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The role of fecal sulfur metabolome in inflammatory bowel diseases

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ABSTRACT

Sulfur metabolism and sulfur-containing metabolites play an important role in the human digestive system, and sulfur compounds and pathways are associated with inflammatory bowel diseases (IBD). In fact, cysteine metabolism results in the production of taurine and sulfate, and gut microbes catabolize them into hydrogen sulfide, a signaling molecule with various biological functions. Besides metabolites originating from sulfur metabolism, several other sulfur-containing metabolites of different classes were detected in human feces, consisting of non-volatile and volatile compounds. Sulfated steroids and bile acids such as taurine-conjugated bile acids are the major classes along with sulfur amino acids and sulfur-containing peptides. Indeed, sulfur-containing metabolites were described in stool samples from healthy subjects, patients suffering from colorectal cancer or IBD. In metabolomics-driven studies, around 50 known sulfur-containing metabolites were linked to IBD. Taurine, taurocholic acid, taurochenodeoxycholic acid, methionine, methanethiol and hydrogen sulfide were regularly reported in IBD studies, and most of them were elevated in stool samples from IBD patients. We summarized from this review that there is strong interplay between perturbed gut microbiota in IBD, and the consistently higher abundance of sulfur-containing metabolites, which potentially represent substrates for sulfidogenic bacteria such as *Bilophila* or *Escherichia* and promote their growth. These bacteria might shift their metabolism towards the degradation of taurine and cysteine and therefore to a higher hydrogen sulfide production.

1. Introduction

Sulfur in endogenous organic sulfur-containing compounds are mostly derived from diet. The two canonical sulfur amino acids Methionine (Met) and Cysteine (Cys) are highly abundant in animal protein sources (Barton et al., 2017). In human body, organic sulfur is either used for protein synthesis, metabolism or conjugation of endogenous and exogenous compounds such as bile acids or drugs. Met is essential for humans and has to be acquired through diet and only plants or microbes are able to synthesize methionine de-novo Met (Ravanel et al., 1998). The majority of dietary Met is used for protein synthesis. Cys is semi-essential and can be produced by transsulfuration of Met and serine with the synthesis of ammonia (NH_3), α-ketobutyrate and Cys (Weinstein et al., 1988). Protein-bound Met and Cys are released during digestion in the gastrointestinal tract with an efficient absorption of both amino acids (~95–99%) across the intestinal epithelium (Nimni et al., 2007). Free sulfur amino acids are passing through portal vein into the liver. Hepatic Met and Cys are utilized for protein synthesis, glutathione synthesis, catabolism of Cys to taurine, sulfate and hydrogen sulfide (H_2S) (Stipanuk, 2004). Usually, fecal and renal excretion of Met and Cys are very low (Sheffner et al., 1948, Eckhardt and Davidson, 1949, Ahlman et al., 1993). In this review we briefly discuss and summarize the current knowledge about sulfur metabolism, including endogenous Cys metabolism, bacterial degradation of Cys, Met, taurine and sulfate. The main goal is to present a comprehensive and systematic overview about fecal sulfur metabolome with the specific focus on inflammatory bowel diseases.

2. Sulfur Metabolism

2.1. Endogenous Cys Metabolism

There are two major pathways of Cys metabolism (cysteinesulfinate dependent or independent), including oxidation or desulfuration with

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main products taurine or sulfate (SO_4^{2-}) (Fig. 1). The cysteinsulfinate dependent pathway starts with the oxidation of the SH group by hepatic Cys dioxygenase (CDO) (Stipanuk et al., 2006). This enzyme is highly specific for Cys, and tightly controlled by dietary proteins especially of animal origin (Stipanuk et al., 2002, Ueki et al., 2011). The product of Cys oxidation is cysteinesulfinate which is transformed by the action of cysteinesulfinate decarboxalyse (CSD) into hypotaurine and oxidized to the final product taurine (Fig. 1). Alternatively, cysteinesulfinate is converted via aminotransferase into pyruvate and sulfite (SO_3^{2-}), followed by oxidation to sulfate, which could be further reduced to H_2S (Bella et al., 2002). In comparison to taurine, SO_4^{2-} seems to be the major catabolite of Cys degradation (Bella and Stipanuk, 1995; Nakamura et al., 2002). The cysteinesulfinate independent Cys catabolism employs at least three enzymatic steps that cleave the sulfur from Cys to deliver endogenous reduced sulfur (H_2S) (Stipanuk and Ueki, 2011). Cystathionine β-synthase (CBS) is using Homocysteine (HomoCys) with either serine or alternatively Cys to produce cystathionine, water or H_2S (Chen et al., 2004, Vicente et al., 2017). The condensation of HomoCys with Cys produces cystathionine and endogenous H_2S, which represents only a small part (5%) of the CBS activity. Cystathionine is further used by cystathionine γ-lyase (CSE) to generate Cys, α-ketobutyrate and NH_3. Cys is then α,β-eliminated by the same enzyme CSE to produce pyruvate and $NH_3$by releasing H_2S (Stipanuk and Ueki, 2011). Both enzymes play an important role in generating endogenous H_2S, which can be further oxidized to SO_4^{2-}. A third Cys degradation pathway is known to act through intermediates by 3-mercaptopyruvate sulfurtransferase (3-MST) to generate H_2S and pyruvate (Shibuya et al., 2008).

2.2. Bacterial Metabolism of Cys and Met

There are four different pathways for bacterial degradation of Cys. The key enzyme cysteine desulfhydrase (CDS) catalyzes the reaction of Cys and water to produce pyruvate, NH_3 and H_2S (Fig. 2A) (Barton et al., 2017). There are three other enzymes (i.e., CSE, CBS and 3-MST) involved in bacterial Cys metabolism, resulting in the production of pyruvate, serine, NH_3 and H_2S (Fig. 2A). Recently, cysteine desulfurase (IscS, Fig. 2A) was found out to be responsible for the synthesis of H_2S from Cys in *Escherichia coli* (*E. coli*) under anaerobic condition (Korshunov et al., 2016, Wang et al., 2019). In fact, CDS is found amongst different gut bacteria of the genera *Clostridium*, *Enterobacter*, *Klebsiella*, *Streptococcus*, *Desulfovibrio* and *Tissierella* (Carbonero et al., 2012). Also, CSE, CBS and 3-MST, which are involved in endogenous Cys degradation, were already described in bacteria, especially in pathogens such as *E. coli* or *Staphylococcus aureus* (Shatalin et al., 2011).

Microbial degradation of Met leads to the production of methanethiol, NH_3, 2-oxobutanoate by the enzyme methionine γ-lyase, which was found in some bacteria including *Pseudomonas putida* or oral microbe *Porphyromonas gingivalis* (Portune et al., 2016). Methanethiol might be converted to dimethyl disulfide or dimethyl trisulfide, excreted or passed through host metabolism to produce dimethyl sulfoxide and finally dimethyl sulfone (He and Slupsky, 2014).

