposite from that of MRP1 [70–72].

It seems differences between MDR regulations and inflammatory responses are the main cause of these conflicting results. Studies have shown that cytokine release is dependent on model, strain, and species. On the other hand, different types of receptors interact with proinflammatory cytokines and the distribution of these receptors is different among different types of cells. Moreover, different cell lines have different contents of transcriptional factors. Thus, cytokines have connections with various types of receptors that cause different sets of intracellular signals and transcription factors to activate/deactivate. Some studies have reported that the cytokine-mediated modulation of MDR genes is influenced by the expression patterns of MDR genes greatly. There is some discrepancy regarding the different effects of COX-2 on MDR expression, which can be associated with the differences among species, tissue origins, or cell types. The net effect of the genes involving in MDR is too complex and it is difficult to list those that lead to the development of the MDR phenotype. The above-mentioned studies highlighted the importance of understanding the molecular effects of inflammation on MDR transporters. Undoubtedly, the importance of understanding the molecular effects of inflammation on MDR transporters is influenced by such studies [73,74].

6. Inflammatory mediators and MDR promoter elements

Although MDR promoters lack TATA boxes, some unique initiation sequences direct the MDR transcription. These elements are not universal for all MDR promoters; however, many similarities are among their structural sequences and activities. MDR1 transcription is involved in transcription start sites (TSS); inverted CCAAT box; GC boxes; C/EBP element; steroid xenobiotics receptor element (SRE); heat shock element (HSE); cAMP response element (CRE); glucocorticoid response elements (GRE); and multiple Sp1, AP-2, AP-1 for transcription regulators [75–77]. It seems BCRP promoter does not contain an SRE that is often found in genes involved in cholesterol and fatty acid metabolism, suggesting that BCRP may not be active in lipid transporting. Moreover, the MRP gene expression may also be controlled through other sequences including NF-κB-like element and progesterone response element (PRE) that could work as repressor and enhancer elements, respectively (Fig. 3) [78–80].

Generally, transcription factors regulate *MDR1*, *BCRP*, and *MRP* genes transcription via binding to promoter response elements. Some studies have reported that SP1, pregnane X receptor (PXR), NF-Y, YB-1, NF-κB, and p53 mutation amplify the *MDR* gene. It was also observed that a proto-oncogene Fos and NF-κB/P63 complex interaction with the

Table 2
Inflammatory mediators and MDR modulation in cancers.

Inflammatory mediator	Inflammation or cancer type	Effect	Target ABC-transporter
IL-1 and IL-6	Ulcerative Colitis	Reduction in the expression	P-gp and BCRP of colonic epithelium
ND	Gastrointestinal inflammation	Reduction in the expression and function	Intestinal MDR1, MRP2, MRP3 and MRP4
ND	Pediatric diarrea	Reduction in the expression and function	P-gp
ND	Intestinal inflammation in IL-10 deficient mice	Reduction in the expression and function	Intestinal P-gp
ND	Endotoxin- treated rats	Reduction in the expression	Jejunums MDR1a and MDR1b
ND	Induced chronic renal failure in rats	Reduction in the expression and function	Intestinal P-gp
ND	Induced colitis in mice and rats	Reduction in the expression and function	Intestinal and colonal P-gp
INF-γ, TNF-α and IL-2	Human and mice colon carcinoma cells	Reduction in the expression	P-gp
IL-6 and TNF-α	Caco-2 (human colorectal adenocarcinoma)	Reduction in the function	P-gp
ND	Obstructive cholestasis	Reduction in the expression	Duodenum BCRP
ND	Turpentin-induced APR in rats	Reduction in the expression and function	Hepatic P-gp
ND	Endotoxin-induced inflammation in rodents	Reduction in the expression	P-gp and MRP2 in liver
IL-6 and IL-1b	Primary rat hepatocytes	Reduction in the expression	P-gp
IL-6	Mice	Reduction in the expression	P-gp
TNF-α, IL-1b or IL-6	Human hepatoma cells	Reduction in the expression and function	P-gp
ND	Cholestasis	Reduction in the expression and function	Hepatic MRP2
IL-6	IL-6 deficient mice	Reduction in the expression	MRP2
ND	LPS-treated rats	Reduction in the expression	MRP2
ND	Endotoxin treated rats	Reduction in the expression	BCRP
TNF-α and IL-1b	Primary placental trophoblasts	Reduction in the expression	P-gp and BCRP
IL-6	Primary placental trophoblasts	Reduction in the protein expression	BCRP
ND	Endotoxin-treated mice	Reduction in the expression	Placental MDR1a
ND	LPS-treated rats	Reduction in the expression	Placental BCRP
ND	Endotoxin-treated mice	Reduction in the expression	Brain P-gp
ND	LPS-treated rats	Reduction in the expression	Brain MDR1a
ND	Gp120 treated rat astrocytes	Reduction in the expression	P-gp
TNF-α	hCME/D3 cell	Reduction in the expression	BCRP
ND	Endotoxin treated rats	Reduction in the expression	Renal MDR1a and MDR1b
TNF-α, IL-1 or IL-6	Human breast cancer cell lines	Induction of the expression and function	BCRP
TNF-α, IL-1 or IL-6	Human gastric and cervical cancer cell lines	Unchanged	BCRP
INF-γ, IL-1b and IL-6	Caco-2 cells	Induction of the expression	MDR1
TNF-α	HCT116	Induction of the expression	MRP1
TNF-α	HCT15	Unchanged	MRP1
TNF-α	Endotoxin treated rats	Induction of the expression	MDR1b
IL-6	Human hepatoma cell	Induction of the expression and function	MRP1 and MRP3
ND	LPS-treated human liver slice	Unchanged	MRP2
TNF-α	Blood brain barrier	Induction of the expression	P-gp
TNF-α	Blood brain barrier	Unchanged	BCRP
ND	Endotoxin-treated mice	Induction of the expression	Renal P-gp
TNF-α	Sulfasalazine-resistant human T cells	Induction of the expression	BCRP
COX-2	Human breast and ovarian tumor specimens	Induction of the expression	P-gp
COX-2	Human hepatocellular carcinoma cells	Induction of the expression	P-gp
COX-2	Rat mesangial cells	Induction of the expression	P-gp
Arachidonic acid, PGE2 and F2a	Primary rat hepatocytes	Induction of the expression	MDR1b
COX-2	Colon cancer cell line, TR-5	Induction of the expression	MRP1
COX-2	Breast cancer cell lines	Induction of the expression and function	BCRP
COX-2	Medullary thyroid carcinoma cells	Induction of the expression	MRP1
COX-2	Human H460 lung cancer cell line	Unchanged	P-gp and MRP1
COX-2	Medullary thyroid carcinoma cells	Reduction in the expression	MRP2

