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MCF-7 Breast Cancer Cell Line, a Model for the Study of the Association Between Inflammation and ABCG2-Mediated Multi Drug Resistance

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1. Introduction

Breast cancer is one of the most common and serious malignancies worldwide. Despite intensive cancer control efforts, it remains the second-leading cause of cancer death among women (Harris et al., 2000). While the overall response rate can be high, the duration of response is relatively short, and most patients with initially responsive tumors will experience a drug-resistance phenotype. Therefore, a lot of studies have centered on the field of drug resistance to improve cancer chemotherapy and management of cancers Gottesman, 2002).

The development of intrinsic or acquired resistance to a wide variety of anticancer drugs is a major obstacle to successful cancer chemotherapy. Some cancers show primary resistance or natural resistance in which they do not respond to standard chemotherapy drugs from the beginning. On the other hand, many types of sensitive tumors respond well to chemotherapy drugs in the beginning but show acquired resistance later (Choi, 2005). Multidrug resistance (MDR) can be defined as the intrinsic or acquired resistance of cancer cells to multiple classes of structurally and mechanistically unrelated antitumor drugs (Teodori et al., 2002). To date, the most widely studied cellular mechanisms of MDR are those associated with drug efflux involving members of the adenosine triphosohate-binding cassette (ABC) membrane transporter family (Mao et al., 2005).

Recently, several human ABC transporters with a potential role in drug resistance have been discovered. Among them, a novel known protein is ATP-binding cassette sub-family G member 2 (ABCG2). Human ABCG2 (also known as MXR, BCRP, and ABCP) was first cloned by Doyle et al. (Doyle et al., 1998) in the drug-resistant breast cancer cell line (MCF-7). ABCG2 is an efflux pump, which transports a variety of xenobiotics and endogenous compounds across cellular membranes. Tissue localization of ABCG2 in the mammary glands, intestine, kidney, liver, ovary, testis, placenta, endothelium and in hematopoietic stem cells indicates that ABCG2 plays an important role in absorption, distribution, and elimination of its substrates (Krishnamurthy et al., 2004; Mao & Unadkat, 2005). The expression of ABCG2 protein and/or mRNA has been detected in numerous types of human cancers (Diestra et al., 2002; Ross et al., 2000), and a large spectrum of anticancer drugs are effluxed by ABCG2

(Doyle et al., 2003). It has also been shown that ABCG2 expression may be associated with poor response to chemotherapy (van den Heuvel-Eibrink et al., 2002, Steinbach, 2002 #216) . Alteration in ABCG2 expression and function can significantly affect the disposition of the transporter drug substrates, it is possible that its overexpression in cancer cells is responsible for decreasing in drug concentration within the cell and a reduced cancer-chemotherapy efficacy (Glavinas et al., 2004; Mao & Unadkat, 2005).

Inflammation is a state consisting of complex cytological and chemical reactions that occur in affected blood vessels and adjacent tissues in response to an injury or abnormal stimulation caused by physical, chemical or biological agents (Ho et al., 2006; Philip et al., 2004). Although inflammation is essential, it can be harmful to the host and therefore it is subject to multiple levels of biochemical, pharmacological, and molecular controls involving a diverse and potentially huge array of cell types and soluble mediators including cytokines (Haddad, 2002). In fact tumors are similar to healing or desmoplastic tissue in many ways and the micro-environment of the tumor highly resembles an inflammation site (Caruso et al., 2004). Breast cancer is a prototype of these kinds of cancer. Indeed, proinflammatory cytokines have been found to be present within the microenvironment of breast carcinomas and secreted by infiltrating host leukocytes, malignant and/or stromal cells of the breast cancer (Basolo et al., 1996; Jin et al., 1997; Lithgow et al., 2005; Miles et al., 1994).

In recent years, it has been demonstrated that the expression and function of the MDR transporters is altered in numerous tissues during an inflammatory response. The current review focuses on the elucidation of the effects of inflammation on the ABCG2 expression and function, using MCF-7 human breast carcinoma cell line.

2. The role of inflammation on the ABCG2 expression and function

In an overview, the results of several studies on the effect of inflammation on the levels of ABCG2 protein expression and function in MCF-7 cells will be reviewed in this paper. In the first part, the observed effects of the proinflammatory cytokines on the ABCG2 protein expression and function will be expressed. In the next section, the effects of cyclooxygenase 2 on drug resistance due to ABCG2 will be reviewed and eventually the influence of treatment with anti-inflammatory drugs indomethacin and dexamethasone on the incidence of drug resistance phenotype will be expressed.

