Ion Channels Involved in Oxidative Stress-Related Gastrointestinal Diseases

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Ion channels (ICs) are integral membrane proteins that play a crucial role in regulating the ions' flow across cell membranes. They are essential for maintaining cellular homeostasis and are involved in various physiological processes. The pathogenesis of various gastrointestinal (GI) disorders, including gastritis, ulcers, inflammatory bowel disease (IBD) and cancer, can be linked to oxidative stress. It is known that reactive species carry out a crucial role in the genesis and progression of these pathologies; however, the contribution of ionic channels in their development is still under discussion. The function of ion channels in the gastrointestinal tract influences a variety of cellular processes.

ion channels oxidative stress reactive species antioxidants

1. Introduction

Oxidative stress (OS) occurs due to an imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and the endogenous antioxidant defense system. This imbalance leads to cellular injury and subsequent dysfunctions that can result in a wide range of disorders [1][2]. Reactive species represent byproducts of normal cellular metabolism and are normally neutralized by a variety of cellular antioxidants: enzymatic, such as catalase (CAT) and superoxide dismutase (SOD), or non-enzymatic, such as glutathione [3].

Reactive species are generated in response to factors like UV radiation, smoking, alcohol consumption, the use of non-steroidal anti-inflammatory drugs (NSAIDs), infections, ischemia-reperfusion injury, and inflammation (**Figure 1**) [4][5]. While low to moderate levels of ROS and RNS have positive effects on several physiological functions, such as fighting pathogens, promoting wound healing, and aiding in tissue repair, they also serve as important signaling biomolecules [6][7]. However, excessive production can disrupt the body's balance and lead to oxidative damage in tissues. For this reason, OS has been implicated in various disease processes, including aging, ischemia-reperfusion injury, hypertension, atherosclerosis, diabetic neuropathies, renal diseases, neurological disorders, inflammatory bowel disease and cancer [8][9].

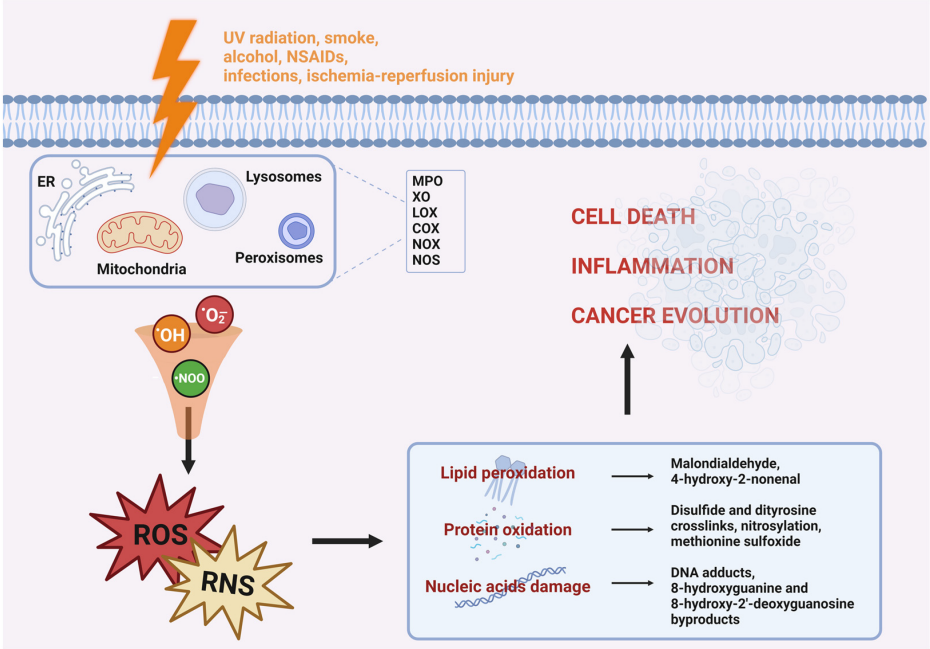

Figure 1. Oxidative stress and its effects on cells. Reactive species are generated by multiple processes at the level of different cell organelles and can be produced in reaction to different noxious stimuli. ROS and RNS thus obtained damaged cellular membranes, proteins, and DNA, contributing to cell death, inflammation and cancer.

In this regard, several exogenous and endogenous bioactive agents are well recognized for their ability to strengthen the antioxidant response against several diseases caused by OS, helping to fight the harmful effects of reactive species and to promote overall health [10][11]. For instance, nutraceuticals represent important sources of different classes of antioxidants and anti-inflammatory compounds, such as polyphenols and many bioactive peptides [12][13], which exhibit remarkable antioxidant activity that can be beneficial in GI diseases [14][15][16] and other conditions related to OS [17][18][19][20]. Furthermore, vitamin E and vitamin C, as well as supplementation with SOD and other endogenous enzymes have been shown to decrease oxidative stress markers and improve disease activity in patients with IBD [21][22].

The GI tract is both a source and a target of OS. Despite the protective barrier provided by the epithelial layer, digested food and pathogens can activate the epithelium, polymorphonuclear neutrophils (PMNs), and macrophages, leading to inflammation and the production of inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6, IL-4 and IL-8) and other mediators involved in oxidative stress [23][24]. Various GI disorders, for instance, gastroduodenal ulcers; GI malignancies, such as gastric and colorectal cancer; gastroesophageal reflux disease (GERD); IBD, which includes Crohn's disease (CD) and ulcerative colitis (UC); and irritable bowel syndrome (IBS), partly arise due to oxidative stress [7][10]. Considering that OS can alter the normal functioning of ion channels, which are essential for maintaining cellular homeostasis in gastrointestinal cells [25], it is crucial to understand the processes and changes initiated by free radicals.

1.1. Oxidative Stress

OS can have various implications on cellular homeostasis, depending on the intensity and duration of the insult. In some cases, an excess of ROS can damage cellular biomolecules, including lipids, proteins, and nucleic acids, leading to various negative consequences (**Figure 1**) [26][27].

Damage to lipids leads to the formation of lipid peroxidation products, such as malondialdehyde and 4-hydroxy-2-nonenal, derived from omega-6 fatty acids. These products exhibit various physiological and protective functions as signaling molecules stimulating gene expression and cell survival. However, they can also have a cytotoxic role by inhibiting gene expression and inducing cell death [28].

Lipid peroxidation is triggered by free radicals that affect unsaturated fatty acids in cell membranes. It involves a series of chain reactions continuing to occur once activated, resulting in progressive and cumulative changes in the structure and functions of the membrane [29]. These alterations include abnormalities in membrane potential, mitochondrial fission and its consequent release of calcium, activation of caspase-3, DNA fragmentation and, ultimately, the initiation of programmed cell death [30].

Damage to proteins can affect their structure and function, impairing metabolic pathways and enzymatic activity. Modifications caused by ROS/RNS include the loss of sulfhydryl groups, and the formation of carbonyls, disulfide crosslinks, methionine sulfoxide, dityrosine cross-links, nitration, nitrosylation, glutathionylation and glyoxidation, among others [31][32]. The oxidation of protein sulfhydryl groups occurs as a result of exposure to different ROS and is considered one of the immediate responses to increased oxidative stress. One of the main targets for oxidation within proteins is the amino acid cysteine, which contains a highly reactive thiol group. The latter undergo various oxidative modifications, including the formation of sulfenic, sulfinic, and sulfonic acids depending on the concentration of oxidants, redox potentials, local pH, charge, temperature, etc. [33][34]. Additionally, in pathological conditions with excessively high concentrations of ROS, other amino acids, such as arginine and lysine, can be altered to aldehydes, and methionine residues can be converted to sulfoxides or sulfones. Some of these modifications are irreversible and permanently affect protein function. Another oxidative modification in proteins is the formation of dityrosine crosslinks, which apparently occurs as a result of the reaction between two tyrosyl radicals, generated by peroxidases and other heme proteins. The addition of carbonyl-containing adducts to the side chains of amino acid residues, such as lysine, arginine, proline, and threonine, is another very common post-translational structural alteration in proteins [35].

Damage to nucleic acids by OS includes strand breaks, base modifications, and the formation of DNA adducts. If not adequately repaired, these damages can lead to genomic instability [36][37]. ROS can react with purines and pyrimidines DNA bases causing various byproducts, such as 8-hydroxyguanine and 8-hydroxy-2′-deoxyguanosine, interfering with normal DNA replication and transcription [36]. Consequently, mutations caused by oxidative stress triggers can activate proto-oncogenes, converting them into oncogenes. Conversely, oncosuppressor genes, which normally control cell growth and prevent tumor formation, can be inactivated by ROS-induced DNA damage leading to uncontrolled cell proliferation and the development of gastrointestinal cancers [38][39].

