Colorectal cancer and endoplasmic reticulum stress – potential targets for therapeutic compounds

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Abstract

Introduction and Objective. Colorectal cancer (CRC), a malignant neoplasm of the gastrointestinal tract, affects the colon and rectum, its incidence is high, being the third most common neoplasm in men, with two million cases/year and survival <70%/5 years. The pathophysiology and progression of CRC are closely related to endoplasmic reticulum stress (ERE) and the unfolded or misfolded protein response (UPR). ERE can be triggered by various oxidative stress and inflammation factors with high UPR load followed by physicochemical and conformational interactions. The aim of the review is to present recent evidence on the relationships between endoplasmic reticulum stress, unfolded protein response and colorectal cancer.

Review Methods. An expanded integrative review was carried out of scientific information from PubMed, LILACS and SciELO health databases. Articles containing key words were selected for abstract fast readings, followed by full text selections of works containing targeted subjects. From a total of 198 articles, 96 were selected (92% ≤ 8 years) for inclusion in the review.

Brief description of the state of knowledge. New developments in CRC research are presented within approaches to molecular pathophysiological pathways, a spectrum of therapeutic targets and suggestive diets with a view of intestinal microbiota and dysbiosis, considering progression stages and evidences correlating CRC to socio-environmental and innate or acquired genetic load. Putative CRC target compounds and drugs, such as Aspirin, Fucoidan, PERK inhibitor, antimicrobial and current natural antioxidants are briefly presented and discussed.

Summary. Chaperone proteins may accumulate misfolded proteins in the endoplasmic reticulum, causing disruption of ERE proteostasis. While CRC progression is closely related to these signaling pathways, a better understanding is vital for new target-specific anticarcinogenic molecules.

Key words

colorectal cancer, endoplasmic reticulum stress, unfolded protein response, CRC signaling pathways

INTRODUCTION

This integrative review was carried out by gathering scientific information from the main free access health databases accessed on the internet (PubMed, LILACS and SciELO). All articles containing at least one of the key words were initially selected for reading the title and abstract. The works that contained the subjects targeted by this review were then selected for the full text to be read. After reading 198 articles in full, 113 were selected for inclusion in the expanded integrative review. The aim of the review was to collect the most recent scientific evidence on the relationships between endoplasmic reticulum stress, the unfolded protein response and colorectal cancer.

Colorectal cancer (CRC) – gastrointestinal tract malignant neoplasm. Colorectal cancer (CRC) is a malignant neoplasm of the gastrointestinal tract that can affect the right, left, sigmoid and rectum colon. Among incident malignant tumours of the gastrointestinal tract, and according to data from the International Agency for Research on Cancer, in 2018, CRC ranked third in terms of incidence, but second in mortality. It is also the third most common type of cancer in men, after lung and prostate cancer, and the second most common type of malignancy in women, after breast cancer. Estimates predict that in 2030 the global burden of CRC will reach approximately 2.2 million new cases per year, thus indicating a 20% increase [1]. In patients with CRC, overall survival is 64–67% at 5 years. Patients with localized cancer have a survival rate of 89–90%, in those with regional neoplasia the 5-year survival rate drops to 70–71%, and patients with distant metastases have a survival expectancy of only 14–15% at 5 years [2].

Colorectal cancer has a multicausal etiopathogenesis. The main risk factors for developing CRC are family history of bowel cancer, personal history of bowel cancer, age equal to or greater than 50 years, excess body weight, diet rich in fats, sugars, processed meats and poor fibre, physical inactivity, diabetes mellitus, smoking and consumption of alcoholic beverages, intestinal inflammation, among others [3]. A more detailed discussion will be presented later in the review. Although known to have a multifactorial pathophysiology, in CRC, endoplasmic reticulum stress (ERE) associated...
with the unfolded protein response (UPR) are the main cytomolecular pathways involved in the genesis, progression, and invasion of colon tumours [4–5]. However, despite some signaling pathways having been described previously, much remains unknown about the ERE and the UPR, as well as several mechanisms related to carcinogenesis which also need clarification. In this sense, the present study aims to revisit and update the evidence on the existing relationships between the ERE/UPR and the CRC, as well as the drugs and inherent compounds that have anticancer and modulating effects.

