Introduction

Oxidative stress (OS) is frequently described as an imbalance between the production of reactive oxygen species (ROS) in biological systems and the ability of the latter to defend themselves through their sophisticated antioxidant machinery.\(^1\,^2\) The term ROS is applied to a collection of highly reactive chemicals, namely free radicals, including superoxide anion (O\(_2^−\)), hydroxyl radical (OH\(^−\)) and singlet oxygen (\(^{1}\)O\(_2\)), or alternatively their non-radical forms.

Role of SLC4 and SLC26 solute carriers during oxidative stress

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Abstract

Bicarbonate is one of the major anions in mammalian tissues and fluids, is utilized by various exchangers to transport other ions and organic substrates across cell membranes and plays a critical role in cell and systemic pH homoeostasis. Chloride/bicarbonate (Cl\(^−/\)HCO\(_3^−\)) exchangers are abundantly expressed in erythrocytes and epithelial cells and, as a consequence, are particularly exposed to oxidants in the systemic circulation and at the interface with the external environment. Here, we review the physiological functions and pathophysiological alterations of Cl\(^−/\)HCO\(_3^−\) exchangers belonging to the solute carriers SLC4 and SLC26 superfamilies in relation to oxidative stress. Particularly well studied is the impact of oxidative stress on the red blood cell SLC4A1/AE1 (Band 3 protein), of which the function seems to be directly affected by oxidative stress and possibly involves oxidation of the transporter itself or its interacting proteins, with detrimental consequences in oxidative stress-related diseases including inflammation, metabolic dysfunctions and ageing. The effect of oxidative stress on SLC26 members was less extensively explored. Indirect evidence suggests that SLC26 transporters can be target as well as determinants of oxidative stress, especially when their expression is abolished or dysregulated.

Keywords

Cl\(^−/\)HCO\(_3^−\) exchangers, oxidative stress, oxidative stress-related diseases, SLC26, SLC4

1 | INTRODUCTION

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intermediates, such as hydrogen peroxide (H$_2$O$_2$), nitric oxide (NO) and hypochlorous acid (HOCl), which are typically less reactive.3,4 In eukaryotes, endogenous ROS represent a normal byproduct of the cell metabolism and mainly arise from the incomplete reduction of O$_2$ during the process of oxidative phosphorylation in the mitochondria.5 In addition, endogenous ROS are produced by various cellular enzymes, including NADPH oxidases (NOXs) and nitric oxide synthase (NOS), peroxisomes, ionizing and UV radiation, as well as by the metabolism of drugs and xenobiotics.6,7 However, the redox state in the cell is normally regulated by a complex endogenous antioxidant system, which is composed of proteins with enzymatic activities, like glutathione peroxidase, catalase (CAT), and superoxide dismutase and non-enzymatic small-molecule compounds, like glutathione, which are able to quickly neutralize ROS and ensure a low production of reactive species. In addition, antioxidant molecules, such as vitamin C, vitamin E, some minerals, carotenoids, and polyphenols, which can be supplied through the diet, can help the activity of endogenous antioxidants, thus promoting the redox homoeostasis of the cell.8

Nevertheless, some oxidants in controlled amount possess important cell defense and signalling functions within the cell. Specifically, cells can generate ROS with function of second messengers, use them for intracellular signalling and for stimulating redox-sensitive pathways in order to modify the cellular levels of cytoprotective regulatory proteins.9,10 For example, the massive ROS production by activated macrophages not only represents a first-line defense against environmental pathogens, but can also stimulate T-cell function, including the production of cytokines.11 However, when oxidants are produced in excess, or when the antioxidant defenses that regulate them are ineffective, the balance between antioxidant and pro-oxidant capacity can be perturbed, thus resulting in OS and ultimately cell death through apoptosis or necrosis. In these conditions, biomolecules such as nucleic acids, membrane lipids, enzymes, and structural proteins can be altered through oxidation to an extent that exceeds repair capacity.12,13 Abnormal ROS levels can influence several cell signalling pathways. In this regard, the role of OS in the pathogenesis of disease is widely acknowledged. A perturbed redox homoeostasis may be the common denominator underlying ageing and different chronic diseases,14-19 although specific mechanisms contributing to OS-induced damage are poorly investigated.

By representing the boundary between the cell interior and the extracellular environment, the cell membrane is most vulnerable to free radical attack.20 The plasma membrane contains a wide range of proteins and lipids that elicit distinct cellular reactions in response to extracellular stimuli and stressors, and each of these can be target of OS. The solute carrier (SLC) superfamily of transporters comprises integral membrane proteins known as the gatekeepers for all cells, as they control the transmembrane flux of inorganic ions, sugars, amino acids, nucleotides, fatty acids, neurotransmitters, and drugs.21 Currently, the human SLC superfamily includes over 458 members grouped into 65 families.22 This organization has been established by the Gene Nomenclature Committee (HGNC) of the Human Genome Organization (HUGO), and arranged such that member proteins within each family share at least 20%-25% sequence similarity with at least one other member of the family.23 The SLC transporters are grouped into four main types according to the transport mode, which are cotransporters, exchangers, facilitated transporters and orphan transporters (with no known substrate), thus playing a central role in a plethora of physiological and pathological functions in almost all cells and tissues.22 These membrane transporters are widely expressed throughout the body, most notably in the epithelia of major organs, such as the liver, intestine, kidney and organs with barrier function, such as the blood-brain barrier, testes and placenta. Many transporters are also expressed in an organ-specific manner, thus facilitating the entry and elimination of endogenous and xenobiotic compounds.24 The substrate specificity of these transporters can be determined by interactions between the amino acid backbone and/or side chains and the substrate, as well as by intramolecular interactions that regulate gating and/or selectivity elements.25

The modulation of the activity of membrane transport systems is part of the cellular response to OS.26 In particular, the link between OS and membrane transport systems during ageing as well as in OS-related diseases is incompletely understood, and is essential for a deeper understanding of mechanisms through which such processes and diseases develop. Indeed, the relationship between ion transport and cellular redox balance is complex. The activity of ion transporters and channels can be stimulated or blocked during OS and, in turn, these molecular entities can even be involved in determining or attenuating OS. To name just a few examples, volume regulated anion channels LRRC8/VRAC can be either activated or inhibited by OS depending on their subunit composition, while LRRC8/VRAC inhibitors seem to lower OS.27 The expression as well as the function of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel is impaired during OS, thus contributing to the progression of airway dysfunctions, including chronic obstructive pulmonary disease (COPD), consequent to alteration of the mucociliary transport in airway epithelial cells.28 On the other hand, CFTR is permeable to not only chloride ions, but also organic anions such as reduced glutathione, and consequently CFTR dysfunction potently contributes to
### Table 1: Link between SLC4A members and oxidative stress (OS)

| Transport mode | Isoform | Tissue distribution | Experimental model | Findings | References |
|----------------|---------|---------------------|---------------------|----------|------------|
| Na\(^+\)-independent Cl\(^-\)/HCO\(_3\)\(^-\) exchangers | SLC4A1 | Erythrocytes, kidney, heart, colon | Erythrocytes exposed to H\(_2\)O\(_2\) | Reduction of transport efficiency (SO\(_4\)\(^{2-}\)) | 62,98 |
| | | | Erythrocytes exposed to thiol-oxidizing agents | Reduction of transport efficiency (SO\(_4\)\(^{2-}\)) | 64,97 |
| | | | Erythrocytes exposed to extracellular pH variations | Oxidation of membrane SH groups | |
| | | Inflammation-associated diseases | | Reduction of transport efficiency (SO\(_4\)\(^{2-}\)) | 102,103 |
| | | | | Oxidation of membrane SH groups | |
| | | | | Acceleration of transport efficiency (SO\(_4\)\(^{2-}\)) | 67,68,71 |
| | | | | Tyrosine phosphorylation increase | |
| | | | | Lipid peroxidation increase | |
| | | | | Protein degradation | |
| Canine Leishmaniasis | SLC4A2 | Kidney, gut, blood vessels, lung | Endothelial cells exposed to high glucose | Reduction of transport efficiency (SO\(_4\)\(^{2-}\)) | 74-76 |
| | | | | Oxidation of membrane SH groups | |
| | | | | Lipid peroxidation increase | |
| | | | | Protein degradation | |
| Diabetes mellitus | SLC4A3 | Brain, heart, retina, pituitary, adrenal gland | No information available | Acceleration of transport efficiency (SO\(_4\)\(^{2-}\)) | 80 |
| | | | | Oxidation of membrane SH groups | |
| | | | | Lipid peroxidation increase | |
| | | | | Reduction of GSH/GSSG ratio | |
| | | | | Protein degradation | |
| | | | | Formation of Methylene blue | |
| | | | | Formation of glycated haemoglobin | |
| | | | | Reduction of transport efficiency (SO\(_4\)\(^{2-}\)) | 93 |
| | | | | Reduction of GSH:GSSG ratio | |
| | | | | Oxidation of membrane SH groups | |
| | | | | Formation of Methylene blue | |
| | | | | Formation of glycated haemoglobin | |
| | | | | Reduction of transport efficiency (O\(_2\)\(^{-}\)) | 111,112 |
| | | Age-related diseases | | Increase of protein expression | 87,89,91 |
| | | | | Apoptosis | |
| | | | | Increase of transport efficiency (O\(_2\)\(^{-}\)) | 112 |
the OS burden at the airway surface in cystic fibrosis. Recent studies have established that the Na+/K+-ATPase can cause OS with mechanisms distinct from its well-understood function of ion pump but rather dependent on the scaffolding properties of the alpha1 subunit, which is targeted by OS and post-translationally modified, thus leading to the activation of a downstream signalling cascade eventually amplifying ROS production.

In this review, we will focus on the impact of OS on plasma membrane SLC transporters, and specifically on the members of SLC4 and SLC26 families of chloride/bicarbonate (Cl−/HCO3−) exchangers, which are essential for maintaining crucial homeostatic functions, such as the regulation of systemic and intracellular pH and ion composition, and the regulation of cell and extracellular fluid volume. We will emphasize their pathophysiological relevance and their role in OS-related conditions, including ageing. In this regard, only isoforms involved in OS events will be considered. Also, we will discuss their potential as targets of antioxidant therapies.

### 2 | THE SLC4 FAMILY

The SLC4 transporters, also known as the bicarbonate-transporter family, are integral membrane proteins that carry bicarbonate (HCO3−) and other electrolytes (Na+ and Cl−) across the plasma membrane. These proteins play a critical role in the acid-base homeostasis of the body by acting as either acid loaders or acid extruders, thus regulating both intra- and extracellular pH. Based on the transport modes, members of the SLC4 family of proteins were classified into three functional groups in mammals: (1) Na+-independent Cl−/HCO3− exchangers, which include SLC4A1, SLC4A2, and SLC4A3; (2) Na+-dependent HCO3− transporters, comprising electrogenic Na+/HCO3− cotransporters (SLC4A4, SLC4A5), electroneutral Na+/HCO3− cotransporters (SLC4A7 – formerly SLC4A6 – and SLC4A10), and an electroneutral Na+-driven Cl−/HCO3− exchanger (SLC4A8); (3) Na+-coupled borate transporter that do not transport bicarbonate, which is represented by the unique member SLC4A11. The classification of SLC4A9 remains unclear because its function is still incompletely characterized.

