ATP-Binding Cassette (ABC) Transporters and Their Role in Inflammatory Bowel Disease (IBD)

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Abstract

Inflammatory bowel disease (IBD) is a chronic, relapsing, idiopathic inflammation of the gastrointestinal tract characterizing chronic colonic inflammation of GIT. This results from the interaction between the various components of the mucosal immune system and the microenvironment. It is considered as an auto immune disease (AID) involving various factors like immune dysregulation, genetic predisposition, dysbiosis of commensal flora and environmental factors. ATP-binding cassette (ABC) transporters are a large superfamily of membrane proteins with various functions and are also expressed on apical lining of intestine. They utilize the energy from ATP hydrolysis for import and export of substrates. The inflammatory changes associated with IBD pathophysiology may affect the inner mucosal layer structure and affects these transporters modifying their absorptive and secretory functions and protective role against toxic compounds. This subsequently affects the drug absorption and hence IBD treatment. Beside this transporters also play role in drug resistance and their expression is modulated during inflammatory conditions like IBD. Therefore regulating the ABC transporter may be useful in controlling the symptoms or treatment of disease. ABC transporters expressed on epithelial lining of intestine could interact with gut pathogens and could involve in dysbiosis leading to various gastrointestinal disease such as IBD. The information outlined in this review may help in designing new studies for further exploration of ABC transporters and their role in gastrointestinal diseases. This might be beneficial to develop improved innovative approaches.

Keywords: ABC transporters; Inflammatory bowel disease (IBD); Gut microbes; Dysbiosis

Introduction

Inflammatory bowel disease (IBD) is a chronic, relapsing, idiopathic inflammation of the gastrointestinal tract [1,2]. It is characterized by chronic colonic inflammation that results from the interaction between the various components of the mucosal immune system and the microenvironment [3]. It is classified as an Auto immune disease (AID) whose pathophysiology remains uncertain. Inflammatory bowel disease (IBD) is a chronic, relapsing, idiopathic inflammation of the gastrointestinal tract characterizing chronic colonic inflammation of GIT. This results from the interaction between the various components of the mucosal immune system and the microenvironment. It is considered as an auto immune disease (AID) involving various factors like immune dysregulation, genetic predisposition, dysbiosis of commensal flora and environmental factors. ATP-binding cassette (ABC) transporters are a large superfamily of membrane proteins with various functions and are also

expressed on apical lining of intestine. They utilize the energy from ATP hydrolysis for import and export of substrates. The inflammatory changes associated with IBD pathophysiology may affect the inner mucosal layer structure and affects these transporters modifying their absorptive and secretory functions and protective role against toxic compounds. This subsequently affects the drug absorption and hence IBD treatment. Beside this transporters also play role in drug resistance and their expression is modulated during inflammatory conditions IBD.

Therefore regulating the ABC transporter may be useful in controlling the symptoms or treatment of disease. ABC transporters expressed on epithelial lining of intestine could interact with gut pathogens and microbes and could involve in dysbiosis leading to various gastrointestinal disease such as IBD. The information outlined in this review may help in designing new studies for further

exploration of ABC transporters and their role in gastrointestinal diseases. This might be beneficial to develop improved innovative approaches. It has been shown that IBD is caused by the enteric microflora in genetically predisposed patients with an immune dysregulation in the gastrointestinal tract. Various components of mucosal immune system and the microenvironment: luminal antigens, intestinal epithelial cells, T- lymphocytes, cells of innate and adaptive immune systems and their secreted mediators contribute to the initiation and perpetuation of gut inflammation in genetically predisposed individual [3]. Genetic predisposition plays a role through the inheritance of a number of contributory genes and genetic polymorphisms. These variant forms of genes may be associated with an abnormal response [4]. However the exact etiology is unknown.

