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Sulfur-Element containing metabolic pathways in human health and crosstalk with the microbiome

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A B S T R A C T

In humans, methionine derived from dietary proteins is necessary for cellular homeostasis and regeneration of sulfur containing pathways, which produce inorganic sulfur species (ISS) along with essential organic sulfur compounds (OSC). In recent years, inorganic sulfur species have gained attention as key players in the crosstalk of human health and the gut microbiome. Endogenously, ISS includes hydrogen sulfide (H_2S), sulfite (SO_3^{2-}), thiosulfate ($S_2O_3^{2-}$), and sulfate (SO_4^{2-}), which are produced by enzymes in the transsulfuration and sulfur oxidation pathways. Additionally, sulfate-reducing bacteria (SRB) in the gut lumen are notable H_2S producers which can contribute to the ISS pools of the human host. In this review, we will focus on the systemic effects of sulfur in biological pathways, describe the contrasting mechanisms of sulfurylation versus phosphorylation on the hydroxyl of serine/threonine and tyrosine residues of proteins in post-translational modifications, and the role of the gut microbiome in human sulfur metabolism.

1. Introduction

Sulfur is among the most biologically abundant elements in the human body with functions including cellular signaling, detoxification of free radicals, structural support, and assisting in energy production [1–5]. Sulfur pools in the human body are vast and include both inorganic sulfur species (ISS) as well as critical organic sulfur-containing compounds (OSCs). In humans, sulfur pools (ISS and OSC) are maintained mainly through dietary intake of methionine along with adequate B-vitamins (B1, B2, B3, B5, B6, B7, B9, B12), and trace elements zinc, nickel, molybdenum, cobalt, potassium, magnesium, iron, calcium, and sodium (Table 1) [6,7]. Methionine is an essential regulator of human sulfur pools through its direct regeneration of universal methyl donor s-adenosyl-L-methionine (SAM) and homocysteine, which replenish cysteine concentrations during the fed-state through the transsulfuration pathway [4]. While cysteine is considered a conditionally essential amino acid, it is the rate-limiting amino acid in the synthesis of glutathione, coenzyme A, iron-clusters, taurine, and tertiary proteins, all of which are considered OSCs because they contain sulfur [4]. As a product of sulfur pathways, ISS are commonly produced and include hydrogen sulfide (H_2S), sulfite (SO_3^{2-}), thiosulfate ($S_2O_3^{2-}$), and sulfate (SO_4^{2-}). Additionally, microbiota residing in the human gut-microbiome are major contributors and regulators of sulfur pools in the body. Through the sulfate reduction pathways of sulfur-reducing bacteria energy is not only extracted for the microorganism, but hydrogen sulfide is produced. In general, microbiota found in the gut-microbiome favor ISS reduction while human metabolic processes favor ISS oxidation to sulfate for its activation to 3′-phosphoadenosine 5′-phosphate (PAPS) and numerous sulfonation/sulfurylation reactions [8–18]. The purpose of this review, is to focus on the systemic effects of sulfur (ISS and OSC) in biological pathways and the role of the gut microbiome in human sulfur metabolism.

2. Inorganic sulfur species – hydrogen sulfide (H_2S)

Among the most remarkable distinctions between sulfur and oxygen is the range of accessible oxidation states available for sulfur biology [19,20] (Fig. 1). The oxidation states of inorganic sulfur species found in the human body include hydrogen sulfide (H_2S) at −2, thiosulfate ($S_2O_3^{2-}$) at +2, sulfite (SO_3^{2-}) at +4, and sulfate (SO_4^{2-}) at +6. Compared to oxygen, sulfur contains an available d-orbital for bond formation, has a larger radius, and is less electronegative (2.58 for sulfur, compared to oxygen at 3.44 on the Pauling scale). While the redox potential for H_2O reduction is strongly positive (+0.82 V), the redox potential for H_2S is more negative (−0.27 V). This redox potential of H_2S is in the same range as NADH and $FADH_2$ (−0.32 V and −0.20 V, respectively), which likely contributes to its ability to carry electrons and detoxify free radicals [1]. Additionally, H_2S has a pKa_1 of close to 7, which is near the physiological pH, which is significant as fluctuating H_2S and HS^- anions have different physiological functions and properties allowing sulfur compounds to determine the cellular redox potential, regulate metabolic pathways, and react to oxidative stress [21]. Notably, the ionized HS^- is

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Table 1
Enzymes in sulfur metabolism pathways described in this review. Additional information obtained from The Human Protein Atlas.

ID	GENE	NAME	CHROMOSOME	EC	COFACTOR/COENZYME	TISSUE RNA EXPRESSION (nTPM)
ENSG00000181915	ADO	2-aminoethanethiol dioxygenase	10	1.13.11.19	Nickel (Ni2+) Fe2+	Testes - 40 Brain - 30 Tongue - 20
ENSG00000101444	AHCY (SAHH)	Adenosylhomocysteinase	20	3.3.1.1	NAD + open, NADH closed	Liver - 180, Kidney (Proximal Tubule) - 160, Pancreas - 160, most tissue
ENSG00000119689	α-KGDHC - DLST	α-ketoglutarate dehydrogenase complex	14	1.2.4.2	TPP (vitamin B1) Mg2+	Tongue - 230 Muscle - 150 Kidney - 100
ENSG00000145692	BHMT	betaine-homocysteine S-methyltransferase	5	2.1.1.5	Zinc (Zn2+) Potassium (K+)	Liver (hepatocytes) - 1150 Kidney (proxima tubule) - 770
ENSG00000132840	BHMT2	betaine-homocysteine S-methyltransferase 2	5	2.1.1.5	Zinc (Zn2+) Potassium (K+)	Liver - 430 Kidney - 333
ENSG00000160200	CBS	Cystathionine beta-synthase	21	4.2.1.22	Heme (Fe2+) Pyridoxal-5-phosphate (PLP)	Liver - 175 Pancreas - 100
ENSG00000129596	CDO1	Cysteine dioxygenase type 1	5	1.13.11.20	Iron (II)	Liver - 500 Adipose - 120
ENSG00000016391	CHDH	Choline dehydrogenase	3	1.1.99.1	FAD+	Liver - 40 Kidney - 40
ENSG00000068120	COASY	Coenzyme A synthase	17	PPAT - 2.7.7.3 DPCK - 2.7.1.24	ATP Magnesium (Mg2+)	Liver - 70 Adrenals - 60
ENSG00000139631	CSAD	Cysteine sulfinic acid decarboxylase	12	4.1.1.29	Heme (Fe2+) Pyridoxal-5-phosphate (PLP)	Liver - 100 Adipose - 70
ENSG00000116761	CTH - CSE - CGL	Cystathionine gamma-lyase	1	4.4.1.1	Heme (Fe2+) Pyridoxal-5-phosphate (PLP)	Liver - 120 Ovary - 35
ENSG00000228716	DHFR	Dihydrofolate reductase 1	5	1.5.1.3	NADP+	Liver - 60 Thymus - 60 Bone Marrow - 60 Tonsils/lymph nodes - 40
ENSG00000178700	DHFR2	Dihydrofolate reductase 2	3	1.5.1.3	NADP+	Ovary - 10 Endometrium - 8 Liver - 7
ENSG00000102967	DHODH	Dihydroorotate dehydrogenase (quinone)	16	1.3.5.2	FAD+	Liver (hepatocytes) - 100
ENSG00000132837	DMGDH	Dimethylglycine dehydrogenase	5	1.5.99.2	FAD+	Liver - 300 kidney - 170
ENSG00000105755	ETHE1/PDO	“ethylmalonic encephalopathy 1 protein” and “per sulfide dioxygenase"	19	1.13.11.18	Iron (Fe2+)	Colon - 260 Rectum - 230
ENSG00000010932	FMO1	Flavin containing dimethylaniline monoxygenase 1	1	1.14.13.8	FAD+ NADP+	Kidney (Proximal Tubule) - 200
ENSG00000094963	FMO2	Flavin containing dimethylaniline monoxygenase 2	1	1.14.13.8	FAD + NADPH Magnesium (Mg2+)	Lung - 100 Adipose - 70 Esophagus - 70 Muscle - 60
ENSG00000007933	FMO3	Flavin containing dimethylaniline monoxygenase 3	1	1.14.13.8	FAD+ NADP+	Liver - 1120
ENSG00000076258	FMO4	Flavin containing dimethylaniline monoxygenase 4	1	1.14.13.8	FAD+ NADP+	Liver - 70 Kideny - 50
ENSG00000131781	FMO5	Flavin containing dimethylaniline monoxygenase 5	1	1.14.13.8	FAD+ NADP+	Liver - 700
ENSG00000165060	FXN	Frataxin	9	1.16.3.1	Iron (Fe2+)	Liver - 46 Bone Marrow - 30 Muscle - 25
ENSG00000001084	y-GCS - GCLC	Glutamate-cysteine ligase	6	6.3.2.2	ATP Magnesium (Mg2+)	Liver - 150 Bladder - 60 Fallopian Tubes - 60
ENSG00000120053	GOT1 - CAT1 - AST1	Aspartate aminotransferase 1	10	2.6.1.3	Pyridoxal 5′-phosphate (PLP)	Tongue - 1010 Heart - 560 Muscle - 500 Liver - 370 Kidney - 140
ENSG00000125166	GOT2 - CAT2 - AST2	Aspartate aminotransferase 2	16	2.6.1.3	Pyridoxal 5′-phosphate (PLP)	Tongue - 730 Skeletal muscle - 700 Liver - 320 Heart - 310
ENSG00000100983	GSS	Glutathione synthetase	20	6.3.2.3	ATP Magnesium (Mg2+)	Testis - 70 Liver - 45