2.3. Bacterial Taurine Metabolism

Taurine is the end product of endogenous oxidative Cys metabolism but can also be obtained through diet (Rana and Sanders, 1986). In human body, it acts as an osmolyte, and neurotransmitter, and has antioxidative, anti-inflammatory and anti-apoptotic effects (Lambert et al., 2015, Stipanuk et al., 2015). The organosulfonate is not further subjected to endogenous metabolism, it is either excreted in the urine or feces or conjugated to organic compounds such as bile acids and fatty acids to increase their water solubility (Lambert et al., 2015). In the lower gastrointestinal tract, taurine can serve as a substrate for microbial metabolism (Cook and Denger, 2006; Lambert et al., 2015). Through an active import (ABC transporter, TauABC) taurine is transported into the microbial cell and depends on the microbe and conditions, there are several pathways to degrade taurine by releasing SO_3^{2-} (Rohwerder, 2020). Taurine is desulfonated by the taurine dioxygenase (TauD) or alkanesulfonate dioxygenase (SsuD) with the generation of SO_3^{2-} and aminoacetaldehyde (Fig. 2B) (Eichhorn et al., 1997, Eichhorn

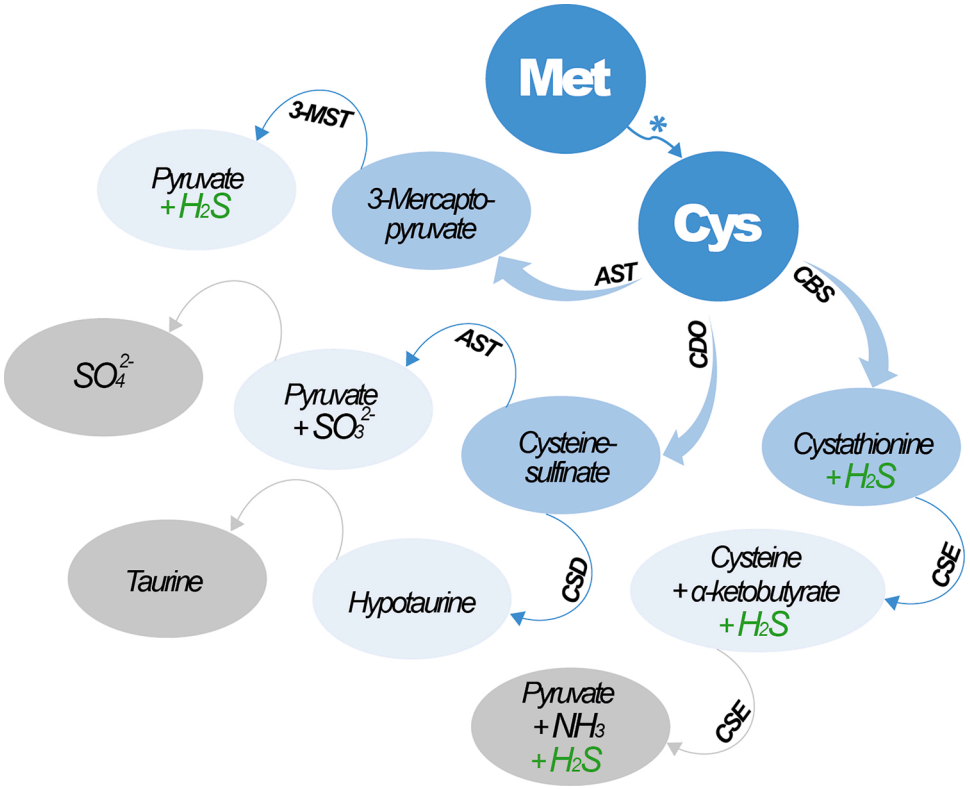

Fig. 1. Cysteine metabolism.
Cys is either derived from food (animal sources) or produced via transsulfuration (*) of Met. Two important pathways of Cys metabolism engage the enzymes Cys dioxygenase (CDO) or cystathionine β-synthase (CBS) and result in the production of two intermediate metabolites, cysteinesulfinate and cystathionine, respectively. Cysteinesulfinate is converted to hypotaurine (cysteinesulfinate decarboxalyse, CSD) and finally oxidized to taurine or an aminotransferase (AST) is producing pyruvate and sulfite (SO_3^{2-}) with final oxidation to sulfate (SO_4^{2-}). The cystathionine pathway results in following products – pyruvate, ammonia (NH_3) and H_2S, generated by the cystathionine γ-lyase (CSE). A third Cys degradation pathway is conducted via 3-mercaptopyruvate sulfurtransferase (3-MST) to generate H_2S and pyruvate.

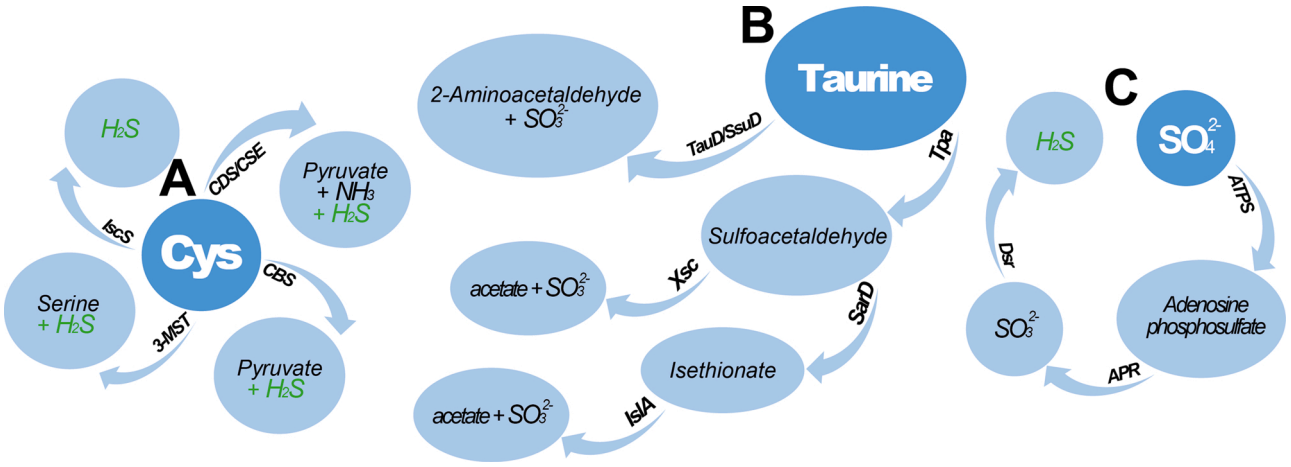

Fig. 2. Microbial metabolism of Cys, Taurine and sulfate.
A: Cys is known to be degraded by at least four enzymes - Cys desulfhydrase (CDS), cystathionine γ-lyase (CSE), 3-mercaptopyruvate sulfurtransferase (3-MST) and Cys desulfurase (IscS), resulting in the production of pyruvate, serine, NH_3 and H_2S.
B: Taurine is desulfonated by a taurine dioxygenase (TauD) or alkanesulfonate dioxygenase (SsuD) under generation of 2-Aminoacetaldehyde and SO_3^{2-}. A deamination of taurine produces sulfoacetaldehyde (taurine:pyruvate aminotransferase, Tpa). This intermediate can be processed by the sulfoacetaldehyde acetyltransferase (Xsc) to acetate and SO_3^{2-}. In addition, sulfoacetaldehyde can be utilized by sulfoacetaldehyde reductase (SarD) and isethionate sulfite-lyase (IslA) to acetate and SO_3^{2-}.
C: Sulfate is undergoing a dissimilatory reduction by the ATP sulfurylase (ATPS), APS reductase (APR) and dissimilatory sulfite reductase (Dsr) to generate H_2S.