Results from research in animal models, human genetics, basic science and clinical trials have provided new insights into the pathogenesis of chronic, immune-mediated, intestinal inflammation. These studies indicate that Crohn's disease and ulcerative colitis are heterogeneous diseases characterized by various genetic abnormalities that lead to overly aggressive T-cell responses to a subset of commensal enteric bacteria. The onset and reactivation of disease are triggered by environmental factors that transiently break the mucosal barrier, stimulate immune responses or alter the balance between beneficial and pathogenic enteric bacteria. Inflammatory bowel disease is mainly of two types:

- a) Ulcerative colitis (UC)
- b) Crohn's disease (CD)

ATP-Binding Cassette (ABC) Transporters

ATP-binding cassette (ABC) transporters are a large superfamily of membrane proteins with varying functions [5,6]. They utilize the energy obtained from ATP hydrolysis for import and export of substrates across the into trans-bilayer. In both cases, a pair of cytoplasmic ABCs (nucleotide-binding domains, NBDs) catalyse ATP hydrolysis, a and pair of transmembrane domains (TMDs) facilitate the translocation of the substrate. The basic domain architecture and schematic mechanism are shown in Figure 1: ABC transporters are mainly of two types (a) ABC importers, (b) ABC exporters. ABC importers, require a substrate binding protein (SBP) that feeds the hydrophilic substrates into the translocation pathway formed by the TMDs. The ABCs (or NBDs) are separate subunits. (b) ABC exporters, which typically have their TMDs fused to the ABCs. ABC importers have been found only in prokaryotes till date, whereas ABC exporter is expressed ubiquitously in all kingdoms of life. ABC transporters have been shown to be associated with various clinical conditions suggesting the importance of understanding their mechanism. There are approximately 50 known ABC transporters in the human. There are 13 genetic diseases associated with defects in 14 of these transporters. The most common genetic disease conditions include cystic fibrosis, Stargardt disease, age-related macular degeneration, adrenoleukodystrophy, Tangier disease, Dubin-Johnson syndrome and progressive familial intrahepatic cholestasis [7].

Conserved Coupling Mechanism For ABC Transporters: The NBD domain is conserved and regarded as a common engine attached to diverse TMDs. NBDs has two sub-domains, one resembling the functionally unrelated RecA protein, and another that has been dubbed the 'helical sub-domain' (Figure 1). NBDs contains many conserved sequence motifs, each with a specific function [8]. For example P-loops (Walker-A motifs) is the most important of them and located in the RecA-like sub-domain, and the LSGGQ motif (denoting the amino acid sequence in single letter code), located in the helical sub-domain. In full transporters, the two NBDs assemble exposing their conserved motifs towards the shared interface in a head-to-tail arrangement. This setting produces two ATP binding and hydrolysis sites between the P-loops of one NBD and the LSGGQ motif of the other, hence the name 'head-to-tail'. In the absence of a nucleotide, there is a gap at the domain interface, with water being able to access the nucleotide-binding sites. When ATP is bound, the interface closes and the nucleotides are sandwiched between the NBDs [9]. During a single transport cycle, two molecules of ATP are consumed, which is consistent with positive cooperativity observed for ATP hydrolysis in several ABC transporters [10]. Exceptions are possible due to mutations for e.g cystic fibrosis transmembrane conductance regulator CFTR where one of the ATP binding sites features mutations that prevent hydrolysis.

Figure 1: Basic domain architecture of ABC transporter [6].

Types of ABC Transporters: In human total 48 ABC transporters are known. These are subdivide in 7 sub families ABCA, ABCB, ABCC, ABCD, ABCE, ABCF and ABCG by the Human Genome Organization. Table 1 displays a list of all 48 known human ABC genes with chromosomal location, and function.

Role of ABC Transporters in IBD

Irrespective of the genetic cause, severe and continuous inflammation causes damage to the intestinal epithelium that may strongly affect its absorptive and secretory functions as well as its protective role against toxic compounds [11]. Cytoprotection is provided by ATP-binding cassette (ABC) transporters that are specialized in exporting toxic compounds of foreign or endogenous origin. Thus by the knowledge of transporters showing change during the IBD helps us to improve drug absorption as well as increase protection given by these transporters.