The Na+-independent Cl−/HCO3− exchangers, and particularly SLC4A1 and SLC4A2, have been well characterized in the context of OS and will be reviewed in the following. For the other SLC4 family members, there is no information available (Table 1).

### 2.1 | The SLC4A1 isoform

The SLC4A1 isoform, also known as anion exchanger 1 (AE1) or band 3 protein (B3p), is encoded by the SLC4A1 gene and—with more than 1 million copies per cell—is the most abundant membrane protein in human erythrocytes. A truncated form of SLC4A1 lacking the first 65 residues is expressed on the basolateral membrane of the alpha intercalated cells of the distal portion of the nephron, where it plays a crucial role in the reabsorption of bicarbonate, and consequently in urinary acid secretion. Some forms of distal renal tubular acidosis are caused by inherited mutations in the SLC4A1 gene.
In 2015, the crystal structure of B3p revealed two domains: an N-terminal cytosolic domain that anchors the cytoskeleton at the membrane and interacts with different erythrocyte proteins and a C-terminal membrane domain that mediates the anion exchange (Figure 1). Moreover, B3p is present as a mixture of dimers and tetramers in membranes and these oligomers form interaction hubs around which integral and peripheral membrane proteins are organized. As an integral membrane protein, B3p is also important for the mechanical properties of red blood cells, such as docking of glycolytic enzymes and maintenance of cell shape by anchoring the actin-spectrin cytoskeleton at the plasma membrane. Defects or deficiencies in B3p may lead to a reduction of cohesion between the cytoskeleton and the lipid bilayer, with a consequent loss of membrane surface area typical of hereditary spherocytosis.

In physiological conditions, B3p mediates electroneutral Cl⁻/HCO₃⁻ exchange across the plasma membrane, a fundamental process for an efficient respiration. Specifically, in peripheral tissues, carbon dioxide, which is generated by metabolic processes, diffuses into the erythrocytes and is hydrated by intracellular carbonic anhydrase II (CAII) to produce bicarbonate, which is in turn transported out
of the cell in exchange for chloride. Conclusively, at the level of pulmonary capillaries, the mechanism is reversed: HCO$_3^-$ enters the erythrocytes via B3p in exchange for Cl$^-$ and is converted by CAII to carbon dioxide, which then diffuses across the plasma membrane to be excreted by the lungs. In this way, more than two thirds of the carbon dioxide molecules are transported in the form of HCO$_3^-$.

Each B3p molecule exchanges 10$^5$ pairs of monovalent anions per second. The Cl$^-$/HCO$_3^-$ exchange is the largest ion-specific flux of a secondary active transporter known in the body, and it is blocked by the unspecific anion exchange inhibitor 4,4′-diisothiocyanato-2,2′-stilbenedisulphonic acid (DIDS) with high affinity.

In experimental conditions, the functional efficiency of B3p can in principle be estimated by measuring the influx or efflux of radiolabelled substrates across the plasma membrane or variations in the intracellular pH and chloride concentration, which can be revealed by sensitive dyes. However, the Cl$^-$/HCO$_3^-$ exchange is so fast that it cannot be easily monitored without the confounding factor of the cellular metabolism, and sophisticated instrumentation is required to follow the time course of extracellular pH. In this respect, B3p transporter can exchange different anions, including SO$_4^{2-}$, even if at different rates. The use of SO$_4^{2-}$ transport to monitor B3p activity offers the advantage that the exchange time is slow enough to employ relatively simple experimental protocols. Moreover, the absence of SO$_4^{2-}$ within the erythrocyte ensures that intracellular SO$_4^{2-}$ determinations are essentially indicative of the anion uptake. This experimental approach has been
recognized as an effective tool to monitor erythrocyte homeostasis in several experimental conditions in vitro and ex vivo. In this regard, the rate constant for $SO_4^{2-}$ transport can be measured by using a turbidimetric method aimed at quantifying the amount of $SO_4^{2-}$ internalized through B3p as a function of time (Figure 2).

2.1.1 SLC4A1 and oxidative stress

Erythrocytes are continuously threatened by oxidative events associated with high ROS levels in the blood stream and are therefore more exposed to OS than other cells. Indeed, erythrocytes are a prime target for oxidative stress due to their main function as $O_2$-carrying cells and may accumulate oxidative damage when crossing a tissue with an intense production of reactive species. Moreover, OS in blood might rise following exposure to xenobiotics, auto-oxidation of haemoglobin or release of ROS from neutrophils and macrophages into the plasma. Thus, erythrocytes have sophisticated antioxidant defense machinery, and these aspects render these cells a good model for OS-related studies. In fact, the oxidants can exert their effects on the plasma membrane with potential consequences on transport systems and, in turn, on erythrocyte homeostasis, which is strictly linked to B3p function. The transporter is particularly susceptible to redox balance variations in red blood cells and reductions in the efficiency of the antioxidant machinery, which encourage the capability of oxidizing molecules to generate ROS, thus resulting in intracellular cytotoxic injury (Figure 3).
A large body of evidence supports the notion that OS induces post-translational modifications of the N-terminus of B3p, which is exposed to the intracellular environment (Figure 1). Oxidized B3p is selectively and abundantly phosphorylated, which can induce B3p aggregation, weaken the interaction with the spectrin-actin cytoskeleton and reduce membrane stability. Lyn is responsible for the phosphorylation of Tyr 359, and Syk is responsible for the phosphorylation of Tyr 8 and Tyr 21. In addition, oxidation induces B3p disulphide cross-linking. The dimerization of B3p is guided by formation of disulphide bridges between two cysteine (Cys) residues located in the dimerization arms of the two monomers. The Cys 201 residue in one monomer and the Cys 317 residue of the paired monomer can easily form intermolecular disulphide bonds following moderate OS, which might block ankyrin binding. It is likely to hypothesize that these modifications might induce conformational changes that could affect B3p ion transport efficiency.

B3p transport efficiency has been firstly investigated in human red blood cells exposed to hydrogen peroxide (H₂O₂). This compound, which is commonly used in in vitro assays to model oxidant conditions, easily permeates the plasma membrane. In this regard, it has been demonstrated that not haemolytic concentrations of H₂O₂ induce OS and reduce B3p transport efficiency (Figure 2). In addition, it has also been reported that the anion transport by B3p can be modulated by oxygen pressure levels in human erythrocytes, being higher with higher oxygen pressure. Taking into account that haemoglobin binds B3p, these findings suggest that the transition of haemoglobin from the deoxygenated to the oxygenated form may play a key role in the regulation of anion exchanger activity. Moreover, OS induced by thiol-oxidizing agents, such as N-ethylmaleimide (NEM) or diamiide, impaired the ability of B3p to drive the uptake of SO₄²⁻ in human erythrocytes. The decreased efficiency of anion transport was linked to changes in the structural state of B3p caused by membrane sulphidrly oxidation, mainly belonging to B3p. In addition, these agents are known to cause B3p cross-linking, thus inducing conformational changes, which in turn could affect the uptake kinetics.

In the last few years, erythrocytes have emerged as the main determinant of blood rheology. As mentioned above, B3p provides an anchoring point between the cell membrane and the cytoskeleton, which are the two main cellular structures that contribute to erythrocyte deformability. Human erythrocytes are capable of extreme changes in shape. Due to their flexibility, red blood cells can easily be compressed to pass through capillaries and can recover rapidly to their original shape. Therefore, potential defects in the integrity of the structure can produce changes in erythrocyte deformability and stability, affecting cell survival, homoeostasis, and rheological properties of blood. Such abnormalities are seen in different pathologies. In this respect, B3p has been studied ex vivo in some OS-related diseases (Table 1).

2.1.2 | SLC4A1 and oxidative stress in inflammation

Several studies explored how OS-linked modifications of B3p contribute to the development of inflammatory diseases. In general, red blood cells respond to OS by activating tyrosine kinases that induce tyrosine phosphorylation (Tyr-P) at the cytoplasmic domain of B3p, thus leading to erythrocyte membrane destabilization. Thus, in normal red blood cells, Tyr-P levels of B3p are closely controlled, but can be altered in pathological conditions. In fact, it has been shown that B3p Tyr-P levels are useful in analyzing erythrocyte membrane functional status and are increased in inflammatory processes associated with systemic OS, such as endometriosis. In addition, the increased B3p Tyr-P levels seen in G6PD deficiency correlated closely with chronic impairment of antioxidant defenses, whereas the lower B3p Tyr-P levels observed in pregnancy are accompanied by a characteristically increased antioxidant defense.

A large number of inflammatory mediators, including the C-reactive protein (CRP), have been proposed as potential markers of inflammatory response. In this respect, Morabito and collaborators have investigated the effect of high serum CRP levels, associated to acute inflammatory diseases of various origins, on anion exchange capability through B3p in human erythrocytes. In this study, the anion exchange rate was accelerated in erythrocytes from patients with high (>8 mg/L) CRP levels. Though CRP levels returned to normal after 1 week, a total restoration of the rate constant for anion exchange was only observed after 2 months, suggesting that erythrocyte function was irreversibly affected and a total erythrocyte turnover was needed to normalize B3p functionality. Lipid peroxidation, which is associated to inflammation, correlated to erythrocytes deformability and could explain the accelerated uptake via B3p. Thus, these studies suggest a link between inflammation and B3p functional and/or structural alterations.