CAAT element of the gene promoter and by c-jun and p-c-jun leads to negative transcriptional regulation. Several studies have investigated the involvement of other transcription factors such as NF-IL6, CREB/ATF, Jun-Fos, STAT, and NF-AT in the control of *MDR* mRNA expression [81–83].

In particular, proinflammatory cytokines can be involved in MDR transcriptional control through these transcription factors. For example, it has been shown that the activation of C/EBPβ (also called NF-IL6) and C/EBPδ transcription factors play an essential role in the *MDR1* transcription induction by IL-6 in breast cancer cells. NF-IL6 activates MDR1 after interaction with the inverted CCAAT box and this effect was negatively regulated by the AP-1 box (−123 to −111) [84,85]. TNF-α mediated *MDR1b* gene up-regulation was reported in rat hepatocytes and hepatoma cells through NF-κB and p53 transcription factors. These promoter-binding sites in the *MDR1b* have been fully investigated. STAT2 and STAT3 are two intracellular mediators that regulate the effects of type-I IFNs through the transcription signaling pathways [58,86].

Recently it has been realized that nuclear hormone receptors can also regulate drug transporters during inflammation. Pregnane X receptor (PXR) was also named as steroid xenobiotics receptor (SXR) responses to some hormones such as bile acids, and steroidal xenobiotics and has been proven for *MDR1a*, *MRP2*, and *MRP3* transcriptional regulation. Primary hepatocyte and colon cells responded to several SXR agonists and enhanced MDR1 expression, suggesting that MDR1 was PXR-targeted in liver and intestine [87,88].

MDR1 transcription induction was also reported through pregnane X receptor in human colon carcinoma cells and DR4 response element was responsible as the distinct binding site. An interesting study on human primary hepatocytes shows that IL-6 can decrease the expression of PXR transcripts and probably PXR dependent gene expression. PXR and nuclear constitutively activated receptor (CAR) elimination are also investigated in rodent and human tissues after exposure to LPS [89]. In spite of the widespread evidence that shows cytokines and inflammation modulate the expression of *MDR* mRNA via nuclear receptors, the exact mechanism, and nature of such relation and interaction remained unclear and should be further studied.

It is reported that inflammatory cytokines may mediate their regulatory effects on MDR activity and expression by activating the ET-NOS-PKC pathway. This pathway involved in endothelin formation and

interaction to endothelin receptor, and activation of several enzymes like nitric oxide synthase (NOS), protein kinase C (PKC), and soluble guanylyl cyclase (SGC). Inducible NOS (iNOS) enzyme plays a critical regulatory role in this pathway. TNF-α has been activated in lipopolysaccharide-treated renal proximal tubule cells and subsequently elevated P-gp expression and bioactivity via triggering NO production pathway. It seems NF-κB activation via NO may repress the P-gp synthesis [90,91]. In addition, epigenetic modifications of the MDR promoters or post-translational histone modifications play a pivotal role in regulating of MDR expression in inflammatory processes [92,93]. The aberrant CpG island methylation was responsible for MDR silencing in some cancer and inflammatory diseases [94–96]. Pro-inflammatory cytokines normally change DNA methylation patterns of variety gene promoters and regulate histone deacetylase [97,98]. It seems that this mechanism would also be considered as one of the MDR regulatory pathway by inflammatory cytokines. However, more works are needed to investigate such links.