Role of ABCC1: MRP1 (multidrug resistance-associated protein 1, encoded by the ABCC1 gene) plays a role in inflammatory responses. It transports glutathione and substrates that are conjugated to reduced glutathione, glucuronide, or sulfate as part of the detoxification machinery of cancer cells. The role of Mrp1 in the inflammatory signaling pathway is evident from studies with Mrp1-/- knock-out mice that show a strongly reduced response to arachidonic acid-induced inflammatory stimuli as measured by decreased ear edema and vascular permeability [12]. Relevant for IBD, however, it was shown that intestinal damage was significantly aggravated in Mrp1-/- knock-out mice exposed to dextran sulfate sodium-induced colitis. These animal studies suggest that Mrp1 serves a dual role during inflammation, both sending out inflammatory signals as well as protecting the intestinal epithelium. The mechanism of the latter and the relevance for IBD patients are unknown to date.

Up-regulation and cytoprotective role of epithelial multidrug resistance-associated protein 1 in inflammatory bowel disease is also known [13]. In their study they found that MRP1 expression is induced in the inflamed intestine of IBD patients, e.g. Crohn disease and ulcerative colitis. Increased MRP1 expression was detected at the basolateral membrane of intestinal epithelial cells. To study a putative role for MRP1 in protecting epithelial cells against inflammatory cues, they manipulated MRP1 levels in human epithelial DLD-1 cells and exposed these cells to cytokines and anti-Fas. Also inhibition of MRP1 (by MK571 or RNA interference) resulted in increased cytokine- and anti-Fas-induced apoptosis of DLD-1 cells. Opposite effects, e.g. protection of DLD-1 cells against cytokine- and anti-Fas-induced apoptosis, were observed after recombinant MRP1 over expression. Inhibition of LTC₄ synthesis reduced anti-Fas-induced apoptosis when MRP1 function was blocked, suggested that (leukotrienes 4) LTC₄ is the pro-apoptotic compound exported by epithelial MRP1 during inflammation. These data showed that MRP1 protects intestinal epithelial cells against inflammation-induced apoptotic cell death and provides a functional role for MRP1 in the inflamed intestinal epithelium of IBD patients.

Role of ABCC4: Multidrug resistance protein 4 (MRP4/ABCC4) belongs to the MRP family of multispecific drug transporters. MRP4 is widely expressed in a range of human blood cells including CD34+ stem cells, erythrocytes, platelets, granulocytes and lymphocytes. MRP4 is localized in the plasma membrane and shows an ATP-dependent transport of a broad range of compounds. Like the other MRPs, MRP4 is an organic anion transporter, but has the unique ability to transport nucleoside monophosphate analogs such as 6-mercaptopurine (6-MP) and 6-thioguanine nucleotide (6-TGN). Drug TPMT is commonly administered in IBD patients which is metabolized to 6-MP. The over expression of MRP4 in cells results in resistance to 6-MP and 6-TGN. Since MRP4 is an ATP-dependent efflux pump, one possible explanation for the resistance observed in cells over-expressing these proteins is the increased removal of an essential thiopurine metabolite from these cells. A single-nucleotide polymorphism in human MRP4 (rs3765534) dramatically reduces MRP4 function and results in the intracellular accumulation of 6-TGN [14].

It was observed that the gene expression changes during UC development may be responsible for resistance to intravenous corticosteroid therapy in children with severe ulcerative colitis [15]. In this study they selected 20 corticosteroid responsive patients and 20 corticosteroid resistant patients for analysis. A total of 41 genes differentially expressed between responders and non-responders were detected with statistical significance. Two of these genes, CEACAM1 and MMP8, possibly inhibited by methylprednisolone through IL8, were both found to be over-expressed in non-responsive patients. ABCC4 (MRP4) as a member of the multi-drug resistance superfamily was a novel candidate gene for corticosteroid resistance. The expression pattern of a cluster of 10 genes selected from the 41 significant hits was able to classify the patients with 80% sensitivity and 80% specificity.