Among inflammatory conditions, Canine leishmaniasis is also associated with ROS generation and a reduction of erythrocyte survival. The leishmaniasis parasite, even though not directly invading red blood cells, causes a decrease in cell membrane fluidity, as well as an increase in cell rigidity, which may account for the reduced B3p transport efficiency observed in erythrocytes from infected dogs. This hypothesis is supported by the significant
shape alterations unrelated to a decrease in cell size detected in erythrocytes from infected animals, suggesting a reorganization of membrane structure. In this regard, both an increase of lipid peroxidation in erythrocytes of infected animals and a marked degradation of membrane proteins, namely B3p and Band 4.1 protein, have also been demonstrated.76

2.1.3  |  SLC4A1 and oxidative stress in metabolic dysfunctions

Diabetes mellitus is a chronic metabolic disorder characterized by insulin deficiency, insulin insensitivity, or both, as well as by hyperglycemia and vascular complications. Oxidative stress is a major participant in the pathophysiology of diabetes and not only promotes the onset of diabetes but also exacerbates its associated complications.77 This condition has been reported to dramatically impact on red blood cells, inducing membrane destruction, decreased deformability, alterations in haemoglobin oxygen binding and modification of the internal structure between membrane and cytoskeleton, thus leading to an altered systemic homeostasis.78

To investigate the possible influence of diabetes on B3p transport efficiency, two different conditions have been considered: erythrocytes from diabetic patients and from healthy volunteers exposed to increasing concentrations of glucose for 24 hours in vitro, according to.79 The anion exchange rate via B3p was accelerated in both conditions.80 Specifically, in the first case, the functional alteration was linked to a modification of B3p conformation, putatively caused by an altered cross linking with haemoglobin, which is glycated in diabetic patients (6.5% or higher in this study), along with an increased OS, as revealed by an increased lipid peroxidation as well as decreased membrane sulphhydril groups abundance and GSH:GSSG ratio. Accordingly, it has been shown that hyperglycaemia may favour the advanced glycation end products formation, of which receptors activate signal transduction pathways, thus inducing ROS production.81 On the contrary, in the second case, although no significant levels of glycated haemoglobin and lipid peroxidation were detected and membrane sulphhydril groups abundance was not altered, a decreased GSH:GSSG ratio was found, which was normalized by pre-exposure to the antioxidant melatonin. These findings suggest that alterations in B3p function may reveal early diabetic changes linked to OS.80

Galactosemia is a group of disorders of galactose metabolism characterized by erythrocyte galactose-1-phosphate levels usually >10 mg/dL. If undiagnosed or left untreated, galactosemia can result in life-threatening complications including failure to thrive, hepatocellular damage, bleeding, sepsis, and neonatal death. Despite adequate treatment, children with galactosemia remain at increased risk for developmental delays, apraxia of speech, abnormalities of motor function, and hypergonadotropic hypogonadism or premature ovarian insufficiency in females.82 OS plays a fundamental role in the pathophysiology of galactosemia, which is also characterized by the formation of glycated haemoglobin.82-84 Remigante et al85 have reported that the rate constant for SO₄²⁻ uptake via B3p is significantly reduced in erythrocytes treated for 1 hour with 0.1-10 mmol/L D-Galactose (D-Gal). This effect was accompanied by the formation of glycated haemoglobin rather than OS, which was mitigated by the endogenous catalase. These findings suggest that B3p dysfunction might contribute to the pathophysiology of galactosemia and further underscore the sensitivity of B3p function for the formation of glycated haemoglobin.

2.1.4  |  SLC4A1 and oxidative stress during ageing

Oxidative stress has also been postulated to play an important role in pathophysiological pathways involved in ageing as well as several age-related diseases. The plasma membrane of red blood cells plays a crucial role in regulating cellular homeostasis, and proteins and lipids involved in this function are very susceptible to oxidative modifications during ageing.86 In fact, proteomic studies have reported that 15% of erythrocytes in patients with Alzheimer’s disease (AD) are elongated and have an altered membrane architecture,87 which favours erythrocyte aggregation and sedimentation in the blood flow. In this regard, the removal of senescent erythrocytes in AD implies conformational changes in B3p, which are involved in both an increase of cell density and reduction in cell volume.88 In addition, in Alzheimer subjects, an accelerated breakdown of B3p has been shown,89-91 in line with what has been recently demonstrated in diabetic patients.80

Unfortunately, no studies exploring possible functional changes of B3p in aged individuals are reported in the literature. Chronic administration of D-Gal has been widely used as a model to mimic a process very similar to the natural ageing, provoking OS via increased production of ROS and changes in antioxidant enzyme activities in the cell.92 In human erythrocytes exposed to 25-100 mmol/L D-Gal for 24 hours, the rate constant of SO₄²⁻ uptake via B3p was increased; however, the total amount of SO₄²⁻ trapped by the cell was significantly reduced. These changes in the transport properties were paralleled by and increased formation of glycated haemoglobin, as well as a marked OS.93 These findings confirm that the biophysical
properties of B3p are sensitive to the oxidative status of the cell as well as to the formation of glycated haemoglobin and further suggest that B3p dysfunction might participate in age-related pathophysiological alterations.

2.1.5 SLC4A1 and beneficial effects of antioxidants

Both the enzymatic and non-enzymatic antioxidant system are essential for the cellular response in order to deal with OS injuries. Also, antioxidants provided by the diet help the activity of endogenous antioxidants and contribute to the maintaining of redox homoeostasis. Magnesium (Mg\(^{2+}\)) deficiency has been associated with an increased production of ROS, increased levels of inflammation, and several age-related diseases. G6PDH-deficient red blood cells, which are exposed to increased OS levels compared with normal red blood cells, exhibited a decreased sulphate uptake via B3p. Magnesium pre-treatment ameliorated the efficiency of anion exchange in these cells. To better investigate the mechanism of the antioxidant effect of Mg\(^{2+}\), the phosphorylation grade of B3p and tyrosine kinase Syk expression have been assayed in normal erythrocytes after OS induced by exposure to NEM. This investigation has shown that the beneficial effect of Mg\(^{2+}\) is not mediated by phosphorylation pathways, but is rather linked to an improvement of the endogenous antioxidant system and protection of SH groups. In fact, pre-exposure to Mg\(^{2+}\) restored B3p ion transport following an increase of intracellular glutathione levels. Furthermore, the reduction of B3p anion exchange efficiency caused by a strong OS (300 \(\mu\)mol/L \(H_2O_2\)) could be prevented or attenuated by a short-time pre-incubation of red blood cells with low (10 \(\mu\)mol/L) \(H_2O_2\) concentrations. This pre-incubation encourages erythrocytes to adapt to a mild and transient OS and favours an increased tolerance to a successive stronger oxidant condition. Such adaptation response, termed preconditioning, could be monitored through B3p functional measurement, did not involve B3p-related Tyr-P pathways but was mediated by an increased activity of catalase. In fact, this strategy allowed red blood cells to optimize the performance of the endogenous antioxidant system, thus preventing the generation and accumulation of ROS and providing a better protection against oxidative damage.

In a recent study, a correlation between melatonin effect, OS injury and B3p anion exchange capability was shown. In particular, the authors reported that pre-treatment of human erythrocytes with melatonin ameliorated the reduction in rate constant for \(SO_4^{2−}\) uptake observed following treatment with \(H_2O_2\). In parallel, exposure of erythrocytes to melatonin also prevented the increase in the rate constant for \(SO_4^{2−}\) uptake observed in a cell-based model of hyperglycaemia represented by red blood cells treated with high glucose concentrations (15-35 mmol/L) for 24 hours.

Apart from haemolysis, exposure of red blood cells to low pH values can evoke alterations of cell membranes. In fact, erythrocytes, when exposed to an external medium of different pH values, may exhibit alterations of cytoskeletal and integral membrane proteins, including B3p, which result in membrane destabilization and ionic imbalance probably caused by oxidative damage. Furthermore, a significant reduction in anion exchange efficiency has been detected, probably due to oxidized haemoglobin, resulting in damage to the cell membrane. According to this model, perturbations of the external medium may reflect on B3p transport efficiency, which critically depends on the interaction with intracellular proteins, such as haemoglobin. In this regard, curcumin protected erythrocyte membranes against OS associated to extracellular pH variations by scavenging free radicals.

B3p is expressed in all cells and tissue of the body, including brain and lymphocytes, and represents an excellent marker protein for post-translational modifications during ageing. In this respect, the anion transport ability of B3p decreased in brains and erythrocytes from old mice and, in addition, this functional reduction was associated to obvious structural changes. In parallel, the anion transport by lymphocytes also declined with age and these alterations could be delayed or prevented by increased levels of vitamin E supplied by the diet. Thus, vitamin E, which acts at membranes level, where the transporter resides, restored the anion exchange via B3p.

2.2 The SLC4A2 isoform

SLC4A2, or anion exchanger 2 (AE2), is an electroneutral \(Cl^-/HCO_3^-\) exchanger that in humans is encoded by the SLC4A2 gene. This transporter is expressed in many tissues, including blood vessels, airways epithelia, proximal colon, and salivary glands cells and regulates the intracellular pH and \(Cl^-\) concentration. In addition to these regulatory functions, AE2 exerts a central role in the transport of superoxide radicals and is also activated by low concentrations of \(NH_4^+\) in several cell types. All AE anion exchangers have a large N-terminal cytoplasmic domain, which is about 700 amino acid long for AE2, followed by a 500 amino acid polytopic transmembrane domain and a short C-terminal cytoplasmic tail. Crosslinking studies in gastric parietal cell membranes suggest that AE2 possesses a dimeric structure.
2.2.1 SLC4A2 and oxidative stress

Diabetes mellitus causes a wide variety of vascular complications that are closely related to the degree of glycaemic control, suggesting that abnormal blood glucose levels are a critical risk factor for the damage of endothelial cells. In a model of hyperglycaemia based on human umbilical vein endothelial cells (HUVECs), high concentrations of glucose induced apoptosis of cells in a time and concentration-dependent manner. Apoptosis was guided by the mitochondrial permeability transition pore (mPTP)/ROS/Caspase-3 pathway and was dependent on AE2. Indeed, glucose upregulated the expression as well as the activity of AE2, as evidenced by an increased intracellular Cl⁻ concentration. Pharmacological inhibition or silencing of the expression of AE2 protected cells from apoptosis.

Turi and collaborators have reported that the expression of AE2 in rat airway epithelial cells is regulated by OS, and this regulation seems to be mediated by transcription factor AP-1, a specific protein able to respond to elevated intracellular concentrations of ROS, including H₂O₂. The transport of superoxide radicals via AE2 raises interesting questions with regard to the regulation of AE2 in the lung. Since superoxide radicals can contribute to oxidant lung injury, the increase of expression of AE2 following OS exposure should provide increased transport of O₂⁻ out of the cell, thus limiting the oxidative damage. Accordingly, AE2 has been demonstrated to protect cell viability in a model of lung reperfusion injury. However, other studies have shown a decreased injury when the function of the AE2 exchanger was blocked. Therefore, the expression of AE2 and its function can be altered by OS, but it remains unclear how such alterations occur and, ultimately, whether this molecular entity can protect or rather injure cells during periods of elevated OS.

3 THE SLC26 FAMILY

The SLC26 family of multifunctional ion transporters and channels comprises 11 genes (SLC26A1-11) of which 10 are protein coding and one (SLC26A10) is a pseudogene. With the exception of SLC26A5, which encodes for the outer hair cells motor protein prestin, these genes encode multifunctional anion exchangers, of which SLC26A7, A9 and A11 can also operate as uncoupled ion transporters in a channel-like mode. The anion exchangers of this family can accept divalent as well as monovalent anions and generally show versatile substrate selectivity, being able to exchange chloride for inorganic anions such as bicarbonate, hydroxyl, sulphate and iodide, or small organic anions such as formate and oxalate. SLC26A3, A4, A6, A7, A9, and A11 can operate in Cl⁻/HCO₃⁻ exchange mode, while SLC26A1 and A2 are selective sulphate transporters.