7. Conclusion

Recent data supported the association between the inflammation and incidence of cancer and the development of multidrug resistance. Different stages of tumor progression such as initiation, promotion, malignant conversion, invasion, and metastasis are greatly influenced by inflammation. In addition to tumor development, inflammation can affect the tumor drug response through different pathways. One of the common mechanisms in cancer drug resistance is the over-expression of membrane-anchored MDR transporters that can be directly affected by inflammation and inflammatory mediators. Cytokine and other inflammatory mediators can modulate MDR at different levels. At transcriptional levels, inflammatory mediators regulate MDR through the interaction between the various transcription factors and different response elements available in MDR promoters. Although the *MDR* promoters have wide sequence similarities and there are common response elements on the *MDR* promoters, the inflammatory mediators show quite diverse effects on *MDR* transcriptional regulation. Although in most cases the inflammatory mediators down-regulate the MDR transcription and sensitize the cancerous cell to chemotherapeutic agents, there are different reports that show these mediators do not have any effect on MDR transcription or in some cases show up-regulatory effects on the MDR transcript levels that reduce the efficacy of chemotherapeutic agents. Inflammatory mediators represented stimulatory or inhibitory effects at both MDR translation and function. These diverse effects confirm the idea that the inflammation-mediated MDR regulation depends on the species, type of inflammatory mediators, tumor, and cell type, and finally MDR pump type. It is strongly recommended to get this regulatory pattern individually and do further prescription based on the personal obtained data. This is so-called personalized medicine and is one of the goals of scientist for obtaining better results in the treatment cycle to move from traditional medicine to personalized medicine in the near future.

Author contributions

F. Elahian coordinated the review and revised the final manuscript. S.A. Mirzaei and F. Dinmohammadi, A. Alizadeh collected the articles and participated in intellectual discussion of the data and manuscript writing.

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Declaration of competing interest

The authors declare that there are no potential conflicts of interest and consent to the publication of this manuscript.