Role of ABCB1

Inflammation is known to suppress the expression and activity of several hepatic drug transporters [16-18]. Goralski et al, 2003 investigated localized CNS inflammation induced by *Escherichia coli* lipopolysaccharide (LPS) modified *mdr1a*/P-gp expression and function in the brain and liver. Their major finding was that the CNS inflammation in male rats produced a loss in the expression of *mdr1a* mRNA in the brain and liver that was maximal 6 h after intracranial ventricle (i.c.v.) administration of LPS. When radioactive H₃-digoxin was used at discrete time points, as a probe for Pgp function in vivo, an increase in brain and liver H₃-radioactivity and plasma level of parent digoxin was produced 6 and 24 h following LPS treatment compared to the saline controls. Digoxin disposition was similarly altered in *mdr1a* (+/+) mice but not in *mdr1a* (-/-) mice 24 h after administering LPS i.c.v. They also shown that in male rats, the biliary elimination of parent digoxin was reduced at 24 h (60%) and 48 h (40%) after LPS treatment and was blocked by the Pgp substrate cyclosporin A. The conditions which impose inflammation in the CNS, produce dynamic changes in *mdr1a*/P-gp expression/function that may alter hepatic drug elimination and the movement of drugs between the brain and the periphery.

In rats the expression and function of intestinal *mdr1* and *mrp2* were found to be reduced in lipopolysaccharide-induced inflammation [19,20]. In their study transport and metabolism were determined in jejunum segments isolated at 24 h from endotoxin-treated or control rats (n = 8). Transport and metabolism of (3)H-digoxin, 5-carboxyfluorescein (5-CF), amiodarone (AM), and 7-benzoyloxyquinoline (7-BQ) were measured for 90 min in the presence and absence of inhibitors. They found that as compared to controls, levels of *mdr1a* and *mrp2* mRNA were significantly decreased by approximately 50% in the jejunum of LPS-treated rats. Corresponding reductions in the basolateral→apical efflux of digoxin, AM, and 5-CF were observed, resulting in significant increases in the apical→basolateral absorption of these compounds. Role of Pgp in IBD was suggested after finding that *mdr1a*-deficient mice developed a ulcerative colitis (UC)-like phenotype that was reversed with antibiotics [21]. They reported that *mdr1a* knockout (*mdr1a* -/-) mice are susceptible in developing a severe, spontaneous intestinal inflammation when maintained under specific pathogen-free animal facility conditions. The intestinal inflammation seen in *mdr1a* -/-

mice had pathology similar to that of human inflammatory bowel disease (IBD) and was defined by dysregulated epithelial cell growth and leukocytic infiltration into the lamina propria of the large intestine. Treating *mdr1a*^{-/-} mice with oral antibiotics prevented both the development of disease and resolved active inflammation. Lymphoid cells isolated from mice with active colitis were functionally reactive to intestinal bacterial antigens, providing evidence that there is enhanced immunologic responsiveness to the normal bacterial flora during IBD.

Gene array data have reported that Pgp is down regulated in patients with UC [22,23]. Drug efflux pump P-glycoprotein, a membrane transporter extruded Glucocorticoids from cells and thereby lowering their intracellular concentration [24]. Natural and synthetic glucocorticoids (GCs) are widely employed in a number of inflammatory, autoimmune and neoplastic diseases, and, despite the introduction of novel therapies, remain the first-line treatment for inducing remission in moderate to severe active Crohn's disease and ulcerative colitis patients. GCs interact with their cytoplasmic receptor, and are able to repress inflammatory gene expression through several distinct mechanisms. The glucocorticoid receptor (GR) is therefore crucial for the effects of these agents: mutations in the GR gene (NR3C1, nuclear receptor subfamily 3, group C, member 1) are the primary cause of a rare, inherited form of GC resistance. In their study they found not only GC mutations but other factors also causes resistant against GCs. This protein is encoded by the ABCB1/MDR1 gene; this gene presents different polymorphic sites that can influence its expression and function.

Decreased ABCB1 (P-glycoprotein) expression in ulcerative colitis was found to be associated with disease activity [25]. The major human efflux transporter ABCB1 showed significantly lower expression levels, that were inversely correlated with those of certain antimicrobial peptides (DEFA5/6) and cytokines (IL1beta and IL8). Cell culture experiments revealed a time-dependent decrease of ABCB1 expression upon IL8 exposure. Disease activity profoundly modified ABCB1 expression, indicated by an inverse correlation of clinical activity index values with ABCB1 mRNA expression ($r = -0.603$; $p = 0.017$) and markedly reduced protein expression in UC patients with moderate and severe symptomology ($p = 0.011$).