**Endoplasmic reticulum and chaperones.** The so-called Heat Shock Proteins (HSP) were first described by Ferruccio Ritossa [6]. This observed that when raising the temperature of Drosophila larvae, there was an increase in gene transcription for translation into proteins, as yet not known. The term molecular chaperone was subsequently applied by Ron Laskey [7] to describe the nuclear protein involved in the synthesis of histone nucleosomes and DNA in amphibian egg extracts. The word ‘chaperone’ is used as an analogy, with the term from the French word ‘chaperone’, meaning ‘to accompany’. Subsequent studies demonstrated various HSPs, which are ubiquitously distributed in eukaryotic cells and form large families, which are classified according to their molecular weight (in kilodaltons – KDa), namely, the main HSPs are distributed in different families, including HSP100s, HSP90s, HSP70s, HSP60s, HSP40s, and some small HSPs (15–40 kDa) [8]. Depending on their subtype, chaperones can be found in various cell compartments, such as the cytosol, nucleus and organelles, e.g. the endoplasmic reticulum and even in the mitochondria. However, the chaperones of interest in this study are the HSPs that reside in the lumen of the endoplasmic reticulum (ER) where they perform several important functions related to proteostasis and cellular protection [9]. The rough endoplasmic reticulum (ER), an organelle connected to the nuclear membrane, is the site of most protein synthesis, translation, folding and quality control processes. These processes must be organized and harmonious so that they can process different spatial conformations of specific proteins, but they must also be sensitive enough to recognize that an unrecoverable protein must be degraded, a task up to the HSPs [9].

However, when HSPs fail, defective proteins may be directed to degradation by the ERAD (Endoplasmic reticulum-associated protein degradation) system, aimed at alleviating ERE [10]. ERAD is activated in a complex pathophysiology [18].

**Activation of unfolded protein response (UPR).** The UPR is the mechanism that cells use to maintain the balance of protein folding in the ER. The correctly folded protein reaches its native or functional state, being addressed to intracellular destinations and respective structures, or may be secreted for action (e.g. digestive enzymes, hormones, transport proteins, among others) [16]. When misfolded proteins accumulate in the ER, the UPR is triggered and the overload recruits chaperones to fold the defective proteins. The UPR operates by reducing the amount of non-folded ER proteins, relieving pressure on the stressed ER, increasing the ER’s folding ability, and degrading some unfolded proteins that take longer to fix. As negative feedback, once activation of the UPR succeeds in reducing unfolded proteins, the UPR will be inactivated, and the cell’s protein folding balance will return to normal. Otherwise, the cell may be routed to apoptosis. [17]. The UPR comprises three transmembrane proteins (IRE1α, PERK and ATF6) that coordinate all signaling cascades for ER rebalancing and for consequent cell protection, or otherwise into apoptosis if the triggering events of stress are irrecoverable. It is known that these proteins work in cooperation, activating and blocking molecules with each other, both in the ER and in the cytosol and nucleus. It is important to recognize the individual and collective role of these proteins to understand the complexity of the control events of this delicate microenvironment, aiming to understand these reactions with the CRC pathophysiology [18].

**Activation and signaling pathway of IRE1α reduce protein load.** Activation of IRE1α (Kinase 1 alpha – type I transmembrane protein) begins when GRP78, as a BIP (Binding Protein) leaves its binding site in the luminal domain of IRE1α, at which point IRE1α homodimers are assembled in the plane of the ER membrane [19–20]. A trans-autophosphorylation then occurs that increases kinase and RNase activity, the reaction of which removes an intron of 26 bases from the mRNA that encodes the binding protein XBP1 (X-box-binding protein 1). This results in the formation of the transcription factor XBP1s (X-box binding protein 1 splicing). XBP1s travels to the nucleus and activates a transcription programme that stimulates the production of chaperones and other transcription factors which control ER quality, with synthesis of phospholipids necessary for ER expansion.
under stress, and activation of ERAD [21]. Another signaling pathway originating from IRE1α activates the degradation of mRNAs associated with the ER, promoting RIDD (IRE1α – Regulated IRE1-dependent decay of mRNAs), reducing protein load and promoting metabolic adaptation. In a third way, IRE1α can also positively modulate c-Jun N-terminal kinase (JNK), a cytoplasmic protein responsible for inducing apoptosis [22–23].