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References

[1] S. Dizdarevic, A.M. Peters, Imaging of multidrug resistance in cancer, Cancer Imaging 11 (2011) 1–8.
[2] L. Knez, E. Sodja, I. Kern, M. Kosnik, T. Cufer, Predictive value of multidrug resistance proteins, topoisomerases II and ERCC1 in small cell lung cancer: a systematic review, Lung Cancer 72 (2011) 271–279.
[3] S.A. Mirzaei, S. Reiisi, P. Ghiasi Tabari, A. Shekari, F. Aliakbari, E. Azadfallah, F. Elahian, Broad blocking of MDR efflux pumps by acetylshikonin and acetoxyisovalerylshikonin to generate hypersensitive phenotype of malignant carcinoma cells, Sci. Rep. 8 (2018) 3446.
[4] H. Qosa, J. Lichter, M. Sarlo, S.S. Markandaiah, K. McAvoy, J.P. Richard, M.R. Jablonski, N.J. Maragakis, P. Pasinelli, D. Trotti, Astrocytes drive upregulation of the multidrug resistance transporter ABCB1 (P-Glycoprotein) in endothelial cells of the blood-brain barrier in mutant superoxide dismutase 1-linked amyotrophic lateral sclerosis, Glia 64 (2016) 1298–1313.
[5] S.P. Hussain, L.J. Hofseth, C.C. Harris, Radical causes of cancer, Nat. Rev. Cancer 3 (2003) 276–285.
[6] C. Gedeon, J. Behravan, G. Koren, M. Piquette-Miller, Transport of glyburide by placental ABC transporters: implications in fetal drug exposure, Placenta 27 (2006) 1096–1102.
[7] S.A. Mirzaei, N. Gholamian Dehkordi, M. Ghamghami, A.H. Amiri, E. Dalir Abdolahinia, F. Elahian, ABC-transporter blockage mediated by xanthotoxin and bergapten is the major pathway for chemosensitization of multidrug-resistant cancer cells, Toxicol. Appl. Pharmacol. 337 (2017) 22–29.
[8] M.F. Rosenberg, Z. Bikadi, E. Hazai, T. Starborg, L. Kelley, N.E. Chayen, R.C. Ford, Q. Mao, Three-dimensional structure of the human breast cancer resistance protein (BCRP/ABCG2) in an inward-facing conformation, Acta Crystallogr. D Biol. Crystallogr. 71 (2015) 1725–1735.
[9] R.W. Robey, K.M. Pluchino, M.D. Hall, A.T. Fojo, S.E. Bates, M.M. Gottesman, Revisiting the role of ABC transporters in multidrug-resistant cancer, Nat. Rev. Cancer 18 (2018) 452–464.
[10] J. Wang, N. Seebacher, H. Shi, Q. Kan, Z. Duan, Novel strategies to prevent the development of multidrug resistance (MDR) in cancer, Oncotarget 8 (2017) 84559–84571.
[11] F. Elahian, B. Moghimi, F. Dinmohammadi, M. Ghamghami, M. Hamidi, S.A. Mirzaei, The anticancer agent prodigiosin is not a multidrug resistance protein substrate, DNA Cell Biol. 32 (2013) 90–97.
[12] D. Hira, T. Terada, BCRP/ABCG2 and high-alert medications: Biochemical, pharmacokinetic, pharmacogenetic, and clinical implications, Biochem. Pharmacol. 147 (2018) 201–210.
[13] S.M. Jackson, I. Manolaridis, J. Kowal, M. Zechner, N.M.I. Taylor, M. Bause, S. Bauer, R. Bartholomaeus, G. Bernhardt, B. Koenig, A. Buschauer, H. Stahlberg, K.H. Altmann, K.P. Locher, Structural basis of small-molecule inhibition of human multidrug transporter ABCG2, Nat. Struct. Mol. Biol. 25 (2018) 333–340.
[14] F. Balkwill, A. Mantovani, Inflammation and cancer: back to Virchow? Lancet 357 (2001) 539–545.
[15] L.L. Munn, Cancer and inflammation, Wiley interdisciplinary reviews, WIREs Syst. Biol. Med. 9 (2017).
[16] M.R. Galdiero, G. Marone, A. Mantovani, Cancer inflammation and cytokines, Cold Spring Harb. Perspect. Biol. 10 (2018).
[17] C. Pouplard, E. Brenaut, C. Horreau, T. Barnetche, L. Misery, M.A. Richard, S. Aractingi, F. Aubin, B. Cribier, P. Joly, D. Jullien, M. Le Maitre, J.P. Ortonne, C. Paul, Risk of cancer in psoriasis: a systematic review and meta-analysis of epidemiological studies, J. Eur. Acad. Dermatol. Venereol. 27 (Suppl. 3) (2013) 36–46.
[18] C. Lin, J. Zhang, Inflammasomes in inflammation-induced cancer, Front. Immunol. 8 (2017) 271.
[19] R.L. Blaylock, Cancer microenvironment, inflammation and cancer stem cells: a hypothesis for a paradigm change and new targets in cancer control, Surg. Neurol. Int. 6 (2015) 92.
[20] S.S. Savant, S. Sriramkumar, H.M. O'Hagan, The role of inflammation and inflammatory mediators in the development, progression, metastasis, and chemoresistance of epithelial ovarian cancer, Cancers 10 (2018).
[21] G. Marelli, A. Sica, L. Vannucci, P. Allavena, Inflammation as target in cancer therapy, Curr. Opin. Pharmacol. 35 (2017) 57–65.
[22] T.P. Raposo, B.C. Beirao, L.Y. Pang, F.L. Queiroga, D.J. Argyle, Inflammation and cancer: till death tears them apart, Vet. J. 205 (2015) 161–174.