Cortada et al. [26] investigated the role of P-gp in therapeutic response of ulcerative colitis by studying its functionality in lymphocytes isolated from peripheral blood. Rhodamine 123 (a fluorescent P-glycoprotein substrate) efflux was studied by flow cytometry as absence and presence of an inhibitor (verapamil, 100 μ M). Rhodamine efflux assay was also performed in 12 patients who required therapeutic change; a significant diminish of rhodamine transport ($p < 0.01$) was observed without inhibitor when patients achieved clinical response. their observation indicates a possible relevant role of P-gp in ulcerative colitis treatment response and indicate advantage of P-gp functional assay in the early detection of individual therapeutic response. Genetic variation in the gene encoding Pgp, ABCB1, appears to be associated with disease distribution as well as susceptibility to UC [27,28]. The author utilized a gene-wide haplotype tagging approach to define the identity of germ-line variations in the ABCB1/MDR1 gene contributing to

IBD susceptibility. Six haplotype tagging single nucleotide polymorphisms (tSNPs) representing the haplotypic variations of the ABCB1/MDR1 gene were identified. The log-likelihood analysis after the genotyping of 249 ulcerative colitis (UC) and 179 Crohn's disease (CD) patients and 260 healthy controls, showed a highly significant association between the common haplotypes and UC ($P = 4.22 \times 10^{-7}$) but not CD ($P = 0.22$).

This significant association was critically dependent on one tSNP, intronic variant rs3789243. All haplotypes with this variant retained a highly significant association ($P = 3.2 \times 10^{-7}$ – 3.6×10^{-12}), whereas significance was lost when rs3789243 was dropped in systematic haplotypic analysis. The effect of this tSNP was independent of C3435T SNP, previously suggested to be the critical variant in disease susceptibility and drug transport. The association with UC was shown to be strongest with the phenotype of extensive disease ($P = 1.7 \times 10^{-7}$). This 'candidate gene' approach provides compelling evidence to support the contribution of the ABCB1/MDR1 gene in determining risk to UC but not to CD and provides new insights into the localization of the critical susceptibility determinants within the gene. Common variants in *mdr1* gene are also found to be associated with an overall susceptibility for UC in north Indians [29]. SNP analysis was conducted in three exonic (C1236T, G2677T/A, and C3435T) locations and one in the promoter (C129T) region of *mdr1* gene [30-39]. Their results indicated that above SNPs in the *mdr1* gene are associated with an overall susceptibility for UC and specific disease phenotypes in North Indians. Other ABCB1 SNPs associated with IBD in different population are summarized in Table 1.

Table 1: ABCB1 polymorphisms in different population.

Population/country	SNP name	Reference
Polish	C3435T	[30]
Japanese	rs3765534	[14]
New Zealand	rs2235046	[31]
	G2677T/A	
	C1236T	
	rs3789243	
	C3435T	
Turkish	G2677T/A	[32]
Canadian	C3535T	[33]
	G2677T/A	
Germany	G2677T/A	[34]
	C3435T	
Hungarian	C3435T	[35]
	G2677T/A	
Spanish	G2677T/A	[36]
	C3435T	
Iranian	C3435T	[37]
Dutch	C3435T	[38]
British	G2677T/A	[39]
	C3435T	