2.1 Proinflammatory cytokines and ABCG2 expression and function

Proinflammatory cytokines including interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are well-known regulators of inflammatory response. Inflammatory components including host leukocytes, chemokines and cytokines are also present in the microenvironment of most probably all tumors including those not casually related to an obvious inflammatory process (Germano et al., 2008).

Numerous in vitro and in vivo investigations reported that inflammation and proinflammatory cytokines are able to modulate the expression or function of different drug transporters including Multi-Drug Resistance transporter 1 (MDR1/ABCB1), Multidrug Resistance-associated Proteins (MRPs/ABCCs) and Lung-resistance Related Protein / Major Vault Protein (LRP/MVP). These modulations appeared to happen at various levels of expression including transcriptional, posttranscriptional, translational, and/or post-translational levels (Bertilsson et al., 2001; Hartmann et al., 2002; Hirsch-Ernst et al., 1998;

Piquette-Miller et al., 1998; Stein et al., 1997; Sukhai et al., 2001; Theron et al., 2003; Vos et al., 1998; Walther et al., 1994; Walther et al., 1995).

The influence of proinflammatory cytokines (IL-1β, IL-6 and TNF-α) on ABCG2 expression and function in human MCF-7 breast cancer cell line were studied using real-time PCR and flow cytometry, respectively. The results showed that, the levels of ABCG2 mRNA, protein expression and function in MCF-7 cells increased significantly after treatment with either IL-1β or TNF-α (Fig. 1).