The SLC26 family was discovered more recently and is less well characterized compared with SLC4. SLC26 members are highly hydrophobic, large (700–1,000 amino acids) proteins sharing relatively low (21%-43%) amino acid identity with the members of the same family. The structure of mammalian SLC26 transporters has long been elusive. Structures of the murine Slc26a9, two bacterial homologues—a bicarbonate transporter from cyanobacteria (BicA) and a proton-coupled fumarate transporter from the bacterium Deinococcus geothermalis (SLC26Dg), and a plant homologue of SLC26—the vacuolar H⁺/SO₄²⁻ symporter SULTR4;1 from Arabidopsis thaliana were solved recently by X-ray crystallography and cryo-electron microscopy. These structures show a shared architecture consisting of 14 transmembrane α-helices organized in two intertwined inverted repeats of seven transmembrane segments each and a large C-terminal cytosolic domain referred to as the sulphate transporter and anti-sigma factor antagonist (STAS) domain. It is widely accepted that mammalian SLC26 members and their lower organism counterparts act as functional homodimers, although the dimerization mechanism was not unequivocally determined and probably differs among family members. Two swapped STAS domains have been determined as major determinants of the homodimeric assembly of murine Slc26a9, Arabidopsis thaliana SULTR4;1 and BicA from Synechocystis sp. while the STAS domain is not a requisite for SLC26Dg dimerization, which indeed relies on contacts between the transmembrane domain and is centred on TM14.

Some of the members of the SLC26 family show restricted tissue distribution, whereas other isoforms are more broadly expressed and orchestrate the ion transport across epithelia such as the intestine and kidney. Pathogenic sequence alterations in SLC26 genes cause inherited diseases, including diastrophic dysplasia (phenotype MIM number 222600) and other osteochondrodysplastic syndromes (SLC26A2), secretory chloride diarrhoea (SLC26A3, phenotype MIM number 214700), Pendred syndrome (SLC26A4, phenotype MIM number 274600) and non-syndromic deafness (SLC26A4 and A5, phenotype MIM numbers 600791 and 613865, respectively), calcium oxalate nephrolithiasis (SLC26A1 and A6, phenotype MIM number 167030), and spermatogenic failure (SLC26A8, phenotype MIM number 606766). SLC26A3, A4, A6, A8 and A9 physically and/or functionally interact with the CFTR chloride channel and regulate the CFTR activity or are regulated by CFTR.

The information regarding the impact of OS on SLC26 function is sparse, and will be reviewed in the following and in Table 2.
SLC26A3/DRA was initially identified as a candidate tumour suppressor gene that was downregulated in adenoma (hence the alias DRA). Later, SLC26A3 was identified by positional cloning as the gene mutated in recessive congenital chloride-losing diarrhoea. This transporter is expressed on the apical membrane of epithelial cells in the intestine and is particularly abundant in the colon and duodenum. SLC26A3 functions as a Cl⁻/HCO₃⁻ exchanger in tandem with NHE3, which mediates a Na⁺/H⁺ exchange, to generate an electroneutral NaCl reabsorption across the intestinal mucosa, or gives rise to HCO₃⁻ secretion in the absence of NHE3.

3.1.1 SLC26A3/DRA and oxidative stress

Oxidative stress plays an essential role in the pathogenesis and progression of inflammatory bowel disease (IBD). It is well known that SLC26A3 expression is reduced in animal models of intestinal inflammation as well as in patients with ulcerative colitis (UC), an effect that was attributed to inhibition of gene transcription by proinflammatory cytokines. Interestingly, H₂O₂ inhibited the SLC26A3 and SLC26A6-mediated Cl⁻/OH⁻ (HCO₃⁻) exchange activity in Caco-2 cells independently of the prostaglandin/COX-dependent pathway, but occurring via a signalling cascade that involved the activation of the Src kinase Fyn, PI3K, PLCγ1 and the Ca²⁺-dependent PKCα. These authors concluded that phosphorylation of the anion exchangers or regulatory proteins, rather than modification of their plasma membrane trafficking, might be involved in modulation of their activity.

In a recent study, the gene expression of SLC26A3 was decreased in the colonic mucosa from patients with active UC compared with patient in remission and non-inflamed donors. In parallel, SOD2 was significantly upregulated in the colonic mucosa from patients with active UC compared with controls, thus denoting an increased OS, and SOD2 levels correlated with severe histological activity in the inflamed mucosa. Together, these findings suggest that OS might contribute to inhibition of expression and function of SLC26A3 in the context of IBD, thus aggravating fluid loss and stool acidification consequent to lack of NaCl reabsorption and HCO₃⁻ secretion.

| Transport mode | Isoform | Experimental model | Findings | References |
|----------------|---------|--------------------|----------|------------|
| Anion exchanger | SLC26A1 | No information available | Reduction of DIDS-sensitive ³⁶Cl⁻ uptake | 135 |
| Anion exchanger | SLC26A2 | No information available | | |
| Anion exchanger | SLC26A3 | CaCo-2 cells exposed to H₂O₂ | Tissue from patients with active ulcerative colitis | |
| Anion exchanger | SLC26A4 | Knockout mouse | Increased OS in the stria vascularis | 142 |
| Anion exchanger | SLC26A5 | Placenta of smoking mothers | Increased transcript levels | 155 |
| Anion exchanger | SLC26A6 | CaCo-2 cells exposed to H₂O₂ | Reduction of DIDS-sensitive ³⁶Cl⁻ uptake | 135 |
| Anion exchanger | SLC26A7 | No information available | | |
| Anion exchanger | SLC26A8 | No information available | | |
| Anion exchanger | SLC26A9 | No information available | | |
| Anion exchanger | SLC26A10 | No information available | | |

### Table 2: Link between SLC26 members and oxidative stress (OS)

Anion exchangers of this family are all Na⁺-independent

| Transport mode | Isoform | Experimental model | Findings | References |
|----------------|---------|--------------------|----------|------------|
| Anion exchanger | SLC26A1 | No information available | Reduction of DIDS-sensitive ³⁶Cl⁻ uptake | 135 |
| Anion exchanger | SLC26A2 | No information available | | |
| Anion exchanger | SLC26A3 | CaCo-2 cells exposed to H₂O₂ | Tissue from patients with active ulcerative colitis | |
| Anion exchanger | SLC26A4 | Knockout mouse | Increased OS in the stria vascularis | 142 |
| Anion exchanger | SLC26A5 | Placenta of smoking mothers | Increased transcript levels | 155 |
| Anion exchanger | SLC26A6 | CaCo-2 cells exposed to H₂O₂ | Reduction of DIDS-sensitive ³⁶Cl⁻ uptake | 135 |
| Anion exchanger | SLC26A7 | No information available | | |
| Anion exchanger | SLC26A8 | No information available | | |
| Anion exchanger | SLC26A9 | No information available | | |
| Anion exchanger | SLC26A10 | No information available | | |
3.2 | SLC26A4/pendrin

SLC26A4/pendrin is an electroneutral Cl⁻/anion exchanger abundantly expressed on the apical membrane of distinct epithelial cells of the *stria vascularis* and endolymphatic duct and sac of the inner ear, as well as in the thyroid and kidney. In the inner ear, pendrin drives HCO₃⁻ secretion and Cl⁻ reabsorption and controls the endolymphatic pH and volume. In the thyroid, pendrin participates in the iodide flux into the thyroid follicle, possibly via its Γ⁻/Cl⁻ exchange activity. In addition, pendrin expression is upregulated in the airways and oesophageal mucosa by the pro-inflammatory cytokines IL-4/IL-13 via a STAT6-mediated pathway. Loss or reduction of function of pendrin consequent to gene mutation causes autosomal recessive forms of non-syndromic as well as syndromic sensorineural hearing loss, ie, DFNB4 and Pendred syndrome, of which a malformation of the inner ear called enlarged vestibular aqueduct (EVA) with or without cochlear incomplete partition type 2 is the main radiological finding. Vestibular dysfunction is also observed in a fraction of patients. In Pendred syndrome, deafness is associated with a partial iodide organification defect in the thyroid that may lead to subclinical or overt hypothyroidism and goiter. In the cortical collecting duct and connecting tubule of the kidney nephron, pendrin is expressed on the apical membrane of β and non-α, non-β intercalated cells, mediates Cl⁻ reabsorption and HCO₃⁻ excretion and controls the systemic electrolyte, vascular volume and acid-base homoeostasis by working in concert with other ion absorbing transport systems, including the sodium chloride cotransporter NCC and the epithelial sodium channel ENaC.

3.2.1 | SLC26A4/pendrin and oxidative stress

A possible link between OS and pendrin expression and function in the inner ear was firstly reported by Wangemann and collaborators, who described hyperpigmentation of the *stria vascularis* in pendrin-knockout mice. Hyperpigmentation of the *stria vascularis* was linked to an increased melanin production in the strial intermediate cells, which are in charge of detoxification of free radicals produced by the metabolically active strial marginal cells. The authors proposed a model where lack of bicarbonate secretion in the endolymph due to the absence of pendrin, with consequent increase of bicarbonate concentration and pH in the intra-strial fluid, may have led to inhibition of cysteine uptake and glutathione synthesis in the intermediate cells and free radical damage of these cells. Oxidative stress in the intermediate cells was proposed to be responsible for the reduced protein expression of KCNJ10/Kir4.1, an inwardly rectifying K⁺ channel essential for the generation and maintenance of the endocholear potential and proper hearing function. In this context, pH control via pendrin would exert a protective role against OS. Accordingly, elevated amounts of oxidized and nitrated proteins were found in the *stria vascularis* of pendrin-knockout mice, and OS reduced Kcnj10 expression in a heterologous system. These findings underscore the physio-pathological relevance of OS, leading to failure of KCNJ10 expression, lack of endocholear potential and deafness in mouse models and possibly in patients with pendrin-related hearing loss.

A recent study has evidenced a significant increase in the SLC26a4 transcript levels in the cochlea of three distinct mouse models of age-related hearing loss linked to chronic OS, represented by mice subjected to intermittent hypoxia alone, high-fat diet plus galactose injection and intermittent hypoxia combined with high-fat diet and galactose injection for 12 weeks, respectively. These changes were paralleled by an increase in the hearing threshold and morphological damage of cochlear hair cells. Although the pathophysiological significance of the altered SLC26a4 transcript levels in these mouse models remains unclear, this study suggests that pendrin transcriptional regulation might respond to OS with compensatory changes.