Role of ABCA1

TNF- α , an important cytokine produced during IBD, decreases ABCA1 expression and attenuates HDL cholesterol efflux in the human intestinal cell line Caco-2 [40]. The regulation of ABCA1 and HDL cholesterol efflux by TNF- α was investigated in the human intestinal cell line Caco-2. They found that in response to cholesterol micelles or T0901317, an LXR non sterol agonist, TNF- α decreased the baso-lateral efflux of cholesterol to apolipoprotein A1 (apoA1). TNF- α , by attenuating ABCA1 promoter activity, markedly decreased ABCA1 gene expression without attenuating the expression of LXR- α , LXR- β , and most other LXR target genes, such as ABCG1, FAS, ABCG8, scavenger receptor-B1 (SR-B1), and apoC1. TNF- α also decreased ABCA1 mass by markedly enhancing the rate of ABCA1 degradation and modestly inhibiting its rate of synthesis. Inhibitors of the nuclear factor- κ B (NF- κ B) pathway, which is activated by TNF- α , partially reverse the effect of TNF- α on ABCA1 protein expression. The results suggested that TNF- α , the major cytokine implicated in the inflammation of Crohn's disease, decreased HDL cholesterol levels by attenuating the expression of intestinal ABCA1 and cholesterol efflux to apoA1.

Role of ABCG2 (BCRP)

Similar to Pgp, BCRP is expressed in organs with a barrier function, indicating a role in tissue defense against xenobiotics [41]. BCRP has been suggested as an important determinant in the absorption of sulfasalazin [42] which is widely used in the treatment of IBD. The role of BCRP in transporting carcinogens, exemplified by benzo[a]pyrene conjugates, aflatoxin B1, and PhIP is also highly interesting in the context of UC, as the colon cancer risk increases with longer duration of colitis greater anatomic extent of colitis, and the fact that certain drugs used to treat inflammation may prevent the development of colorectal cancer. Two of the efflux transporters of importance for the barrier function of the gut mucosa, Pgp and BCRP, are expressed at strongly reduced levels during active inflammation in patients with UC [43]. In their study colonic and rectal mucosa from patients with UC were compared with tissues from control subjects (n = 15). The mRNA expression (Taq Man) of the efflux transporters and the pro-inflammatory cytokines interleukin (IL)-1 β and IL-6 was determined. Western blot was used in the analysis of protein expression and the tissue localization of BCRP was determined. BCRP and Pgp expression was strongly reduced in individuals with active inflammation compared with controls and were negatively correlated with the levels of IL-6 mRNA.

The BCRP staining of colonic epithelium seen in healthy mucosa was diminished in inflamed tissues, with concurrent disruption of epithelial F-actin structure. Impeded protein folding and function of ABCG2 in active inflammatory bowel disease was also known [44]. Their study revealed decreased expression of ABC (ATP-binding cassette) transporters such as ABCG2 (ABC transporter G2) in patients with active IBD, thereby limiting the protection against various luminal threats. Correct ER (endoplasmic reticulum)-dependent protein folding is essential for the localization and function of secreted and membrane-bound proteins. Inflammatory triggers, such as cytokines and nitric oxide, can impede protein folding,

which causes the accumulation of unfolded proteins inside the ER. NO is increased during the IBD and this NO inhibited the formation of disulfide bond and these disulfide bonds are essential for the function of xenobiotic transporters, such as ABCG2, it can be assumed that these proteins are not properly folded and therefore reduced in expression during inflammation.

As a result, the unfolded protein response is activated which can lead to a cellular process named ER stress. The protein folding impairment affects the function and localization of several proteins, including those involved in protection against xenobiotics. Absence of ABCG2-mediated mucosal detoxification in patients with active inflammatory bowel disease is due to impeded protein folding [45]. Their study showed that xenotoxic damage in inflammatory diseases, including IBD was compounded by reduced activity of the xenobiotic transporter ABCG2 (ATP-binding-cassetteG2) during the inflammatory state. An association between the activation of the unfolded protein response pathway and inflammation prompted them to investigate the possibility that reduced ABCG2 activity was causally linked to this response. To this end, they correlated expression of ABCG2 and the unfolded protein response marker GRP78 (glucose-regulated protein of 78 kDa) in colon biopsies from healthy individuals and patients with inactive or active IBD, ischaemic colitis or infectious colitis. In addition, tissue specimens from the small bowel from healthy individuals and from patients with inactive or active Crohn's disease were co-stained for ABCG2 and GRP78.