Oxidative stress can also influence cellular signaling regulation and gene expression. It can modulate transcription factors, such as activator protein-1 (AP-1), nuclear factor kappa B (NF-κB), and/or NF-E2-related factor (Nrf2), which control the expression of genes involved in inflammatory response and apoptosis. Additionally, it can interfere with cellular signaling pathways, including mitogen-activated protein kinases (MAPKs) and tyrosine kinases. It can also disrupt the cellular response to various external signals (**Figure 1**) [40].

1.2. Reactive Oxygen and Nitrogen Species

Molecular oxygen (O_2) is involved in energy production through mitochondrial respiration; however, it also paradoxically contributes to cell death because ROS are derived from its chemical reduction. ROS include radical compounds such as superoxide ($O_2^{\bullet-}$), hydroxyl radicals (•OH), lipid hydroperoxides, and non-radical reactive compounds including singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), chloramines (RNHCl) and ozone (O_3) [7][41].

Reactive nitrogen species are unstable compounds that include both radical species as nitric oxide (•NO) and nitrogen dioxide ($\bullet NO_2$), and non-radical species as peroxynitrite ($ONOO^-$) and dinitrogen trioxide (N_2O_3), that possess unpaired electrons in their outermost electron orbit. RNS often interact with reactive oxygen species, such as peroxynitrite, leading to nitrosative stress. RNS are a group of free radicals that are produced by nitric oxide synthase, which is expressed within the intestinal submucosa and mucosal regions [42][43].

ROS and RNS can be generated within various intracellular organelles, including mitochondria, endoplasmic reticulum, peroxisomes, nuclei, cytosol, plasma membranes, and even extracellular spaces (**Figure 1**). The primary source of ROS in cells is provided by complexes I and III of the mitochondrial electron transport chain, which are responsible for the conversion of approximately 1% to 3% of total oxygen to superoxide. Indeed, it is during cellular respiration that the accumulation of high-energy electrons can result in the production of oxygen-free radicals [44][45].

Moreover, numerous enzymes, such as nicotinamide adenine dinucleotide phosphate oxidase (NOX), phospholipase A2 (PLA2), nitric oxide synthase (NOS), cyclooxygenases (COXs), xanthine oxidase (XO), lipoxygenases (LOXs) and myeloperoxidase (MPO) can generate reactive species as part of their normal metabolic processes (**Figure 1**) [46].

NADPH oxidase, a membrane-bound enzyme complex present in the plasma membrane and phagosomes of phagocytes, is responsible for respiratory burst that occurs when phagocytic cells consume a large amount of oxygen during phagocytosis, leading to the release of $O_2^{\bullet-}$ into the extracellular space or phagosomes. It consists of multiple subunits, including gp91PHOX, p22PHOX, p67PHOX, p47PHOX, p40PHOX, and Rho GTPases. Activation of NADPH oxidase involves the relocation of cytosolic components to the cell membrane, where they assemble and activate the catalytic core, flavocytochrome b. There are six homologs of NADPH oxidase, collectively known as the NOX family, with different intracellular localizations. Among them, NOX1 and DUOX2 (dual oxidase 2) play some significant roles in gastrointestinal pathology, particularly in *Helicobacter pylori*-induced

gastric inflammation, IBD and tumor development. DUOX is found in all segments of the intestine, while NOX1 is present only in the ileum, cecum, and colonic epithelium [7][47][48].

Lipoxygenases are non-heme iron enzymes that catalyze the dioxygenation of polyenoic fatty acids, resulting in the production of hydroperoxyl derivatives such as hydroperoxyeicosatetraenoic acids (HPETEs). HPETEs can be further converted into pro-inflammatory hydroxyl derivatives, leukotrienes and lipoxins. In any case, LOX-mediated oxidation of arachidonic acid generates reactive oxygen species. LOX enzymes are found in various cells of the gastrointestinal tract and play a role in inflammation and diseases such as atherosclerosis, gastric inflammation, and peritonitis [49][50][51].

Myeloperoxidase is a heme-enzyme localized in lysosomes of neutrophils, macrophages, and monocytes. This is an enzyme that generates highly reactive HOCl and other ROS; HOCl reacts with H_2O_2 to generate single oxygen and chloride ion. MPO activity increases in *H*. *pylori* infection and contributes to gastric inflammation and the development of gastric cancer [52].

Nitric oxide synthase is an enzyme that produces the signaling molecule NO. There are three types of NOS: neuronal NOS (nNOS or NOS I), endothelial NOS (eNOS or NOS III), and inducible NOS (iNOS or NOS II) [53]. These isozymes catalyze the conversion of L-arginine to L-citrulline and NO; at low levels of L-arginine, NOS can produce hydrogen peroxide in addition to NO. While NO is a weak oxidant, it can react with superoxide to form peroxynitrite. Additionally, both NO and peroxynitrite in can generate nitrite and nitrate ions, which can accumulate in cells along with their intermediates (e.g., nitrogen dioxide, nitrogen trioxide, nitrogen monoxide). This accumulation can lead to the nitration and nitrosation of nucleic acids, proteins, and lipids, thereby disrupting their function. Nitrated lipids can elicit various physiological responses and can also produce NO [54][55]. NOS is expressed in the GI tract and plays a role in GI mucosal defense and injury. NO is involved in maintaining the normal functions of the GI mucosa and has a cytoprotective role: it regulates gastric mucosal blood flow, epithelial secretion, and barrier function, thereby maintaining GI mucosal integrity. However, excessive expression of iNOS is observed in conditions like chronic ulcerative colitis and peptic ulcers, indicating potential involvement of reactive nitrogen species generated by iNOS in both normal and pathophysiological conditions of the GI tract [7].

Cyclooxygenase is an enzyme that plays a crucial role in the release of arachidonic acid from cell membrane lipids and its subsequent conversion into prostanoids. There are two isoforms of COX: COX-1, constitutively expressed in most tissues and is involved in various physiological functions. COX-2 is an inducible isoform that is constitutively expressed at low levels in some tissues and upregulated in others in response to inflammation and tumorigenesis; and a reported splice variant known as COX-3. The peroxidase activity of COX leads to the generation of radicals, like NAD• and NADP•, which can eventually produce superoxide. Both COX-1 and COX-2 are physiologically found in the gastric mucosa, and enhanced levels are often observed at the edges of ulcers. COX-2 has been linked to early cancerous alterations in the gastrointestinal mucosa, such as Barrett's esophagus, gastritis induced by *H. pylori*, and inflamed colonic mucosa. It is also involved in the progression of cancers related to these conditions [56][57].

1.3. Antioxidant Defense in the GI Tract

The human body exhibits two fundamental forms of antioxidant defense: enzymatic and non-enzymatic. The major enzymatic antioxidants include catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPX) and glutathione reductase (GSR) (**Figure 2**) [4].

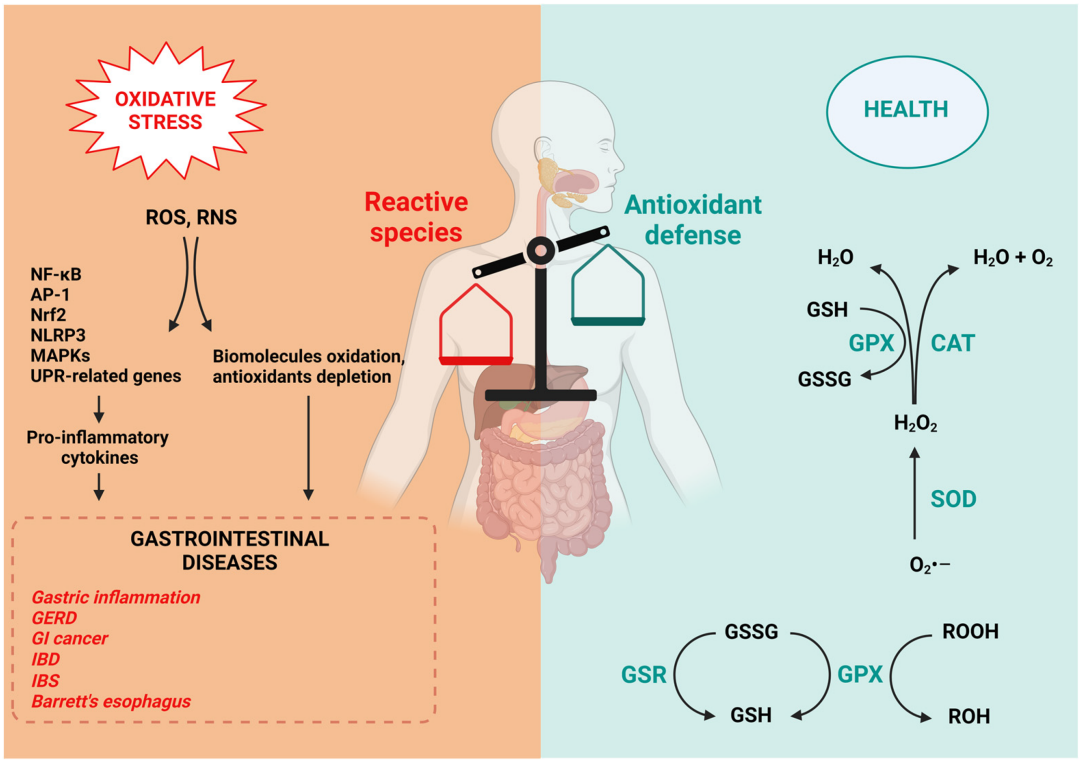

Figure 2. Unbalance between reactive species and antioxidant defense and its implications on the gastrointestinal diseases. The overproduction of free radicals due to the influence of external factors causes oxidative damage and induction of several transcription factors, which activate pro-inflammatory cytokines that together with direct oxidative damage and consequent antioxidants depletion determine the onset of GI disorders. On the other side, SOD, GPX, GSH and CAT are the lead actors that act directly in ROS-scavenging.