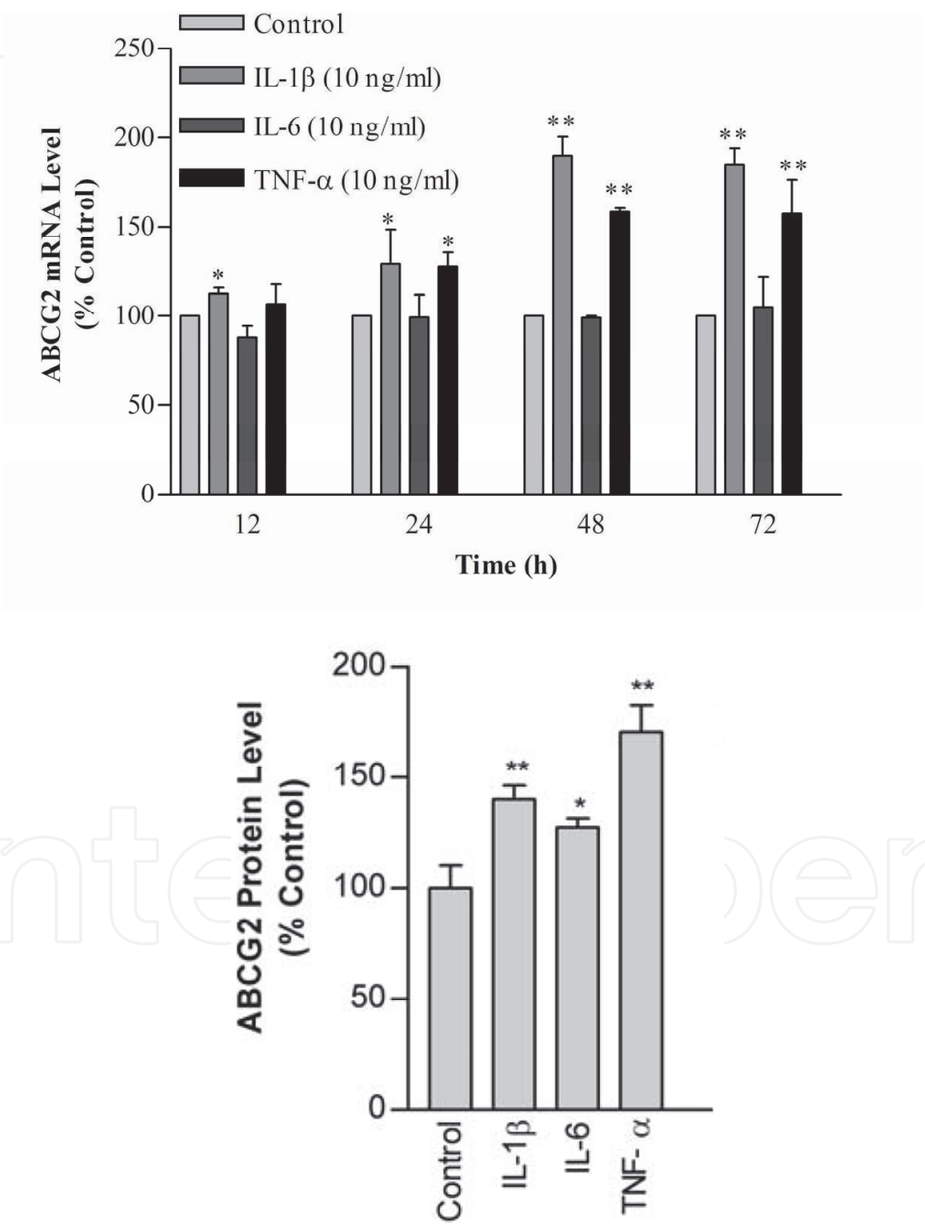


Fig. 1. The effects of proinflammatory cytokines on ABCG2 mRNA expression (A) and protein levels (B) in MCF-7 cells.

A;Cells were treated with 10 ng/ml of each cytokine for 12–72 h and real-time RT-PCR analysis was performed on total RNA extracted from control and treated cells. Values were normalized to the β-actin content of samples and expressed as mean (% control) ±SD (n = 3); *P<0.05; **P<0.01 versus control (0 ng/ml). B; After 72-h incubations with IL-1β (50 ng/ml), IL-6 (50 ng/ml) or TNF-α (50 ng/ml), expression of ABCG2 protein was measured by flow cytometry. Each value represents MFI mean (% control) of at least three independent experiments ± SD; *P<0.05, **P<0.01 versus controls.

Pradhan and colleagues also found that under proinflammatory conditions two transcription factors, estrogen receptor (ER) and NF-κB are cooperatively recruited to the promoter region of the ABCG2 gene at adjacent sites. ER allows the NF-κB family member p65 to access a latent NF-κB response element located near the estrogen response element (ERE) in the gene promoter; in turn, this p65 recruitment is required to stabilize ER occupancy at the functional ERE. Once present together on the ABCG2 promoter, ER and p65 act synergistically to potentiate mRNA and subsequent protein expression. This study has important implications for patients with ER-positive breast tumors, as it reveals a mechanism whereby inflammation enhances the expression of an ER target gene, which in turn can exacerbate breast tumor progression by promoting drug resistance mechanism whereby inflammation enhances the expression of an ER target gene, which in turn can exacerbate breast tumor progression by promoting drug resistance (Pradhan et al., 2010).
On the other hand, while IL-6 had no significant effects on ABCG2 mRNA expression and function in MCF-7 cells, it could slightly increase ABCG2 protein expression in these cells. This shows that IL-6 probably modulates ABCG2 expression by affecting ABCG2 protein translation and/or stability, but not ABCG2 transcription. For unknown reasons, this modulation did not result in the increased activity of the protein (Mosaffa et al., 2009).
In contrast to the results obtained for MCF-7 cells, in its mitoxantrone-resistance derivative, MCF-7/MX cells, none of the cytokines (even at high concentrations and long incubation times) exerted significant effects on ABCG2 mRNA levels. Because MCF-7/MX cells overexpress ABCG2 mRNA, it is likely that although modulation of the signaling pathway(s) responsible for increased transcription of ABCG2 in IL-1β and TNF-α-treated MCF-7 cells, has already happened in MCF-7/MX cells, but treatment with these cytokines could not cause further induction in ABCG2 mRNA levels (Mosaffa et al., 2009).
The results showed that IL-1β increased ABCG2 function and TNF-α enhanced both ABCG2 protein expression and function in MCF-7/MX cells. This lack of correspondence between mRNA and expression/function data suggests that perhaps in addition to the transcriptional regulatory effects of IL-1β and TNF-α, these two cytokines can also mediate ABCG2 expression and function via translational and/or post-translational effects (Mosaffa et al., 2009).