**Activation of PERK signaling pathway to minimize translation.** PERK is a type I transmembrane protein, with the serine/threonine kinase end facing the cytosolic kinase space, and which constitutes the most sensitive ERE sensor. In an ERE situation, the chaperone GRP78 uncouples from PERK at its luminal end in the ER, and then undergoes oligomerization and trans-autophosphorylation [24]. Activation of PERK phosphorylates serine 51 of the eIF2α subunit (eukaryotic translation initiation factor 2), and consequently, translation attenuation occurs. The rapid global reduction in translation decreases the amount of newly synthesized proteins that migrate into the ER, attenuating protein folding and relieving the burden on the ER. However, some mRNAs escape translation inhibition and activate transcription factor 4 (ATF4), which migrates to the nucleus and modulates the expression of genes responsible for amino acid metabolism, redox balance, protein folding, cell survival and autophagy [25]. In the nucleus, ATF4 finds the C/EBP homologous protein gene (CHOP/GADD153) and encodes a transcription factor that regulates apoptosis. ERE that induces apoptosis [26–28].

The main mechanism that explains CHOP-induced apoptosis is the production of ROS induced by the expression of ER oxidoreductin-1 alpha (ERO1α) [29]. PERK also signals eIF2α by activating the transcription of the nuclear factor-κB (NF-κB) through the translational repression of the kappa inhibitor β (IκB), inducing the regulation of apoptosis [30]. Figure 1 shows an overview of UPR signaling and the intranuclear effects resulted by its activation.

![Figure 1. UPR signaling pathways overview and intranuclear events activated by gene expression of XBP1s, ATF4 and ATF6p50, and schematic representation of how drugs affect UPR in CRC (green and red boxes).](image)

**Table 1. Main cellular and biochemical-molecular heat shock proteins characteristics and potential targets for therapeutic tools. Source: Modified and adapted from ZAMER et al. (2021)**

<table>
<thead>
<tr>
<th>Main family</th>
<th>HSPs variants</th>
<th>Cellular compartmentalization</th>
<th>Biochemical functions and processes</th>
<th>Prognosis</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSP90</td>
<td>HSP90</td>
<td>Cytoplasm, Cell Membrane, ECM.</td>
<td>Stabilizes MutS p53, promotes F-FDG accumulation, inhibits E-cadherin, mediates EMT.</td>
<td>Poor prognosis, an independent risk factor for OS.</td>
<td>[97–98]</td>
</tr>
<tr>
<td>GRP94</td>
<td>ER</td>
<td>Activates immune cells.</td>
<td>Increased tumour size and pT stage.</td>
<td></td>
<td>[99–100]</td>
</tr>
<tr>
<td>TRAP1</td>
<td>Mitochondrial Matrix</td>
<td>Protects the mitochondria from ROS accumulation.</td>
<td>Invasion and reduced OS.</td>
<td></td>
<td>[101–102]</td>
</tr>
<tr>
<td>HSP70</td>
<td>Cytosol</td>
<td>Activates RTK, stabilizes β-catenin.</td>
<td>Prognostic marker in primary CRC.</td>
<td></td>
<td>[103–104]</td>
</tr>
<tr>
<td>GRP75</td>
<td>Mitochondria</td>
<td>Promotes P53 retention and Wnt/β-catenin pathway, EMT.</td>
<td>Poor OS and poor prognosis.</td>
<td></td>
<td>[105]</td>
</tr>
<tr>
<td>GRP78</td>
<td>ER</td>
<td>Activates UPR.</td>
<td>Primary tumour depth of CRC, and reduced recurrence-free survival.</td>
<td></td>
<td>[106]</td>
</tr>
<tr>
<td>sHSP</td>
<td>HSP27</td>
<td>Cytosol</td>
<td>EMT, downregulates cell cycle-associated molecules, regulates Ca2+ influx, promotes the “Warburg effect”.</td>
<td></td>
<td>[107–108]</td>
</tr>
<tr>
<td>HSPB3</td>
<td>Cytosol</td>
<td></td>
<td>Poor RFS and OS.</td>
<td></td>
<td>[109]</td>
</tr>
<tr>
<td>HSPB5</td>
<td>Cytosol</td>
<td>Inhibits NF-κB.</td>
<td>Tumour grade, potential prognostic maker.</td>
<td></td>
<td>[110]</td>
</tr>
<tr>
<td>HSP60</td>
<td>Mitochondria</td>
<td>Enhances IGFBP7 activity, promotes adenine accumulation, activates AMPK.</td>
<td>Prognostic marker for the late stage of CRC and liver metastasis, early diagnostic marker.</td>
<td></td>
<td>[111–112]</td>
</tr>
<tr>
<td>HSP110</td>
<td>ER, cytosol, ECM</td>
<td>Activates STAT3 pathway. Favour anti-inflammatory macrophages.</td>
<td>Bad prognosis, poor OS, metastasis.</td>
<td></td>
<td>[113]</td>
</tr>
</tbody>
</table>