Superoxide dismutases are metal ion cofactor-requiring enzymes crucial for cellular protection. They catalyze the dismutation of $O_2^{\bullet-}$ into O_2 and H_2O_2. In humans, there are three forms of SOD: cytosolic copper and zinc-containing enzyme (Cu-Zn-SOD), present in the mitochondrial inter-membranous space; manganese-requiring mitochondrial enzyme (Mn-SOD), present in the mitochondrial matrix; and extracellular Cu-Zn containing SOD (EC-SOD) [58]. Reduced SOD activity in the gut has been linked to gastric ulcers, while increased SOD activity has been associated with ulcer healing in patients. On the other hand, the overall activities of SODs are higher in IBD pathogenesis. This increased SOD activity serves to protect intestinal tissues from oxidative damage caused by inflammation and OS [59]. Moreover, higher levels of Mn-SOD expression have been linked to colorectal cancer. It has also been observed to be increased in normal mucosa of gastric adenocarcinoma as well as in squamous cell esophageal carcinoma tissues. In contrast, Cu-Zn-SOD levels are slightly lower in cancer tissues compared to normal tissues [60].

Glutathione peroxidase catalyzes the conversion of reduced glutathione (GSH) to oxidized glutathione (GSSG) and can reduce H_2O_2 to H_2O and lipid hydroperoxides (ROOH) to stable alcohols. GPX, in conjunction with glutathione reductase (GSSG-R), helps maintain reduced levels of GSH, thus protecting cells from peroxide damage. There are various subtypes of GPX: GPX1, found in the cytosol of most cells; GPX2, identified in the cytosol and primarily found in the gastrointestinal tract; GPX3, present in the plasma as a glycoprotein; GPX4, located in mitochondria, where it interacts with cholesterol and lipoproteins that have been harmed by free radicals [61]. It is known that GPX isoforms are transcriptionally upregulated by oxidative mechanisms and as a result of the OS response. GPX2 expression is detected in various parts of the GI tract and is induced in gastric cancer cells. It has been observed that patients with active or remission-phase UC exhibit a significant increase in GPX activity associated with inflamed mucosa [62].

Catalase, primarily located in peroxisomes, is responsible for catalyzing the reduction of H_2O_2 to H_2O and O_2; it is predominantly distributed in the liver, kidneys, and erythrocytes [63]. CAT can be classified into the following types: typical or monofunctional catalases (e.g., mammalian catalase), bifunctional catalase peroxidases, and pseudocatalase. Mammal-type catalases function as tetramers and demonstrate comparatively lower rates of peroxidase activity. Catalase-peroxidases are characterized by their bifunctionality, serving as both catalase and peroxidase enzymes. Unlike monofunctional catalases, pseudo-catalases, also known as non-heme manganese-containing catalases, function as dimers or tetramers. These non-heme catalases comprise three well-defined and sequenced enzymes originating from various bacterial species. It is plausible that a group of pathogens linked to gastrointestinal conditions might contribute to changes in CAT expression. Diminished CAT activity has been noticed in patients with CD, as well as in patients with colorectal cancer, gastric adenocarcinoma, and *H. pylori*-positive gastric ulcers [64][65].

Among the endogenous non-enzymatic antioxidants, GSH is one of the most important (**Figure 2**). It is present at the intracellular level and is a water-soluble tripeptide that contains a thiol group derived from cysteine. GSH acts as the major soluble antioxidant in the cytoplasm, nucleus, and mitochondria. Its homeostasis is maintained through de novo synthesis, regeneration by GSSG and uptake via transport systems. GSH works in combination with GPX, GSr and GST to establish an antioxidant defense in the intestinal mucosa. Reduced GSH levels are associated with colitis, and antioxidant therapies can help restore health [7][62].

1.4. Oxidative Stress in GI Diseases

The loss of redox homeostasis is implicated in the pathogenesis of various gastrointestinal disorders (**Figure 2**).

Barrett's esophagus is a metaplasia of esophageal squamous epithelium characterized by increased production of superoxide anions and subsequent lipid peroxidation, which corresponds to the inactivation of SOD. The elevation of superoxide in Barrett's esophagus was triggered by one of the NOX isoforms, specifically NOX5. The overexpression of NOX5 is mediated by the calcium-dependent activation of Rho kinase (ROCK2) [66]. Additionally, a variant of NOX5 known as NOX5-S, which lacks calcium-binding domains, has also been observed to stimulate

the generation of H_2O_2, resulting in DNA damage, thereby contributing to the progression from Barrett's esophagus to adenocarcinoma [67].

As previously mentioned, NOX1 and DUOX2 play a significant role in *H. pylori*-induced gastric inflammation and gastric carcinoma oncogenesis. Specifically, *H. pylori* infection can lead to the development of peptic ulcers, which are characterized by excessive production of H_2O_2 and $O_2^{\bullet-}$ primarily derived from infiltrating leukocytes and neutrophils, as well as NOX activity. This excessive production of ROS leads to mitochondrial dysfunction, DNA alterations, and widespread tissue damage [68][69].

The advancement of IBD is affected by an intricate equilibrium of redox-sensitive pro-inflammatory pathways, like the NLRP3 inflammasome and NF-κB, and the adaptive upregulation of antioxidant enzymes, such as Mn-SOD and glutathione peroxidase 2 [70].

The excessive production of reactive oxygen species due to mitochondrial dysfunction plays a significant part in the development of IBD, including Crohn's disease and ulcerative colitis. These conditions are distinguished by persistent inflammation of the gastrointestinal tract.

In ulcerative colitis, inflammation typically affects the mucosa and submucosa of the colon. It usually begins in the rectum and then spreads to adjacent areas, often involving the peri-appendiceal region. Pro-inflammatory cytokines, along with ROS, NOS, and increased levels of MPO, are implicated in the pathogenesis and development of ulcerative colitis. Furthermore, in ulcerative colitis, there is a loss of mucosal antioxidant defense, which contributes to inflammation and disease progression [71][72]. NO produced by iNOS stimulates the production of TNF-α in the colon. This TNF-α production leads to neutrophil infiltration by promoting the production of intercellular adhesion molecule (ICAM) and P-selectin production. The resulting neutrophil infiltration and activation contribute to tissue damage in the colon. Although both forms of IBD share similar characteristics, H_2O_2 and HOCl have been shown to play an important role in the pathophysiology of ulcerative colitis, while •OH and $O_2^{\bullet-}$ are primarily implicated in Crohn's disease [73][74].

All areas of the gastrointestinal tract can be affected by Crohn's disease, but the terminal ileum or perianal region is commonly involved. The features of Crohn's disease include elevated levels of memory T cells and increased expression of major histocompatibility complex class II molecules (MHC). In the inflamed mucosa of Crohn's disease patients, there is increased activity of XO, Mn-SOD, iNOS, and TNF-α, resulting in decreased antioxidant levels [74][75].

Furthermore, accumulated ROS could also act as secondary chemical messengers that activate intracellular signal pathways, such as p38 MAPK and NF-κB. These pathways have the ability to influence cellular processes such as cell proliferation, differentiation, and apoptosis [40].

NF-κB is a crucial transcription factor that regulates the expression of genes involved in inflammation, immune responses, and cell survival. ROS can activate the NF-κB pathway by various mechanisms, including direct

oxidation and inactivation of inhibitors of NF-κB (IκBs). This leads to the release and translocation of NF-κB into the nucleus. Once in the nucleus, NF-κB promotes the expression of various proinflammatory cytokines in the intestinal epithelial cells, such as TNF-α, IL-1, IL-8, and facilitates inflammation and carcinogenesis [76].

MAPKs are highly conserved serine/threonine protein kinases, including extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinases (JNK), and p38. They are involved in the regulation of cellular responses to stress and inflammation. ROS can activate MAPKs by directly oxidizing and activating upstream kinases or by modulating phosphatases that control MAPK activation. Activated MAPKs translocate to the nucleus and phosphorylate various transcription factors, thereby leading to the production of pro-inflammatory mediators and amplifying the inflammatory response in the gastrointestinal tract [77].