et al., 2000). Alternatively, taurine undergoes deamination by the taurine:pyruvate aminotransferase (Tpa) with production of sulfoacetaldehyde. The aldehyde is either forwarded to sulfoacetaldehyde acetyltransferase (Xsc) enzyme linked pathway or in to the newly discovered anaerobic desulfonation pathway (Fig. 2B). Here, isethionate and acetaldehyde are intermediate metabolites produced by the enzymes isethionate-forming sulfoacetaldehyde reductase (SarD) and isethionate sulfite-lyase (IslA) (Peck et al., 2019; Xing et al., 2019a,b). The C–S cleavage by the thiamine pyrophosphate (TPP)-dependent enzyme sulfoacetaldehyde acetyltransferase (Xsc) rather appears to be a pathway described in non-human associated microbes (Denger et al., 1999; Ruff, Denger et al. 2003). Several species from *Escherichia*, *Shigella* or *Salmonella* genera degrade sulfonates under aerobic growth (Uria--Nickelsen et al., 1993). Under anaerobic conditions, only few gut microbes are known to degrade free taurine such as *Bilophila wadsworthia* (*B. wadsworthia*) and not yet characterized species of the *Veillonellaceae* family (Laue et al., 1997a,b, Feng et al., 2017).

2.4. Dissimilatory Sulfate Reduction

In addition to microbial Cys or taurine degradation, dissimilatory sulfate reduction is another microbial pathway that consumes inorganic SO_4^{2-} to synthetize H_2S (Fig. 2C). The group of anaerobic sulfate-reducing bacteria can use SO_4^{2-} by a dedicated enzymatic machinery. An ATP sulfurylase (ATPS) is generating adenosine phosphosulfate. Next, adenosine phosphosulfate is reduced to SO_3^{2-} and finally to H_2S under use of four hydrogens (acting as an electron donor) by both APS reductase (APR) and the dissimilatory sulfite reductase (Dsr) (Kushkevych et al., 2020). The reduction of SO_4^{2-} to H_2S is the primary goal of sulfate-reducing bacteria and these microbes cannot survive without SO_4^{2-} (Barton et al., 2017). There are five genera in sulfate-reducing bacteria group, including *Desulfovibrio*, *Desulfobacter*, *Desulfomonas*, *Desulfobulbus* and *Desulfotomaculum* (Dordević et al., 2020). Most abundant human SO_4^{2-}-reducing microbe is *Desulfovibrio piger* DSM 749 (*D. piger*), which reduces SO_4^{2-} (but also sulfate ester and sulfonates) to generate H_2S with the use hydrogen, lactate or formate as electron donors, whereas lactate is most preferred substrate by *D. piger* (Marquet et al., 2009). Several other organic substances can act as electron donors such as short chain fatty acids, amino acids, ethanol and organic acids (Dordević et al., 2020). Rey et al. reported that two main sulfate-reducing bacteria are detected in human feces belonging to the *Desulfovibrio* class (*D. piger* and *D. intestinalis*). They found that increased gene expression of sulfatase (N-acetylglucosamine-6-sulfatase) in *Bacteroides* species correlates with higher proportional levels of *D. piger* and H_2S levels. A low-carbohydrate diet caused the host's mucus (e.g. chondroitin sulfate) to be degraded by *Bacteroides thetaiotaomicron (B. thetaiotaomicron)*, releasing SO_4^{2-} which is then used by *D. piger* (Rey et al., 2013).

3. Sulfur Metabolome of Human Stool

In human body, the most important sulfur-containing metabolites are the canonical amino acids Met and Cys. Met transsulfuration provides Cys, and Cys degradation provides SO_4^{2-} and taurine for conjugation of organic host or environmental substances. To get an in-depth look at the amount of sulfur-containing metabolites in the human body, we accessed two databases: the Human Metabolome Database (HMDB) and Human Fecal Metabolome (Karu et al., 2018, Wishart et al., 2018). According to the Human Metabolome Database (HMDB), 620 different sulfur-containing metabolites were detected, by taking the metabolite information collected in serum, urine, cerebrospinal fluid, saliva and feces into account (Wishart et al., 2018). We like to mention here that sulfur-containing metabolites are not only compounds that are part of sulfur metabolism, but they are usually found in human body, for example sulfated drugs or food-derived compounds. In this review, we want to focus on sulfur-containing metabolites detected in human feces. In fact, we selected sulfur-containing metabolites from the feces xml dataset from HMDB (total number of fecal metabolites = 6737, downloaded at 15.06.2020 from https://hmdb.ca/downloads), which resulted in 108 different sulfur-containing compounds (2 inorganic compounds were excluded), 29 volatile and 79 non-volatile compounds (Fig. 3A). Of note, in urine 509 metabolites were curated from HMDB, 471 in serum, 33 in cerebrospinal fluid and 37 in saliva. Afterwards, we performed a classification procedure of 108 fecal analytes, using ClassyFire (Djoumbou Feunang et al., 2016), which allows to get a more condense overview of the metabolites. With the help of the ClassyFire tool, it is possible to derive chemical taxonomies of metabolites, by using their InChIKey information. This classification procedure can result in up to 11 different levels, where we only took the class level for further exploration. The calculation results in 29 different classes of 108 fecal