[23] G.J. Szebeni, C. Vizler, K. Kitajka, L.G. Puskas, Inflammation and cancer: extra- and intracellular determinants of tumor-associated macrophages as tumor promoters, Mediat. Inflamm. 2017 (2017) 9294018.
[24] X. Qu, Y. Tang, S. Hua, Immunological approaches towards cancer and inflammation: a cross talk, Front. Immunol. 9 (2018) 563.
[25] D.G. DeNardo, J.B. Barreto, P. Andreu, L. Vasquez, D. Tawfik, N. Kolhatkar, L.M. Coussens, CD4(+) T cells regulate pulmonary metastasis of mammary carcinomas by enhancing protumor properties of macrophages, Cancer Cell 16 (2009) 91–102.
[26] H. Wang, S. Yin, Natural killer T cells in liver injury, inflammation and cancer, Expert Rev. Gastroenterol. Hepatol. 9 (2015) 1077–1085.
[27] S. Kraus, N. Arber, Inflammation and colorectal cancer, Curr. Opin. Pharmacol. 9 (2009) 405–410.
[28] M. Abdullah, A.A. Rani, A.W. Sudoyo, D. Makmun, D.R. Handjari, B.S. Hernowo, Expression of NF-kB and COX2 in colorectal cancer among native Indonesians: the role of inflammation in colorectal carcinogenesis, Acta Med. Indones. 45 (2013) 187–192.
[29] S. Hirschberger, L.C. Hinske, S. Kreth, MiRNAs: dynamic regulators of immune cell functions in inflammation and cancer, Cancer Lett. 431 (2018) 11–21.
[30] T. Atsumi, R. Singh, L. Sabharwal, H. Bando, J. Meng, Y. Arima, M. Yamada, M. Harada, J.J. Jiang, D. Kamimura, H. Ogura, T. Hirano, M. Murakami, Inflammation amplifier, a new paradigm in cancer biology, Cancer Res. 74 (2014) 8–14.
[31] Y. Fan, R. Mao, J. Yang, NF-kappaB and STAT3 signaling pathways collaboratively link inflammation to cancer, Protein Cell 4 (2013) 176–185.
[32] J.V. Fernandes, R.N. Cobucci, C.A. Jatoba, T.A. Fernandes, J.W. de Azevedo, J.M. de Araujo, The role of the mediators of inflammation in cancer development, Pathol. Oncol. Res. 21 (2015) 527–534.
[33] M. Ghandadi, A. Sahebkar, Interleukin-6: a critical cytokine in cancer multidrug resistance, Curr. Pharm. Des. 22 (2016) 518–526.
[34] E.A. Ho, M. Piquette-Miller, Regulation of multidrug resistance by pro-inflammatory cytokines, Curr. Cancer Drug Targets 6 (2006) 295–311.
[35] V. Petrovic, S. Teng, M. Piquette-Miller, Regulation of drug transporters during infection and inflammation, Mol. Interv. 7 (2007) 99–111.
[36] A. Kawase, Alterations in expression and function of ABC transporters and ERM proteins in inflammation, Yakugaku Zasshi 134 (2014) 925–929.
[37] G. Englund, A. Jacobson, F. Rorsman, P. Artursson, A. Kindmark, A. Ronnblom, Efflux transporters in ulcerative colitis: decreased expression of BCRP (ABCG2) and Pgp (ABCB1), Inflamm. Bowel Dis. 13 (2007) 291–297.
[38] A. Kawase, S. Norikane, A. Okada, M. Adachi, Y. Kato, M. Iwaki, Distinct alterations in ATP-binding cassette transporter expression in liver, kidney, small intestine, and brain in adjuvant-induced arthritic rats, J. Pharm. Sci. 103 (2014) 2556–2564.
[39] M. Miyoshi, M. Nadai, A. Nitta, J. Ueyama, A. Shimizu, K. Takagi, T. Nabeshima, K. Saito, T. Hasegawa, Role of tumor necrosis factor-alpha in down-regulation of hepatic cytochrome P450 and P-glycoprotein by endotoxin, Eur. J. Pharmacol. 507 (2005) 229–237.
[40] Y. Yagdiran, J. Tallkvist, K. Artursson, A. Oskarsson, Staphylococcus aureus and lipopolysaccharide modulate gene expressions of drug transporters in mouse mammary epithelial cells correlation to inflammatory biomarkers, PLoS One 11 (2016) e0161346.
[41] E.T. Morgan, K.B. Goralski, M. Piquette-Miller, K.W. Renton, G.R. Robertson, M.R. Chaluvadi, K.A. Charles, S.J. Clarke, M. Kacevska, C. Liddle, T.A. Richardson, R. Sharma, C.J. Sinal, Regulation of drug-metabolizing enzymes and transporters in infection, inflammation, and cancer, Drug Metab. Dispos. 36 (2008) 205–216.
[42] J.H. Wang, D.A. Scollard, S. Teng, R.M. Reilly, M. Piquette-Miller, Detection of P-glycoprotein activity in endotoxemic rats by 99mTc-sestamibi imaging, J. Nucl. Med. 46 (2005) 1537–1545.
[43] A.M. Hartz, B. Bauer, G. Fricker, D.S. Miller, Rapid modulation of P-glycoprotein-mediated transport at the blood-brain barrier by tumor necrosis factor-alpha and lipopolysaccharide, Mol. Pharmacol. 69 (2006) 462–470.