Recently, it has been suggested that these particulate stimuli can trigger a calcium influx mediated via transient receptor potential melastatin 2 (TRPM2), leading to activation of the NLRP3 inflammasome in irritable bowel syndrome. These findings indicate that the generation of ROS, which is a critical factor in mucosal immunity, may serve as an essential upstream event for NLRP3 inflammasome activation [78]. Activation of NF-κB can rapidly enhance the expressions of pro-IL-1β and pro-IL-18, which are then cleaved into the mature IL-1β and IL-18 by caspase-1 in the inflammasome. Subsequently, NLRP3 inflammasome initiates pyroptosis by the cleaving of gasdermin D (Gsdmd), which forms pores in the plasma membrane and acts as the executioner molecule for pyroptosis [79][80].

There is also a relationship between the unfolded protein response (UPR) and inflammation in the GI tract. The UPR is a consequence of altered endoplasmic reticulum (ER) homeostasis, which initially results in a condition called ER stress. This condition is characterized by an accumulation of damaged and improperly folded proteins within the ER lumen caused by various factors, including elevated levels of reactive oxygen species. Once the cell is affected by an ER stress, the UPR signaling pathway is activated. This pathway exerts a protective action to restore cell balance, when the stress is mild and of short duration. However, if the stress becomes too intense and prolonged, the UPR can initiate apoptotic processes that lead to cell death [81].

One of the UPR transducers, activated IRE1α, not only serves as a bifunctional enzyme but also interacts with TRAF2 (TNF receptor-associated factor 2) to activate JNK (c-Jun NH2-terminal kinase) and NF-κB. Additionally, it induces TNF-α and IL-6, which in turn further activate NF-κB, thus amplifying inflammatory responses in bowel diseases [82][83].

It is interesting to note that the degradation UPR-mediated of miR-17, a microRNA that represses the expression of the thioredoxin-interacting protein (TXNIP) by IRE1α, results in the stabilization of TXNIP. The elevated levels of TXNIP protein activate ROS overproduction and NLRP3 inflammasome. This activation leads to the cleavage of caspase-1 and the secretion of interleukin 1β, further contributing to the inflammatory response [84]. TXNIP is indeed implicated in various biological processes, including energy metabolism, insulin secretion, oxidative stress, and inflammatory response. Recent studies have highlighted the emerging role of TXNIP in the pathogenesis of complex diseases, such as metabolic disorders, neurological disorders, and inflammatory diseases [85]. Moreover,

Zhenzhen et al. have demonstrated the significant impact of TXNIP on ischemia/reperfusion (I/R) injury in multiple organs, including intestinal I/R injury [86].

2. Ion Channels and Oxidative Stress

Ion channels (ICs) are integral membrane proteins that play a crucial role in regulating the ions' flow across cell membranes. They are essential for maintaining cellular homeostasis and are involved in various physiological processes [87]. However, the function of ICs in OS conditions can be two-faced, potentially providing both benefits to the cell and contributing to pathological states.

It is remarkable to recognize that oxidative stress not only causes damage to DNA, proteins, and lipids, but it also directly regulates key pathways involved in cellular signaling controlled by ICs and protein kinases. The effect of ROS on ICs forms part of a regulatory circuit that allows cells to respond to the oxidative potential by compensating for the stress, similar to how transcription factors are activated in response to oxidative stress, leading to the expression of antioxidant components. Additionally, activation by OS can serve as a second messenger in signaling cascades driven by changes in ion channel activity in response to hormones and neurotransmitters. However, excessive production of reactive species and constant activation of OS lead to alterations of ICs that extend beyond ion fluxes and can impact diverse cellular processes, including membrane excitability, signal transduction, neurotransmission, muscle contraction, hormone secretion, cell proliferation, and apoptosis. Thus, OS-induced dysfunction of ICs and transporters can contribute to the pathogenesis of various disorders, including cardiovascular diseases, neurodegenerative conditions, cancer, and metabolic and liver diseases [88][89].

Therefore, understanding the interplay between ion channels and oxidative stress is essential for unraveling the mechanisms underlying cellular responses to oxidative stress and their implications in disease pathophysiology.

The presence of ROS/RNS can directly interact with ion channels and induce post-translational modifications, such as oxidation, nitrosylation, or nitration of specific amino acid residues. These modifications occur on amino acids that are particularly susceptible to modification by ROS/RNS due to the presence of sulfur atoms, hydroxyl groups, or aromatic rings [90].

Several types of ICs are known to be affected by oxidative stress. For instance, voltage-gated ion channels, such as sodium, potassium, and calcium channels, can experience altered gating properties and ion selectivity. Oxidative stress can also modulate ligand-gated ion channels, including receptors for neurotransmitters and hormones, thereby affecting their sensitivity and signaling pathways [88]. Additionally, OS can impact intracellular calcium homeostasis by altering the activity of calcium release channels in the ER (e.g., ryanodine receptors) and calcium uptake channels in the plasma membrane (e.g., store-operated calcium channels) [91].

Ion transporters, including those responsible for sodium, potassium, calcium, and chloride ion transporters, are also influenced by oxidative stress. ROS can affect the activity and expression levels of these ICs, leading to

disruptions in ion gradients and cellular ionic balance. Moreover, OS can impair the function of sodium-potassium ATPase, compromising ion homeostasis and cellular energy metabolism [92].

2.1. Ion Channels Involved in Oxidative Stress-Related GI Diseases

Ion channels play a critical role in the physiopathology of the gastrointestinal tract. Intestinal epithelial cells use ion channels present on the submucosal nerves and enterochromaffin cells to transport ions which in turn drive fluid secretions. ICs also regulate the normal function of the GI smooth muscle, which is critical for optimal motility. In this regard, in tissues that require coordinated contractions (such as smooth, cardiac, and striated muscle), electrical depolarizations play a fundamental role in ensuring proper electromechanical coupling. Therefore, the coordination of electrical activity is so well tuned that even small perturbations can lead to functional abnormalities [93][94].

The chronic inflammation present in some gastrointestinal diseases, such as IBD, may contribute to increased oxidative stress in the gut. OS can lead to dysregulation of ICs in the gastrointestinal tract, by altering electrolyte transport, as well as increasing the secretion of mucus and water, and reducing absorption of nutrients, which contribute to the development of inflammation and tissue damage [95]. There are several types of ion channels involved in gastrointestinal pathologies, including chloride, calcium, potassium, and sodium channels. The main ones are disclosed below.

2.2. Calcium Channels

Calcium channels are critical for smooth muscle contraction, gene expression, neurotransmitter release, and hormone secretion in the gastrointestinal tract [96].

2.2.1. Voltage-Gated Ca^{2+} Channels

The family of voltage-gated Ca^{2+} channel (CaV) consists of five main subgroups: L-type (CaV 1.1–1.4), N-type (CaV 2.2), P/Q-type (CaV 2.1), R-type (CaV 2.3), and T-type (CaV 3.1–3.3) Ca^{2+} channels [97].

CaV channels were among the first Ca^{2+} channels to be discovered as being responsive to changes in cellular redox status. Voltage-sensitive calcium channels L-type have been described in smooth muscle cells (SMCs) and interstitial cells of Cajal (ICCs), known to be the pacemaker cells and control the contraction of the smooth muscle cells of the gastrointestinal tract [98][99].

Calcium influx in gastrointestinal smooth muscle is primarily mediated by the voltage-gated L-type Ca^{2+} channel, which is responsible for the upstroke of the action potential. The Ca^{2+} channel is a multimeric complex consisting of a central pore-forming and voltage-sensing α subunit along with auxiliary β and α2δ subunits [100]. Links have been reported between L-type calcium channel activity, oxidative stress, and gastrointestinal pathologies, including IBD [101].

In the inflamed colon, the circular smooth muscle cells exhibit a decrease in the expression of L-type calcium channels on their membranes. This down-regulation potentially leads to a reduction in calcium influx. Despite this decrease, the functional and pharmacological properties of the channels appear to be normal. However, acetylcholine, a neurotransmitter involved in muscle contraction, fails to activate these channels in the inflamed cells. This inability to activate the channels may be due to additional defects in the receptor signaling cascade upstream. The reduced expression of L-type calcium channels could dampen the contractions of circular smooth muscle in the inflamed colon, contributing to the motility and digestion abnormalities observed during inflammatory disorders [102][103][104][105].

Furthermore, in the context of OS, the expression of tyrosine-nitrated calcium channels on the plasma membrane is increased, which hinders the binding of Src tyrosine kinase. The enhanced production of nitric oxide leads to the formation of peroxynitrite, which oxidizes tyrosine residues and results in the formation of 3-nitrotyrosine. This OS-induced modification alters the gating kinetics of calcium channels, leading to decreased calcium influx [106][107].