(*continued on next page*)

Table 1 (*continued*)

ID	GENE	NAME	CHROMOSOME	EC	COFACTOR/COENZYME	TISSUE RNA EXPRESSION (nTPM)
						Kidney - 45 GI - 40 Skin - 30 Brain - 20
ENSG00000151224	MAT1A	Methionine adenosyltransferase 1A	10	2.5.1.6	ATP Magnessium (Mg2+) Potassium (K+)	Liver (hepatocytes) - 1400
ENSG00000168906	MAT2A	Methionine adenosyltransferase 2A	2	2.5.1.6	ATP Magnessium (Mg2+) Potassium (K+)	Pancreas - 900 Thyroid - 400 Brain White Matter - 300
ENSG00000038274	MAT2B	Methionine adenosyltransferase 2B	5	2.5.1.7	NADP+	Nonspecific - 100 (Kidney, duodenum, lymph)
ENSG00000128309	MPST, TST2	Mercaptopyruvate sulfurtransferase	22	2.8.1.2	Zinc (Zn2+)	Liver - 400 GI TRACT - 100
ENSG00000177000	MTHFR	Methylenetetrahydrofolate reductase	1	1.5.1.20	FAD+ NADP+	Epidydemis - 60 Bone - 30
ENSG00000116984	MTR	Methionine synthase	1	2.1.1.13	B12 Zinc (Zn2+) Cobalt (Co3+)	Parathyroid - 30 Muscle - 20 Cardiomyocytes - 20
ENSG00000124275	MTRR	5-methyltetrahydrofolate-homocysteine methyltransferase reductase	5	2.1.1.3	FAD+, NADP+	Parathyroid - 20 Tongue 20 Muscle - 16
ENSG00000152782	PANK1	Pantothenate kinase 1	10	2.7.1.33	ATP Magnesium (Mg2+)	Liver - 110 Kidney - 40 Tongue - 30 GI-tract - 20
ENSG00000125779	PANK2	Pantothenate kinase 2	20	2.7.1.33	ATP Magnesium (Mg2+)	Testis - 25 Tonsils - 20 Bone Marrow - 20 Esophagus - 20
ENSG00000120137	PANK3	Pantothenate kinase 3	5	2.7.1.33	ATP Magnesium (Mg2+)	Liver - 40 GI Tract - 30 Breast - 25
ENSG00000157881	PANK4	Pantothenate kinase 4	1	2.7.1.33	ATP, Maganase (Mn2+), Nickel (Ni2+), Cobalt (Co2+)	Skeletal Muscle - 35 Heart - 20 Tongue - 20
ENSG00000138801	PAPSS1	3′-phosphoadenosine 5′-phosphosulfate synthase 1	4	ATPS - 2.7.7.4, APSK - 2.7.1.25	ATP, Magnesium (Mg2+)	Brain - 65 Salvilary gland - 65 Stomach - 60 Skin - 50
ENSG00000198682	PAPSS2	3′-phosphoadenosine 5′-phosphosulfate synthase 2	10	ATPS - 2.7.7.4 , APSK - 2.7.1.25	ATP, Magnesium (Mg2+)	Adrenal - 135 Liver - 80 Colon - 80 Lung - 70 Placenta - 60
ENSG00000138621	PPCDC	Propionyl-CoA decarboxylase, alpha subunit	15	4.1.1.36	Coenzyme A, FMN	Parathyroid - 20 Bone Marrow - 20 Adrenal - 20 Esophagus - 20
ENSG00000127125	PPCS	Propionyl-CoA synthase	1	6.3.2.51	B5, ATP, Magnesium (Mg2+)	Liver - 100 Kidney - 90 Pancreas - 70 Testis - 70
ENSG00000123453	SARDH	Sarcosine dehydratase	9	1.5.8.3	FAD+, Pyridoxal-5-phosphate (PLP)	Liver - 115 Pancreas - 40 Testis - 40
ENSG00000073578	SDHA	Succinate dehydrogenase complex, subunit A	5	1.3.5.1	FAD+	Heart - 600 Skeletal muscle - 480 Liver - 250
ENSG00000117118	SDHB	Succinate dehydrogenase complex, subunit B	1	1.3.5.1	Iron–Sulfur [Fe–S]	Tongue - 580 Skeletal muscle - 500 Liver - 310
ENSG00000143252	SDHC	Succinate dehydrogenase complex, subunit C	1	1.3.5.1	Iron–Sulfur [Fe–S]	Liver - 300 Tongue - 280 Kidney - 280 Skeletal muscle - 280
ENSG00000204370	SDHD	Succinate dehydrogenase complex, subunit D	11	1.3.5.1	Iron–Sulfur [Fe–S], Heme	Tongue - 450 Liver - 350 Skeletal muscle - 330 Kidney - 320
ENSG00000176974	SHMT1	Serine hydroxymethyltransferase 1	17	2.1.2.1	Pyridoxal-5-phosphate (PLP)	Liver- 400 Kidney - 170
ENSG00000182199	SHMT2	Serine hydroxymethyltransferase 2	12	2.1.2.1	Pyridoxal-5-phosphate (PLP)	Liver - 180 Pancreas - 60

(*continued on next page*)

Table 1 (*continued*)