[44] P.T. Ronaldson, R. Bendayan, HIV-1 viral envelope glycoprotein gp120 triggers an inflammatory response in cultured rat astrocytes and regulates the functional expression of P-glycoprotein, Mol. Pharmacol. 70 (2006) 1087–1098.
[45] E. Siewert, C.G. Dietrich, F. Lammert, P.C. Heinrich, S. Matern, C. Gartung, A. Geier, Interleukin-6 regulates hepatic transporters during acute-phase response, Biochem. Biophys. Res. Commun. 322 (2004) 232–238.
[46] M.G. Elferink, P. Olinga, A.L. Draaisma, M.T. Merema, K.N. Faber, M.J. Slooff, D.K. Meijer, G.M. Groothuis, LPS-induced downregulation of MRP2 and BSEP in human liver is due to a posttranscriptional process, Am. J. Physiol. Gastrointest. Liver Physiol. 287 (2004) G1008–G1016.
[47] D.A. Evseenko, J.W. Paxton, J.A. Keelan, Independent regulation of apical and basolateral drug transporter expression and function in placental trophoblasts by cytokines, steroids, and growth factors, Drug Metab. Dispos. 35 (2007) 595–601.
[48] B. Weksler, I.A. Romero, P.O. Couraud, The hCMEC/D3 cell line as a model of the human blood brain barrier, Fluids Barriers CNS 10 (2013) 16.
[49] B. Poller, J. Drewe, S. Krahenbuhl, J. Huwyler, H. Gutmann, Regulation of BCRP (ABCG2) and P-glycoprotein (ABCB1) by cytokines in a model of the human blood-brain barrier, Cell. Mol. Neurobiol. 30 (2010) 63–70.
[50] F. Mosaffa, H. Lage, J.T. Afshari, J. Behravan, Interleukin-1 beta and tumor necrosis factor-alpha increase ABCG2 expression in MCF-7 breast carcinoma cell line and its mitoxantrone-resistant derivative, MCF-7/MX, Inflamm. Res. 58 (2009) 669–676.
[51] F. Mosaffa, F. Kalalinia, H. Lage, J.T. Afshari, J. Behravan, Pro-inflammatory cytokines interleukin-1 beta, interleukin 6, and tumor necrosis factor-alpha alter the expression and function of ABCG2 in cervix and gastric cancer cells, Mol. Cell. Biochem. 363 (2012) 385–393.
[52] A.M. Belliard, B. Lacour, R. Farinotti, C. Leroy, Effect of tumor necrosis factor-alpha and interferon-gamma on intestinal P-glycoprotein expression, activity, and localization in Caco-2 cells, J. Pharm. Sci. 93 (2004) 1524–1536.
[53] C. Forster, M. Burek, I.A. Romero, B. Weksler, P.O. Couraud, D. Drenckhahn, Differential effects of hydrocortisone and TNFalpha on tight junction proteins in an in vitro model of the human blood-brain barrier, J. Physiol. 586 (2008) 1937–1949.
[54] B. Bauer, A.M. Hartz, D.S. Miller, Tumor necrosis factor alpha and endothelin-1 increase P-glycoprotein expression and transport activity at the blood-brain barrier, Mol. Pharmacol. 71 (2007) 667–675.
[55] J. Marki-Zay, K. Tauberne Jakab, P. Szeremy, P. Krajcsi, MDR-ABC transporters: biomarkers in rheumatoid arthritis, Clin. Exp. Rheumatol. 31 (2013) 779–787.
[56] C.J. Gibson, M.M. Hossain, J.R. Richardson, L.M. Aleksunes, Inflammatory regulation of ATP binding cassette efflux transporter expression and function in microglia, J. Pharmacol. Exp. Ther. 343 (2012) 650–660.
[57] B. Liu, L. Qu, H. Tao, Cyclo-oxygenase 2 up-regulates the effect of multidrug resistance, Cell Biol. Int. 34 (2009) 21–25.
[58] G. Sethi, M.K. Shanmugam, L. Ramachandran, A.P. Kumar, V. Tergaonkar, Multifaceted link between cancer and inflammation, Biosci. Rep. 32 (2012) 1–15.
[59] F. Elahian, F. Kalalinia, J. Behravan, Dexamethasone downregulates BCRP mRNA and protein expression in breast cancer cell lines, Oncol. Res. 18 (2009) 9–15.
[60] S. Agarwal, G.V. Reddy, P. Reddanna, Eicosanoids in inflammation and cancer: the role of COX-2, Expert. Rev. Clin. Immunol. 5 (2009) 145–165.
[61] A. Sorokin, Cyclooxygenase-2: potential role in regulation of drug efflux and multidrug resistance phenotype, Curr. Pharm. Des. 10 (2004) 647–657.
[62] L. Hilovska, R. Jendzelovsky, P. Fedorocko, Potency of non-steroidal anti-inflammatory drugs in chemotherapy, Mol. Clin. Oncol. 3 (2015) 3–12.
[63] D.A. Dixon, F.F. Blanco, A. Bruno, P. Patrignani, Mechanistic aspects of COX-2 expression in colorectal neoplasia, Recent Results Cancer Res. 191 (2013) 7–37.