The regulation of calcium channels is crucial for the process of calcium-induced gene transcription and one of the transcription factors closely associated with the activation of L-type calcium channels is the cyclic AMP response element-binding protein (CREB). Following cell depolarization, CREB undergoes specific phosphorylation at the Ser133 site within the nucleus. Oxidative stress impacts excitation-transcription coupling, resulting in reduced depolarization-mediated expression of phospho-CREB due to tyrosine nitration of the calcium channel. The particular post-translational modification is noteworthy, as S-nitrosylation enhances L-type calcium currents, whereas tyrosine nitration predominantly occurs in colon inflammation [108][109][110].

2.2.2. Calcium-Permeable Non-Selective Ion Channels

The transient receptor potential (TRP) channels comprise a superfamily of non-selective calcium-permeable ion channels. In particular, they are a class of cationic channels that can act as signal transducers by modulating membrane potential or intracellular calcium concentration. This ICs family can be divided into seven subgroups: TRPC (Canonical), TRPV (Vanilloid), TRPM (Melastatin), TRPA (Ankyrin), TRPML (Mucolipin), TRPP (Polycystic), and TRPN (NOMPC-like). All seven members of the subfamily share a similar structural organization. They consist of six transmembrane spanning domains (S1–S6), with the pore region formed by hydrophobic residues between S5 and S6. Additionally, they possess three to four ankyrin repeats, coiled-coil domains in the N- and C-terminus, a C-terminal proline-rich region, a Calmodulin/IP3 binding region and a 25-amino acid motif, known as TRP domain. This TRP domain, loosely conserved among almost all TRP channels, is located at the C-terminal end of the sixth transmembrane segment [111].

These channels are involved in multiple cellular functions, including cell death, chemokines production, pain sensation and thermosensation. Their activation mechanisms involve not only the direct detection of temperature and/or chemical compounds and changes in extracellular or intracellular ion concentrations but also the detection of second messengers. Some TRP channels, including TRPM2, TRPM7, TRPC5, TRPV1, and TRPA, sense

reactive species either indirectly through second messengers or directly via oxidative modification of cysteine residues [112][113].

TRP channels in the GI tract function as molecular detectors of chemical and physical signals and act as secondary responders to G protein-coupled receptors (GPCRs) or ion channel receptors, thereby regulating calcium balance. These channels are expressed not only in the sensory neurons of the ganglia and enteric nervous system that innervate the GI tract but also in non-neuronal cells such as intestinal epithelial cells, enteroendocrine cells, and immune cells. Among the TRP channel subfamilies, TRPV, TRPA, and TRPM have been identified as particularly relevant in inflammatory bowel disease. They can be activated by various endogenous stimuli and have been extensively studied as potential targets for therapeutic drugs. Alterations in the expression of these TRP channels have been observed in patients with IBD and animal models of colitis, indicating their involvement in the disease [114][115][116].

TRPM2

The TRPM2 ion channel exhibits permeability to divalent ions such as Ca^{2+} and Mg^{2+}, as well as monovalent ions including Na^{+} and K^{+}. It contains an enzymatic region known as the NudT9-H domain, which possesses ADP-ribose (ADPR)-hydrolase activity. TRPM2 is expressed in various gastrointestinal cells, including enterocytes of the intestinal epithelium, enteroendocrine cells, pancreatic β-cells, smooth muscle cells, and some immune cells present in the intestinal mucosa. Under normal physiological conditions, TRPM2 channels play a crucial role in immune modulation by regulating the release of various cytokines, such as TNF-α, IL-6, IL-8, and IL-10, in human monocytes. They are also involved in the maturation and chemotaxis of dendritic cells, which are essential for immune responses. In addition to their role in immune modulation, TRPM2 channels are also implicated in other functions such as regulating endothelial permeability and insulin secretion [117][118].

The expression of TRPM2 in various gastrointestinal cells suggests its involvement in the control of gastrointestinal function and responses to pathological conditions.

One notable characteristic of TRPM2 is its modulation by oxidative stress. It is hypothesized that oxidative/nitrosative stress triggers a biochemical pathway within mitochondria, leading to the production of ADP-ribose. This molecule acts as a diffusible second messenger that can activate TRPM2 channels located on the cell's plasma membrane [119][120].

Under OS, H_2O_2 promotes the generation of intracellular ADPR in mitochondria. This event leads to the activation of two enzymes in the nucleus: PARP-1 (poly ADP-ribose polymerase) and poly ADP-ribose glycohydrolase (PARG). PARP-1 binds to damaged DNA and catalyzes the cleavage of NAD^{+} into nicotinamide and intracellular ADPR. Both H_2O_2 and ADPR can synergistically activate TRPM2. Intracellular ADPR binds to the C-terminal NudT9-H domain of the channel, leading to increased calcium influx. This influx triggers the phosphorylation of Pyk2, which enhances Ras-dependent ERK activation. Amplified ERK activates the transcription of the CXCL8

gene, inducing the nuclear translocation of RelA, an NF-κB subunit in human monocytes. This cascade ultimately leads to the upregulation of pro-inflammatory cytokines [121][122].

Ca^{2+} influx through TRPM2 also activates both extrinsic and intrinsic cell death pathways, resulting in the activation of caspase-3 and the cleavage of PARP [123].

Structural properties play a significant role in the oxidative modulation of TRPM2. A shorter isoform of TRPM2 (TRPM2-S) lacking specific transmembrane domains has been identified. TRPM2-S directly interacts with the full-length isoform (TRPM-L) and acts as a dominant negative mutant, inhibiting TRPM2-mediated Ca^{2+} influx. Interestingly, co-transfecting TRPM2-L and TRPM2-S suppresses H_2O_2-induced cell death by inhibiting OS-induced TRPM2 activity. These findings suggest that the dominant negative effects of TRPM2-S protect cells from oxidative damage [124][125].

In the gastrointestinal tract, TRPM2 channels are expressed in mucosal macrophages, mast cells and enteric neurons and they have been shown to contribute to the progression of experimental colitis and food allergy in mice. Notably, TRPM2 deficiency suppresses the exacerbation of inflammation in a mouse model of dextran sulfate sodium (DSS)-induced colitis. TRPM2 has been suggested to play an important role in the colon, leading to the production of cytokines and chemokines (such as CXCL2) by macrophages, neutrophils, and T lymphocytes [126][127].

However, the physiological and pathological roles of TRPM2 in the gastrointestinal tract are not well understood. It is hypothesized that TRPM2 plays an important role in visceral nociception and the development of hypersensitivity because several lines of evidence indicate that TRPM2 channels are likely expressed in neurons [128][129].

Matsumoto et al. have founded that intestinal manipulation activates resident muscle macrophages via TRPM2, leading to the release of inflammatory cytokines and chemokines, which in turn promote the infiltration of macrophages and neutrophils into the muscle layer, resulting in dysmotility. Therefore, TRPM2 could be an interesting target for the treatment of dysmotility associated with postoperative ileus [130].

TRPM2 is also found in pancreatic β-cells, where its activity has been linked to insulin secretion and H_2O_2-mediated apoptosis of insulin-secreting cells, suggesting a role of TRPM2 in diabetes [131].

TRPV1

TRPV1 is primarily found in sensory nerve fibers throughout the gastrointestinal tract, including the esophagus, stomach, small intestine, and colon. It is also expressed in certain non-neuronal cells such as epithelial cells, smooth muscle cells, and immune cells within the gastrointestinal tract [132][133]. TRPV1 is a channel that responds to heat, capsaicin and acidic pH, and it can be upregulated or sensitized by pro-algesic pathways associated with functional GI disorders. In patients with conditions such as IBS and non-erosive reflux disease, upregulation of TRPV1, even in the absence of overt inflammation, has been observed [134][135].

During OS, when TRPV1 is exposed to hydrogen peroxide, it exhibits enhanced responses to capsaicin, acid, and receptor phosphorylation, indicating sensitization. This sensitization occurs through the formation of inter-cysteine disulfide bonds within the cytoplasmic termini of TRPV1. Several cysteine residues, including C772 and C783, play a critical role in this sensitization process. Oxidized TRPV1 receptors are more resistant to desensitization induced by capsaicin, while desensitized receptors can be reactivated by strong OS. This oxidative modulation of TRPV1 operates independently of phosphorylation, desensitization, and extracellular pH, and it amplifies the channel's response to noxious stimuli [135][136].

Furthermore, TRPV1 is also expressed on the plasma membrane of esophageal epithelial cells, and its activation by capsaicin and acid can induce significant production of IL-8 suggesting that TRPV1 activation on esophageal epithelial cells may contribute to esophageal inflammation through cytokine release. In a study, it was observed that the activation of TRPV1 receptors by capsaicin led to a significant increase in the production of ROS within Het1A cells. Interestingly, when a TRPV1 antagonist was applied, the elevated levels of ROS-modified proteins induced by capsaicin treatment were blocked. These findings suggest that capsaicin may specifically trigger ROS production through a TRPV1-dependent pathway [137][138][139].