2.2 Cyclooxygenase-2 and ABCG2 expression and function

Cyclooxygenases (COX), also known as prostaglandin endoperoxide synthases or prostaglandin H synthases, comprise a group of enzymes that participate in the conversion of arachidonic acid to prostaglandins (PGs) that affect a number of physiological and pathological states in neoplastic and inflamed tissues (Smith et al., 1996). There are two isoforms of the enzyme that have been identified, COX-1 and COX-2. Constitutively expressed COX-1 supplies normal tissues with prostaglandins required to maintain physiological organ functions (O'Neill et al., 1993), such as cytoprotection of the gastric

mucosa (Chan et al., 1995) and regulation of renal blood flow (Tanioka et al., 2003). On the other hand, COX-2 is highly induced by growth factors (epidermal growth factor (EGF)), cytokines (IL-1β, IL6, TNF-α (Davies et al., 2002; Zhang et al., 2006)), and carcinogens (phorbol esters (Liu et al., 1996; Rigas et al., 2005)) via protein kinase C (PKC) and RAS-mediated signaling at sites of inflammation. Therefore, it is assumed that COX-2 plays an important role in the prostaglandin E2 (PGE2) production involved in pathophysiological processes (Trebino et al., 2003). COX-2 may be implicated in tumor promotion through modulating cell proliferation, inhibiting apoptosis, control of cell migration, cell adhesion, tumor invasion and suppression of immune response (Cao et al., 2002). In recent years, it has been reported that COX-2 modulates ABC transporter expression and is involved in the development of the MDR phenotype (Ratnasinghe et al., 2001, Fantappiè O, 2002 #78, Puhlmann, 2005 #103).

Kalalinia et al. studies had aimed to explore the potential link between COX-2 expression and development of multidrug resistance phenotype due to ABCG2 expression in MCF-7 cell line. In one study they used of 12-O-tetradecanoylphorbol-13-acetate (TPA) for induction of COX-2 expression in MCF-7 cells. TPA often employed in biomedical research to activate the signal transduction enzyme protein kinase C (PKC). The effects of TPA on PKC result from its similarity to one of the natural activators of classic PKC isoforms, diacylglycerol (DAG).

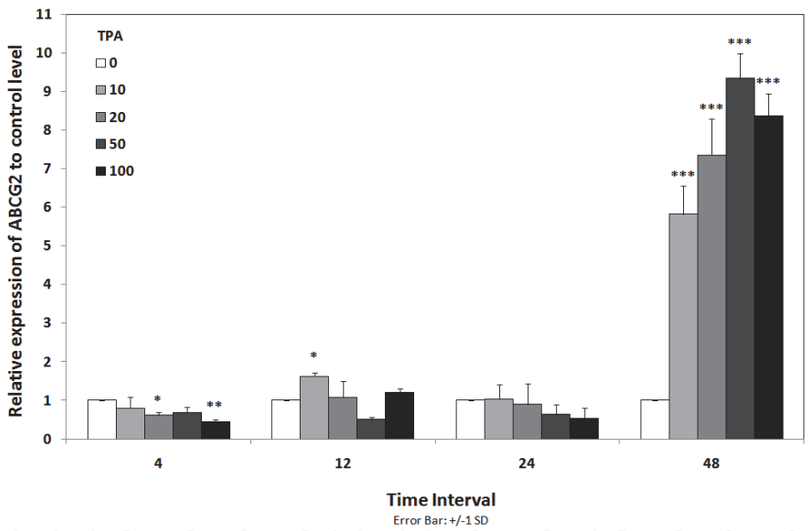
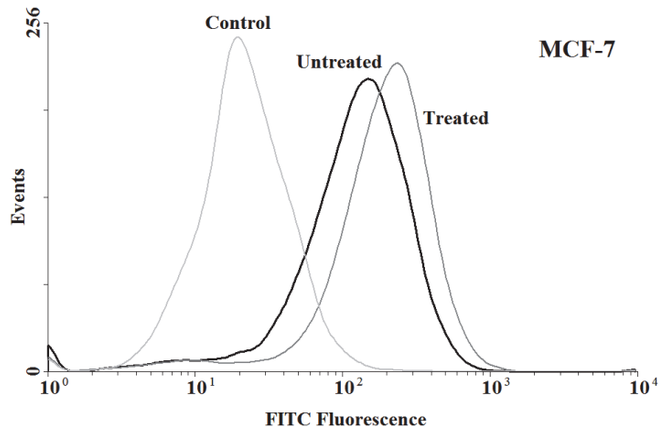