For abbreviations see Terminology

**Interrelation between IRE1α, PERK and ATF6 systems**

**ER membrane anchored ATF6 signaling pathway.** ATF6 is a type II protein anchored in the ER membrane, with a domain...
of the transcription factor CREB/ATF bZip at the amino terminus located in the luminal portion of the organelle. With the accumulation of unfolded or misfolded proteins in the ER, the chaperone GRP78 leaves its binding site on ATF6 on the luminal side of the ER, freeing ATF6 to migrate to the Golgi apparatus where it is cleaved to give rise to the ATF6p50 complex. This travels to the nucleus where it activates ATF6α target genes that include the chaperones GRP78, GRP94, ERAD components, the UPR genes XBP1, 58 kDa protein kinase inhibitor (P58IPK/DNAJC3) and CHOP [21,24]. ATF6 activation during ERE requires the integrated participation of PERK/eIF2α/ATF4 signaling pathways. ATF6α has been shown to promote ERAD induction when heterodimerizing with XBP1. This ATF6-XBP1 heterodimer has eight times more affinity for the UPR element than the XBP1 homodimer [21]. Two are the main final effects resulting from the interaction of the various UPR constituents, cell adaptation and survival and apoptosis. To achieve these effects, dozens of molecules from the three main ERE signalers interact with each other in complex cascades involving primarily the activation of IRE1α, PERK and ATF6 [4].

Pathways for cell adaptation and survival. Four pathways are possible to achieve cell adaptation and survival. The first involves the activation of PERK, and subsequently NRF2, ARE and Keap1, and finally, the modulation of redox enzymes. The second pathway for adaptation requires the initial activation of PERK, followed by eIF2α, ATF4 and finally the modulation of ERAD genes and chaperones. The third pathway starts with IRE1α activation, followed by XBP1, XBP1s and finally the activation of ERAD genes and chaperones. The fourth and final interactive signaling pathway that culminates in cell adaptation and survival begins when ATF6 is activated, in sequence, ATF6 travels to the Golgi apparatus where it is cleaved into ATF6p50, which finally modulates the action of ERAD genes and chaperones [4].

For apoptosis to occur, five paths are possible to be traversed. The first requires PERK activation, followed by eIF2α, ATF4, and finally CHOP. The second pathway starts with PERK activation, followed by phosphorylated eIF2α, GADD34, dephosphorylated eIF2α, and finally ROS. The third pathway starts with the activation of IRE1α followed by TRAF2, ASK1, and finally JNK. The fourth pathway starts when IRE1α is activated, followed by XBP1, XBP1s and CHOP molecules. The fifth and final signaling pathway for apoptosis occurs when ATF6 is activated, and in sequence ATF6 travels to the Golgi apparatus where it is cleaved into ATF6p50, which finally triggers the CHOP transcription factor [4].