ID	GENE	NAME	CHROMOSOME	EC	COFACTOR/COENZYME	TISSUE RNA EXPRESSION (nTPM)
ENSG00000081800	SLC13A1	Solute carrier family 13 member A1	7	NA	Sodium (Na+)	Kidney (Proximal Tubule) - 80
ENSG00000145217	SLC26A1	Solute carrier family 26 member 1	4	NA	NA	Liver - 18 Adrenals - 10
ENSG00000155850	SLC26A2 - DTDST	diastrophic dysplasia sulfate transporter	5	NA	NA	Colon - 210 Rectum - 200
ENSG00000137767	SQOR	Sulfide quinone oxidoreductase	15	1.8.5.8	FAD+	Colon - 210 Rectum - 180 Muscle - 130 Esophagus - 110
ENSG00000196502	SULT1A1	Sulfotransferase family 1A member 1	16	2.8.2.1	3-phospho-5-adenosyl sulfate (PAPS)	Liver - 250 Duodenum - 140 Small intestines - 100 Adrenals - 100
ENSG00000197165	SULT1A2	Sulfotransferase family 1A member 2	16	2.8.2.1	3-phospho-5-adenosyl sulfate (PAPS) Calcium (Ca2+)	Liver - 50 Duodenum - 50 Small intestine - 50
ENSG00000261052	SULT1A3	Sulfotransferase family 1A member 3	16	2.8.2.1	3-phospho-5-adenosyl sulfate (PAPS)	Duodenum - 240 Small Intestine - 140 BRAIN - 50
ENSG00000213648	SULT1A4	Sulfotransferase family 1A member 4	16	2.8.2.1	3-phospho-5-adenosyl sulfate (PAPS)	Small Intestine - 70 Colon - 50 Adipose - 30 Breast - 30
ENSG00000173597	SULT1B1	Sulfotransferase family 1B member 1	4	2.8.2.1	3-phospho-5-adenosyl sulfate (PAPS)	Duodenum - 100 Small Intestine - 100
ENSG00000198203	SULT1C2	Sulfotransferase family 1C member 2	2	2.8.2.1	3-phospho-5-adenosyl sulfate (PAPS)	Stomach (gastric mucus cells) - 170 Kidney - 70
ENSG00000196228	SULT1C3	Sulfotransferase family 1C member 3	2	2.8.2.1	3-phospho-5-adenosyl sulfate (PAPS)	Breast - 370
ENSG00000198075	SULT1C4	Sulfotransferase family 1C member 4	2	2.8.2.1	3-phospho-5-adenosyl sulfate (PAPS)	Brain - 30 Gall bladder - 30 Ovary - 30,
ENSG00000109193	SULT1E1	Sulfotransferase family 1E member 1	4	2.8.2.1	3-phospho-5-adenosyl sulfate (PAPS) Sodium (Na+)	Liver - 40 Duodenum - 30 Vagina - 30 Skin - 20
ENSG00000105398	SULT2A1	Sulfotransferase family 2A member 1	19	2.8.2.1	3-phospho-5-adenosyl sulfate (PAPS)	Liver - 1080 Duodenum - 240 Small intestine 100 Duodenum - 60 Parathyroid - 40
ENSG00000088002	SULT2B1a	Sulfotransferase family 2B member 1a	19	2.8.2.1	3-phospho-5-adenosyl sulfate (PAPS) Sodium (Na+)	Esophogus - 300 Skin (karatinocytes), 200 Vagina 150 Cervix - 70 Salivary glands - 50
ENSG00000088002	SULT2B1b	Sulfotransferase family 2B member 1b	19	2.8.2.1	3-phospho-5-adenosyl sulfate (PAPS) Sodium (Na+)	Esophogus - 300 Skin (karatinocytes) - 200 Vagina 150 Cervix - 70
ENSG00000130540	SULT4A1	Sulfotransferase family 4A member 1	22	2.8.2.1	3-phospho-5-adenosyl sulfate (PAPS)	Brain (cerebral cortex) - 100 Brain (white matter) - 30
ENSG00000138068	SULT6B1	Sulfotransferase family 6B member 1	2	2.8.2.1	3-phospho-5-adenosyl sulfate (PAPS)	Testes - 5 Brain - 3
ENSG00000139531	SUOX	Sulfite oxidase	12	1.8.3.1	Molybdenum (Mo) Cobalt (Co) Heme (Fe2+)	Liver - 70 Parathyroid - 50 Kidney - 40 Muscle - 40
ENSG00000138336	TET1	Ten-eleven translocation methylcytosine deoxigenase 1	10	NA	Zinc (Zn2+) Iron (Fe2+)	Brain - 5
ENSG00000168769	TET2	Ten-eleven translocation methylcytosine deoxigenase 2	4	NA	Zinc (Zn2+) Iron (Fe2+)	Bone marrow - 25 Skin - 10
ENSG00000187605	TET3	Ten-eleven translocation methylcytosine deoxigenase 3	2	NA	Zinc (Zn2+) Iron (Fe2+)	Bone marrow - 20 Skin - 15 Brain - 13
ENSG00000169902	TPST1	Tyrosylprotein sulfotransferase 1	7	2.8.2.20	NA	Liver - 50 Gallbladder – 40 Urinary bladder - 40
ENSG00000128294	TPST2	Tyrosylprotein sulfotransferase 2	7	2.8.2.20	NA	Pancreas - 400 Epididymis - 100 Liver - 70
ENSG00000176890	TS/**TYMS**	Thymidylate synthase	18	2.1.1.45	Tetrahydrofolate (THF)	Thymus - 115 Bone - 90

(*continued on next page*)

Table 1 (*continued*)

ID	GENE	NAME	CHROMOSOME	EC	COFACTOR/COENZYME	TISSUE RNA EXPRESSION (nTPM)
ENSG00000128311	TST	Thiosulfate sulfurtransferase	22	2.8.1.1	Zinc (Zn2+)	Tonsil - 45 lymph - 40 Liver - 560 GI Tract - 150 Adrenals - 150
ENSG00000112299	VNN1	Vanin 1	6	3.5.1.92	NA	Liver – 220 Duodenum 140 Gallbladder - 90
ENSG00000112303	VNN2	Vanin 2	6	3.5.1.92	NA	Spleen – 60 Tonsils & Lymph nodes – 40 Bone Marrow - 30
ENSG00000093134	VNN3	Vanin 3	6	3.5.1.92	NA	Liver – 35 Bone Marrow - 35

more reactive than the un-ionized H_2S and exerts its biological effects through binding electrophiles in a process known as sulfhydration or attaching to other reactive sulfur species (thiols) to form disulfide bonds in a process known as persulfhydration. These post-translational processes, sulfhydration and persulfidation, also apply to thiol containing molecules (R–SH) such as cysteine and are regarded as fundamental molecular mechanisms for sensing/regulating oxidative stress [22–24].

In healthy humans, the plasma baseline levels of H_2S have been reported to lie in the range of 34 μM–274 μM; however, this does not specify the concentration of ionized to un-ionized H_2S forms [25,26]. By assuming the plasma pH is about 7.4, the ionized HS^- is the predominate form at 80% of the concentration, while the un-ionized H_2S exists at 20%. This is important for two major reasons; first, HS^- anions are biologically more reactive, attaching to proteins found on platelets which inhibit aggregation and also attaching to potassium-ATP channels causing vasodilation [2,19,27–31]. Secondly, since the ionized HS^- form carries an overall negative charge, it requires facilitated diffusion and therefore specific transporters, such as anion exchange protein AE1 present on erythrocytes to enter cells [29]. On the other hand, the 20% H_2S at the physiological plasma pH of 7.4 is more hydrophobic and penetrates the lipid bilayer of the cell membrane through simple diffusion. Inside the cell, where the pH of the cytosol is closer to a neutral 7, un-ionized H_2S and ionized HS^- anions would become roughly equal in concentration. In the basic environment of the mitochondria, where the pH can reach above 8, the concentration of the HS^- anion again predominates at more than 90% of the sulfide concentration. Lastly, in a more acidic environment such as the lysosomes with a pH below 5, nearly 99% of un-ionized H_2S predominates [21].

In recent years, accumulating evidence continues to show a key reciprocal relationship between hydrogen sulfide and oxygen in regulating metabolism and electron flow within the mitochondria [3,32–34]. More specifically, Kumar et al. and others have shown that under conditions of excess HS^- concentrations, oxidative phosphorylation is inhibited by HS^- binding to cytochrome *a*3 (cytochrome oxidase) of mitochondrial complex IV in the electron transport chain. Inhibition of Complex IV by HS^- anions results in increased electrons at complex II, III, and the Coenzyme Q (CoQH2) pools. Although electrons readily escape as free radicals, the majority of electrons are shunted in a reverse flow through complex II to the sulfide quinone oxidoreductase (SQOR) reducing fumarate to succinate along with thiosulfate or oxidized glutathione (GSSH), depending on sulfur acceptor availability [1,3,20,32–37]. A sulfide-driven metabolic flux may be a protective mechanism used in mammalian cells to avoid free radical damage during conditions of low pH, high proliferation, or hypoxia. In hypoxia, succinate accumulation is observed, and restoration of Complex II activity through pure oxygen reperfusion induces rapid succinate oxidation met with an already abundant CoQH2 pool causing electrons to leak as reactive oxygen species (ROS) and free radical tissue damage to occur [36]. To avoid tissue damage in reperfusion cases according to these mechanisms, hypothermic therapy and gentle rewarming of organs mixed with oxygen and sulfide monitoring may ameliorate the events and significantly reduce succinate-driven ROS production [37] (Fig. 2).