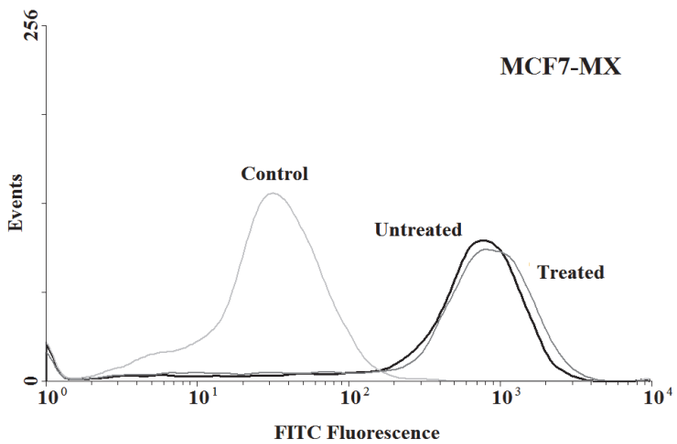
Fig. 2. Effects of TPA on the levels of ABCG2 mRNA in MCF-7 cells.
Cells were treated with TPA (0-100 nM for 4-48 h) and ABCG2 mRNA expression was measured by real-time RT-PCR using total RNA extracted from control and treated cells. Relative expression levels for each gene were normalized to that of the β-actin. The results were expressed as: (target/reference ratio) treated samples / (target/reference ratio) untreated control sample. Values were expressed as mean ± SD (n = 3); *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

The real-time PCR analysis showed that COX-2 inducer TPA caused a considerable increase up to 9-fold in ABCG2 mRNA expression in parental MCF-7 cells (Fig. 2). While a slight increase in ABCG2 expression was observed in the resistant cell line MCF-7/MX. The results

of flow cytometry showed a slight increase of ABCG2 expression at protein level in MCF-7, while no significant changes in the level of ABCG2 protein expression was observed in MCF-7/MX (Fig. 3). As we mentioned earlier, in the drug resistant MCF-7/MX cells, ABCG2 is already overexpressed, and its expression may be at a threshold maximum level, so an induction with TPA treatment may not be causing any detectable increase in ABCG2 mRNA level. Likewise, a close association between MDR and COX-2 has been reported in non-Hodgkin's lymphomas (Szczuraszek et al., 2009), non-small cell lung cancer (Surowiak et al., 2008) and breast cancer cases (Surowiak et al., 2005). Adenovirus-mediated transfer of rat COX-2 cDNA into renal rat mesangial cells increased P-glycoprotein (P-gp/MDR1) expression, and this was blocked by COX-2 inhibitor NS398, suggesting that COX-2 products may be implicated in this response (Miller et al., 2006; Patel et al., 2002). All of these studies strongly suggest that COX-2 could be involved in the development of the MDR phenotype (Sorokin, 2004).



(A)



(B)

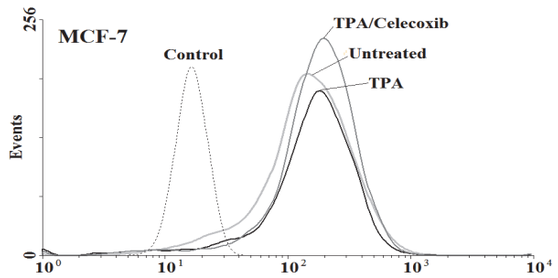
Fig. 3. Effect of TPA on ABCG2 protein levels in MCF-7 (A) and MCF-7/MX (B) cells. After 48 h incubation with TPA (10 nM), expression of ABCG2 protein was measured by flow cytometry. Each histogram shows the overlay of the treated sample (dark gray), untreated sample (black) and secondary antibody as negative control (light gray).

Different studies showed that incubation of MDR cells with PKC activator TPA stimulate P-gp phosphorylation, reduce drug accumulation, and enhance drug resistance (Ramachandran et al., 1998). Fine et al. demonstrated that phorbol 12,13-dibutyrate [P(BtO)2] led to an increase in protein kinase C activity and induced a drug-resistance phenotype as a result of increased phosphorylation of an unknown 20-kDa particulate protein (Fine et al., 1988). Similar to TPA treatment, diacylglycerol (DAG), a physiological stimulant of PKC, also increased the expression of MDR1 mRNA and protein. Whereas, protein kinase inhibitor staurosporine suppressed the induction of MDR1 expression by TPA and DAG (Chaudhary et al., 1992). These reports suggest that MDR gene expression in different cell types is regulated by a PKC-mediated pathway.
ABCG2 function was measured by flow cytometric mitoxantrone efflux assay. In long term exposure TPA enhanced the ABCG2 function, which was more considerable in MCF-7/MX than parental MCF-7 cells (Kalalinia et al., 2010). There is considerable precedent that PKC activation is associated with increased transport processes. Fine et al showed that, protein kinase C activity was 7-fold higher in the drug-resistant mutant MCF-7 cells compared with the control MCF-7 cells, sensitive parent cells (Fine et al., 1988). Fine et al reported that exposure of drug-sensitive cells to the phorbol 12, 13-dibutyrate [P (BtO)2] caused an enhanced PKC activity and induced drug-resistance phenotype, whereas drug-resistant cells in the same exposure to P(BtO)2 showed further increased in drug resistance. So phorbol ester might be the reason of decreased drug accumulation by inducing phosphorylation of a drug efflux pump or carrier protein (Fine et al., 1988).