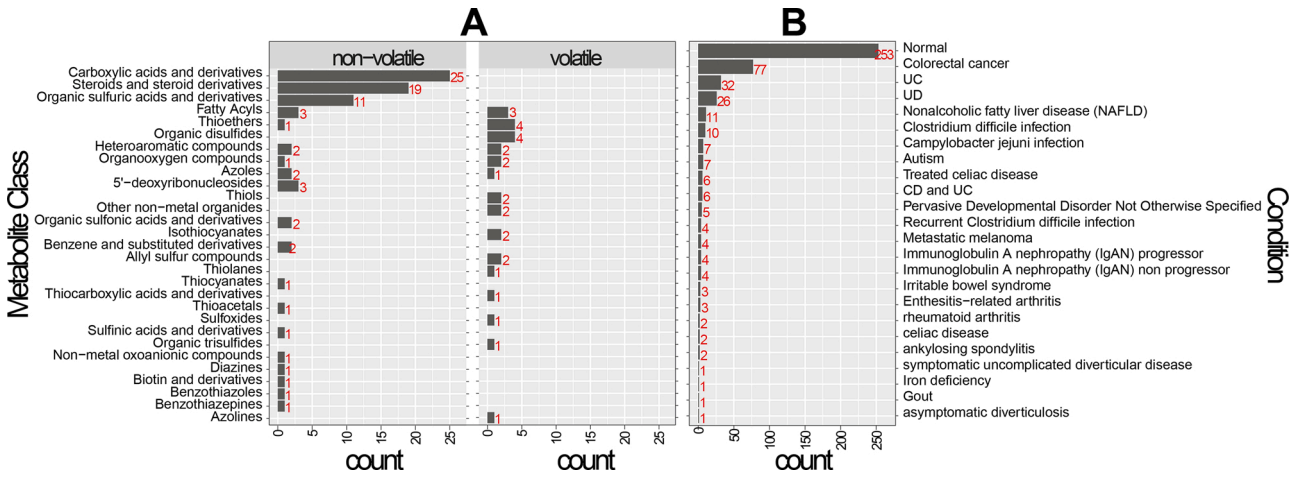

Fig. 3. Sulfur-containing metabolites in Human Fecal Metabolome database.
A: In total 108 sulfur-containing metabolites were reported in Human Metabolome Database and Human Fecal Metabolome database. Of those, 79 metabolites were non-volatile and 29 were of volatile nature. The compounds could be classified into 29 categories, whereas the class - Carboxylic acids and derivatives – has the highest count of metabolites, followed by Steroids and steroid derivatives and Organic sulfuric acids and derivatives.
B: In Human Fecal Metabolome database, most of the metabolites were described under normal conditions, directly followed by colorectal cancer, ulcerative colitis (UC) and Crohn's disease (CD).

metabolites (Fig. 3A). The class of carboxylic acids and derivatives, steroids and steroid derivatives, and organic sulfuric acids and derivatives have the highest count with more than 10 metabolites per class in the non-volatile group (Fig. 3A) and further details are listed in Table S1. Carboxylic acids and derivatives are mainly represented by amino acids and derivatives (14) as well as dipeptides (11) with units of Cys or Met (Table S1). Steroids and steroid derivatives consist of two subclasses including sulfated steroids (8) and bile acids, alcohols and derivatives (11). Organic sulfuric acids and derivatives are mainly composed of phenylsulfates (9) such as p-cresol sulfate, organic sulfuric acids and derivatives (1) and arylsulfates (1). The group of phenylsulfates contains metabolites of microbial degradation of aromatic amino acids, drugs or xenobiotics, and are usually urinary metabolites (Table S1). Several bile acids, Met, Cys (as cystine) and sulfated steroids are the earliest identified sulfur-containing metabolites, which were detected in human fecal sample material (Sheffner et al., 1948, Morohashi et al., 1961; Norman, 1964; Gustafsson et al., 1969, Tanida et al., 1981). Surprisingly, fecal concentrations of sulfur-containing metabolites are very sparsely collected in databases. The Human Fecal Metabolome has collected concentration values of 19 compounds (15 non-volatile, 4 volatile), mainly values of bile acids and two amino acids, Met and taurine. According to the Human Fecal Metabolome database, the most abundant sulfur-containing metabolites in human feces are Met, carbon disulfide and dimethyl sulfide. As mentioned above, earlier studies focused on the identification of certain classes or metabolites, present in human stool samples. A more holistic or comprehensive identification of sulfur-containing metabolites or their verification in new matrices such as human feces are tedious, and the identification of metabolites is also a more general problem in metabolomics (Peisl et al., 2018). But given the access to different chromatographic opportunities, detection techniques including mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy in metabolomics facilities, there should be an enormous potential. There are several approaches worth to mention such as stable isotope profiling, enzymatic or chemical hydrolysis or the generation of specific knockouts that can be performed in metabolomics-driven studies to unravel sulfur-containing metabolites. The use of stable isotopes of principal sulfur amino acids Met, Cys, or other important sulfur-containing compounds such as SO_4^{2-} or taurine (partly, fully or ^{34}S labelled) could be helpful, if available, to identify new metabolites, already applied in plant metabolomics (Giavalisco et al., 2011, Gläser et al., 2014). A high proportion of non-volatile fecal sulfur-containing metabolites are mostly conjugates of SO_4^{2-} or taurine, and an enzymatic or chemical hydrolysis could be a method of choice to derive identification of novel metabolites or verify known metabolites through their unconjugated form (Tanida et al., 1981). Ballet et al. identified 41 sulfate conjugated metabolites in five different human feces samples by using a promiscuous arylsulfatase from the snail *Helix pomatia* (Ballet et al., 2018). With this approach, several microbiota related metabolites were identified including *p*-cresyl sulfate, ferulic acid 4-sulfate, L-tyrosine-O-sulfate, phenyl sulfate and dihydroxybenzoate sulfate. Some of them (e.g. *p*-cresyl sulfate) were chemically synthetized and characterized with NMR spectroscopy (Ballet et al., 2018). Cell or organism-based experiments with knockouts of genes (related or unrelated to sulfur metabolism) could provide some insights into the regulation of metabolites or pathways by these genes. Comparative metabolomics performed in knock-out mice of fatty acid amide hydrolase enabled the identification of sulfur-containing lipid class – so called – N-acyl taurines (Saghatelian et al., 2004). This class was also observed in fecal samples of *db/db* mice, together with other sulfur-containing metabolites, determined by an *in silico* deconjugation of detected mass signals (Walker et al., 2014). Some of the annotated metabolites were also verified by MS/MS experiments. In LC–MS/MS based experiments, monitoring of specific fragments such as 124.0 (taurine), 79.9 (SO_3^-) or 96.9 (HSO_4^-) in negative electrospray ionization mode provides first hints of sulfate or taurine conjugates (Lafaye et al., 2004, Saghatelian et al., 2004; Ballet et al., 2018, Metwaly et al., 2020). Ideally, for the description of novel sulfur-containing metabolites a whole repertoire of identification and characterization steps should be performed as for example done for the determination of bacterial sulfonolipids (Walker et al., 2017). This include purification, determination of accurate mass by high resolution MS and their isotope pattern, tandem MS, in-depth analysis with NMR and synthesis. Recently, a microbial-derived metabolite, isocaproyltaurine was discovered by performing a comparative multi-omics approach. In fact, isocaproyltaurine was highly significant and increased in fecal samples of children with inflammatory bowel diseases and positively tested for *Clostridioides difficile* (Bushman et al., 2020). Besides, the pathogen could produce this taurine conjugate in-vitro, proving its microbial origin (Bushman et al., 2020).