Recent studies demonstrate a new retro-interaction between activated XBP1, ATF6 and PERK-eIF2α, with the potential to activate or silence signaling pathways involved in tumourigenesis and resistance to chemotherapy. During tumour proliferation, cancer cells acquire several adaptive characteristics that allow them to survive and thrive even in the face of unfavorable microenvironmental conditions such as ERE [31]. New knowledge shows that UPR activation is primarily responsible for many tumour characteristics, including genomic instability, angiogenesis, invasion, proliferation, cell Nrf2/nci, survival and escape from apoptosis. These researchers have demonstrated a novel cross-interaction between activated XBP1 and ATF6 and PERK-eIF2α. It was found that the interaction between XBP1 and PERK-eIF2α is directly responsible for the antiproliferative effect of XBP1.

The results of this review show the relevance of the action of PERK-eIF2α in reducing tumour cell viability. From this research, sufficient fronts of knowledge can be opened to leverage treatments using the effects of the XBP1 and PERK-eIF2α interaction in the prevention or treatment of intestinal malignancies [24,32].

Antagonistic mechanisms observed by UPR activation by the ERE

Survival of cancer cells by UPR activation. Generally, normal cells under homeostatic circumstances, maintain their UPR in an inactive state under basal conditions, activating it only in situations of physiological challenges that induce the ERE [33]. UPR activation can both induce tumour cell adaptation and survival and promote apoptosis of these cells. Furthermore, the UPR may play an inverse role in the metastasizing effect. There are several mechanisms used by neoplastic cells to survive and thrive in the hostile tumour microenvironment, and in the presence of chemotherapeutic agents. The activation of some UPR signaling pathways are essential for tumour cells to adapt to hypoxia regimes, nutrient deprivation, ROS production and the action of antitumour defense system cells [34–35].

Unlike normal cells, cancer cells commonly express typical activation of UPR signaling seeking adaptation, while modulating anti-apoptotic signals. These facts clearly demonstrate that neoplastic cells can acquire the ability to self-select, allowing them to survive in unfavourable environments [35–36]. The positive modulation of IRE1α induces the expression of XBP1, XBP1s and ERAD, further facilitating the survival of the malignant cell [21,37]. PERK activation via ARE, Keap1 and ATF4 may also favour the survival of neoplastic cells in hostile environments with nutrient deficiency, ATP shortage, ROS production and hypoxia [4,38].

Life and death of cancer cells control though the CHOP pathway: Tumour growth is usually stopped by Tumour Infiltrating Myeloid Cells, like Dendritic Cells (BMDC). However, the signaling emitted by the tumour, still not elucidated, changes the BMDC to a phenotype that does not undergo cell-mediated antitumour immunity. In this way, this apparatus negatively regulates the cross-presentation of the high affinity antigen and fails when trying to present the tumour antigens to the TCD8+ receptors, thus determining the activation of T cells without proliferation, preventing the immune system from identifying and destroying the tumour cells [39]. In the PERK signaling pathway, CHOP is a key mediator that induces apoptosis in the presence of ERE. The PERK-eIF2α-ATF4–CHOP sequence is a CHOP-determining pathway that culminates in apoptosis. In addition, ATF6 also makes an important contribution to the production of CHOP in the first moments of stress, and XBP1 regulates CHOP in a more attenuated way. When stress is intense and chronically sustained, CHOP induces DNA damage34 (GADD34), increasing the formation of ROS which, in turn, aggravates the ERE and determines the death of the tumour cell [26]. Nuclear factor E2-related factor 2 (ATF4atf), PERK’s downstream signal protein, promotes cell adaptation and cancer growth. NRF2–Kelch-like ECH-associated protein 1 (Keap1) and NRF2 antioxidant response element (ARE), can counteract the harmful effects of ROS on tumour cells and restore the redox balance of the tumour.
microenvironment, promoting cancer survival at adverse agents such as chemotherapy [31,40]. ATF6p50, ATF4 and XBP1s act synergistically to stimulate CHOP and induce apoptosis. The JNK pathway initiated by IRE1α, TRAF2 (TNF receptor-associated factor 2) and ASK1 (Apoptosis signal-regulating kinase 1) activation can trigger both apoptotic and necrotic cell death. Furthermore, the generation of ROS stimulated by the action of eIF2α can also cause tumour apoptosis [41]. CHOP (a 29 kDa bZIP transcription factor) is a vital canonical mediator of ER-based apoptosis. When activated, it triggers several apoptosis-facilitating factors, including conformational modeling of Bim, a pro-apoptotic member of the B2 cell lymphoma (BCL-2) family, death receptor 5 (DR5), and repeat binding factor, telomere 3 (TRB3) [42].