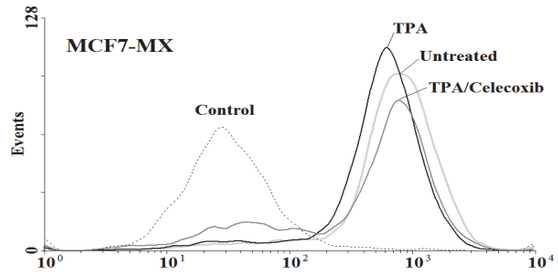
2.3 Celecoxib (a selective inhibitor of COX-2) and ABCG2 expression and function

Numerous studies showed that COX-2 inhibitors (coxibs) enhance the efficacy of different anticancer therapy methods. Different mechanisms have been suggested to contribute to the antitumor activity of coxibs such as the inhibition of cell cycle progression, induction of apoptosis, inhibition of angiogenesis and decreased invasive potential of tumor cells (Fife et al., 2004; Gasparini et al., 2003; Hashitani et al., 2003; Masferrer et al., 2000). Another mechanism by which COX-inhibitors could sensitize cells to chemotherapeutic drugs is functional blockade of membrane transporter proteins of the ABC-transporter family (Patel et al., 2002; Zatelli et al., 2005).
Kalalinia et. al. investigated the relationship between the inhibition of COX-2 and expression of ABCG2 in parental and resistance breast cancer cell lines. They reported that treatment of MCF-7 and MCF-7/MX cells with celecoxib up-regulates ABCG2 expression at mRNA levels. The results also indicated that, celecoxib reversed the inhibitory effects of TPA on ABCG2 protein expression and increased its expression to the basal level in MCF-7/MX, while co-treatment of MCF-7 cells with TPA and celecoxib caused increased ABCG2 protein expression to a small amount more than TPA lonely (Fig. 4). In the same way , Zrieki et al. showed that treatment of human colorectal Caco-2 cell line with COX-1/ COX-2 inhibitor naproxen led to an stimulation of ABCG2 expression which corresponded to the significant decrease of Rho123 retention achieved in activity study. In contrast, treatment with selective COX-2 inhibitors nimesulide did not influence the expression of ABCG2 at protein level (Zrieki et al., 2008). Several studies have shown that specific COX-2 inhibitors could prevent or reduce the development of chemoresistance phenotype by downregulation of the expression and function of P-glycoprotein (MDR1) (Huang et al., 2007; Kim et al., 2004; Roy et al., 2010; Zatelli et al., 2005; Zatelli et al., 2007). Xia et al. found that celecoxib significantly inhibited MDR1 expression without any effects on pump function of P-gp.

They demonstrated that the inhibitory effect of celecoxib on MDR1 was COX-2-independent but directly correlated to hypermethylation of MDR1 gene promoter (Xia et al., 2009). In addition, it is shown that COX-2 inhibitors induced PGH2 generation and NF-κB activation, which result in inhibition of P-gp expression and function in breast cancer cells (Zatelli et al., 2009).



(A)



(B)

Fig. 4. Effects of celecoxib on the expression of ABCG2 at protein levels in MCF-7 (A) and MCF-7/MX (B) cell lines were studied by flow cytometry.
Cells were fixed and permeabilized by formaldehyde and methanol, blocked with BSA and then incubated with primary monoclonal antibody BXP-21. After washing, cells were incubated with a FITC-conjugated goat anti-mouse antibody. Each histogram shows the overlay of the TPA treated sample (black), TPA and celecoxib treated sample (dark gray), untreated sample (ligh gray) and secondary antibody as negative control (broken light gray).

