

Blocking MRP1 may Enhance ER-Stress Induced DNA Damage by an Accumulation of Nuclear LTC4

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The ATP-binding cassette multidrug-resistance associated protein 1 (MRP1 for human, Mrp1 for rodent) was cloned in 1992 by Cole SP, *et al* [1]. The discovery of MRP1 is significant in cancer resistant field primarily because MRP1 was the second membrane efflux transporter associated with multidrug resistant being identified after the discovery of P-glycoprotein (P-gp) by Juliano RL and Ling V back in 1976 [2]. P-gp confers cancer chemotherapy resistance for multiple structurally unrelated compounds with weakly amphipathic and relatively hydrophobic properties. Similarly, substrates for MRP1 are quite diverse, however, with a narrower substrate recognition spectrum. MRP1 mediates an efflux of endo and xenobiotics that are conjugated with either glutathione (GSH), glucuronide or sulfate. MRP1 also mediates the extrusion of nonconjugate hydrophobic compounds in the presence of GSH. Both P-gp and MRP1 were found to be expressed in several cancer resistant cells.

MRP1 is ubiquitously expressed in various tissues [3-5] and is localized in plasma membrane and intracellular organelles including nuclear envelop [6,7]. The function of MRP1 has been expanding beyond the efflux-transporter mediated chemotherapy resistance. Dvash E., *et al*, have recently published an article reported that leukotriene C4 (LTC4), a classic MRP1 substrate, plays a major role in triggering oxidative DNA damage and cell death [8]. Independently, studies have shown that doxorubicin-induced oxidative stress causes a more severe nuclear injury in cardiac tissues in mice lacking Mrp1 [9,10]. These studies imply that MRP1 may have a role in regulating cell survival by regulating intracellular levels of LTC4 in addition to mediating cancer resistance.

Endoplasmic reticulum (ER) stress and oxidative DNA damage have been associated with several pathophysiology and pathogenesis of disorders, including cardiovascular diseases and cancers. Triggering of ER stress may occur under variety of conditions, leading to an accumulation of unfold and/or misfolded proteins in the ER and a subsequently activation of the unfolded protein response (UPR). This evolutionarily conserved mechanism is aimed to restore ER homeostasis, however, if sustained the UPR can trigger cell death possibly via UPR-induced overexpression of C/EBP γ homologous protein (CHOP), which blocks expression of anti-apoptotic protein, BCL-2 [11, 12].

In Brefeldin A-mediated-ER stress model, the ER stress causes a translocation of LTC4 synthesis machinery including 5-lipoxygenase (5-LO), 5-LO activating protein (FLAP) and microsomal glutathione S-transferase 2 microsomal glutathione S-transferase 2 (MGST2) into the nucleus of non-hematopoietic cells, triggering biosynthesis of LTC4 (Figure 1). Knocking down CHOP mRNA significantly attenuated ER-stress induced MGST2 expression and LTC4 synthesis, indicating that MGST2 activation is downstream of CHOP [8]. Intriguingly, ER stress also induces translocation of cysLT receptors (i.e., cysLTR1 and cysLTR2) into the nucleus during death-promoting phase of the UPR [8]. This allows a subsequent interaction between LTC4 and its receptors in the nucleus, resulting in oxidative stress as indicated by an accumulation of reactive oxygen species (ROS). Knocking down mgst2 mRNA or blocking cysLTRs with pranlukast or motelukast abrogates the ER stress induced ROS accumulation and diminished oxidative DNA damage indicated by high levels of 8-hydroxy-2'-deoxy guanosine (8-OHdG) and γ -H2AX [8]. Potentially, the source of ROS being generated in the nucleus is mediated by NADH/NADPH oxidases (NOXs), and more specifically NOX4. It has been demonstrated that NOX4 was found predominantly in the nucleus during ER stress, and

the NOX4 has a critical role in Ras-induced DNA damage [8,13]. Knocking down NOX4 mRNA significantly diminishes ER stress-induced ROS production [8].