3. Inorganic sulfur species – thiosulfate ($S_2O_3^{2-}$)

Thiosulfate has been shown to possesses antioxidant, anti-inflammatory, and antihypertensive properties [20,38–50]. Clinically, low concentrations of thiosulfate have been shown to reduce hypertension, left ventricular hypertrophy, fibrosis, and even rescue a failing heart [42]. Currently, sodium thiosulfate is an FDA approved medicine used for treating acute cyanide poisoning, carbon monoxide toxicity, and calcific uremic arteriolopathy found in dialysis patients [38,40,42–44,48,51]. Systemically, thiosulfate ($S_2O_3^{2-}$) mainly serves as a superoxide scavenger to be excreted in the urine but can also be a major sulfur source for sulfonation/sulfurylation pathways [42] (Fig. 1).

Thiosulfate and sulfite are produced within the mitochondria of various tissues by the thiosulfate sulfurtransferase (TST) using inorganic sulfide anions (HS^-) and glutathione-persulfide substrates [49]. For thiosulfate to be produced, a sulfhydryl group is donated to glutathione by sulfur-donating enzymes such as the membrane-bound sulfide quinone oxidoreductase (SQOR). TST can then use the sulfhydryl group from glutathione-persulfide to produce thiosulfate using an additional inorganic sulfide during sulfur oxidation [49]. Thiosulfate (S = +2) can be excreted into the plasma and or further oxidized to sulfite (S = +4) for sulfate-PAPS production (Fig. 1 and 2).

4. Inorganic sulfur species – sulfite (SO_3^{2-})

Inorganic sulfite (SO_3^{2-}) and sulfur dioxide (SO_2) have both shown to cause a wide-range of allergic reactions and inflammatory symptoms at high concentrations [52]. While both sulfur dioxide (S = +4) and inorganic sulfite (S = +4) share similar sulfur oxidation states, sulfur dioxide has been described to exist as an aerosolized pollutant whereas inorganic sulfite is a dissolved ISS in human plasma [52]. Notably, mast cells and basophils have been reported to be sulfite-sensitive and induce histamine degranulation independent of calcium or IgE cross-linking upon exposure [53]. This means, inhalation of high concentrations of sulfur dioxide pollutants, ingestion of high volume sodium sulfites found

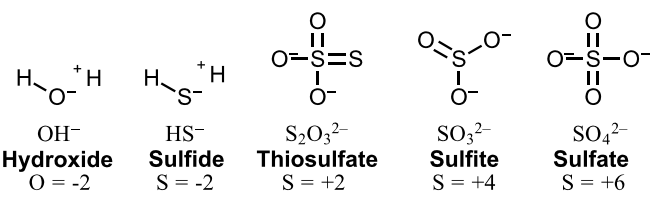

Fig. 1. 2-D molecular structure of hydroxide anion (left) and inorganic sulfur species (sulfide, thiosulfate, sulfite, and sulfate) at the physiological plasma pH of about 7.4.

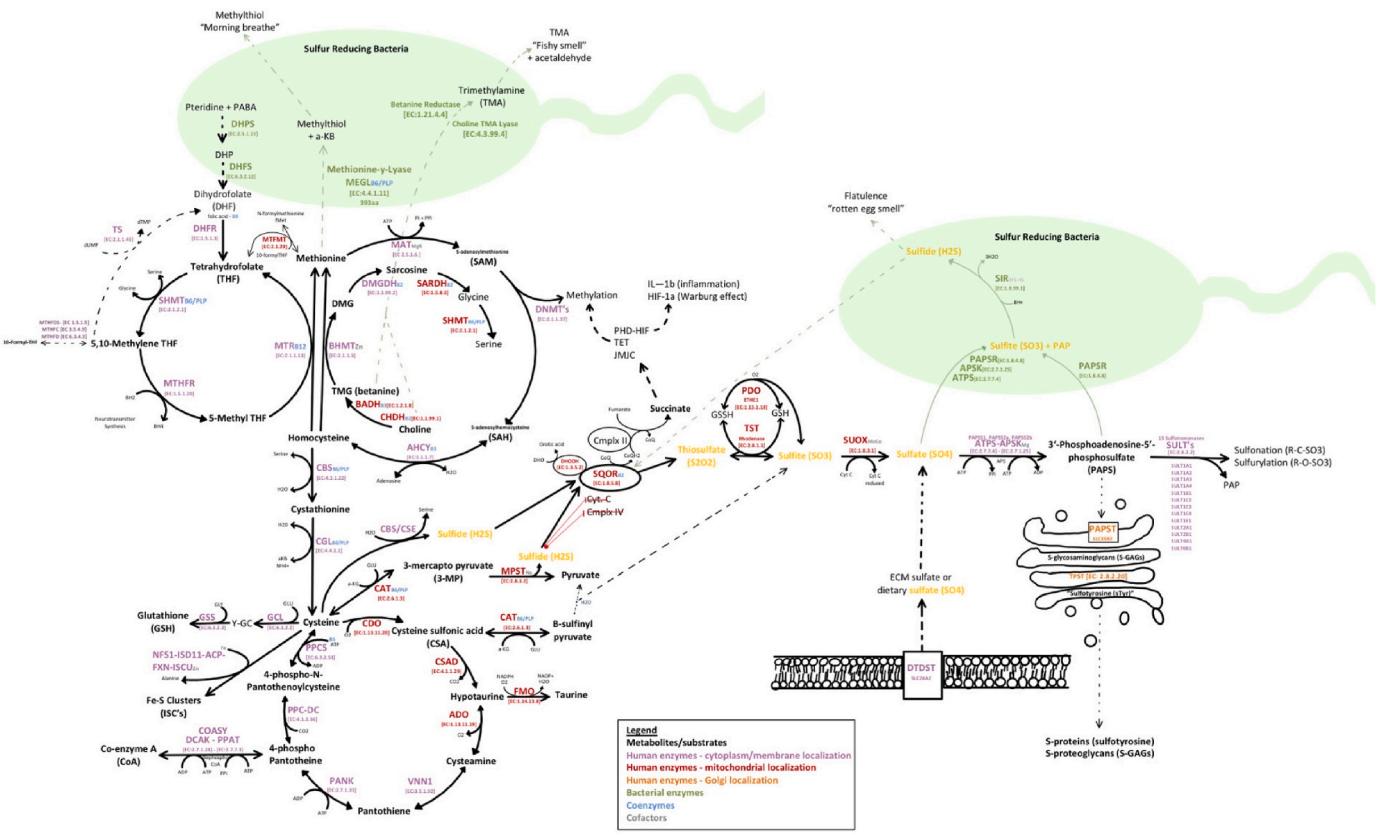

Fig. 2. –In humans, sulfur pathways require sufficient intake of methionine along with adequate B-vitamins (B2, B3, B5, B6, B7, B9, B12), and trace elements zinc, nickel, molybdenum, cobalt, potassium, magnesium, iron, calcium, and sodium (Table 1) [4,6,7,19,68,71,77,174]. Methionine is essential as it can regenerate critical organic sulfur compounds, including the universal methyl donor s-adenosyl-L-methionine (SAM), homocysteine, cysteine, glutathione (GSH), iron-clusters (Fe–S), coenzyme A (CoA), hypotaurine, and taurine [4]. As a by-product of transsulfuration pathways, inorganic sulfur species (ISS) are produced. Specifically, the Cystathionine β-synthase (CBS), cystathionine γ-lyase (CGL), and 3-mercaptopyruvate sulfurtransferase (MST) enzymes produce endogenous H_2S, mitochondrial SQOR, ETHE1/PDO, and TST enzymes produce SO_3^{2-} and $S_2O_3^{2-}$, and mitochondrial SUOX produces endogenous SO_4^{2}. Additionally, extracellular sulfate can also be transported into cells by SLC26A1 or SLC26A2 (DTDST) sulfate/chloride antiporters [63]. The oxidation of inorganic sulfur species (H_2S, SO_3^{2-} and $S_2O_3^{2-}$) then occurs step-wise in the mitochondria where thiosulfate and GSSH are oxidized by either iron-dependent persulfide dioxygenase (PDO/ETHE1) or by thiosulfate sulfur transferase (TST/rhodanese) to produce sulfite (SO_3^{2-}) and regenerate reduced glutathione (GSH) [40,42,43,45,47,49,175]. The final and most oxidized inorganic sulfur species produced from sulfite (S = +4), is inorganic sulfate (SO_4^{2-}) (S = +6), by molybdenum-dependent sulfite oxidase (SOUX), which resides in the intermembrane space of the mitochondria [54]. Sulfate is readily used as a substrate for sulfonation/sulfurylation reactions after activation to 3′-phosphoadenosine-5′-phosphosulfate (PAPS) by PAPS synthase [13,14].

in food additives, or dysfunctional sulfur oxidation pathways resulting in higher plasma sulfite concentrations may all be risk factors for anaphylaxis, especially in sulfite-sensitive patients (Fig. 1).