In MCF-7 cell line, celecoxib in presence of TPA 10 nM caused reduction of ABCG2 function in a dose- and time-dependent manner (Kalalinia et al., 2010). Another study provides evidence that NS-398, selective COX-2 inhibitor, sensitizes chemoresistant breast cancer cells to the cytotoxic effects of doxorubicin and notably enhances intracellular DOX accumulation and retention in vitro. It was shown that these effects depended on the inhibition of P-gp expression and function in both native and chemoresistant MCF-7 cells (Zatelli et al., 2007).

2.4 The influence of indomethacin on ABCG2 expression and function

Several preclinical and clinical trials have shown that nonsteroidal anti-inflammatory drugs (NSAIDs), used as classical COX inhibitors, could reduce the incidence of cancers (Cha et al., 2007; Kang et al., 2005; Lin et al., 2005). Although the exact anticancer mechanisms of NSAIDs are not fully understood, it seems to be related closely to their suppression of COX

enzyme and subsequent reduction in prostaglandin production (Kismet et al., 2004; Zatelli et al., 2005). Modulation of the efficacy of cancer chemotherapy by NSAIDs has not been examined in detail.

Elahian et. al. investigated the pharmacological silencing of ABCG2 in MCF-7 cells through the use of indomethacin, in the hopes of opening a novel way in management of breast cancer. MTT assay showed that indomethacin did not significantly change the survival of MCF-7 and MCF-7/MX cells, but cotreatment of mitoxantrone with indomethacin increased the mitoxantrone cytotoxicity and reduced the IC50 of mitoxantrone in these cells. Altough indomethacin sensitized MCF-7 cells to mitoxantrone, but it did not alter mitoxantrone accumulation in MCF-7 cells, compared to the control (Elahian et al., 2010). It might suggest that indomethacin exerts the sensitising effects through a mechanism not involving the inhibition of ABCG2, but possibly reducing the synthesis of COX and its end-products (Spugnini et al., 2006; Verdina et al., 2008). Indeed, further studies would be necessary to clarify the molecular mechanisms involved in the potentiation of mitoxantrone cytotoxicity by indomethacin in MCF-7 and MCF-7/MX cells. Real-time PCR results showed that indomethacin-treated MCF-7 cells indicated no significant change in the amount of ABCG2 mRNA expression. This observation has been also confirmed on the level of ABCG2 protein expression (Elahian et al., 2009). As a result, expression of a MDR phenotype in human malignant cells may not always be sensitive to potentiation of drug cytotoxicity by NSAIDs (Roller et al., 1999). The present results also confirmed other studies that show NSAIDs' effects are cell and efflux transporter specific (Nozaki et al., 2007).

2.5 The influence of dexamethasone on ABCG2 expression and function

Glucocorticoides are efficacious in the reducing of chemotherapy adverse side effects and show their intrinsic anticancer activity (Vee et al., 2009) (Pavek et al., 2005). Some glucocorticoids, such as beclomethasone, 6α-methylprednisolone, dexamethasone, and triamcinolone, at micromolar concentrations, are shown to efficiently decrease the transport of ABCG2 substrates (Pavek et al., 2005).

Glucocorticoide receptor agonists regulate gene expression in various ways, at the transcriptional (Adcock, 2001), posttranscriptional (Korhonen et al., 2002), and posttranslational levels (Kritsch et al., 2002). Direct interaction of ligand-activated GR with control elements of target genes could regulate gene transcription in a positive or negative way. However, there are different mechanisms for the negative regulation of gene transcription by glucocorticoides. They could interfere with general transcription factors such as activator protein-1 (AP-1) (Herrlich, 2001) and nuclear factor-κB (NF-κB) (Almawi et al., 2002), resulting in decreased transcription of AP-1- and NF-κB -responsive genes. Genomic organization of the ABCG2 gene revealed the presence of several AP-1 sites in the ABCG2 promoter (Bailey-Dell et al., 2001). So it could be a direct target of transcriptional repression in a similar way. On the other hand, it has been reported that dexamethasone mediates negative regulation of gene expression by destabilizing the mRNA of some target genes (Garcia-Gras et al., 2000; Lasa et al., 2002).