In the thyroid, iodide reaches the follicular lumen via pendrin and is subsequently incorporated (organified) into thyroglobulin (Tg) by the thyroid peroxidase (TPO), which requires H₂O₂ as cofactor. H₂O₂ is generated by dual oxidases (DUOXs). In a normal thyroid, TPO and DUOX expression is restricted to the apical membrane of thyrocytes or confined within Caveolin-1-positive intracellular vesicles. Similar to what was observed in the inner ear of pendrin-knockout mice, OS was augmented in the thyroid of a patient with Pendred syndrome, as evidenced by greatly increased lipid peroxidation as well as catalase and peroxiredoxin PRDX5 expression. In parallel, TPO and DUOX showed greatly enhanced expression, lost their normal apical distribution and were mislocalized within the cytosol, while the expression of Caveolin-1 was absent. These authors linked the increased OS in the thyroid tissue with aberrant, intracellular thyroid hormone biosynthesis, a process that would require H₂O₂ production within the cytosol. Although the mechanism by which TPO and DUOX were mislocalized remained unexplained, these findings underscore the importance of proper pendrin activity in protecting from dramatic OS-related pathological changes in the thyroid.

Pendrin transcript was found downregulated (~4.6 and ~6.0 fold after 52 and 100 weeks, respectively) in the kidney from F344 male rats exposed to 400 ppm (high) potassium bromate in drinking water. Potassium bromate is a nephrotoxic compound and a kidney and
thoracic carcinogen, can induce deafness and promotes OS, as evidenced by de-regulation of OS-related genes. Although the mechanism leading to decreased pendrin mRNA levels remained unexplained, this study suggests that pro-oxidant compounds might suppress pendrin transcription in the kidney and perhaps other organs, including the inner ear. Further studies are needed to verify this hypothesis.

Similarly to thyroid, the airway and lung epithelium has the ability to generate $H_2O_2$ at the apical membrane through DUOX1 and DUOX2. $H_2O_2$ serves to oxidize luminal SCN$^-$ to OSCN$^-$ (hypothiocyanite) in a reaction catalyzed by lactoperoxidase and other peroxidases. Both anions are pro-oxidant species, have an antimicrobial role and play an important function in the innate mucosal defense. Pendrin is a major determinant of the IL-4/IL-13-stimulated SCN$^-$ secretion at the luminal surface of human bronchial epithelial cells and lung. When upregulated by ILs in the context of airway inflammation and allergic asthma, SCN$^-$ secretion may lead to increased OSCN$^-$ production. OSCN$^-$ in low doses can be sensed by the OS-sensitive PKA, which dimerizes and activates NF-xB, a transcription factor critical for inflammatory responses. High doses of OSCN$^-$ can induce necrosis of epithelial cells, further triggering inflammation. The implications of these findings are that (i) a defective SCN$^-$ secretion via pendrin might be linked to increased bacterial colonization of the airway epithelium and (ii) inhibition of pendrin activity or peroxidase-dependent conversion of SCN$^-$ to OSCN$^-$ might be beneficial in treating asthma and other chronic inflammatory airway conditions. These studies highlight how ion transport, OS and inflammation are tightly interconnected and their dysregulation might profoundly affect mucosal function and health.

### 3.3 SLC26A5/prestin

SLC26A5/prestin is the transmembrane sensor-motor protein of the outer air cells (OHC) of the mammalian organ of Corti and enables changes in length of these cells depending on the frequency of a sound stimulus, which is the basis of the mechanism of cochlear amplification of sounds. Although prestin shares high homology with other members of the SLC26 family of proteins including pendrin and DRA, it does not transport ions across the plasma membrane, but instead changes its structure by voltage-dependent translocation of anions within the molecule itself. Targeted deletion of prestin exons 3-7 in mice resulted in loss of OHC electromotility in vitro and a 40-60 dB loss of cochlear sensitivity in vivo. A limited number of SLC26A5 mutations has been identified in patients with hearing loss; one of these mutations was linked to autosomal recessive deafness DFNB61 but later was found non-pathogenic. Due to the limited number of patients, whether any of the identified SLC26A5 mutations are true causes of hearing loss remains unclear.

#### 3.3.1 SLC26A5/prestin and oxidative stress

Katbamna et al have shown that prenatal smoke exposure ($\geq 10$ cigarettes/d) leads to significant reductions in the cochlear response amplitudes and auditory brainstem recording (ABR) wave latencies in newborns. These alterations in the auditory function were paralleled by a dysregulation of the expression of placental genes, including SLC26A5, which was upregulated 8.95 fold, again suggesting an adaptive change. Also, several OS pathway genes were found dysregulated. The authors suggested that placental gene expression might be a good surrogate of foetal gene expression. The study raises the possibility that prenatal exposure to OS might damage the hearing function in the newborn by targeting genes involved in regulating the hearing function.

Oxidative stress following production of ROS is a hallmark of noise-induced hearing loss and mainly targets OHC. Prestin was used to selectively target ROS-scavenging nanoparticles to OHC in a guinea pig model of noise-induced hearing loss. This innovative strategy allowed for preservation of the morphological integrity of OHC and led to significant improvement of the hearing function, denoting that protection of OHC and their delicate molecular machinery from OS is crucial in the prevention and treatment of noise-induced hearing loss.

### 3.4 SLC26A6/PAT1/CFEX

SLC26A6 putative anion transporter 1 (PAT1) and chloride-formate exchanger (CFEX) was cloned based on the homology to the genes encoding SLC26A3 and SLC26A4, was found most abundantly expressed in the kidney and pancreas, but was also detected in other tissues, including the intestine. SLC26A6 can work in Cl$^-$/HCO$_3^-$, Cl$^-$/OH$^-$, chloride/oxalate and chloride/formate exchange modes. Mutant mice lacking Slc26a6 develop calcium oxalate urolithiasis, have significant hyperoxaluria and elevation in plasma oxalate concentration, both resulting from a defect in intestinal oxalate excretion, which leads to an enhanced net absorption of oxalate. In the human pancreas and intestine, SLC26A6 is co-expressed with SLC26A3 and CFTR and participates in chloride-dependent HCO$_3^-$ secretion by acting synergistically with CFTR; in addition, SLC26A6 mediates oxalate excretion in
the intestine and kidney proximal tubule and Cl\(^{-}/\)HCO\(_{3}^{-}\) exchange in the myocardium. These findings imply a role of SLC26A6 in the development of intestinal and pancreatic diseases, nephrolithiasis and arrhythmia.\(^{161}\)

3.4.1 | SLC26A6/PAT1/CFEX and oxidative stress

In normal rat proximal tubular epithelial (NRK-52E) cells, SLC26A6 expression correlated with oxalate-induced cell injury, apoptosis, crystal adhesion, ROS formation and lipid peroxidation. Accordingly, selective attenuation of SLC26A6 expression in the kidney of rats with lentivirus-transfected siRNAs decreased SOD generation, cell apoptosis and crystal formation.\(^{162}\) This study highlights that SLC26A6-mediated oxalate excretion in the kidney might be a determinant of stone formation as well as OS-induced cell injury and identifies SLC26A6 as a target of potential protective therapeutic approaches.

4 | CONCLUDING REMARKS

Several studies have investigated in detail the impact of OS on some transporters of the SLC4 family in different experimental conditions (Table 1). In particular, great attention has been reserved to SLC4A1. In this regard, human erythrocytes exposed to various oxidizing agents or extracellular pH variations have shown both a reduction in transport efficiency and changes in the structural state of SLC4A1. Instead, in ex vivo or in vitro models of inflammation, diabetes mellitus and ageing, the SLC4A1 ion transport was found accelerated. While the reasons of this apparent discrepancy are only partly elucidated, it becomes increasingly obvious that the activity of SLC4A1 is sensitive to OS and increases or decreases in ion transport efficiency most likely reflects the formation and/or the amount of glycated haemoglobin and methaemoglobin, as well as the integrity of the lipid bilayer ad the intricate intracellular network of interacting proteins (Figure 3).

The potential impact of OS on the expression and activity of SLC26 family members was less extensively studied compared with SLC4A1. For several SLC26 members, there is no information available in this context. The current knowledge denotes a dual role of these transporters in being potential targets as well as determinants of OS (Figure 3). For example, function and possibly expression of SLC26A3 and SLC26A6 can be reduced during OS. Similarly, SLC26A4 and SLC26A5 gene expression appeared dysregulated in OS. In turn, lack of expression of SLC26A4 was associated with increased OS in the human thyroid and mouse cochlea. At the same time, SLC26A4 upregulation in the context of inflammation and SLC26A6 appeared aggravating or mediating OS (Table 2). More studies are needed to explain how SLC26 members sense, respond to or determine OS. Particularly intriguing is the hypothesis of a possible dysfunction of SLC26A4 and SLC26A5 mediated by OS in noise-induced and/or age-related hearing loss.

Further research should establish whether and how members of the SLC4 and SLC26 family of proteins can be safely and effectively targeted by antioxidants in the prevention and treatment of OS-related conditions, including inflammation, metabolic dysfunctions, hearing loss and ageing.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to performing the literature search and writing the manuscript. All authors have read and agreed to the final version of the manuscript.