Under physiological conditions, sulfite (S = +4) is endogenously produced in the mitochondria and then further oxidized to inorganic sulfate (SO_4^{2-}) (S = +6), by molybdenum-dependent sulfite oxidase (SOUX), which resides in the intermembrane space of the mitochondria [54]. Since SOUX is the rate-limiting enzyme for sulfite oxidation, single nucleotide polymorphisms (SNPs) or molybdenum deficiencies effecting enzymatic function can cause a wide range of sulfite sensitivities due to increased plasma sulfite (Fig. 1 and 2).

5. Inorganic sulfate (SO_4^{2-}) & 3′-phosphoadenosine-5′-phosphosulfate (PAPS)

In humans, inorganic sulfate is a vital ISS that is produced through sulfite oxidation by either molybdenum-dependent sulfite oxidase (SOUX) residing in the intermembrane space of the mitochondria or by the moonlighting functions of endothelial nitric oxide synthase (eNOS) [15,54,55]. Inorganic sulfate can also be consumed through diet or produced as a degradative product of the extracellular matrix by sulfatase enzymes [56–59].

In humans, inorganic sulfate is activated through ATP and magnesium-dependent PAPS synthase (PAPSS1 or PAPSS2a/b) and then incorporated into biomolecules such as glycoproteins, glycosaminoglycans (GAGS), cholesterols, or even proteins in sulfonation/sulfurylation reactions by several sulfotransferase enzymes (SULTs/TPSTs). Inorganic sulfate levels in the plasma are retained by reabsorption of the filtered sulfate in the renal proximal tubule which requires the SLC13A1 (Solute Carrier Family 13 Member 1) which is a sodium-sulfate cotransporter (NaS1) located in the apical brush-border membrane and together with the SLC26A1-encoded sulfate-anion exchange transporter in the contra luminal basolateral membrane, allows for sulfate re-entry into blood circulation [60–62]. Of these two transport proteins, SLC13A1 Na-sulfate cotransport is believed to be the rate-limiting step in plasma sulfate retention and loss of this transporter may deplete the circulating sulfate pools and negatively affect general sulfonation/sulfurylation capacity [60–62]. When in circulation, inorganic sulfate can be transported into cells by SLC26A1 or SLC26A2 (DTDST) sulfate/chloride antiporters (Fig. 2) [63].

Upon entering the cell, inorganic sulfate is activated/adenylated using ATP to form adenosine phosphosulfate (APS) by ATP sulfurylase and then phosphorylated to form PAPS by the magnesium-dependent APS kinase activity [13,14]. Notably, the ATP sulfurylase and APS kinase activities are fused into a single polypeptide known as PAPSS which forms the universal sulfuryl donor. In humans there are two major

isoforms PAPSS1 and PAPSS2 with a 77% identity in amino acid sequence. In addition, there is a splice variant PAPSS2b which contains an extra five amino acid sequence GMALP [13,14]. As the rate-limiting enzymes in the sulfurylation pathway, PAPSS supplies the sulfuryl group from PAPS to several different sulfotransferase (SULT) enzymes for sulfonation/sulfurylation reactions [64]. Among the thousands of end-products in sulfonation/sulfurylation, cholesterol sulfate (Ch-S), complex glycosaminoglycans (GAGS), and sulfotyrosine (proteins) are arguably the most vital for cellular homeostasis.

6. Organic sulfur compounds – methionine: folate-dependent and independent cycles

Methionine is an essential regulator of cellular homeostasis and sulfur pools through its direct regeneration of universal methyl donor s-adenosyl-L-methionine (SAM) and homocysteine, which replenish cysteine concentrations during the fed-state through the trans-sulfuration pathway [4]. The magnesium-dependent methionine adenosyltransferase (MAT1A or MAT2A/B) produces SAM from methionine using ATP. SAM is the universal methyl group donor used by nearly all methyltransferase reactions in every cellular compartment, second only to ATP in the number of biological reactions that use it [65]. When the methyl group is transferred from SAM, the remaining molecule is s-adenosyl-L-homocysteine (SAH) which functions as a feedback inhibitor of SAM-dependent methyltransferases. SAH can then be reversibly hydrolyzed to produce homocysteine and adenosine by the B3/NAD^+-dependent SAH hydrolase (SAHH; AHCY) [66]. Notably, AHCY is the only reversible enzyme in the methionine cycle and as such

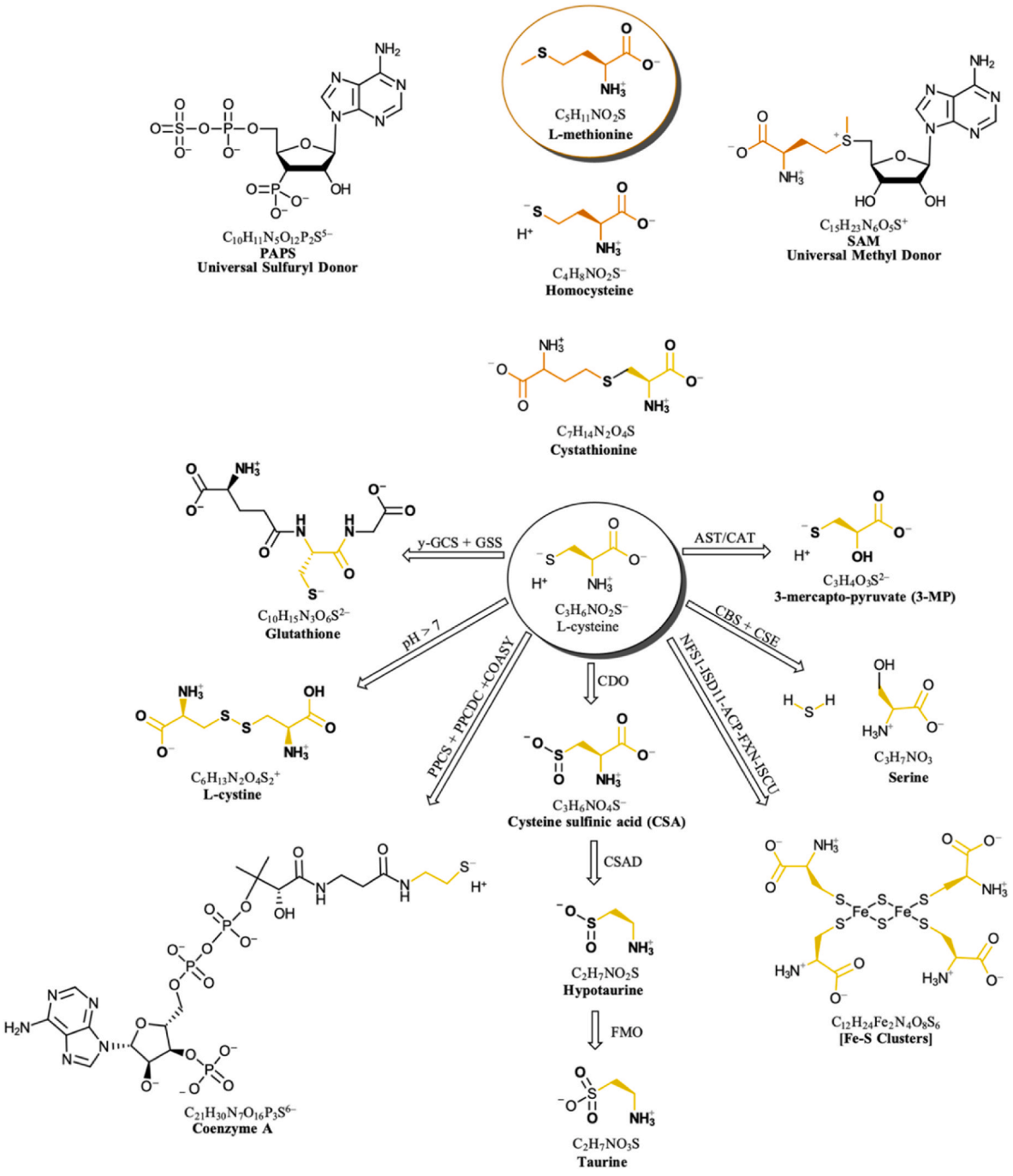

Fig. 3. Organic sulfur compounds (OSC's) in human metabolism described in this review.