Investigating the effects of dexamethasone on ABCG2 expression in MCF-7 cells showed that dexamethasone decreased the mRNA level of ABCG2 gene in comparison with control in MCF-7 and MCF-7/MX cell lines. Flow cytometry analysis indicated that a decrease in the level of ABCG2 protein was observed in dexamethasone treated MCF-7/MX cells. While the level of ABCG2 protein expressed as a ratio of the corresponding control was unchanged in

MCF-7 treated cells (Elahian et al., 2009). Cotreatment with different concentrations of mitoxantrone and dexamethasone increased the sensitivity of MCF-7 and MCF-7/MX cells to the toxic effects of mitoxantrone. In addition, the flow cytometry results showed that dexamethasone could inhibit the efflux and consequently caused increase in the accumulation of mitoxantrone in MCF-7/MX cells. However, ABCG2 inhibition by dexamethasone was not significant in MCF-7 cells (Elahian et al., 2010).
These studies also confirmed that suppression role of dexamethasone on ABCG2 expression in MCF-7/MX cells was more significant than MCF-7 cells. It could be a confirmation for higher level of ABCG2 in MCF-7/MX cells compared with their parental cells and also confirmed other studies that show hormonal regulation of MDR gene expression is cell type specific (Demeule et al., 1999; Imai et al., 2005).

3. Conclusion

In this review we aimed to focuse on the explanation the role of inflammation on the ABCG2 expression and function, using MCF-7 human breast carcinoma cell line. Pro-inflammatory cytokines have been found to be present within the micro-environment of tumors and inflammation. They are able to modulate the expression and function of different drug transporters. Mosaffa et al. showed that that proinflammatory cytokines IL-1β and TNF-α induce ABCG2 mRNA and protein expression and increase its function in MCF-7 cells. In MCF-7/MX, these cytokines increased ABCG2 protein expression and function, but they have no influence on the transporter mRNA levels.
Cyclooxygenase-2 (COX-2) is induced by mitogenic and inflammatory stimuli such as growth factors and cytokines, which results in enhanced synthesis of PGs in neoplastic and inflamed tissues. Kalalinia et al. studies had aimed to explore the potential link between COX-2 expression and development of multidrug resistance phenotype in MCF-7 cell line. They reported that COX-2 inducer TPA (12-O-tetradecanoylphorbol-13-acetate) caused a considerable increase up to 9-fold in ABCG2 mRNA expression in parental MCF-7 cells, while a slight increase in ABCG2 expression was observed in the resistant cell line MCF-7/MX. They also showed a positive corrolation between ABCG2 protein expression and COX-2 protein level in each cell line. On the other hand, celecoxib (a selective inhibitor of COX-2) up-regulated the expression of ABCG2 mRNA in MCF-7 and MCF-7/MX cells, which was accompanied by increased ABCG2 protein expression. Furthermore, TPA could increase ABCG2 function in all cell lines with the greatest stimulatory effects in MCF-7/MX (more than 6 times the control level). In addition, celecoxib inverted the effects of TPA on ABCG2 function. This effect was more obvious in MCF-7/MX.
Several studies have demonstrated that anti-inflammatory drugs like NSAIDs and some glucocorticoids could be effective in chemosensitizing of the many carcinoma cell lines to cytotoxic agents. The pharmacological modulation of ABCG2 in MCF-7 cells by dexamethasone and indomethacin was investigated by elahian et al. . They showed that dexamethasone induced downregulation of ABCG2 mRNA compared to controls in both MCF-7 and MCF-7/MX cell lines, whereas no changes were noted in the presence of indomethacin. The level of ABCG2 protein was decreased in dexamethasone treated MCF-7/MX cells. Cotreatment of mitoxantrone with different concentrations of dexamethasone and indomethacin sensitized parental and resistant MCF-7 cells to mitoxantrone cytotoxicity. Dexamethasone also increased the accumulation of mitoxantrone in the MCF-7/MX cell line, indicating an inhibitiory effect on the ABCG2 protein.

In this review, we describe the effects of proinflammatory cytokines (IL-1β and TNF-α), inflammatory mediator (COX-2) and anti-inflammatory drugs (celecoxib and dexametashone) on the expression of ABCG2 which addressed concerning to finding a new adjutant therapy for patients with cancer experiencing resistance to cancer treatment.

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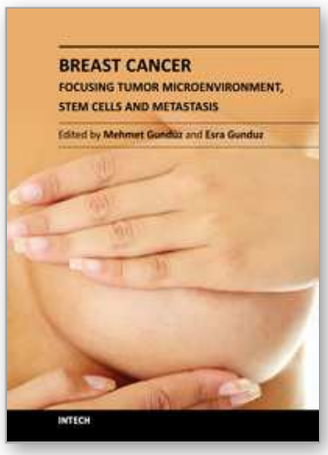

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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed characteristics of breast cancer cell, role of microenvironment, stem cells and metastasis for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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