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REFERENCES

1. Burton GJ, Jauniaux E. Oxidative stress. Best Pract Res Clin Obstet Gynaecol. 2011;25(3):287-299.
2. Pizzino G, Irrera N, Cucinotta M, et al. Oxidative stress: harms and benefits for human health. Oxid Med Cell Longev. 2017;2017:8416763.
3. Lushchak VI. Free radicals, reactive oxygen species, oxidative stress and its classification. Chem Biol Interact. 2014;224:164-175.
4. Halliwell B. The antioxidant paradox: less paradoxical now? Br J Clin Pharmacol. 2013;75(3):637-644.
5. Mailloux RJ. An update on mitochondrial reactive oxygen species production. Antioxidants (Basel). 2020;9(6):472.
6. Magnani F, Mattevi A. Structure and mechanisms of ROS generation by NADPH oxidases. Curr Opin Struct Biol. 2019;59:91-97.
7. Juan CA, Perez de la Lastra JM, Plou FJ, Perez-Lebena E. The chemistry of reactive oxygen species (ROS) revisited: outlining their role in biological macromolecules (DNA, lipids and proteins) and induced pathologies. Int J Mol Sci. 2021;22(9):4642.
8. Neha K, Haider MR, Pathak A, Yar MS. Medicinal prospects of antioxidants: a review. Eur J Med Chem. 2019;178:687-704.
9. Zhang J, Wang X, Vikash V, et al. ROS and ROS-mediated cellular signaling. Oxid Med Cell Longev. 2016;2016:4350965.
10. Schieber M, Chandel NS. ROS function in redox signaling and oxidative stress. Curr Biol. 2014;24(10):R453-R462.
11. Droge W. Free radicals in the physiological control of cell function. Physiol Rev. 2002;82(1):47-95.
12. Jones DP. Radical-free biology of oxidative stress. *Am J Physiol Cell Physiol.* 2008;295(4):C849-C868.
13. Halliwell B. Reactive species and antioxidants. Redox biology is a fundamental theme of aerobic life. *Plant Physiol.* 2006;141(2):312-322.
14. Yan LJ. Pathogenesis of chronic hyperglycemia: from reductive stress to oxidative stress. *J Diabetes Res.* 2014;2014:137919.
15. Moldogazieva NT, Mokhosoev IM, Mel’nikova TI, Porozov YB, Terentiev AA. Oxidative stress and advanced lipoxidation and glycation end products (ALEs and AGEs) in aging and age-related diseases. *Oxid Med Cell Longev.* 2019;2019:3085756.
16. Uttara B, Singh AV, Zamboni P, Mahajan RT. Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. *Curr Neuropharmacol.* 2009;7(1):65-74.
17. Giacco F, Brownlee M. Oxidative stress and diabetic complications. *Circ Res.* 2010;107(9):1058-1070.
18. Hegab Z, Gibbons S, Neyes L, Mamas MA. Role of advanced glycation end products in cardiovascular disease. *World J Cardiol.* 2012;4(4):90-102.
19. Klaunig JE. Oxidative stress and cancer. *Curr Pharm Des.* 2018;24(40):4771-4778.
20. Akki R, Siracusa R, Cordaro M, et al. Adaptation to oxidative stress at cellular and tissue level. *Arch Physiol Biochem.* 2019:1-11.
21. Hediger MA, Romero MF, Peng JB, Rolfs A, Takanaga H, Bruford EA. The ABCs of solute carriers: physiological, pathological and therapeutic implications of human membrane transport proteins.Introduction. *Pflugers Arch.* 2004;447(5):465-468.
22. Zhang Y, Zhang Y, Sun K, Meng Z, Chen L. The SLC transporter in nutrient and metabolic sensing, regulation, and drug development. *J Mol Med Biol.* 2019;11(1):1-13.
23. Povey S, Lovering R, Bruford E, Wright M, Lush M, Wain H. The HUGO gene nomenclature committee (HGNC). *Hum Genet.* 2001;109(6):678-680.
24. Lin L, Yee SW, Kim RB, Giacomini KM. SLC transporters as therapeutic targets: emerging opportunities. *Nat Rev Drug Discovery.* 2015;14(8):543-560.
25. Pizzagalli MD, Bensimon A, Superti-Furga G. A guide to plasma membrane solute carrier proteins. *FEBS J.* 2020;288(9):2784–2835. http://dx.doi.org/10.1111/febs.15531
26. Marino A, Dossena S, Tamma G, Donnini S. Oxidative stress and membrane transport systems. *Oxid Med Cell Longev.* 2018;2018:9625213.
27. Friard J, Laurain A, Rubera I, Duranton C. LRRC8/VRAC channels and the redox balance: a complex relationship. *Cell Physiol Biochem.* 2021;55(S1):106-118.
28. Shi J, Li H, Yuan C, Luo M, Wei J, Liu X. Cigarette smoke-induced acquired dysfunction of cystic fibrosis transmembrane conductance regulator in the pathogenesis of chronic obstructive pulmonary disease. *Oxid Med Cell Longev.* 2018;2018:6567578.
29. Hudson VM. New insights into the pathogenesis of cystic fibrosis: pivotal role of glutathione system dysfunction and implications for therapy. *Treat Respir Med.* 2004;3(6):353-363.
30. Bartlett DE, Miller RB, Thiesfeldt S, Lakhani HV, Shapiro JI, Sodhi K. The role of Na/K-ATPase signaling in oxidative stress related to aging: implications in obesity and cardiovascular disease. *Int J Mol Sci.* 2018;19(7):2139.
31. Alper SL. Molecular physiology of SLC4 anion exchangers. *Exp Physiol.* 2006;91(1):153-161.
32. Jeong YS, Hong JH. Governing effect of regulatory proteins for Cl(-)/HCO3(-) exchanger 2 activity. *Channels (Austin).* 2016;10(3):214-224.
33. Liu Y, Yang J, Chen LM. Structure and function of SLC4 family [formula: see text] transporters. *Front Physiol.* 2015;6:355.
34. Wang LY, Tian Y, Wen HS, et al. SLC4 gene family in spotted sea bass (Lateolabrax maculatus): structure, evolution, and expression profiling in response to alkalinity stress and salinity changes. *Genes (Basel).* 2020;11(11):1271.
35. Pena-Munzenmayer G, George AT, Shull GE, Melvin JE, Catalan MA. Aε4 (Slc4a9) is an electroneutral monovalent cation-dependent Cl-/HCO3- exchanger. *J Gen Physiol.* 2016;147(5):423-436.
36. Steck TL. The organization of proteins in the human red blood cell membrane. A review. *J Cell Biol.* 1974;62(1):1-19.
37. Tanner MJ. Band 3 anion exchanger and its involvement in erythrocyte and kidney disorders. *Curr Opin Hematol.* 2002;9(2):133-139.
38. Alper SL. Molecular physiology and genetics of Na+-independent SLC4 anion exchangers. *J Exp Biol.* 2009;212(Pt 11):1672-1683.
39. Arakawa T, Kobayashi-Yurugi T, Alquel Y, et al. Crystal structure of the anion exchanger domain of human erythrocyte band 3. *Science.* 2015;350(6261):680-684.
40. Zhang D, Kiyatkin A, Bolin JT, Low PS. Crystallographic structure and functional interpretation of the cytoplasmic domain of erythrocyte membrane band 3. *Blood.* 2000;96(9):2925-2933.
41. Kodippilli GC, Spector J, Hale J, et al. Analysis of the mobilities of band 3 populations associated with ankyrin protein and junctional complexes in intact murine erythrocytes. *J Biol Chem.* 2012;287(6):4129-4138.
42. Ramasyami A. Atypical hereditary spherocytosis phenotype associated with pseudohypokalaemia and a new variant in the band 3 protein. *BMJ Case Rep.* 2020;13(12):e238428.
43. Reithmeier RA, Casey JR, Kalli AC, Sansom MS, Alquel Y, Iwata S. Band 3, the human red cell chloride/bicarbonate anion exchanger (AE1, SLCA4A1), in a structural context. *Biochim Biophys Acta.* 2016;1858(7 Pt A):1507-1532.
44. Frumence E, Genetet S, Ripoche P, et al. Rapid Cl−/HCO3− exchange kinetics of AE1 in HEK293 cells and hereditary stomatocytosis red blood cells. *Am J Physiol Cell Physiol.* 2013;305(6):C654-C662.
45. Wang DN. Band 3 protein: structure, flexibility and function. *FEBS Lett.* 1994;346(1):26-31.
46. Ramjeesingh M, Gaar A, Rothstein A. The amino acid conjugate formed by the interaction of the anion transport inhibitor 4,4′-diisothiocyanato-2,2′-stilbenedisulfonic acid (DIDS) with band 3 protein from human red blood cell membranes. *Biochim Biophys Acta.* 1981;641(1):173-182.
47. Chow EI, Crandall ED, Forster RE. Kinetics of bicarbonate-chloride exchange across the human red blood cell membrane. *J Gen Physiol.* 1976;68(6):633-652.
48. Jennings ML. Proton fluxes associated with erythrocyte membrane anion exchange. *J Membr Biol.* 1976;28(2-3):187-205.
49. Romano L, Passow H. Characterization of anion transport system in trout red blood cell. *Am J Physiol.* 1984;246 (3 Pt 1):C330-C338.
50. Bissinger R, Bhuyan AAM, Quadri SM, Lang F. Oxidative stress, erythropoiesis and anemia: a pivotal mechanistic nexus in systemic diseases. *FEBS J.* 2019;286(5):826-854.
51. Mrakic-Spota S, Gussoni M, Montorsi M, Porcelli S, Vezzoli A. Assessment of a standardized ROS production profile in humans by electron paramagnetic resonance. *Oxid Med Cell Longev*. 2012;2012:973927.

52. Podsiedlik M, Markowicz-Piasecka M, Sikora J. Erythrocytes as model cells for biocompatibility assessment, cytotoxicity screening of xenobiotics and drug delivery. *Chem Biol Interact*. 2020;332:109305.

53. Mohanty JG, Nagababu E, Rifkind JM. Red blood cell oxidative stress impairs oxygen delivery and induces red blood cell aging. *Front Physiol*. 2014;5:84.

54. Remigante A, Morabito R, Marino A. Band 3 protein function and oxidative stress in erythrocytes. *J Cell Physiol*. 2021;236(9):6225-6234.

55. Crupi R, Morabito R, Remigante A, et al. Susceptibility of erythrocytes from different sources to xenobiotics-induced lysis. *Comp Biochem Physiol C Toxicol Pharmacol*. 2019;221:68-72.

56. Farag MR, Alagawany M. Erythrocytes as a biological model for screening of xenobiotics toxicity. *Chem Biol Interact*. 2018;279:73-83.

57. Ferru E, Giger K, Pantaleo A, et al. Regulation of membrane-cytoskeletal interactions by tyrosine phosphorylation of erythrocyte band 3. *Blood*. 2011;117(22):5998-6006.

58. Pantaleo A, Ferru E, Pau MC, et al. Band 3 erythrocyte membrane protein acts as redox stress sensor leading to its phosphorylation by p (72) Syk. *Oxid Med Cell Longev*. 2016;2016:6051093.

59. Ferru E, Giger K, Pantaleo A, et al. Oxidized and poorly glycosylated band 3 is selectively phosphorylated by Syk kinase to form large membrane clusters in normal and G6PD-deficient red blood cells. *Biochem J*. 2009;418(2):359-367.

60. Thevenin BJ, Willardson BM, Low PS. The redox state of cytines 201 and 317 of the erythrocyte anion exchanger is critical for ankyrin binding. *J Biol Chem*. 1989;264(27):15886-15892.

61. Yamaguchi T, Nakano T, Matsumoto M, Terada S. Effects of chemical modification of cytines 201 and 317 of band 3 on hemolytic properties of human erythrocytes under hydrostatic pressure. *Ipn J Physiol*. 1998;48(3):205-210.

62. Morabito R, Romano O, La Spada G, Marino A. H2O2-induced oxidative stress affects SO4= transport in human erythrocytes. *PLoS One*. 2016;11(1):e0146485.

63. Galtieri A, Tellone E, Romano L, et al. Band-3 protein function in human erythrocytes: effect of oxygenation-deoxygenation. *Biochim Biophys Acta*. 2002;1564(1):214-218.

64. Teti D, Crupi M, Busa M, et al. Chemical and pathological oxidative influences on band 3 protein anion-exchanger. *Cell Physiol Biochem*. 2005;16(1-3):77-86.