TRPV1 activation in esophageal epithelial cells can specifically induce ROS production, which can potentially modify intracellular biomolecules, including TRPV1 itself. Bile acids and low pH can induce oxidative stress and DNA damage in esophageal tissues and cells by, suggesting the possibility that acid-induced OS through TRPV1 activation may occur in esophageal epithelial cells [140].

TRPV1 is involved in gastroesophageal reflux disease, a gastrointestinal disorder associated with the malfunctioning of the lower esophageal sphincter (LES), leading to the reflux of stomach acid and digestive juices into the esophagus. While the primary cause of GERD is the weakening of the LES, the involvement of TRPV1 receptors has also been observed [138][141].

TRPV1 receptors, when activated, can contribute to the sensation of heartburn and chest discomfort experienced by GERD patients. Acidic substances, such as stomach acid, can stimulate and activate TRPV1 receptors in the esophagus, leading to the perception of pain and irritation. The activation of TRPV1 receptors in the esophagus may also enhance sensitivity to pain and contribute to the development of esophageal hypersensitivity, which is a characteristic feature of GERD.

Research suggests that TRPV1 antagonists, which inhibit the activity of TRPV1 receptors, could potentially provide therapeutic benefits in managing GERD symptoms. By blocking TRPV1 receptors, these antagonists may help decrease esophageal sensitivity to acid reflux and alleviate the discomfort and pain associated with it [142][143].

TRPA1

The ion channel TRPA1 is recognized for its excitatory characteristics and is thought to be involved in diverse sensory processes, including cold perception, burning sensation and discomfort associated with acid reflux, as well as inflammation pain in the context of IBD. While it is well-established that TRPA1 is expressed in a subset of

sensory neurons, particularly nociceptors, its functional role in the gastrointestinal tract, especially in non-neuronal cells, such as enteroendocrine cells, remains largely unexplored. TRPA1 exhibits significant expression in both human and rat enteroendocrine cells, suggesting that it may function as a sensor molecule in these cells to regulate gastrointestinal functions [144][145][146].

TRPA1 is found mainly on the cell plasma membrane and presents in the intracellular portion of cysteine residues, which have been identified as key players in its activation. Agents that modify cysteine, such as N-methyl maleimide, have been shown to activate TRPA1, while agents that reduce cysteine have the opposite effects [147][148]. These findings suggest that cysteine oxidation in TRPA1 may be important for its activation. Considering that H_2O_2 induces oxidative modification of protein cysteine residues, it is possible that H_2O_2 may activate TRPA1 inducing the activation of sensory neurons in the pain pathway [149]. This mechanism may be related to the neurogenic inflammation in the gastrointestinal tract in gastroesophageal reflux disease. Experimental evidence revealed that berberine attenuated neurogenic inflammation in the gastrointestinal tract mainly by suppressing the production of substance P (SP) [150]. Additionally, Zou et al. showed that berberine can also suppress the upregulation of TRPA1 induced by airway hyperresponsiveness (AHR), a common symptom observed in GERD patients [151].

Nrf2 is a transcription factor that participates in the regulation of cellular response to oxidative stress. It has been widely reported that Nrf2 is dissociated from the Cul3-kelch-associated ECH-associated protein 1 (Keap1)-Nrf2 complex by ROS, after which Nrf2 enters the nucleus to mediate the expression of TRPA1. Given that Nrf2 can mediate the expression of TRPA1, and that ROS are activators of TRPA1, it has been hypothesized that ROS not only activate TRPA1 but also regulate TRPA1 expression via Nrf2. Furthermore, the influx of Ca^{2+} through TRPA1 activates the ERK and AKT signaling pathways leading to apoptosis by activating calcium/calmodulin-dependent kinase II (CaMKII), a serine/threonine protein kinase. CaMKII undergoes autophosphorylation in the presence of Ca^{2+} and CaM, and it subsequently activates various downstream effectors. Hydroxyl radical scavengers have shown effectiveness in alleviating ROS or oxidative stress-related diseases by blocking TRPA1 activation. Additionally, TRPA1 has been found to be upregulated in various cancer cells, including colorectal cancer. This suggests a potential role of TRPA1 in cancer development and progression [152][153][154][155][156].

Moreover, elevated cytosolic Ca^{2+} concentrations induce Ca^{2+} uptake into the mitochondrial matrix in cells, leading to depolarization of the inner mitochondrial membrane and alteration of the outer membrane permeability. These events trigger the release of cytochrome c and Apaf-1-dependent activation of the apoptosome, which is a multi-subunit protein complex that serves as a platform for caspase activation, ultimately leading to apoptosis. An increase in intracellular Ca^{2+} levels also leads to membrane depolarization and subsequent activation of UPR [156][157][158].

2.3. Chloride Channels

Chloride ion channels are important regulators of fluid and electrolyte transport in the gastrointestinal tract, and their dysfunction has been implicated in the pathogenesis of several GI disorders. There are several types of

chloride channels expressed in the gastrointestinal tract, including the cystic fibrosis transmembrane conductance regulator (CFTR), calcium-activated chloride channels (CaCCs) and Chloride intracellular channel 1 (CLIC1).

2.3.1. Cystic Fibrosis Transmembrane Conductance Regulator

Cystic fibrosis is a genetic disorder characterized by the abnormal folding of the CFTR protein. One of the most common mutations associated with cystic fibrosis is the deletion of phenylalanine at position 508 (ΔF508) in the CFTR protein. These mutations impair the function of CFTR, leading to disrupted chloride and fluid transport across epithelial cells in various organs, including the lungs, pancreas, and gastrointestinal tract. In the latter, CFTR dysfunction can result in reduced chloride secretion and increased sodium and water absorption. This imbalance leads to the production of thick and sticky mucus that obstructs the pancreatic ducts, bile ducts, and small intestine, causing complications and impairing normal digestive processes [159][160].

In CF, misfolded CFTR proteins are retained within the ER and undergo rapid degradation by the ERAD (ER-associated protein degradation). This holds true for the most common mutation, ΔF508. The retention of misfolded proteins can lead to ER stress, which activates UPR with the purpose of regulating the protein load within the ER. This involves increasing the expression of chaperones and limiting overall protein synthesis in cells. Moreover, UPR limits the endogenous expression of CFTR (wild type and ΔF508) by the activation of its transducer ATF6 (activating transcription factor 6) to limit gastrointestinal tract manifestations of cystic fibrosis, including mucous inspissation, dysmotility, constipation, and GERD [161][162][163].

Oxidative stress can modulate CFTR channel activity through direct oxidation of cysteine residues or via downstream signaling pathways. OS modulates intracellular signaling pathways mediated by protein kinase A (PKA) and protein kinase C (PKC), which are known regulators of CFTR function. ROS-mediated activation of these pathways can modulate CFTR phosphorylation and alter its activity and localization. In addition, CFTR is involved in maintaining cellular redox balance by regulating the transport of GSH. CFTR dysfunction in CF may result in reduced GSH levels and compromised antioxidant defenses, leading to increased oxidative stress in the GI tract [164][165][166].

The interplay between CFTR dysfunction and OS contributes to the pathogenesis of various GI disorders. Conditions such as Crohn's disease and ulcerative colitis are characterized by increased OS and impaired CFTR function. The elevated oxidative stress in these conditions exacerbates inflammation, disrupts ion and fluid transport, and compromises the integrity of the intestinal barrier [167][168].

The regulation of CFTR expression in oxidative stress conditions involves the HIF-1/Nrf2 pathway. Nrf2, which is normally located in the cytoplasm, translocates to the nucleus in response to cellular stress. In the nucleus, Nrf2 activates target genes by binding to antioxidant response elements. However, the effect of Nrf2 on CFTR expression is context-dependent and varies based on tissue type, cell conditions (normoxic or hypoxic), and possible cancer stage. Nrf2 has been reported to both positively and negatively regulate CFTR expression, and its downregulation is observed in patients with CF and CF knockout mouse models. The CFTR gene contains CREs

(cAMP response elements) within a topologically associating domain. Under normoxic conditions, repressor proteins, including BACH1, bind to the −44 kb ARE located in the TAD, leading to CFTR repression. However, oxidative stress, induced by compounds like sulforaphane (SFN), displaces repressors and activates CFTR expression in airway epithelial cells [169][170][171][172].

The regulation of CFTR expression in intestinal epithelial cells, especially colorectal cancer (CRC) cells, remains less understood. Stress conditions like gut ischemia, hypoxia, dysbiosis, and inflammation have been linked to CFTR dysregulation. Hypoxia and HIF-1 signaling repress CFTR expression in CRC cells, which is commonly observed in epithelial cancers [173][174][175].