In all biopsies from patients with active inflammation, irrespective of the underlying disease, an absolute negative correlation was observed between epithelial ABCG2 expression and GRP78 expression, suggesting that inflammation-dependent activation of the unfolded protein response is responsible for suppression of ABCG2 function. The link between the unfolded protein response and functional ABCG2 expression was further corroborated by live imaging of ABCG2-expressing cells, which showed that various inflammatory mediators, including nitric oxide, activate the unfolded protein response and concomitantly reduce plasma membrane localization as well as transport function of ABCG2. Thus a novel mechanism for explaining xenobiotic stress during inflammation emerges in which intestinal inflammation activates the unfolded protein response, in turn abrogating defenses against xenobiotic challenge by impairing ABCG2 expression and function. ABC transporters and their interaction with gut microbes

ABC transporters and their interaction with gut microbes

ABC transporters have been shown to play a important role in tissue defense. The multidrug resistance protein (MDR) affects the host-bacterial interactions at the mucosal frontier of GIT. The intestinal barrier function regulates transport and host-defense mechanisms at the mucosal frontier and plays a critical role in the pathophysiology of various gastrointestinal diseases including IBD. The ABC efflux transporters are also expressed at the apical surface of the epithelial cells of the intestine suggesting their possible interaction with gut microbes. The expression of P-gp increases distally from the duodenum to the colon [46] and able to interact

with enteric pathogens like *Listeria monocytogenes*, *Salmonella enterica* serovar Typhimurium [47]. However the expression of MRP2 is highest in the duodenum and decreases distally to undetectable at the terminal ileum and colon [48]. In the small intestine MRP2 is exclusively localized to the apical brush border membrane of villi suggesting an important role in drug disposition. MRP2 expression also decreases in intensity from the villus tip to the crypts, where no expression has been observed [49]. MRP2 is functionally upregulated during *S. typhimurium* infection and its expression associates with active states of intestinal inflammation [50].

MRP2 upregulation is considered to be involved in neutrophil recruitment by the apical efflux of the eicosanoid heparin A3 (HXA3), a potent neutrophil chemoattractant which is associated with active states of intestinal inflammation [51]. Breast cell receptor protein (BCRP/ABCG2), another apically expressed ABC transporter, is found throughout the small intestine and colon [52]. However there are no reports showing their interaction with microbes or pathogens. In the intestine, CFTR gene expression shows a decreasing gradient along the crypt-villus and proximal-distal axes as well [53]. CFTR is a Cl⁻ channel, rate limiting step for intestinal Cl⁻ secretion (i.e., fluid secretion in cholera and other enterotoxin-mediated secretory diarrheas). These characteristics are crucial to make this transporter a target for therapeutic intervention of enterotoxin-mediated secretory diarrheas, such as cholera.

The expression of the CFTR protein by intestinal epithelium is markedly increased during serovar *S. typhi* infection of enterocytes that causes enhanced CFTR-dependent entry of *S. typhi* into epithelial cells [54]. However the products of certain commensal bacteria are also able to trigger CFTR in epithelial cells [55]. The dysbiosis of host gut microbiome in case of IBD is well reported [56], however there are not many reports revealing the interaction of commensal microbes with ABC transporters. ABC transporters and the host genotype affecting the ABC transporter functionality might be important in modifying the gut microbiome. Thus exploring ABC transporters and their interaction with host microbiome can help to design therapeutic intervention to identify novel targets for controlling mucosal inflammation and novel drugs for MDR inhibitors.

Discussion and Conclusion

The evidences discussed in this review indicate the importance of ABC transporters in host defense at the mucosal frontier and their involvement with IBD pathophysiology. It has been shown in the literature that some of the patients suffering from ulcerative colitis for a prolonged time may develop colon cancer. However, reports are lacking showing exclusive expression profile of ABC transporters in mucosa of gut during active condition of Ulcerative colitis that are oppositely regulated during colon cancer. In this context, it is important to explore further, how ABC transporters correlate with clinical symptoms and outcome in IBD, how they might be important in colon cancer. The information outlined in this review may help to open up the avenues for early detection of colon cancer in UC patients. The scientific reports discussed in this review would increase the understanding of the vital role of ABC transporters in IBD and other gastrointestinal diseases. This

can give directions to move the field forward and provide the basis in designing more studies towards the development of improved innovative approaches.

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