[64] T. Yu, X. Lao, H. Zheng, Influencing COX-2 activity by COX related pathways in inflammation and cancer, Mini-Rev. Med. Chem. 16 (2016) 1230–1243.
[65] L.D. Weidner, P. Kannan, N. Mitsios, S.J. Kang, M.D. Hall, W.H. Theodore, R.B. Innis, J. Mulder, The expression of inflammatory markers and their potential influence on efflux transporters in drug-resistant mesial temporal lobe epilepsy tissue, Epilepsia 59 (2018) 1507–1517.
[66] M. Ma, X. Yang, L. Zhao, X. Wang, L. Liu, W. Jiao, Y. Wei, B. Shan, Celecoxib enhances sensitivity to chemotherapy drugs of T-cell lymphoma, Oncol. Lett. 15 (2018) 4649–4656.
[67] J. Castro-Lopez, M. Teles, C. Fierro, K. Allenspach, M. Planellas, J. Pastor, Pilot study: duodenal MDR1 and COX2 gene expression in cats with inflammatory bowel disease and low-grade alimentary lymphoma, J. Feline Med. Surg. 20 (2018) 759–766.
[68] P.A. Thompson, M. Khatami, C.J. Baglole, J. Sun, S.A. Harris, E.Y. Moon, F. Al-Mulla, R. Al-Temaimi, D.G. Brown, A. Colacci, C. Mondello, J. Raju, E.P. Ryan, J. Woodrick, A.I. Scovassi, N. Singh, M. Vaccari, R. Roy, S. Forte, L. Memeo, H.K. Salem, A. Amedei, R.A. Hamid, L. Lowe, T. Guarnieri, W.H. Bisson, Environmental immune disruptors, inflammation and cancer risk, Carcinogenesis 36 (Suppl. 1) (2015) S232–S253.
[69] F. Elahian, F. Kalalinia, J. Behravan, Evaluation of indomethacin and dexamethasone effects on BCRP-mediated drug resistance in MCF-7 parental and resistant cell lines, Drug Chem. Toxicol. 33 (2010) 113–119.
[70] F. Kalalinia, F. Elahian, M. Hassani, J. Kasaeeian, J. Behravan, Phorbol ester TPA modulates chemoresistance in the drug sensitive breast cancer cell line MCF-7 by inducing expression of drug efflux transporter ABCG2, Asian Pac. J. Cancer Prev. 13 (2012) 2979–2984.
[71] F. Kalalinia, F. Elahian, J. Behravan, Potential role of cyclooxygenase-2 on the regulation of the drug efflux transporter ABCG2 in breast cancer cell lines, J. Cancer Res. Clin. Oncol. 137 (2011) 321–330.
[72] R.M. Ruggeri, S. Sciacchitano, E. Vitarelli, F. Trimarchi, G. Barresi, M. Trovato, Immunoexpression of multidrug-resistance protein 2 and cyclooxygenase 2 in medullary thyroid carcinomas, Arch. Pathol. Lab. Med. 130 (2006) 1014–1019.
[73] F. Kalalinia, F. Elahian, F. Mosaffa, J. Behravan, Celecoxib up regulates the expression of drug efflux transporter ABCG2 in breast cancer cell lines, Iran J. Pharm. Res. 13 (2014) 1393–1401.
[74] M.H. Sherman, Stellate cells in tissue repair, inflammation, and cancer, Annu. Rev. Cell Dev. Biol. 34 (2018) 333–355.
[75] B. Wang, S. Ngoi, J. Wang, S.S. Chong, C.G. Lee, The promoter region of the MDR1 gene is largely invariant, but different single nucleotide polymorphism haplotypes affect MDR1 promoter activity differently in different cell lines, Mol. Pharmacol. 70 (2006) 267–276.
[76] M. Saxena, G. Yeretssian, NOD-like receptors: master regulators of inflammation and cancer, Front. Immunol. 5 (2014) 327.
[77] K. Balamurugan, E. Sterneck, The many faces of C/EBPdelta and their relevance for inflammation and cancer, Int. J. Biol. Sci. 9 (2013) 917–933.
[78] E. Elinav, R. Nowarski, C.A. Thaiss, B. Hu, C. Jin, R.A. Flavell, Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms, Nat. Rev. Cancer 13 (2013) 759–771.
[79] J. Candido, T. Hagemann, Cancer-related inflammation, J. Clin. Immunol. 33 (Suppl. 1) (2013) S79–S84.
[80] M. Sinreih, S. Stupar, L. Cemazar, I. Verdenik, S. Frkovic Grazio, S. Smrkolj, T. Lanisnik Rizner, Data on expression of genes involved in estrogen and progesterone action, inflammation and differentiation according to demographic, histopathological and clinical characteristics of endometrial cancer patients, Data Brief 12 (2017) 632–643.
[81] T. Cooks, C.C. Harris, p53 mutations and inflammation-associated cancer are linked through TNF signaling, Mol. Cell 56 (2014) 611–612.
[82] C.C. Fraser, G protein-coupled receptor connectivity to NF-kappaB in inflammation and cancer, Int. Rev. Immunol. 27 (2008) 320–350.