3.1. Sulfur Metabolome in Inflammatory Bowel Diseases

We gathered information of most reported sulfur-containing metabolites in HMDB and the Human Fecal Metabolome databases. Most of them were described under normal conditions (healthy), followed by abnormal conditions (disease) such as colorectal cancer, ulcerative colitis and Crohn's disease (Fig. 3B). Under normal conditions, following metabolites including the essential amino acid Met, carbon disulfide, dimethyl trisulfide, dimethyl disulfide and taurine appeared at most (count>10) in Human Fecal Metabolome database. In the disease category, we like to focus on the role of sulfur metabolome in inflammatory bowel diseases (IBD). Crohn's disease (CD) and ulcerative colitis (UC) are the two principal types of IBD and are reflected by an imbalance of immune system and local inflammation in the gastrointestinal tract. Both CD and UC were associated with changes in the gut microbiota composition, metagenomes, metatranscriptomes and metabolomes (Franzosa et al., 2019a,b, Lloyd-Price et al., 2019a,b). Alterations in the metabolite levels or metabolomes could be investigated at different levels, regarding sample material (urine, plasma, feces or others), study subjects (children or adults), design (cross-sectional or longitudinal) or analytical tools (chromatography, ionization, detection). There are a multitude of techniques applied in the field of metabolomics research to study the pathology of IBD, in targeted or a not-targeted manner. One possibility is for example to analyze, volatile organic compounds in breath by selected ion flow tube MS (Hicks et al., 2015), or measuring highly abundant metabolites in urine with NMR spectroscopy (Stephens et al., 2013) or targeting specific pathways or metabolite classes in IBD such as tryptophan and its metabolites (Nikolaus et al., 2017). Since gut microbiota is one the suspects that may contribute to IBD pathology, profiling of microbiota derived metabolites could potentially provide valuable biomarkers or new targets for drug treatment or serve as potential drug candidates (Schirmer et al., 2019). Metabolites in stool were investigated in several IBD studies by performing a non-targeted metabolomics approach (Smirnov et al., 2016, Gallagher et al., 2020). Short chain fatty acids and amino acids were amongst others that seem to play a key role in IBD pathology and discrimination to healthy condition. With respect of sulfur-containing metabolites, we elaborated 39 studies (1990−02.2021, Web of Science and Google Scholar) that performed metabolomics studies in IBD patients, with the restriction that stool samples of humans (infants and adults) were analyzed and the name of the sulfur-containing metabolite is part of the main manuscript. Table 1 summarizes all human IBD studies that mentioned sulfur-containing metabolites in either healthy subjects, CD or UC patients or generally in IBD. Most (n = 27) of the studies used gas or liquid chromatography coupled to MS (GC- or LC–MS) to analyze fecal metabolome and sulfur-containing metabolites were only a small part of the analyzed compound lists. None of them focused on the determination of sulfur-containing metabolites in IBD, except the targeted analysis of H_2S by methylen blue method (Table 1). Interestingly, 11 metabolites listed in Table 1 could be mapped with cysteine and methionine metabolism of KEGG metabolic pathways, followed by sulfur metabolism (10 metabolites), biosynthesis of cofactors (6 metabolites) and primary bile acid biosynthesis (4 metabolites). Thirty-two metabolites could not be mapped into any metabolic pathways of KEGG (Kanehisa and Goto, 2000).

3.1.1. Non-volatile Sulfur-containing Metabolites in IBD

Taurine and Met are the most frequent metabolites, recorded in IBD studies, whereas taurine was mostly associated with UC pathology (Table 1). Primarily, taurine was reported to be significantly increased in IBD patients, consistently observed in different cross-sectional studies, which were conducted in adults or children with IBD (Le Gall et al., 2011, Bjerrum et al., 2015; Kolho et al., 2017; Franzosa et al., 2019a,b), in longitudinal (Lloyd-Price et al., 2019a,b, Bushman et al., 2020) or in intervention studies such as exclusive enteral nutrition in children or vagus nerve stimulation in adults (Alghamdi et al., 2018, Diederen et al., 2020; Sinniger et al., 2020). A few animal studies provide evidence for the protective effect of taurine in IBD (Son et al., 1998, Giriş et al., 2008; Zhao et al., 2008, Shimizu et al., 2009). The anti-oxidative and cyto-protective property of taurine may play an essential role in improving symptoms of IBD (Son et al., 1998, Bao et al., 2017). Rats treated with TNBS (2,4,6-trinitrobenzene sulphonic acid) serve as a model of human UC, in which taurine treatment significantly reduced colitis scores. Furthermore, taurine significantly reduced neutrophil myeloperoxidase, that is a sign of inflammation and malondialdehyde, which is a toxic product generated through oxidative stress. Two other rodent studies observed that taurine application improved several signs of inflammation, including body weight loss, diarrhea, colon shortening and decreased myeloperoxidase activity induced by dextran sodium sulfate (DSS) treatment as well as macrophage inflammatory protein 2 (Zhao et al., 2008, Shimizu et al., 2009).

Met was significantly altered in fecal water of CD subjects alongside two other sulfur-containing metabolites HomoCys and methionine sulfoxide (Meelu et al., 2014). Both amino acids Met and Cys were significantly increased in feces of pediatric CD patients, whereby patients received either anti-tumor necrosis factor therapy or dietary treatment (Ni et al., 2017). In another study of young Finnish patients, Met was significantly increased in UC patients compared to controls, CD or unclassified IBD, as well as four other sulfur-containing metabolites (Table 1) (Kolho et al., 2017). More recently, Met and several other molecules were increased in fecal samples of pediatric CD patients (Wang et al., 2021). Interestingly, Met-restricted diet decreased colitis score, myeloperoxidase activity, interleukin 1β and tumor-necrosis factor α in DSS treated mice, compared to the DSS control group. Also, they observed upregulated catalase, superoxide dismutase and glutathione peroxidase in colitis mice, fed a Met restricted diet (Liu, Yu et al. 2017). Others showed that bacterial Met residues of proteins are oxidized by myeloperoxidase of neutrophils to their respective Met sulfoxides and contribute thereof to the bacterial killing (Rosen et al., 2009). The metabolite Met sulfoxide appeared to be significantly associated with CD (summarized in Table 1), which is probably a degradation product of overexpressed and reactive myeloperoxidase in IBD (Hansberry et al., 2017).

Amongst others, the primary bile acid, taurocholic acid (TCA) was once reported to be increased in patients with ileal CD (Jansson et al., 2009), or in patients with UC (Kolho et al., 2017). TCA was not significantly affected in patients with primary sclerosing cholangitis with UC (90 % of patients), that underwent a fecal microbiota transplantation (Allegretti et al., 2019). In another study, TCA was increased in CD objects (Das et al., 2019). A significant enrichment of primary bile acids (TCA and taurochenodeoxycholic acid (TCDCA)) was observed in dysbiotic CD patients (Lloyd-Price et al., 2019a,b), in CD patients with ileocolonic resection (Fang et al., 2020) or pediatric CD (Wang et al., 2021). It is argued that the increased excretion of bile acids is caused by the inefficient uptake of bile acids in the ileum (distortion of enterohepatic recirculation) (Fitzpatrick and Jenabzadeh, 2020). Also, dietary input such as milk-fat, may increase TCA concentration in gut, which in turn trigger the bloom of microbes especially the abundance of *B. wadsworthia* and promoted colitis in mono-colonized germfree IL-$10^{-/-}$ mice. It is also interesting that *B. wadsworthia* is lacking bile salt hydrolases (BSH) to release taurine, but still H_2S production was observed in cultures, incubated with TCA (Devkota et al., 2012, Ridlon et al., 2016). Others showed that oral administration of another taurine-conjugated bile acid tauroursodeoxycholic, glycoursodeoxycholic or ursodeoxycholic could reduce the severity of colitis in mice, treated with DSS alone (Van den Bossche et al., 2017). However, ursodeoxycholic acid and cholic acid as well their taurine-conjugated derivatives are structurally quite different. Moreover, cholic acid is metabolized to deoxycholic acid, which is potentially toxic or carcinogenic (Jia et al., 2018) and cholic acid compared to ursodeoxycholic acid showed adverse side effects for example in treating primary biliary cirrhosis (Güldütuna et al., 1993). Furthermore, microbial BSHs could

Table 1
A summary of sulfur-containing metabolites, reported in metabolomics-driven studies of human IBD.