The role of CFTR in carcinogenesis is complex and may vary depending on the tissue and cancer context. Loss of CFTR may protect CRC cells from ROS-induced apoptosis by retaining antioxidants such as GSH, thereby promoting cell survival. Initial evidence suggests that loss of CFTR in CRC cells enhances their survival when exposed to oxidative stress. Overall, the regulation of CFTR expression in OS conditions involves intricate molecular pathways, including the HIF-1/Nrf2 pathway. The relationship between CFTR, oxidative stress, and carcinogenesis is multifaceted and context-dependent, requiring further investigation to fully understand its implications in different tissues and cancer types [176][177][178].

2.3.2. Calcium-Activated Chloride Channels

Calcium-activated chloride channels are extensively expressed in various tissues and implicated in physiological processes such as sensory transduction, epithelial secretion, and smooth muscle contraction. CaCCs are mainly found on the plasma membrane of the epithelial cells of the gastrointestinal tract and of the interstitial cells of Cajal. Activation of CaCCs enables the efflux of chloride ions from cells. This process is crucial for facilitating digestion and maintaining appropriate hydration levels within the GI tract [179].

CaCCs are heterogeneous groups of ligand-gated chloride ion channels that include proteins from several structurally diverse families: accessory chloride channel (CLCA), bestrophin (BEST), and calcium-dependent chloride channel anoctamin (ANO or TMEM16) channels. The TMEM16 is highly expressed in the human gastrointestinal interstitial cells of Cajal. Some CLCA isoforms, both human and mouse, may have roles as tumor suppressors, particularly in mammary carcinoma. One member of the CLCA family, mCLCA6, is highly expressed in the intestine and stomach, with trace amounts in the spleen and liver, while mCLCA3 overexpression has been linked to mucus overexpression in cystic fibrosis. Overall, CaCCs are activated by an increase in intracellular calcium levels, and their function is modulated by OS [180][181][182].

Oxidative stress can directly influence CaCCs through several mechanisms in the GI tract: ROS induces oxidative modifications of CaCC proteins, such as the oxidation of critical cysteine residues. These modifications can alter the channel's gating properties, stability, and trafficking, leading to aberrant chloride transport and fluid secretion. CaCCs are activated by intracellular calcium concentration and phosphorylation of Ca^{2+}/calmodulin protein kinase.

The intracellular hydroxyl radicals directly increase the activity of CaCC channels, going to targeting, reversibly or irreversibly, exposed cysteine -SH residues [183][184].

Dysregulation of CaCCs due to oxidative stress has been implicated in various GI disorders. For instance, in inflammatory bowel disease, increased OS can lead to CaCC dysfunction, contributing to altered chloride transport and excessive fluid secretion. This can result in diarrhea and electrolyte imbalances [185].

2.3.3. Chloride Intracellular Channels

CLIC1 is a member of the CLIC protein family and plays an important role in the transport of chloride ions across cellular membranes. Emerging evidence suggests that CLIC1 is involved in various cellular processes, including cell proliferation, apoptosis, and ion homeostasis [186][187].

There is still controversy regarding the functional expression of CLIC1. For most researchers actively working on protein properties, CLIC1 functions as a selective chloride channel with unique characteristics that are transiently expressed on the membrane in response to specific stimuli. However, since it is considered unlikely for a hydrophilic protein to undergo drastic changes enabling insertion into the membrane and formation of an ion channel, not everyone considers it as such. Furthermore, the recordings made on the membrane could potentially be attributed to modulation by CLIC1 on other resident chloride channels in the membrane. In this latter case, CLIC1 would function as a second messenger or an additional functional subunit [188][189].

Over the past 10 years, several research groups have demonstrated, using different experimental approaches, that CLIC1 could realistically form an ion pathway. According to this view, CLIC1 would be an example of an ion-permeable protein transiently expressed in the cell membrane. However, the mechanism of protein anchoring and insertion into the lipid bilayer is still unknown [190].

CLIC1 has been shown to be involved in cell cycle regulation being detected on the plasma membranes of cells in the G2/M phase. During this period, the current density is approximately twice that recorded in the G1/S phase, and inhibition of CLIC1 function prolongs the average cell cycle time in cell culture. It is known that there are oxidative fluctuations during the cell cycle that drive cells through all phases of the cell cycle. Therefore, it is not surprising that CLIC1 is hyperactivated in all diseases involving OS, including GI tumors. The behavior of CLIC1, migrating to the plasma membrane in response to changes in the redox state of cells, given the protein's high affinity for GSH, suggests that CLIC1 should be explored as a potential therapeutic target [191][192].

CLIC1 is overexpressed due to increased ROS, particularly hydrogen peroxide. The overexpressed channel suppresses the nuclear translocation of Nrf2 and cellular antioxidant capacity, promoting cellular senescence and endothelial dysfunction. The main characteristics of Nrf2 are to some extent mimicked by Nrf2-dependent genes and their proteins, including heme oxygenase-1 (HO-1). HO-1 exerts beneficial effects through protection against oxidative damage, regulation of apoptosis, modulation of inflammation, and contribution to angiogenesis. Conversely, Nrf2/HO-1 activation is essential in the mechanism by which CLIC1 activation is blocked and in the

expression of antioxidant systems. In fact, the nuclear translocation of Nrf2 is blocked by CLIC1 overexpression but enhanced by the treatment with an IAA94 inhibitor or CLIC knockdown [193][194][195].

Upregulation of the CLIC1 protein has been linked to the progression of gallbladder and gastric cancers, where it promotes cell proliferation via regulation of MAPK/AKT pathways and facilitates fibroblast formation. In fact, Li et al. demonstrated that the expression levels of integrin α3 (ITGα3), integrin αv (ITGαv), integrin β1 (ITGβ1) and Bcl-2 decreased in gastric tumor cells after CLIC1 knockdown, as well as AKT-phosphorylation, ERK-phosphorylation, and p38-phosphorylation. Therefore, it has been hypothesized that CLIC1 may play an important role in the initiation and progression of gastric cancer and its mechanism may be related to the regulation of integrin family proteins, leading to the sequential regulation of PI3K/AKT, MAPK/ERK and MAPK/p38. Furthermore, the upregulation of CLIC1 protein is associated with the metastatic capacity of colorectal cancer cells, where it has been demonstrated to control cell volume and ROS levels [196][197].

2.4. Potassium Channels

The remarkable diversity of genes encoding K^+ channels represents the largest group of ion channels in the human genome. These genes often have splice variants, undergo post-translational modifications, or form complexes with regulatory subunits, further expanding the functional variability of K^+ channels. This variability underscores the significance of fine-tuning K^+ conductance and raises questions about additional functions these channels may serve. Voltage-gated, Ca^{2+}-activated, inward rectifier channels, and 2P-domain channels are the general classifications of K^+ channels [198][199][200].

While sodium (Nav) channels are typically associated with the rapid depolarization of excitable cells, voltage-gated K^+ (Kv) channels are responsible for the repolarization phase during an action potential. In non-excitable cells like those in the GI epithelium, these channels primarily function to hyperpolarize the PM. This negative membrane potential is essential for Ca^{2+} signaling, intracellular pH regulation, and cell volume control. Due to their wide-ranging impact, K^+ channels are implicated in various cellular and tissue functions, including cell proliferation, differentiation, contractility, circadian rhythms, wound healing, cell cycle progression, autophagy, metabolism, angiogenesis, stem cell dynamics, making them vital for cellular functions in various tissues, such as smooth muscles, pancreatic β-cells, myocardium, and neurons. However, the mechanisms underlying the loss of control over K^+ channels are still not fully understood [187][201].

Research indicates that the functional characteristics of the human ether-related gene (HERG) potassium channels may be affected by ROS, possibly through interactions involving cysteine or histidine residues. Methionine is also susceptible to oxidation; when an oxygen atom is added to its sulfur-containing region, it forms methionine sulphoxide (MetO), which possesses distinct physicochemical properties compared to methionine. Protein oxidation in methionine residues frequently leads to functional impairments, including a reduction in cellular electrical excitability [202][203].

2.4.1. The ATP-Sensitive Potassium Channels

In the maintenance of plasma membrane potential, K^+ channels play a vital role. They work in conjunction with transporters such as the Na^+/K^+-ATPase, H^+/K^+-ATPase, and the Na^+-K^+-$2Cl^-$ cotransporter (NKCC) to facilitate the exit of K^+ ions from the cell, thereby maintaining a net negative charge at the membrane potential. This hyperpolarized membrane potential is crucial for driving the active transport of various molecules against their concentration gradients. Particularly in the GI epithelium, which requires continuous transport of water, electrolytes, and nutrients, K^+ channels are significant [199][200].