is a key regulator of the SAM to SAH molar ratio, commonly referred to as the "methylation index" or "indicator of methylation capacity." [67] When SAH and homocysteine concentrations increase faster than methionine regeneration, SAM utilizing enzymes are inhibited by SAH and the SAM concentrations then act in a feed-forward mechanism to allosterically activate the B6-dependent cystathionine beta-synthase (CBS) which metabolizes homocysteine through the transsulfuration pathway and allows the methionine cycle to continue [68,69]. While mammals assimilate methionine primarily through the diet, methionine is also regenerated from homocysteine by the folate cycle which utilizes the zinc and B12-dependent methionine synthase (MS; MTR) and or the zinc-dependent betaine-homocysteine S-methyltransferase (BHMT) with betaine (trimethylglycine; TMG) being the one-carbon donor produced from choline in the mitochondria of the liver and the kidneys [70–72]. It has been reported that ~50% of methionine regeneration occurs through the folate cycle and ~50% of methionine regeneration occurs by zinc-dependent BHMT (Fig. 2 and 3) [71,72].

7. Transsulfuration – homocysteine to cysteine

In order to maintain cellular homeostasis and cysteine concentrations, dietary intake of methionine is vital because it replenishes cysteine through the transsulfuration pathway [73]. Transsulfuration from homocysteine to cysteine occurs by two steps; first, through a condensation reaction combining homocysteine with a serine amino acid by the enzyme CBS, which is the rate-limiting step of the transsulfuration pathway [74]. Secondly, cystathionine is hydrolyzed by cystathionine gamma lyase (CGL; CSE) into cysteine producing alpha keto-butyrate and ammonia by-products. Studies have shown, SAM allosterically activates CBS and inhibits of methylenetetrahydrofolate reductase (MTHFR) increasing the irreversible reaction of homocysteine to cysteine [21,74–79] (Fig. 2).

8. Organic sulfur compounds – cysteine to glutathione (GSH), coenzyme A, taurine etc

While cysteine and the disulfide form cystine are relatively insoluble and toxic at high concentrations [80], cysteine is a crucial OSC and intermediate in the synthesis of proteins [81], coenzyme A [82–86], taurine [87–90], iron-sulfur clusters [91–93], zinc-finger complexes/metalloproteins [94,95], and glutathione (GSH or γ-glutamyl-cysteinyl-glycine) [71,77,78,80,92,96–102]. Intracellular cysteine is maintained in the 80–100 μM range in most tissues except in the kidney, where its concentration is only ~1 mM [58]. In the mitochondria, cysteine can be oxidized to hypotaurine and taurine [81,103,104], used by cysteine desulfurase (NFS1) to generate iron–sulfur (Fe–S) clusters [91–93], or function in sulfhydration and persulfidation reactions [22,23,30,105]. In the cytosol under conditions of abundant ATP concentrations and pantothenate (B5), cysteine is combined with B5 through a series of reactions that utilize three ATP molecules to form coenzyme A [82–86] (Fig. 2).

Under conditions of increased oxidative stress, cysteine concentrations are shifted toward producing glutathione (GSH; γ-glutamyl-cysteinyl-glycine), which represents the most abundant low molecular weight thiol present in the human body with an intracellular concentration of 1–10 mM [71]. GSH is among the most important thiols in the human body because of its ability to scavenge free radicals and regulate superoxides [16,106]. Low GSH levels are associated with rheumatoid arthritis, Alzheimer's, Parkinson's, cirrhosis, human immunodeficiency virus (HIV), asthma, cystic fibrosis, diabetes, hemorrhagic strokes, atherosclerosis, and benign cancers [71]. GSH is synthesized from the precursor of three common amino acids; cysteine, glutamate, and glycine by two ATP-dependent reactions catalyzed by γ-glutamylcysteine synthetase (GCS; GCL) and by GSH synthetase (GSS), respectively [98]. While cysteine is the rate-limiting substrate in GSH synthesis [71,96–99,107,108], the concentration of GSH is also enzymatically regulated. Specifically, GSH concentrations are increased by upregulation of the GCS enzyme through the nuclear erythroid factor 2-related factor 2 (NRF2) pathway and GSH concentrations are decreased by the γ-glutamyltranspeptidase (GGT) enzyme present on the external surface of certain cell types [71,77,78,96,109–111] (Table 1 and Fig. 3).

Most prominently, cysteine oxidation to taurine accounts for around 50% of cysteine pool utilization in most tissues [112]. Taurine serves various cellular functions including osmotic pressure regulation, cellular membrane stabilization, calcium signaling regulation, mitochondrial biogenesis upregulation, neurotransmitter inhibition through weak binding of the GABA-a receptor, conjugation of bile salts, and as a radical scavenger [87,88,112–114]. The process of cysteine oxidation to taurine occurs by two main pathways; first, through the oxidation of cysteine to form cysteine sulfonic acid (CSA) by the mitochondrial enzyme cysteine dioxygenase (CDO), followed by the decarboxylation to hypotaurine by cysteine sulfonic acid decarboxylase (CSAD) and an oxidation to taurine by the flavin-containing monooxygenase (FMO) enzyme [90]. Secondly, taurine can be formed through the breakdown of coenzyme A [103,104] (Fig. 2, Fig. 3).

9. Sulfur in post-translational modifications (S-PTMs)

Among the mechanisms for cellular signaling and sensing in both eukaryotic and prokaryotic cells, post-translational modifications (PTMs) are an abundant group of mechanisms where biochemical alterations significantly affect the diversity of protein localization, stability, and function (Fig. 2). In contrast to the better-known system of phosphorylation/dephosphorylation, the PTM system of sulfurylation is relatively less understood. Upon phosphorylation the recipient molecule receives two negative charges, whereas the recipient molecule upon sulfurylation receives one negative charge. Aside from this crucial difference, the bond angle, bond distance and the chemical natures are not very different at the macroscopic levels. Yet the charge differences alone can make some uniqueness to the sets of molecules that are being either phosphorylated or sulfurylated [115,116]. From the global analysis it is apparent that many eukaryotic proteins/enzymes are hormonally regulated by phosphorylation/dephosphorylation mechanisms, and small molecules (primary metabolites) are phosphorylated to keep the phosphorylated compounds trapped inside the cell. On the contrary, it is tempting to speculate that molecules that are sulfurylated are mostly secondary metabolites in nature and are typically directed outside of the cell although not exclusively. Some examples of sulfurylated macromolecules (>10,000 Da) include proteoglycans (glycosaminoglycans), cholecystokinin (CCK), thyroglobulin (TG), and glycoprotein receptors (TSHr, LH/hCGr, FSHr) [117–119]. Some small molecules that get sulfurylated include dopamine, estrogen, pregnenolone, glycan moiety of high endothelial venule, and selectin proteins [119–121]. Importantly, the recipient amino acid residues of the proteins that are often phosphorylated are serine, threonine and less frequently tyrosine. In contrast, the peptide/protein residue that is sulfurylated is only tyrosine. Since sulfurylated serine or threonine have not been discovered thus far in humans, we speculate that phosphorylation happens uniquely to serine/threonine residues of proteins (Venkatachalam unpublished) whereas tyrosine residues of peptide/proteins can be either phosphorylated or sulfurylated [120]. Thus, in broad terms clear evolutionary differences between sulfuryl versus phosphoryl transfer processes and their specificities must be understood for targeted therapies.

10. Sulfotyrosine

Of the potential post-translational modifications (PTMs) that can occur on a tyrosine residue, sulfurylation (R_1-*O*-(SO_3^{2-})) of tyrosine is the most abundant PTM and is vital for the biological activity of many proteins directed out of the cell [122]. With a pK_a near 1.5, the sulfuryl group of the sulfotyrosine remains fully ionized at any pH found in the

Table 2
The dominant human gut microbial phyla are *Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia*, with the two phyla Bacteroidetes and Firmicutes representing 90% of gut microbiota [137]. It is estimated that the gut microbiome contains 39 trillion microbial cells compared to 37 trillion human cells [138]. Additional enzyme information was obtained from KEGG pathways.