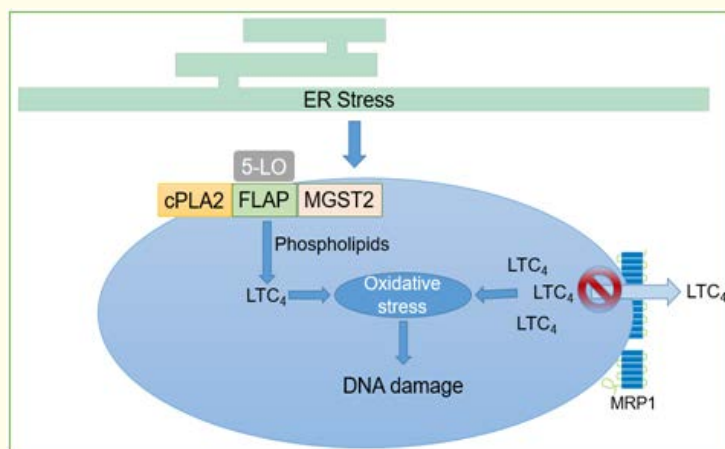


Figure 1: ER stress-mediated oxidative DNA damage. ER stress induces LTC₄ biosynthesis in the nucleus. In a condition that ER stress is sustained, the late unfolded protein response may occur, leading to oxidative stress and DNA damage and cell death. The condition may be enhanced or accelerated if the MRP1 is inhibited. Abbreviations: 5-LO, 5-lipoxygenase; cPLA2, cytosolic phospholipase A2; FLAP, 5-LO activating protein; LTC₄, leukotriene C₄; MGST2, microsomal glutathione S-transferase 2; MRP1, multidrug-resistance associated protein 1.

LTC₄ is the potent lipid mediator and is associated with pathophysiology of asthma. In allergic asthma model, airway inflammation in mice lacking Mrp1 was significantly less severe than that in wild-type littermates. This study indicates that Mrp1 plays a pivotal role in the development of airway inflammation through regulation of antigen-specific IgE mediated LTC₄ extrusion from sensitized mast cells [14]. It was suggested that inhibition of MRP1 could be beneficial in controlling cellular damage. Surprisingly, blockade of MRP1 in Brefeldin A-mediated ER stress model revealed that an accumulation of ROS was more pronounced than in the vehicle treatment control. These studies suggest that the localization of MRP1 is critical in determining the outcomes of the treatment interventions. Blocking MRP1-mediated LTC₄ efflux may prevent inflammation because less of the inflammatory mediators will be released from cells such as mast cells. However, blocking MRP1 that are localized in the nuclear membrane envelope may enhance oxidative damage due to an accumulation of LTC₄ in the nucleus. This situation can be further exemplified in chemotherapeutic agents that induce ER and oxidative stress.

Chemotherapeutic agents such as doxorubicin, vincristine and 5-fluorouracil are known to cause oxidative stress. Not to surprise, doxorubicin has been shown to be capable of inducing the expression of CHOP, LTC₄ synthesis machinery, LTC₄ receptors, and translocating them to the nucleus [8]. The nuclear damage induced by doxorubicin was more pronounced in MRP1 deficient mice than that in wild-type littermates [9], indicating that the Mrp1 play an important role in protecting nucleus from ER stress and oxidative stress especially when the insults are from within the nucleus. Thus, blocking MRP1 may enhance ER-stress induced DNA damage by an accumulation of toxic substances including LTC₄ in the nucleus.

In summary, the physiologic roles of MRP1 seems to be more diverse than predicted. The function of MRP1 that most recognized by the scientific community is as a plasma membrane efflux transporter for glutathione, glucuronide and sulfate conjugated compounds. This MRP1 function involves metabolisms and pharmacokinetics of diverse xenobiotics and hence drug efficacy and toxicity. As the substrates for MRP1 expand from small molecules to endogenous compounds, many of which are lipid mediators and signaling molecules, it is conceivable that MRP1 has emerged as a membrane transporters impact drug metabolism and detoxification process to a broader range of biologic processes that involve cell survival and pathophysiology of diseases.

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