The ATP-sensitive potassium channels consist of regulatory sulfonylurea subunits (SUR1, SUR2A, or SUR2B) along with pore-forming potassium channel subunits (Kir6.1 or Kir6.2). They are influenced by physiological and pathophysiological factors, including hypoxia, hyperglycemia, ischemia, and OS, enabling them to regulate cellular excitability based on metabolic conditions [204].

These channels have various functions in GI tissues: regulation of insulin secretion, protection against cellular stress, and adaptation to metabolic changes [205][206].

ROS can either decrease or increase K_{ATP} channel activity, depending on the tissue and the specific isoforms expressed. Redox regulation has been linked to the N-terminus of the Kir6.2 subunit, particularly Cys42. This mutation made the channel unresponsive to sulfhydryl reactive agents, suggesting that the Kir subunit is a possible site for redox regulation. The modification of Cys42 through sulfhydryl alters the channel allosterically, rather than causing direct pore blockage. NO activates K^+-ATP channels through S-nitrosylation of the SUR1 subunit, while S-glutathionylation of Cys176 in the Kir6.1 subunit inhibits the Kir6.1/SUR2B channel. Protein S-glutathionylation is promoted by oxidative or nitrosative stress. These post-translational modifications are associated with OS and can impact channel function. The effects of NO on K_{ATP} channel activity are complex. Stimulation and inhibition of channel activity have been reported depending on the concentration of NO. Indirect effects of NO on K_{ATP} channels have been ascribed to interference with mitochondrial metabolism and the cGMP/protein kinase G pathway, while high concentrations of NO can inhibit K_{ATP} channels directly [207][208][209].

Interestingly, the loss of K_{ATP} channel activity in β-cells provided partial protection against apoptosis induced by hydrogen peroxide and nitric oxide. This protection appeared to be due to the upregulation of antioxidant enzymes, including SOD, GPX and CAT, which help to detoxify ROS and RNS. This upregulation of antioxidant enzymes seemed to be a result of increased calcium levels in the cytosol and mitochondria, which occurs when K_{ATP} channels are genetically or pharmacologically inhibited [210][211].

The enhanced oxidative stress associated with type 2 diabetes mellitus contributes to disease pathogenesis. ROS and RNS can cause oxidative stress, which affects the function of β-cells in the pancreas leading to apoptotic cell death. Previous studies have demonstrated that ROS/RNS can impact the activity of ATP-sensitive potassium channels in β-cells by inhibiting the production of ATP in the mitochondria. Both hydrogen peroxide and alloxan, a diabetogenic agent that is believed to generate H_2O_2, can open K_{ATP} channels and change the electrical potential of the β-cells membrane. Oxidative damage increases the production of ROS in mitochondria, and these ROS can

trigger the opening of a pore in the mitochondrial membrane, generating a collapse of the membrane potential and depletion of ATP [212][213].

There is a growing body of evidence indicating that hydrogen sulfide (H_2S), similar to nitric oxide and carbon monoxide, functions as a signaling molecule that plays a crucial role in both normal physiology and the development of various diseases. In the case of IBD, H_2S has been found to have a protective role in the gastrointestinal tract.

In experimental models of colitis, it has been observed that colonic inflammation leads to increased activity of ATP-sensitive potassium channels in the smooth muscle cells of the colon. The precise molecular mechanisms underlying this alteration are not yet fully understood, but it appears that these K_{ATP} channels may be potential targets for the effects of H_2S. However, oxidative stress is implicated in this process. H_2S can modify the K_{ATP} channels by S-sulfhydrating cysteine residues, particularly in the SUR2B subunit. This modification enhances the activity of K_{ATP} channels in the smooth muscle cells of the colon, thereby improving colonic function and aiding in the resolution of inflammation [214][215][216].

During colonic inflammation, there is an increased production of H_2S, which contributes to the resolution of the inflammatory state. Animal models of colitis have shown that inhibiting K_{ATP} channels leads to significant mortality, underscoring the importance of these channels in the context of ulcerative colitis and highlighting their potential as therapeutic targets.

In the DSS colitis mouse model, it has been observed that the response to the K_{ATP} channel agonist lemakalim is significantly enhanced in inflamed smooth muscle cells, along with a down-regulation of calcium currents. Further investigation revealed increased bursting activity of individual K_{ATP} channels in inflamed mice. The major isoforms of K_{ATP} channels in mouse colonic smooth muscle are Kir6.1 and SUR2B. Gene expression analysis showed up-regulation of Kir6.1 mRNA and down-regulation of SUR2B mRNA during inflammation. However, the impact of these changes on protein expression remains unclear, as protein expression was not assessed [217][218].

2.4.2. Kv Channels

Kv channels are present in gastrointestinal smooth muscle cells, contributing to the regulation of muscle excitability and contraction. These channels regulate the resting potential and action potential of smooth muscle cells, affecting the motility of the gastrointestinal tract. In enteric neurons, Kv channels influence the generation and propagation of electrical impulses [219].

Some endocrine cells found in the gastrointestinal tract, such as the Langerhans cells in the intestine, express Kv channels. These channels can influence the secretion of hormones and the regulation of chemical signals in the gastrointestinal environment. Since Kv channels are implicated in the regulation of gastrointestinal motility, their alterations may contribute to motor dysfunctions related to functional abdominal pain and intestinal motility disorders.

Kv consists of four α subunits; each α subunit contains six transmembrane segments and contributes to the formation of the conductive pore for potassium ions. In addition to the α subunits, Kv receptors may also include accessory or regulatory subunits that influence their activity. Some examples of common accessory subunits are β and γ subunits, which can regulate the function and properties of voltage-gated potassium channels.

The auxiliary subunits, known as Kvb subunits, interact with the pore-forming α -subunits and influence the inactivation rate of Kv channels. Kvb1 and 3 possess a long N-terminus that induces channel inactivation, whereas Kvb2 lacks the N-terminus and accelerates the self-inactivating Kv channels. Interestingly, Kvb subunits have been proposed to act as sensors of lipid oxidation by reducing oxidized phospholipids generated during OS. These oxidized phospholipids can alter the inactivation properties of Kv channels, suggesting that the b-subunits modulate the detection of metabolic changes during oxidative stress [110][220][221].

Furthermore, both Kvb1 and Kvb2 exhibit aldo-keto reductase activity, functioning as redox enzymes. They can convert aldehydes to alcohols using NADPH as a cofactor. The cofactor is bound to the b-subunits, and its oxidation enhances the current flow through Kv1 channels. The oxidation of the cofactor is voltage dependent. Thus, the Kv1-Kvb complex enables the translation of the cellular redox state into changes in cellular excitability, effectively conveying the impact of oxidative conditions on cellular function [222].

Voltage-gated Kv7 (KCNQ family) potassium channels are present in numerous neuronal populations and have a crucial function in controlling membrane potential. They achieve this by producing a hyperpolarizing potassium current, which effectively reduces cellular excitability representing an important pharmacological target for hyperexcitability disorders [223][224]. Research has revealed that certain members of the Kv7 family (Kv7.2, Kv7.3, and Kv7.5) can combine to form heterotetramers responsible for carrying the ‘M’ current. This stabilizing potassium current is sensitive to inhibition by muscarinic receptor stimulation in neurons [225].

Recently, Peiris et al. identified Kv7 channels in enteric nervous system neurons along the gastrointestinal tract in humans and mice, including afferent fibers innervating the distal colon. In particular, activation of neuronal Kv7.3 channels has been shown to suppress both mechanically and chemically induced sensory responses [226]. Although, the impact of Kv7 channel activation on epithelial electrolyte transport remains unclear and requires further investigation.

According to the results of Nickerson et al., activation of Kv7 channels leads to a significant reduction in Cl^- secretion by the mouse distal colon epithelium. This effect is probably attributed to the Kv7 channels present in the enteric neurons of the submucosal plexus, which decrease neuronal excitability and consequently inhibit stimulatory signals reaching the epithelial layer [227]. All these insights have promising clinical implications for the potential development of therapeutic interventions to mitigate CNS hyperexcitability in gastrointestinal disorders such as IBD and IBS.

ROS generated by oxidative stress are known to induce increased KCNQ currents in neurons [228]. This is mainly due to the methylation of protein arginine, which constitutes a post-translational modification that enhances the

function of the KCNQ/M channel.

A critical characteristic of M-channels is their reliance on membrane phosphatidylinositol-4,5-bisphosphate (PIP2) to be able to open [229]. These channels contain numerous arginine residues within their PIP2-binding domain, and these residues can be subject to methylation by protein arginine methyltransferases (Prmts). Prmts are enzymes that catalyze the transfer of a methyl group to arginine residues and are highly expressed in the CNS [230]. The observation that decreased methylation lowers PIP2 affinity suggests that methylation of arginine residues enhances the channel-PIP2 interaction. The augmentation of KCNQ currents in response to oxidative stress has been linked to a significant reduction in apoptosis activation, which may help prevent neuronal death [231].

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