PHYLUM	SUMMARY	COMMON BACTERIA	BACTERIAL SULFUR REDUCING ENZYMES
Bacteroides	Gram Negative (−) Anaerobic Rod-shaped	Alistipes (−) Rod Bacteroides cellulosilyticus(−) Rod Bacteroides dorei(−) Rod Bacteroides fragilis(−) Rod Bacteroides ovatus(−) Rod Bacteroides vulgatus(−) Rod Bacteroides xylanisolvens(−) Rod Faecalibacterium prausnitzii(−) Rod Oscillibacter (−) Rod Parabacteroides(−) Rod Porphyromonas gingivalis(−) Rod Prevotella (−) Rod	3-mercaptopyruvate sulfurtransferase (3-MST; sseA) PAPS Reductase (PAPSR/CysH) Desulfhydrase enzymes Sulfite Reductase (CysJ/CysI; SIR) O-acetylserine(thiol)lyas (OASS) enzymes. ArylSulfatases Cystathionine-gamma-synthase (metB) Cystathionine-gamma-lyase (mccB) Cystiene synthase (cysK, cysM) Desulfurylases (dcyD, malY, metC) Cysteine desulfhydrases (dcyD/CDS, CdsH, LCD/DES1) Methionine Gamma Lyase (MGL) GlycoSulfatase
Firmicutes	Gram Positive (+) Aerobic/Anaerobic/Facultative Rod/Coccus-shaped	Bacillus anthrax (+) Rod Staphylococcus (+) Coccus Streptococcus (+) Coccus Clostridium difficile(+) Rod Clostridium perfinges(+) Rod Clostridium tetanus(+) Rod Lactobacillus(+) Rod Roseburia(+) Rod Fusobacterium (−) Spindle rod Eubacteria (+) Rod Haemophilis influenzae(−) Rod Listeria(+) Rod	3-mercaptopyruvate sulfurtransferase (3-MST; sseA) PAPS Reductase (PAPSR/CysH) Desulfhydrase enzymes Sulfite Reductase (CysJ/CysI; SIR) O-acetylserine(thiol)lyas (OASS) enzymes. ArylSulfatase Cystathionine-gamma-synthase (metB) Cystathionine-gamma-lyase (mccB) Cystiene synthase (cysK, cysM) Desulfurylases (dcyD, malY, metC) Cysteine desulfhydrases (dcyD/CDS, CdsH, LCD/DES1) Methionine Gamma Lyase (MGL)
Proteobacteria	Gram Negative (−) Anaerobic/Facultative Rod-shaped	Desulfovibrio (−) Rod Corynebacterium diphtheria(+) Rod Escherichia Coli(−) Rod Klebsiella(−) Rod Proteus (−) Rod Salmonella (−) Rod Shigella (−) Rod Vibrio cholerae(−) Rod Campylobacter jejuni(−) Spiral rod Helicobacter pylori(−) Spiral rod	3-mercaptopyruvate sulfurtransferase (3-MST; sseA) PAPS Reductase (PAPSR/CysH) Desulfhydrase enzymes Sulfite Reductase (CysJ/CysI; SIR) O-acetylserine(thiol)lyas (OASS) enzymes. ArylSulfatases Cystathionine-gamma-synthase (metB) Cystathionine-gamma-lyase (mccB) Cystiene synthase (cysK, cysM) Desulfurylases (dcyD, malY, metC) Cysteine desulfhydrases (dcyD/CDS, CdsH, LCD/DES1) Methionine Gamma Lyase (MGL) GlycoSulfatase
Actinomycetota (Actinobacteria)	Gram Positive (+) Aerobic/Anaerobic Rod/Coccus/Branching	Mycobacterium Leprae (+) Rod Mycobacterium Tuberculosis(+) Rod Nocardia (+) Rod Rhodococcus (+) Coccus/Branching Streptomyces (+) Coccus/Branching Actinomyces(+) Branching rod Bifidobacterium (+) Branching rod Collinsella (+) Cocci/Branching	3-mercaptopyruvate sulfurtransferase (3-MST; sseA) PAPS Reductase (PAPSR/CysH) Desulfhydrase enzymes Sulfite Reductase (CysJ/CysI; SIR) O-acetylserine(thiol)lyas (OASS) enzymes. ArylSulfatases Cystathionine-gamma-synthase (metB) Cystathionine-gamma-lyase (mccB) Cystiene synthase (cysK, cysM) Desulfurylases (dcyD, malY, metC) Cysteine desulfhydrases (dcyD/CDS, CdsH, LCD/DES1) Methionine Gamma Lyase (MGL)

biological system and therefore can serve to increase the plasma solubility and half-life of proteins, influence binding interactions, and even regulate the peptide/protein activities [122]. Sulfurylation of tyrosine occurs in the Golgi apparatus where the pH is more acidic (pH 6.0–6.8) and is directed by two protein-tyrosine sulfotransferases (TPST1/TPST2), each with different specificities and expression patterns [117,119] (Fig. 2). The catalyzed reaction involves the transfer of a sulfuryl group from the 3′-phosphoadenosine-5′-phosphosulfate (PAPS) to the hydroxyl group of tyrosine residues which are surrounded by clusters of acidic residues, glutamate and aspartate [119,121,123].

11. Sulfated Glycosaminoglycans (S-GAGs)

Sulfated Glycosaminoglycans (S-GAGs) are highly sulfated macromolecules that are found on the surface of every cell and in the extracellular matrix (ECM) throughout the human body [124,125]. S-GAGs are a diverse class of long, linear, and heterogeneous polysaccharides characterized by disaccharide repeats composed of alternating units of uronic acid and amino-sugar, forming chains that range from 1 to 25,000 disaccharide units [124,125]. Heparin (HP), heparan sulfate (HS), dermatan sulfate (DS), chondroitin sulfate (CS), and keratan sulfate (KS) are all S-GAGs that play an important role in cell-cell communications, structural support, cell adhesion and signaling [46,124–130].

The biosynthesis of S-GAGs begins in the cytoplasm with the formation of a tetrasaccharide linkage to the core proteins, catalyzed by the sequential actions of four glycosyltransferases, which adds one xylose, two galactose, and one glucuronic acid residues (Xyl-gal-gal-glucA). These blocks are then transported into the Golgi lumen through a transmembrane antiporter, where the polymerization and sulfurylation of HP, HS, DS, CS, and KS occurs followed by anterograde vesicle transport to the outer cell membrane [110,111,124,125,129,131]. The sulfurylation of HP and HS typically occurs at positions 2, 3, and 6 of the glucuronic or iduronic acids. The sulfurylation of DS and CS typically occur at positions 4 and 6 of the N-acetylgalactosamine (GalNAc) residues. Lastly, sulfurylation of KS occurs at position 6 of both the N-acetylglucosamine and galactose [122,124].

Inversely, the degradation of the S-GAGs occurs both extracellularly and within the lysosomes [124]. Within the lysosomes, acid hydrolases degrade S-GAGs by the sequential removal of monosaccharides followed by the removal of the sulfur groups; sulfonate/sulfamate groups ($R–NH–SO_3^{2-}$) and sulfuryl/sulfate groups ($R\text{-}O\text{-}SO_3^{2-}$) [110,111,131]. If any of the 12 enzymes participating in S-GAG degradation malfunctions, the lysosomal accumulation of the substrates result in disorders known as mucopolysaccharidoses (MPS) [57,110,111,131]. Overall, S-GAGs are essential in providing structural support and negative charge to cells, and are particularly abundant in the cardiovascular endothelium and the glycocalyx, a protective barrier for epithelial cells in the gut [125,132] (Fig. 2).

12. Sulfur homeostasis in the gut microbiome and crosstalk

The human gut is home to a diverse community of microorganisms, including bacteria, viruses, fungi, and protozoa. It is estimated that the gut microbiome contains tens of thousands of different species of microorganisms, with the majority being bacteria [11,133–136] (Table 2). The dominant gut microbial phyla are *Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia*, with the two phyla Bacteroidetes and Firmicutes representing 90% of gut microbiota [137]. Bacteroidetes consists of a diverse group of bacteria, the predominant genera being *Bacteroides* and *Prevotella.* Firmicutes also consists of a diverse group of bacteria, the predominant genera being *Clostridium*, *Staphylococcus, Lactobacillus*, and *Bacillus* [137]. The *Actinobacteria*phylum is proportionally less abundant and mainly represented by the *Bifidobacterium* genus. Overall, it is estimated that the gut microbiome contains 39 trillion microbial cells compared to 37 trillion human cells [138].