It has already been demonstrated that CHOP leads to oxidative stress through the induction of ERO1α, which in sequence transfers electrons from the protein disulphide isomerase to O2 producing the potent free radical H2O2. Another effect of ERO1α is to release Ca2+ from the ER through the inositol 1,4,5-triphosphate receptor. Knowing that Ca2+ is essential for chaperones to exercise their protein folding functions in the ER, Ca2+ depletion implies a negative regulation of the protein folding capacity. Thus, the Ca2+ released from the ER is carried to the mitochondria, where it determines vigorous oxidative stress and apoptosis signaling [43]. Therefore, CHOP stimulation is not advantageous for cancer cells as it promotes apoptosis in the ERE environment. Therefore, molecules that stimulate CHOP activation in tumour tissues can be considered promising targets for antineoplastic therapy in CRC.

PERK pathway and induction of metastasis. The predominant pathway of the UPR responsible for metastasis is PERK, as it is through its activation that the initiation of angiogenesis occurs. This mechanism is due to increased expression of vascular endothelial growth factor (VEGF), which acts as an angiogenic agent and contributes to the survival of endothelial cells, through the action of VEGFA, VEGFB, VEGFC, VEGFD, VEGFF and placental growth factor (PIGF) [44–45]. The transformation of epithelial tissue into mesenchymal tissue (EMT – Epithelial to Mesenchymal Transition) favours both tumour progression and resistance to chemotherapy; however, few weak points have been identified in this mechanism. Utilizing selective small molecules as cellular probes, EMT induction has been shown to greatly sensitize tumour cells to agents that disrupt ER function. It was noted that the sensitivity to perturbations was caused by the synthesis and secretion of large amounts of extracellular matrix proteins by EMT cells. Thus, it was observed that EMT cells exhibited a branched ER morphology and activated the PERK-eIF2α axis of the UPR. Therefore, PERK activation is essential for EMT cells to invade and metastasize [46].

Interactions between UPR pathways and chaperones in colorectal cancer tissues. GRP78 (BiP) is a chaperone of the HSF70 family. A signal oligopeptide determines that GRP78 resides in the lumen of the ER and there performs tasks such as protein folding and assembly, proteasomal degradation of defective proteins, Ca2+ binding and activation of transmembrane UPR sensors [47–48]. Unfolded or misfolded proteins accumulate on the luminal side of the GRP78 (BiP) as a substrate (SBD) for GRP78, which through the binding domain sends a signal to the ATPase domain, forcing it to disconnect from IRE1α and PERK, ceasing to exert action blockade on these two proteins. GRP78 expression is increased in several types of solid tumours, including CRC, and recent studies show that GRP78 exhibits antagonistic characteristics in tumour cells. GRP78 limits the early development of tumours through numerous suppressive mechanisms, such as dormancy induction [8]. On the other hand, in more advanced stages of tumour progression, when neoplastic cells are exposed to excessive ER stress, GRP78 stimulates cancer progression through its adaptation, survival and metastatic invasion [49–50]. On the surface of the cancer cell, GRP78 interferes with some signaling pathways in the cytoplasmic membrane, regulating proliferation, apoptosis and tumour immunity [8]. GRP78 also plays a key role in tumour angiogenesis, a mechanism attributed to VEGF induction [51]. The expression of GRP78 has already been well studied in CRC tissues using immunohistochemical techniques. In this study it was proven that GRP78 exhibits a comparatively much more pronounced expression in CRC histological sections than in normal colon tissues [8,49]. Such evidences, collectively point to the fact that GRP78 is over-expressed in cultured CRC cell lines as well as in colorectal cancer tissues, and plays an important role in regulating the sensitivity of cancer cells to chemotherapeutic-induced apoptosis [8,49].