65. Nigra AD, Casale CH, Santander VS. Human erythrocytes: cytoskeleton and its origin. *Cell Mol Life Sci*. 2020;77(9):1681-1694.

66. De Franceschi L, Bertoldi M, Matte A, et al. Oxidative stress and beta-thalassemic erythroid cells behind the molecular defect. *Oxid Med Cell Longev*. 2013;2013:985210.

67. Bordin L, Fiore C, Dona G, et al. Evaluation of erythrocyte band 3 phosphotyrosine level, glutathione content, CA-125, and human epididymal secretory protein E4 as combined parameters in endometriosis. *Fertil Steril*. 2010;94(5):1616-1621.

68. Bordin L, Zen F, Ion-Popa F, Barbetta M, Baggio B, Clari G. Band 3 tyr-phosphorylation in normal and glucose-6-phosphate dehydrogenase-deficient human erythrocytes. *Mol Membr Biol*. 2005;22(5):411-420.

69. Bordin L, Quartesian S, Zen F, Vianello F, Clari G. Band 3 tyr-phosphorylation in human erythrocytes from non-pregnant and pregnant women. *Biochim Biophys Acta*. 2006;1758(5):611-619.

70. Ansar W, Ghosh S. C-reactive protein and the biology of disease. *Immunol Res*. 2013;56(1):131-142.

71. Morabito R, Remigante A, Cordero M, et al. Impact of acute inflammation on Band 3 protein anion exchange capability in human erythrocytes. *Arch Physiol Biochem*. 2020;1-7.

72. Spengler MI, Svetaz MJ, Leroux MB, Bertoluzzo SM, Parente FM, Bosch P. Lipid peroxidation affects red blood cells membrane properties in patients with systemic lupus erythematosus. *Clin Hemorheol Microcirc*. 2014;58(4):489-495.

73. Ciaramella P, Oliva G, Luna RD, et al. A retrospective clinical study of canine leishmaniasis in 150 dogs naturally infected by Leishmania infantum. *Vet Rec*. 1997;141(21):539-543.

74. De Luna R, Ferrante M, Severino L, et al. Decreased lipid fluidity of the erythrocyte membrane in dogs with leishmaniasis-associated anaemia. *J Comp Pathol*. 2000;122(2-3):213-216.

75. Morabito R, Remigante A, Cavallaro M, Taormina A, La Spada G, Marino A. Anion exchange through band 3 protein in canine leishmaniasis at different stages of disease. *Pflugers Arch*. 2017;469(5-6):713-724.

76. Biswas T, Pal JK, Naskar K, Ghosh DK, Ghosal J. Lipid peroxidation of erythrocytes during anemia of the hamsters infected with Leishmania donovani. *Mol Cell Biochem*. 1995;146(2-3):99-105.

77. Ighodaro OM. Molecular pathways associated with oxidative stress in diabetes mellitus. *Biomed Pharmacother*. 2018;108:656-662.

78. Szablewski L, Sulima A. The structural and functional changes of blood cells and molecular components in diabetes mellitus. *Biol Chem*. 2017;398(4):411-423.

79. Viskupicova J, Blaskovic D, Galiniak S, et al. Effect of high glucose concentrations on human erythrocytes in vitro. *Redox Biol*. 2015;5:381-387.

80. Morabito R, Remigante A, Spinelli S, et al. High glucose concentrations affect band 3 protein in human erythrocytes. *Antioxidants (Basel)*. 2020;9(5):365.

81. Verma N, Liu M, Ly H, et al. Diabetic microcirculatory disturbances and pathologic erythropoiesis are provoked by deposition of amyloid-forming amylin in red blood cells and capillaries. *Kidney Int*. 2020;97(1):143-155.

82. Berry GT. Classic galactosemia and clinical variant galactosemia. In: Adam MP, Ardinger HH, Pagon RA, et al., *GeneReviews(R)*. Seattle: University of Washington; 1993. https://www.ncbi.nlm.nih.gov/books/NBK1518/. Accessed November 15, 2021.

83. Haskovic M, Coelho AI, Bierau J, et al. Pathophysiology and targets for treatment in hereditary galactosemia: a systematic review of animal and cellular models. *J Inherit Metab Dis*. 2020;43(3):392-408.

84. Howard NJ, Monaghan H, Martin JM. Hemoglobin A1 in galactosemia, a possible role in monitoring dietary compliance. *Acta Paediatr Scand*. 1981;70(5):695-698.

85. Remigante A, Morabito R, Spinelli S, et al. d-Galactose decreases anion exchange capability through band 3 protein in human erythrocytes. *Antioxidants (Basel)*. 2020;9(8):689.

86. Pandey KB, Rizvi SI. Markers of oxidative stress in erythrocytes and plasma during aging in humans. *Oxid Med Cell Longev*. 2010;3(1):2-12.
87. Mohanty JG, Shukla HD, Williamson JD, Launer LJ, Saxena S, Rifkind JM. Alterations in the red blood cell membrane proteome in Alzheimer’s subjects reflect disease-related changes and provide insight into altered cell morphology. Proteome Sci. 2010;8:11.

88. Stevenson A, Lopez D, Khoo P, Kalaria RN, Mukaetova-Ladinska EB. Exploring erythrocytes as blood biomarkers for Alzheimer’s disease. J Alzheimers Dis. 2017;60(3):845-857.

89. Bosman GJ, Bartholomeus IG, de Man AJ, van Kalmthout PJ, de Grip WJ. Erythrocyte membrane characteristics indicate abnormal cellular aging in patients with Alzheimer’s disease. Neurobiol Aging. 1991;12(1):13-18.

90. Kay MM, Rapcsak SZ, Bosman GJ, Goodman JR. Posttranslational modifications of brain and erythrocyte band 3 during aging and disease. Cell Mol Biol (Noisy-le-grand). 1996;42(7):99-944.

91. Kay MM, Flowers N, Goodman J, Bosman G. Alteration in membrane protein band 3 associated with accelerated erythrocyte aging. Proc Natl Acad Sci USA. 1989;86(15):5834-5838.

92. Cebe T, Yanar K, Atukeren P, et al. A comprehensive study of myocardial redox homeostasis in naturally and mitemically aged rats. Age (Dordr). 2014;36(6):9728.

93. Remigante R, Spinelli S, Trichilo V, et al. d-Galactose induced early aging in human erythrocytes: role of band 3 protein. J Cell Physiol. 2021. Online ahead of print.

94. Guo Q, Li F, Duan Y, et al. Oxidative stress, nutritional antioxidants and beyond. Sci China Life Sci. 2020;63(6):866-874.

95. Remigante A, Morabito R, Marino A. Natural antioxidants beneficial effects on anion exchange through band 3 protein in human erythrocytes. Antioxidants (Basel). 2019;9(1):25.

96. Barbagallo M, Veronese N, Dominguez LJ. Magnesium in aging, health and diseases. Nutrients. 2021;13(2):463.

97. Morabito R, Remigante A, Marino A. Protective role of magnesium against oxidative stress on SO4(=) uptake through band 3 protein in human erythrocytes. Cell Physiol Biochem. 2019;52(6):1292-1308.

98. Morabito R, Remigante A, Di Pietro ML, Giannetto A, La Spada G, Marino A. SO4(=) uptake and catalase role in preconditioning after H2O2-induced oxidative stress in human erythrocytes. Pflugers Arch. 2017;469(2):235-250.

99. Angeloni C, Motori E, Fabbri D, et al. H2O2 preconditioning modulates phase II enzymes through p38 MAPK and PI3K/Akt activation. Am J Physiol Heart Circ Physiol. 2011;300(6):H2196-2205.

100. Morabito R, Remigante A, Marino A. Melatonin protects band 3 protein in human erythrocytes against H2O2-induced oxidative stress. Molecules. 2019;24(15):2741.

101. Ivanov IT. Low pH-induced hemolysis of erythrocytes is related to the entry of the acid into cytosole and oxidative stress on cellular membranes. Biochim Biophys Acta. 1999;1415(2):349-360.

102. Morabito R, Falliti G, Geraci A, Spada GL, Marino A. Curcumin protects -SH groups and sulphate transport after oxidative damage in human erythrocytes. Cell Physiol Biochem. 2015;36(1):345-357.

103. Celedon G, Gonzalez G, Pino J, Lissi EA. Peroxynitrite oxidizes erythrocyte membrane band 3 protein and diminishes its anion transport capacity. Free Radic Res. 2007;41(3):316-323.

104. Poulin JE, Cover C, Gustafson MR, Kay MB. Vitamin E prevents oxidative modification of brain and lymphocyte band 3 proteins during aging. Proc Natl Acad Sci USA. 1996;93(11):5600-5603.

105. Chernova MN, Stewart AK, Jiang L, Friedman DJ, Kunes YZ, Alper SL. Structure-function relationships of AE2 regulation by Ca(ii)(2+)
sensitive stimulators NH(4+)
and hyperpnicity. Am J Physiol Cell Physiol. 2003;284(5):C1235-C1246.

106. Faber S, Lang HJ, Hock FJ, Scholkens BA, Mutschler E. Intracellular pH regulation in bovine aortic endothelial cells: evidence of both Na+/H+ exchange and Na+-dependent Cl-/HCO3(-) exchange. Cell Physiol Biochem. 1998;8(4):202-211.

107. Wang HS, Chen Y, Vaira Mani K, Shull GE. Critical role of bicarbonate and bicarbonate transporters in cardiac function. World J Biol Chem. 2014;5(3):334-345.

108. Alper SL, Chernova MN, Stewart AK. How pH regulates a pH regulator: a regulatory hot spot in the N-terminal cytoplasmic domain of the AE2 anion exchanger. Cell Biochem Biophys. 2002;36(2-3):123-136.

109. Zolotarev AS, Shumukler BE, Alper SL. AE2 anion exchanger poly-peptide is a homooligomer in pig gastric membranes: a chemical cross-linking study. Biochemistry. 1999;38(26):8521-8531.

110. Queiroz M, Sena CM. Perivascular adipose tissue in age-related vascular disease. Ageing Res Rev. 2020;59:101040.

111. Huang QR, Li Q, Chen YH, et al. Involvement of anion exchanger-2 in apoptosis of endothelial cells induced by high glucose through an mPTP-ROS-Caspase-3 dependent pathway. Apoptosis. 2010;15(6):693-704.

112. Turi JL, Jaspers I, Dailey LA, et al. Oxidative stress activates anion exchange protein 2 and AP-1 in airway epithelial cells. Am J Physiol Lung Cell Mol Physiol. 2002;283(4):L791-L798.

113. Kennedy TP, Rao NV, Hopkins C, Pennington L, Tolley E, Hoidal JR. Role of reactive oxygen species in reperfusion injury of the rabbit lung. J Clin Invest. 1989;83(4):1326-1335.