Sulfur-containing metabolites	Origin	Group	Technique	Study
Taurine Conjugated Bile Acids	Host/Microbe	CD & UC	GC-MS	(Ejderhamn et al., 1991)
Sulphated Bile acids	Host	NS		
Taurine Conjugated Bile Acids	Host/Microbe	UC	GC-MS	(Ejderhamn et al., 1992)
Sulphated Bile acids	Host	UC		
H_2S	Host/Microbe	UC	Infrared/GC	(Levine et al., 1998)
Methanethiol	Host/Microbe	NS		
Dimethyl sulfide	Microbe	NS		
H_2S	Host/Microbe	UC	Methylen Blue Method	(Pitcher et al., 2000)
Cysteine	Food	NS	NMR	(Marchesi et al., 2007)
Carbon disulfide	Microbe	H	GC-MS	(Garner et al., 2007)
Dimethyl sulfide	Microbe	H		
Dimethyl disulfide	Microbe	H		
Dimethyl trisulfide	Microbe	H		
Methanethiol	Host/Microbe	H		
Dimethyl sulfoxide	Host	H		
Methyl (methylthiol) methyl disulfide	Food	H		
H_2S	Host/Microbe	H		
Allyl isothiocyanate	Food	H		
12 minor sulfur-containing volatiles (less than 20 %)	Mostly Food	H/UC		
Taurocholic acid	Host	Ileal CD	FT-ICR-MS	(Jansson et al., 2009)
Taurine	Host	UC	NMR	(Le Gall et al., 2011)
Sulphated Bile acids	Host	Active IBD	LC-MS	(Duboc et al., 2013)
Lithocholic acid 3-sulfate	Host/Microbe	Active IBD		
S-methyl 3-methylbutanethioate	Food	CD	GC-MS	(Ahmed et al., 2013)
Dimethyl disulfide	Microbe	CD	GC-MS	(Walton et al., 2013)
Dimethyl sulfide	Microbe	H	GC-MS	(De Preter et al., 2013)
Methyl propyl disulfide	Food	H		
Carbon disulfide	Microbe	CD		
Methyl 2-propenyl disulfide	Food	H		
Methanethiol	Host/Microbe	H		
H_2S	Host/Microbe	CD		
H_2S	Host/Microbe	CD	Methylen Blue Method	(Gerasimidis et al., 2014)
Methionine sulfoxide	Food	CD	LC-MS	(Meelu et al., 2014)
Homocysteine	Host	CD		
Methionine	Food	CD		
Taurine	Host	UC	NMR	(Bjerrum et al., 2015)
Dimethyl sulfide	Microbe	H	GC-MS	(De Preter et al., 2015)
Methyl propyl disulfide	Food	H		
Methyl 2-propenyl disulfide	Food	H		
Carbon disulfide	Microbe	CD		
3,4-dimethylthiophene	Food	H		
3-methyl thiophene	Food	UC		
2,4-Dithiapentane	Food	UC		
Methanethiol	Host/Microbe	H		
Thiocyanic acid	Microbe	UC		
Dimethyl disulfide	Microbe	H		
Dimethyl trisulfide	Microbe	H		
Methanethiol	Host/Microbe	H	GC-MS	(Ahmed et al., 2016)
Carbon disulfide	Microbe	Inactive UC		
Dimethyl disulfide	Microbe	Inactive UC		
Dimethyl trisulfide	Microbe	H		
8-[(Aminomethyl)sulfanyl]-6-sulfanyloctanoic acid	Host	H (Iron deficiency)	FT-ICR-MS	(Lee et al., 2017)
Chenodeoxycholic acid sulfate	Host	CD	LC-MS	(Jacobs et al., 2016)
3-sulfodeoxycholic acid	Host/Microbe	CD		
Taurine	Host	IBD		
Taurochenodeoxycholic acid	Host	CD		
Homocystine	Host	CD	LC-MS	(Ni et al., 2017)
Cysteine	Food	CD		
Methionine sulfoxide	Food	CD		
Methionine	Food	CD		
Methionine	Food	UC	LC-MS	(Kolho et al., 2017)
Cystathionine	Host	UC		
Taurine	Host	UC		
Taurocholic acid	Host	UC		
Taurochenodeoxycholic acid	Host	UC		
gamma-glutamylcysteine	Host	CD		
Methionine	Food	NS	IEC-UV	(Bosch et al., 2018)
Taurine	Host	CD	LC-MS	(Alghamdi et al., 2018)
Thiamine	Food	H	LC-MS	(Franzosa et al., 2019a)
Taurine	Host	CD		
Taurine	Host	IBD	LC-MS	(Lloyd-Price et al., 2019a)
Taurocholic acid	Host	Dysbiotic CD		
Taurochenodeoxycholic acid	Host	Dysbiotic CD		
Biotin	Food/Microbe	UC and UC with succesful FMT	LC-MS	(Paramsothy et al., 2019)

(*continued on next page*)

Table 1 (*continued*)

Sulfur-containing metabolites	Origin	Group	Technique	Study
Tauro β-muricholic acid	Host	NS of FMT in PSC with UC	LC-MS	(Allegretti et al., 2019)
Taurochenodeoxycholic acid	Host	NS of FMT in PSC with UC		
Taurocholic acid	Host	NS of FMT in PSC with UC		
Taurodeoxycholic acid	Host/Microbe	NS of FMT in PSC with UC		
Taurolithocholic acid	Host/Microbe	NS of FMT in PSC with UC		
3-methyl-thiopropionic acid	Host	Non-remitted IBD	LC-MS	(Aden et al., 2019)
Methyl 2-(methylthio)acetate	Food	Non-remitted IBD		
Taurocholic acid	Host	CD	LC-MS	(Das et al., 2019)
Taurochenodeoxycholic acid	Host	CD		
Taurodeoxycholic acid	Host/Microbe	CD		
Taurolithocholic acid	Host/Microbe	NS		
Tauroursodeoxycholic acid	Host/Microbe	NS		
Taurolithocholic acid	Host/Microbe	H	GC-MS&LC-MS	(Weng et al., 2019)
Taurine	Host	CD	NMR	(Sinniger et al., 2020)
Methionine	Food	NS	NMR	(Mackner et al., 2020)
Taurocholic acid	Host	NS in CD and EEN	LC-MS	(Connors et al., 2020)
Taurochenodeoxycholic acid	Host	NS in CD and EEN		
Taurodeoxycholic acid	Host/Microbe	NS in CD and EEN		
Taurolithocholic acid	Host/Microbe	NS in CD and EEN		
Tauroursodeoxycholic acid	Host/Microbe	NS in CD and EEN		
Nineteen sulfate-containing metabolites	Diverse	Active CD (pre- and post-HSCT)	LC-MS	(Metwaly et al., 2020)
Eleven sulfate-containing metabolites	Diverse	Inactive CD (post-HSCT)		
O-sulfo-L-tyrosine	Host	IBD	LC-MS	(Bushman et al., 2020)
Taurine	Host	IBD with CDI		
3-sulfo-L-alanine	Host	IBD with CDI		
N-acetyltaurine	Host	IBD with CDI		
Ergothioneine	Food	IBD with CDI		
Hypotaurine	Host	IBD with CDI		
N-palmitoyltaurine	Host	IBD with CDI		
N-oleoyltaurine	Host	IBD with CDI		
Isocaproyltaurine	Microbe	IBD with CDI		
Taurocholic acid	Host	CD with ileocolonic resection	LC-MS	(Fang et al., 2020)
Tauroursodeoxycholic acid	Host/Microbe	CD with ileocolonic resection		
Taurine	Host	NS	LC-Fluorescence	(Diederen et al., 2020)
Methionine	Food	CD		
Ursocholanic acid conjugated to sulfate and taurine	Unknown	CD/UC Responder	LC-MS	(Ding et al., 2020)
Unknown BA conjugated to sulfate and taurine	Unknown	CD/UC Non-responder		
Diketo-chenodeoxycholic acid isomer conjugated to taurine	Unknown	CD/UC Responder		
L-Cystine	Food	NS	LC-MS	(Wang et al., 2021)
Methionine	Food	CD		
Taurochenodeoxycholic acid	Host	CD		
Taurocholic acid	Host	CD		
Tauro-α-muricholic acid	Host	NS		