In general, microbiota found in a healthy human gut form colonies and biofilms on the mucus layers of the host intestinal tissues which is spatially segregated and maintained by the secretion of thrombin from the epithelium [139]. In homeostasis, the mucus layers and thrombin keep the biofilms at bay, through proteolytic degradation of its matrix-associated proteins [139]. In the small intestine, antimicrobial peptides, IgA, IL-33, IL-10 and transforming growth factor-β (TGFβ), as well as cells such as CD103+ dendritic cells and regulatory T-cells are produced to also maintain gut homeostasis while the large intestine relies on a thick continuous mucus layer to compartmentalize the microbiome [32,140–144]. It is worth noting that bacterial composition and colonization is dynamic, not only diverse between individuals, but also in a single individual as trillions of microorganisms are constantly exposed to gut-environment changes (pH, temperature, etc.), diet-choices by the host, and other microbes. Among the diversity of the trillions of microorganisms, there are numerous metabolic processes that allow microbes to utilize elements and metabolites. Apart from sulfur, nitrogen, carbon, and phosphorus are heavily involved in the metabolic flux and contribute to the complexity of the overall gut-microbiome metabolism and its homeostasis.

Due to the dynamic complexity of the gut-microbiome, the mechanisms by which bacteria interact with the human host is complex and multifaceted. Some major mechanisms by which bacteria interact with the human host is through fermenting and producing metabolites such as short-chain fatty acids, like acetate, propionate, and butyrate, as well as more complex metabolites such as the hormones serotonin (5-HT) [145,146], cholecystokinin (CCK), gastric inhibitory peptide (GIP) and glucagon-like peptide 1 (GLP-1) [147], and various vitamins [147]. The metabolites can then affect the human host through direct metabolite PTM or indirect metabolic pathways, including chromatin regulation [10,148–150], chemical regulation of the gut–brain axis [16,135], and contributions to the immunomodulatory functions of the host [143,144].

Among the various metabolites and necessary elements, sulfur plays a crucial role in shaping the overall composition and contributions of the gut microbiome. Studies have reported that in healthy humans, concentrations of H_2S were highest in the colon and commonly ranged from 0.3 to 3.4 mM [151–154]. Low physiological H_2S levels exert anti-inflammatory benefits, stabilize mucus layers in the gut, prevent fragmentation and adherence of the microbiota biofilm to the epithelium, inhibit the release of invasive pathogens, and help resolve inflammation and tissue injury [19,27,28,35,153,155,156]. In contrast, at excessive concentrations in the gut, H_2S can cause mucus disruption, inflammation, and can then diffuse into the bloodstream where it has been reported to enter red blood cells and bind hemoglobin (Hb), methemoglobin (metHb), and glutathione disrupting systemic redox homeostasis, oxygen utilization, and free radical scavenging [157,158].

While oxygen is the final electron acceptor in oxidative phosphorylation for human metabolism, many microbes utilize ISS or OSC's rather than oxygen as electron acceptors for energy producing pathways. Sulfur-reducing bacteria (SRBs) such as those residing in the human gut, for example, rely on metabolizing OSCs through assimilatory pathways and ISS through dissimilatory pathways for energy which require sulfur species to be electron acceptors and produce H_2S or reduced sulfur species as final products [9–11]. Two key enzymes able to complete the final step of sulfite reduction ubiquitous among microbes are the dissimilatory sulfite reductase (Dsr) and anaerobic sulfite reductase (Asr) enzymes [113]. While studies have mainly focused on bacteria harboring Dsr enzymes, Asr may be a more important contributor of sulfate reduction in the human gut [113].

Cowley et al. describes the diversity and distribution of sulfur enzymes within the gut microbiome with great detail [113]. Although the assimilatory metabolism of OSC's like methionine by methionine gamma lyase (mgl) and 3′-phosphoadenosine 5′-phosphate by PAPS Reductase (PAPSR), and sulfite by sulfite reductase (SIR) are common within the microbiome, cysteine-metabolizing enzymes are by far the most expressed and highly conserved genes across nearly all microbiota residing in the human gut-microbiome [113]. Genes associated with cysteine metabolism include cysteine synthase (cysK, cysM), cysteine desulfurase (iscS, sufS), cystathionine-γ-synthase (metB), desulfuryalases (dcyD, malY, metC, and mgl) as well as the three human orthologs cystathionine-β-synthase (CBS), cystathionine-γ-lyase (CSE/mccB), and 3-mercaptopyruvate sulfurtransferase (3MST) [113]. Additionally, cysteine desulfhydrase (dcyD/CDS, CdsH, LCD/DES1) are enzymes that produces H_2S from cysteine and have been described in diverse intestinal pathogens such as *Salmonella typhi* [80,159], *Mycobacterium tuberculosis,* [31,80,159] *Helicobacter pylori* [160], and the protozoan *Leishmania major,* [161] as well as various oral microorganisms, including *Streptococcus, Prevotella, and Fusobacterium* [109,159,161–167].

In addition to cysteine metabolizing enzymes, arylsulfatases, glycosulfatases, and O-acetyl-L-serine sulfhydrylase (OASS) are enzymes that produce reduced sulfur products. Arylsulfatases are involved in the degradation of sulfated compounds and have been purified from *Clostridium perfringens* [57,58]. Glycosulfatase enzymes are also involved in the degradation of sulfated compounds and have been described primarily in the intestinal *Prevotella* and *Bacteroides fragilis* and have also been identified in the stomach *Helicobacter pylori* [160]. Conversely, the prevalent O-acetyl-L-serine sulfhydrylase (OASS) and homocysteine synthase mediate the microbial synthesis of cysteine from O-acetyl-L-serine and sulfide in bacteria and archaea [168].

The detailed mechanisms of the cross-talk between the gut microbiome and the human host are complex, dynamic, and still to be fully determined. While the mutually beneficial relationship of the host provides an environment and nutrients for the bacteria to thrive, the bacteria contribute to various aspects of human health. The functional contributions of the gut microbiome to host health are immense [8,12,16,135]. To name a few, microbiota maintain gut-barrier function in the mucus layers of the GI tract [139,153,169–173], support gut motility [145,148], secrete hormones like serotonin (5-HT) [145,146], cholecystokinin (CCK), gastric inhibitory peptide (GIP) and glucagon-like peptide 1 (GLP-1) [147], regulate chromatin [10,148–150], contribute

to the gut–brain axis [16,135], and contribute to immunomodulatory functions of the host [143,144] (Table 2).

13. Conclusion

Sulfur pools in the human body are vast and include both inorganic sulfur species (ISS) as well as critical organic sulfur-containing compounds (OSCs). Endogenously produced ISS includes hydrogen sulfide (H_2S), sulfite (SO_3^{2-}), thiosulfate ($S_2O_3^{2-}$), and sulfate (SO_4^{2-}). Endogenous OSCs include methionine, cysteine, universal methyl donor s-adenosyl-L-methionine (SAM), homocysteine, cystathionine, cysteine, glutathione (GSH), coenzyme A (CoA), hypotaurine, taurine, and others [4]. Through this review, we have explored the systemic effects of sulfur in biochemical pathways, including mechanisms of regulation by post-translational modifications, and explored the role of the gut microbiome in human sulfur metabolism. While this review has attempted to be thorough, the growing body of literature on the interconnectedness of sulfur pathways and crosstalk with gut microbiota, as well as, human brain sulfurylation are vast warranting further investigation and an up to date review. In future studies, we feel it is important to characterize rate-limiting enzymes including MTHFR, CBS, GCL, PAPSS, eNOS, SUOX, SQOR, and others within the sulfur pathways as they have implications for human health and disease. By investigating specific rate-limiting enzymes and sulfur pathway variations, we can begin to create pharmacological agents to treat associated diseases.

Declaration of competing interest

This is to attest that we do not have or claim “conflict of interest”.

Data availability

Data will be made available on request.

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