[83] Z. Davoudi, A. Akbarzadeh, M. Rahmatiyamchi, A.A. Movassaghpour, M. Alipour, K. Nejati-Koshki, Z. Sadeghi, H. Dariushnejad, N. Zarghami, Molecular target therapy of AKT and NF-kB signaling pathways and multidrug resistance by specific cell penetrating inhibitor peptides in HL-60 cells, Asian Pac. J. Cancer Prev. 15 (2014) 4353–4358.
[84] G.K. Chen, S. Sale, T. Tan, R.P. Ermoian, B.I. Sikic, CCAAT/enhancer-binding protein beta (nuclear factor for interleukin 6) transactivates the human MDR1 gene by interaction with an inverted CCAAT box in human cancer cells, Mol. Pharmacol. 65 (2004) 906–916.
[85] Q. Chen, Y. Bian, S. Zeng, Involvement of AP-1 and NF-kappaB in the up-regulation of P-gp in vinblastine resistant Caco-2 cells, Drug Metab. Pharmacokinet. 29 (2014) 223–226.
[86] J.D. Fleming, P.G. Giresi, M. Lindahl-Allen, E.B. Krall, J.D. Lieb, K. Struhl, STAT3 acts through pre-existing nucleosome-depleted regions bound by FOS during an epigenetic switch linking inflammation to cancer, Epigenetics Chromatin 8 (2015) 7.
[87] Y. Dong, Z. Wang, G.F. Xie, C. Li, W.W. Zuo, G. Meng, C.P. Xu, J.J. Li, Pregnane X receptor is associated with unfavorable survival and induces chemotherapeutic resistance by transcriptional activating multidrug resistance-related protein 3 in colorectal cancer, Mol. Cancer 16 (2017) 71.
[88] K. Hirooka-Masui, R. Lesmana, T. Iwasaki, M. Xu, K. Hayasaka, M. Haraguchi, A. Takeshita, N. Shimokawa, K. Yamamoto, N. Koibuchi, Interaction of silencing mediator for retinoid and thyroid receptors with steroid and xenobiotic receptor on multidrug resistance 1 promoter, Life Sci. 92 (2013) 911–915.
[89] S.R. Pondugula, P. Pavek, S. Mani, Pregnane X receptor and cancer: context-specificity is key, Nucl. Recept. Res. 3 (2016).
[90] S. Heemskerk, J.G. Peters, J. Louisse, S. Sagar, F.G. Russel, R. Masereeuw, Regulation of P-glycoprotein in renal proximal tubule epithelial cells by LPS and TNF-alpha, J. Biomed. Biotechnol. 2010 (2010) 1–10.
[91] S. Ohnishi, N. Ma, R. Thanan, S. Pinlaor, O. Hammam, M. Murata, S. Kawanishi, DNA damage in inflammation-related carcinogenesis and cancer stem cells, Oxidative Med. Cell. Longev. 2013 (2013) 387014.
[92] R. Henrique, A.I. Oliveira, V.L. Costa, T. Baptista, A.T. Martins, A. Morais, J. Oliveira, C. Jeronimo, Epigenetic regulation of MDR1 gene through post-translational histone modifications in prostate cancer, BMC Genomics 14 (2013) 898.
[93] K.K. To, O. Polgar, L.M. Huff, K. Morisaki, S.E. Bates, Histone modifications at the ABCG2 promoter following treatment with histone deacetylase inhibitor mirror those in multidrug-resistant cells, Mol. Cancer Res. 6 (2008) 151–164.
[94] C. Wang, W. Sun, G. Wright, A.Z. Wang, Z. Gu, Inflammation-triggered cancer immunotherapy by programmed delivery of CpG and Anti-PD1 antibody, Adv. Mater. 29 (2017).
[95] T. Tahara, T. Arisawa, T. Shibata, H. Yamashita, D. Yoshioka, I. Hirata, Effect of promoter methylation of multidrug resistance 1 (MDR1) gene in gastric carcinogenesis, Anticancer Res. 29 (2009) 337–341.
[96] J. Liu, X. Zhang, A. Liu, D. Zhang, Y. Su, Y. Liu, D. You, L. Yuan, X. Kong, X. Wang, P. Sun, Altered methylation of glucosylceramide synthase promoter regulates its expression and associates with acquired multidrug resistance in invasive ductal breast cancer, Oncotarget 7 (2016) 36755–36766.
[97] G. Chen, P. Ghosh, H. Osawa, C.Y. Sasaki, L. Rezanka, J. Yang, T.J. O'Farrell, D.L. Longo, Resistance to TGF-beta 1 correlates with aberrant expression of TGF-beta receptor II in human B-cell lymphoma cell lines, Blood 109 (2007) 5301–5307.
[98] M.P. Ceballos, G. Decandido, A.D. Quiroga, C.G. Comanzo, V.I. Livore, F. Lorenzetti, F. Lambertucci, L. Chazarreta-Cifre, C. Banchio, M.L. Alvarez, A.D. Mottino, M.C. Carrillo, Inhibition of sirtuins 1 and 2 impairs cell survival and migration and modulates the expression of P-glycoprotein and MRP3 in hepatocellular carcinoma cell lines, Toxicol. Lett. 289 (2018) 63–74.