Abbreviation: Ulcerative colitis (UC); Healthy Controls (H); Crohn's disease (CD); Primary Sclerosing Cholangitis (PSC); Fecal Microbiota Transfer (FMT); Not Significant (NS); Inflammatory Bowel Diseases (IBD); Hematopoietic Stem Cell Transplantation (HSCT), Exclusive enteral nutrition (EEN); *Clostridioides difficile* Infection (CDI).

alter bile acid pool or individual bile acid profiles in IBD. Increased BSH activity was observed in DSS treated mice, especially for BSHs within Bacteroidetes phylum, together with increased ratios of deconjugated to taurine-conjugated bile acids (Parasar et al., 2019).

3.1.2. *Sulfur-containing Volatiles in IBD*

Sulfur-containing volatiles such as H_2S, carbon disulfide, dimethyl disulfide or the Met degradation product – methanethiol – were also reported in the context of IBD, summarized in Table 1. The gasotransmitter H_2S frequently appeared to be significantly increased in UC patients and its role in IBD is discussed elsewhere in more detail (Singh and Lin, 2015). Methanethiol was mostly significantly increased in healthy controls, whereas for dimethyl disulfide and carbon disulfide no consistent group pattern was observed (Table 1). A general reduction of sulfur compounds was found by De Preter et al., whereby carbon disulfide was significantly increased in CD patients, and methanethiol and dimethyl disulfide were significantly increased in healthy subjects (De Preter et al., 2015). These volatiles are most likely of bacterial origin and are degradation products of sulfur amino acid rich proteins or free sulfur amino acids (Walton et al., 2013). Dimethyl sulfide, dimethyl disulfide or dimethyl trisulfide are either endogenous, microbial or non-enzymatic degradation products of Met metabolism (Hayward et al., 1977, Walton et al., 2013, He and Slupsky, 2014). Gram-negative anaerobic bacteria produce volatile sulfur compounds, whereas H_2S, methanethiol and dimethyl sulfide are major components of bacterial metabolism (Nani et al., 2017). Dimethyl sulfide is also one of the important sulfur-containing metabolites, reported in IBD studies (Table 1), and mostly increased in healthy controls. Some common human oral bacteria are able to produce volatile sulfur compounds. Using Met as a substrate, *Campylobacter ureolyticus*, *Porphyromonas gingivalis*, *Fusobacterium nucleatum* and *Prevotella intermedia* produced large amounts of methanethiol (>1000 parts per billion), whereas Cys incubation with the aforementioned bacteria resulted in higher H_2S production (Salako and Philip, 2011). Although, the bacteria tested originated from oral cavity, *Fusobacterium nucleatum* is also a member of gut microbiota and its presence is linked to colorectal cancer (Castellarin et al., 2012). Carbon disulfide is either derived from microbial metabolism or is an anthropogenic product of industrial processes. Also, carbon disulfide is synthetized from sulfur amino acids (Smeulders et al., 2013). Several sulfur compounds including H_2S, methanethiol and mercaptoacetate damaged colonocytes, whereby H_2S has the strongest impact and significantly decreased butyrate production in the colon (Roediger et al., 1993). To overcome the toxic effects and tissue damage through H_2S or methanethiol, there is a protective oxidation pathway in cecal and colonic mucosa, which utilize both substances to generate thiosulfate (Furne et al., 2001). Colonic and fecal thiosulfate is shown to

be increased in a colitis mouse model, which is not ascribed to the degradation of SO_4^{2-} moiety of DSS (Daeffler et al., 2017). Additionally, reactive oxygen species generated under inflammatory conditions oxidize thiosulfate to tetrathionate, which is then used as an electron acceptor under anaerobic conditions. This allows the outgrowth of *Salmonella enterica* serotype Typhimurium which induces acute gut inflammation in a mouse model (Winter et al., 2010).