114. Nozik-Grayck E, Piantadosi CA, van Adelsberg J, Alper SL, Huang YC. Protection of perfused lung from oxidative injury by inhibitors of anion exchange. Am J Physiol. 1997;273(2 Pt 1):L296-L304.

115. Mount DB, Romero MF. The SLC26 gene family of multifunctional anion exchangers. Pflugers Archiv Eur J Physiol. 2004;447(5):710-721.

116. Dorwart MR, Shcheynikov N, Yang D, Mualem S. The soluble carrier 6 family of proteins in epithelial ion transport. Physiology (Bethesda). 2008;23:104-114.

117. Alper SL, Sharma AK. The SLC26 gene family of anion transporters and channels. Mol Aspects Med. 2013;34(2-3):494-515.

118. Walter JD, Sawicka M, Dutzler R. Cryo-EM structures and functional characterization of murine SLC26a9 reveal mechanism of uncoupled chloride transport. eLife. 2019;8:e46986.

119. Wang C, Sun B, Zhang X, et al. Structural mechanism of the active bicarbonate transporter from cyanobacteria. Nat Plants. 2019;5(11):1184-1193.

120. Geertsma ER, Chang YN, Shaik FR, et al. Structure of a prokaryotic fumarate transporter reveals the architecture of the SLC26 family. Nat Struct Mol Biol. 2015;22(10):803-808.

121. Wang L, Chen K, Zhou M. Structure and function of Arabidopsis thaliana sulfate transporter. Nat Commun. 2021;12(1):4455.

122. Wang Y, Morabito M, Zhang XF, Webb E 3rd, Oztekin A, Cheng X. Shear-Induced Extensional Response Behaviors of Tethered von Willebrand Factor. Biophys J. 2019;116(11):2092-2102.

123. Chang YN, Jaumann EA, Reichel K, et al. Structural basis for functional interactions in dimers of SLC26 transporters. Nat Commun. 2019;10(1):2032.
124. Soleimani M, SLC26 Cl-/HCO3- exchangers in the kidney: roles in health and disease. *Kidney Int. 2013;84(4):657-666.

125. Seidl U, Nikolovskaya K. Slc26 family of anion transporters in the gastrointestinal tract: expression, function, regulation, and role in disease. *Compr Physiol. 2019;9(2):839-872.

126. Berg P, Svendsen SL, Sorensen MV, et al. Impaired renal HCO3(-) excretion in cystic fibrosis. *J Am Soc Nephrol. 2020;31(8):1711-1727.

127. El Khouri E, Touré A. Functional interaction of the cystic fibrosis transmembrane conductance regulator with members of the SLC26 family of anion transporters (SLC26A8 and SLC26A9): physiological and pathophysiological relevance. *Int J Biochem Cell Biol. 2014;52:58-67.

128. Knauf F, Thomson RB, Heneghan JF, et al. Loss of cystic fibrosis transmembrane regulator impairs intestinal oxalate secretion. *J Am Soc Nephrol. 2017;28(1):242-249.

129. Tse CM, Yin J, Singh V, et al. cAMP stimulates SLC26A3 activity in human colon by a CFTR-dependent mechanism that does not require CFTR activity. *Cell Mol Gastroenterol Hepatol. 2019;7(3):641-653.

130. Schweinfest CW, Henderson KW, Suster S, Kondoh N, Papas TS. Identification of a colon mucosa gene that is down-regulated in colon adenomas and adenocarcinomas. *Proc Natl Acad Sci USA. 1993;90(9):4166-4170.

131. Hoglund P, Haila S, Socha J, et al. Mutations of the Down-regulated in adenoma (DRA) gene cause congenital chloride diarrhea. *Nat Genet. 1996;14(3):316-319.

132. Tian T, Wang Z, Zhang J. Pathomechanisms of oxidative stress in inflammatory bowel disease and potential antioxidant therapies. *Oxid Med Cell Longev. 2017;2017:4535194.

133. Yang H, Jiang W, Furth EE, et al. Intestinal inflammation reduces expression of DRA, a transporter responsible for congenital chloride diarrhea. *Am J Physiol. 1998;275(6):G1445-G1453.

134. Xiao F, Juric M, Li J, et al. Loss of downregulated in adenoma (DRA) impairs mucosal HCO3(-) secretion in murine ileocolonic inflammation. *Inflamm Bowel Dis. 2012;18(1):101-111.

135. Saksena S, Gill RK, Tyagi S, Alrefai WA, Ramaswamy K, Dudeja PK. Role of Fyn and F13K in H2O2-induced inhibition of apical CI-/OH- exchange activity in human intestinal epithelial cells. *Biochem J. 2008;416(1):99-108.

136. Camarillo GF, Goyon EI, Zuñiga RB, Salas LAS, Escárcega AEP, Yamamoto-Furusho JK. Gene expression profiling of mediators associated with the inflammatory pathways in the intestinal tissue from patients with ulcerative colitis. *Mediators Inflamm. 2020;2020:1-11. http://dx.doi.org/10.1155/2020/9238970

137. Dossena S, Rodighiero S, Vezzoli V, et al. Functional characterization of wild-type and mutated pendrin (SLC26A4), the anion transporter involved in Pendred syndrome. *J Mol Endocrinol. 2009;43(3):93-103.

138. Vanoni S, Scantamburlo G, Dossena S, Paulmichl M, Nofziger C. interleukin-mediated pendrin transcriptional regulation in airway and esophageal epithelia. *Int J Mol Sci. 2019;20(3):731.

139. Dossena S, Nofziger C, Tamma G, et al. Molecular and functional characterization of human pendrin and its allelic variants. *Cell Physiol Biochem. 2011;28(3):451-466.

140. Roesch S, Rasp G, Sarikas A, Dossena S. Genetic determinants of non-syndromic enlarged vestibular aqueduct: a review. *Audiol Res. 2021;11(3):423-442.

141. Soleimani M, Valenti G. Pendrin and its partners in the kidney: roles in vascular volume and acid base regulation. In: Dossena S, Paulmichl M, eds. *The Role of Pendrin in Health and Disease. Switzerland: Springer; 2017:121-137.

142. Wangemann P, Itza EM, Albrecht B, et al. Loss of KCNJ10 protein expression abolishes endocochlear potential and causes deafness in Pendred syndrome mouse model. *BMC Med. 2004;2:30.

143. Singh R, Wangemann P. Free radical stress-mediated loss of KCNJ10 protein expression in stria vascularis contributes to deafness in Pendred syndrome mouse model. *Am J Physiol Renal Physiol. 2008;294(1):F139-F148.

144. Park DJ, Ha S, Choi JS, Lee SH, Park JE, Seo YJ. Induced short-term hearing loss due to stimulation of age-related factors by intermittent hypoxia, high-fat diet, and galactose injection. *Int J Mol Sci. 2020;21(19):7068.

145. Senou M, Khalifa C, Thimmesch M, et al. A coherent organization of differentiation proteins is required to maintain an appropriate thyroid function in the Pendred thyroid. *J Clin Endocrinol Metab. 2010;95(8):4021-4030.

146. Geter DR, Ward WD, Knapp GW, et al. Kidney toxicocnomics of chronic potassium bromate exposure in f344 male rats. *Transl Oncogenics. 2006;1:33-52.

147. Pedemonte N, Caci E, Sordo E, et al. Thiocyanate transport in resting and IL-4-stimulated human bronchial epithelial cells: role of pendrin and anion channels. *J Immunol. 2007;178(8):5144-5153.

148. Nofziger C, Dossena S, Suzuki S, Izuhara K, Paulmichl M. Pendrin function in airway epithelia. *Cell Physiol Biochem. 2011;28(3):571-578.

149. Suzuki S, Ogawa M, Ohta S, et al. Induction of airway allergic inflammation by hypothiocyanite via epithelial cells. *J Biol Chem. 2016;291(53):27219-27227.

150. Park J, Lee HJ, Song D, et al. Novel pendrin inhibitor attenuates airway hyperresponsiveness and mucin expression in experimental murine asthma. *J Allergy Clin Immunol. 2019;144(5):1425-1428.e1412.

151. Izuhara K, Suzuki S, Ogawa M, et al. The significance of hypothiocyanite production via the pendrin/DUOX/peroxidase pathway in the pathogenesis of asthma. *Oxid Med Cell Longev. 2017;2017:1054801.

152. Zheng J, Shen W, He DZ, Long KB, Madison LD, Dallos P. Prestin is the motor protein of cochlear outer hair cells. *Nature. 2000;405(6783):149-155.

153. Mio K, Kubo Y, Ogura T, Yamamoto T, Arisaka F, Sato C. The motor protein prestin is a bullet-shaped molecule with inner cavities. *J Biol Chem. 2008;283(2):1137-1145.

154. Liberman MC, Gao J, He DZ, Wu X, Jia S, Luo J. Prestin is required for electromotility of the outer hair cell and for the cochlear amplifier. *Nature. 2002;419(6904):300-304.

155. Katbammna B, Klutz N, Pudrith C, Lavery JP, Ide CF. Prenatal smoke exposure: effects on infant auditory system and placental gene expression. *Neurotoxicol Teratol. 2013;38:61-71.

156. Henderson D, Bielefeld EC, Harris KC, Hu BH. The role of oxidative stress in noise-induced hearing loss. *Ear Hear. 2006;27(1):1-19.

157. Zhao Z, Han Z, Naveena K, et al. ROS-responsive nanoparticle as a berberine carrier for OHC-targeted therapy of noise-induced hearing loss. *ACS Appl Mater Interfaces. 2021;13(6):7102-7114.
158. Lohi H, Kujala M, Kerkela E, Saarialho-Kere U, Kestila M, Kere J. Mapping of five new putative anion transporter genes in human and characterization of SLC26A6, a candidate gene for pancreatic anion exchanger. Genomics. 2000;70(1):102-112. http://dx.doi.org/10.1006/geno.2000.6355
159. Chernova MN, Jiang L, Friedman DJ, et al. Functional comparison of mouse slc26a6 anion exchanger with human SLC26A6 polypeptide variants: differences in anion selectivity, regulation, and electrogenicity. J Biol Chem. 2005;280(9):8564-8580.
160. Jiang Z, Asplin JR, Evan AP, et al. Calcium oxalate urolithiasis in mice lacking anion transporter Slc26a6. Nat Genet. 2006;38(4):474-478.
161. Zhang J, Liu Z, Chang A, et al. Abnormal mRNA splicing but normal auditory brainstem response (ABR) in mice with the presten (SLC26A5) IVS2-2A>G mutation. Mutat Res. 2016;790:1-7.
162. Jiang H, Gao X, Gong J, et al. Downregulated expression of solute carrier family 26 member 6 in NRK-52E cells attenuates oxalate-induced intracellular oxidative stress. Oxid Med Cell Longev. 2018;2018:1724648.

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