4. The Interplay between Sulfur-containing Metabolites, Sulfur Metabolism in Bacteria and IBD

Metabolomics-driven studies revealed an important association between sulfur-containing metabolites and IBD, and most of them were increased in IBD patients (Table 1). There is a strong shift towards higher excretion of sulfur-containing metabolites in stool of IBD patients, hinting towards a dysmetabolism (Duboc et al., 2013). These differences can be due to a changes in intake (food/diet), metabolism (host or bacteria) or de-novo synthesis (host or bacteria). Their individual contribution to the fecal metabolome imbalances observed in IBD is generally difficult to rule out, without performing other experiments, such as correlation to dietary intake or gut microbial community patterns. A simplified scheme is shown in Fig. 4, which illustrates the link between several sulfur-containing metabolites, sulfur metabolism and bacteria in IBD. The increase in taurine-conjugated bile acids (TCA and TCDCA) may be explained by the diet but also by a reduced activity of BSH. Recently, fecal BSH activity was found to be significantly reduced in active IBD (Kostic et al., 2014, Khodakivskyi et al., 2021). In general, bacteria within the Firmicutes phylum are the most dominant bile acid hydrolyzers in human gut (Jones et al., 2008). A depletion of Firmicutes phylum was already observed in several IBD studies, with most prominent reduction in the bile-sensitive *Faecalibacterium prausnitzii* (Lopez-Siles et al., 2012, Kostic et al., 2014). In detail, BSHs are distributed amongst several gut microbial genera, including *Bacillus*, *Staphylococcus*, *Enterococcus*, *Lactobacillus, Clostridium*, *Bifidobacterium* or *Bacteroides*, whereas highest enzyme activity was found for *Lactobacillus* (Song et al., 2019). Consistent with increased taurine-conjugated bile acids, several BSH positive genera are decreased in IBD, especially in CD (Kostic et al., 2014, Das et al., 2019). Interestingly, despite reduced hydrolysis of bile acids, still higher levels of taurine are reported in all studies. This indicates that deconjugation is not the primary source of taurine pool in the gut. Dietary Met and Cys could promote the endogenous production of taurine, which may be simply produced to remove excess levels of both amino acids in the gut. Nevertheless, high amounts of taurine as a substrate in the gut could facilitate its microbial degradation. This results in the production of SO_3^{2-}, which is passed into dissimilatory sulfate reduction pathway with the synthesis of H_2S (Fig. 4). *B. wadsworthia* and *E. coli* are two common taurine users and *E. coli* is also increased in human IBD (Uria-Nickelsen et al., 1993, Laue et al., 1997a,b, Lloyd-Price et al., 2019a,b). The end-product of bacterial Cys degradation is H_2S and there are several studies providing evidence of altered Cys metabolism in IBD. Both, an elevated L-cysteine desulfidase and dissimilatory sulfite reductase alpha subunit from *Bilophila* were reported in a treatment-naïve pediatric IBD cohort (Zhang et al., 2018). Along with this finding, there was also significant contribution of other Cys metabolism proteins, including 8 aspartate aminotransferase and 6 malate dehydrogenase proteins. These enzymes are catalyzing the degradation of cysteic acid to 3-sulfopyruvic acid and (2R)-3-sulfolactic acid. Most of them were increased in IBD, and were assigned to different genera such as *Bacteroides*, *Prevotella*, *Alistipes*, *Akkermansia* and *Enterobacter* (Zhang et al., 2018). Consistent with elevated Met and Cys in stool samples of IBD patients, different gut microbial pathways were characterized in IBD patients, with prominent increase of *Cysteine and Methionine metabolism*, *Sulfur metabolism*, *Sulfate transport system* and *Cysteine metabolic process*, and some of them were even greater increased in ileal CD (Morgan et al., 2012). As implicated above, Cys degrading bacteria are distributed among the common colonic genera, including *Streptococcus*, *Prevotella*, *Fusobacterium*, *Clostridium*, *Enterobacter, Klebsiella* and *Desulfovibrio* (Carbonero et al., 2012). *Fusobacterium*, *Prevotella* and *Streptococcus* correlated strongly with CD severity, but no evidence of the involvement of sulfate-reducing bacteria in CD was observed (Mottawea et al., 2016). Additionally, components of the mitochondrial H_2S detoxification complex were significantly reduced in CD patients (Mottawea et al., 2016). Interestingly, *E. coli* is repeatedly associated with IBD pathology and is capable to metabolize Cys (Schirmer et al., 2019). Hence, the microbial Cysteine desulfhydrase was also described in *E.coli*, a study of its activity in IBD subjects would be of great interest, and its contribution to the H_2S pool. Taken together, elevated presence of sulfur-containing metabolites in IBD could favor certain microbial communities and drive them towards sulfur metabolism and ultimately enhanced H_2S production.

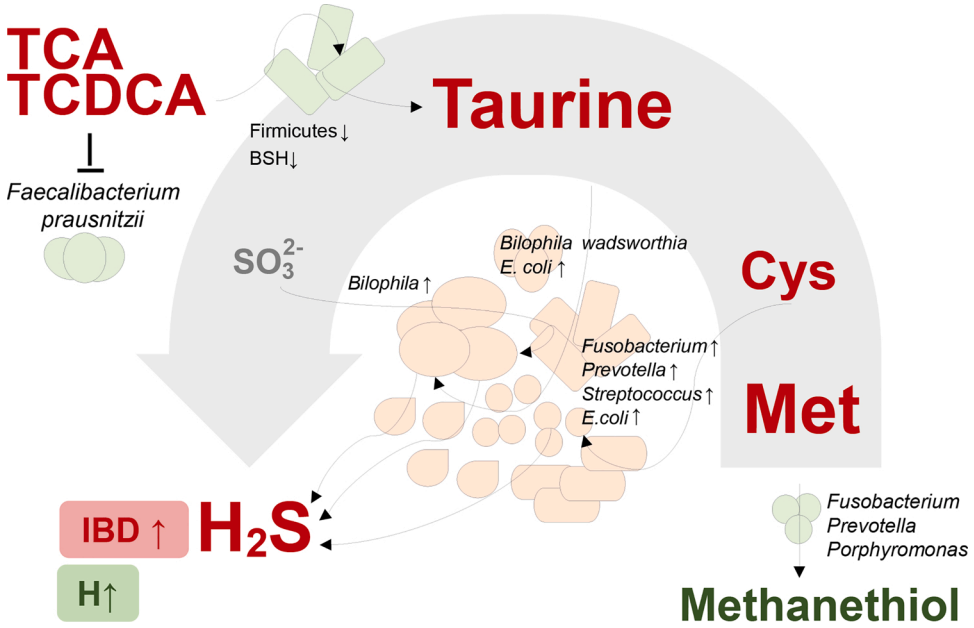

Fig. 4. An illustrative summary of the interplay between sulfur-containing metabolites, gut bacteria and IBD.
The figure shows IBD-relevant sulfur-containing metabolites, including taurine, taurine-conjugated bile acids, Met, Cys and H_2S; TCA (taurocholic acid), TCDCA (taurochenodeoxycholic acid), BSH (Bile salt hydrolase), H_2S (hydrogen sulfide), SO_3^{2-} (sulfite), Cys (cysteine), Met (methionine), H (Healthy Controls), Inflammatory Bowel Disease (IBD).

5. Summary and Conclusion

In this review, we attempt to describe the role of sulfur-containing metabolites in human body, with specific focus on intestinal metabolome and inflammatory bowel diseases. The sulfur amino acid Cys plays an important role and its metabolism results in the synthesis of taurine and sulfate and H_2S. However, the human fecal metabolome does not only contain metabolites of Cys degradation. A total number of 108 different sulfur-containing metabolites were detected in human fecal metabolome. Metabolomics-driven studies reported about 50 different sulfur-containing metabolites altered between healthy controls and patients with inflammatory bowel diseases, but none of the studies focused on the sole determination of sulfur-containing metabolites in this disease. In addition, the capture of full metabolic pathways was absent and only small parts of sulfur metabolism were analyzed. Despite this, taurine, methionine, TCA, TCDCA, H_2S and methanethiol appeared to have an important role in inflammatory bowel diseases. Except methanethiol, all metabolites were significantly increased in stool samples of IBD patients, suffering either from UC or CD, whereas methanethiol was increased in healthy subjects. The presence of sulfidogenic bacteria such as *B. wadsworthia* or *E. coli* could benefit from the vast abundance of sulfur-containing metabolites in IBD, resulting in increased H_2S production. Interestingly, mouse studies indicate a protective effect of some sulfur-containing metabolites such as taurine. There is big lack of comparability in metabolomics-driven studies, because only a small fraction of the studies provide fecal metabolite concentration values, and often statistical analysis relies on relative data derived from MS or NMR analysis. Also, metabolomics studies suffer from descriptive and associative nature, providing less evidence of direct involvement of sulfur-containing metabolites in IBD. Still, there is an enormous potential to establish metabolite biomarkers with the goal to improve and facilitate IBD diagnosis, hence metabolomics studies deliver a series of sulfur-containing metabolites that were consistently altered in IBD.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijmm.2021.151513.

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