IRE1α as a protagonist in the angiogenesis of CRC development. IRE1α presents at least three output signaling pathways, XBP1 mRNA splicing, RIDD from other mRNAs, and direct interactions with downstream mediators such as TRAF2, ASK1 and JNK [35]. Augmentation of XBP1 splicing has been demonstrated in several types of cancer and it is associated with more aggressive tumour behaviour and decreased survival [21]. In a mouse model, activated IRE1α triggered the TRAF2 adapter protein, which then strongly interacted with JNK, resulting in Caspase 12 activation and subsequent apoptosis [52]. Yet, XBP1 is a biomarker of CRC invasion and metastasis, and its expression accelerates cancer cell invasion, suppressed by knockout of XBP1 using small interfering RNA (siRNA). When XBP1s is silenced, VEGF receptor 2 (VEGF-R2) levels, recognized as inducers of tumour angiogenesis, are drastically reduced [37,51]. XBP1s inhibits the expression of the tumour suppressor TAp73, a member of the p53 protein family, by binding directly to the TAp73 promoter and suppressing its transcriptional activity. Furthermore, it was observed that the over-expression of TAp73 nullified the effect of XBP1s in increasing the proliferation of CRC cells and in the potential stimulus of colony formation, indicating that TAp73 is an inducer of tumourigenesis when induced by XBP1s [53]. Nonetheless, angiogenesis represents an essential phase in the development of CRC and IRE1α is the initial protagonist in this context. Solid tumours initially develop in the absence of vascularization, but as they grow they are exposed to various growth-restrictive conditions, such as hypoxia, hypoxia and nutrient (glucose) deprivation. IRE1α activation is a common determinant that triggers hypoxia and hypoglycaemia-dependent signaling pathways leading to VEGF-A over-expression [37]. An experiment using an animal model lacking IRE1α failed to increase VEGF-A expression under conditions of hypoxia and hypoglycaemia, thus proving that IRE1α-dependent signaling pathways play...
an indispensable role in response to ischemia, indicating that IRE1α as a potentially useful therapeutic target to reduce angiogenesis and tumour growth [54].

**The PERK pathway in redox balance for cellular oncogenic adaptation.** ATF4 and NRF2 are the two downstream PERK transcription factors that contribute to cellular adaptation and oncogenesis [55]. NRF2 uses ARE and Keap1 to regulate the expression of genes responsible for modulating antioxidant enzymes, promoting the adaptation and survival of cancer cells. NRF2-Kelch-like ECH-associated protein 1 (NRF2-Keap1), as well as NRF2-ARE, can counteract the harmful effects of ROS on CRC cells and restore redox balance to favour neoplastic progression [38,56]. On the other hand, evidence shows that PERK can phosphorylate and facilitate the relocation and nuclear activity of FOXO (Forkhead box O), an important anti-tumour signaling of the PERKA pathway, also from the FOXO family of transcription factors, recognized as tumour suppressors that promote cell cycle arrest and apoptosis, in order to prevent the accumulation of genomic damage induced by genotoxic agents and oxidative stress. In this way, FOXO inhibition releases cancer progression and acts as a facilitator of metastases and angiogenesis, indispensable factors for tumour progression and survival [57–58]. Hypothetically, the opposite, i.e. FOXO stimulation, would be an interesting way of potential antit-umour treatment.

**ATF6 pathway cytoprotective responses dependent on the microbiota.** Several studies suggest that ATF6 activation does not generate obvious antagonistic effects. Its signaling induces cytoprotective responses, such as ER biogenesis, upregulation of chaperones and activation of the ubiquitin/proteasome system, generating the degradation of unfolded/misfolded proteins [59]. Increased nuclear translocation of the ATF6 fragment, called ATF6p50, is observed in several types of cancer, and its over-expression has been correlated with a greater likelihood of metastasis and relapse [4]. Despite this, ATF6 is considered a marker of low-grade dysplasia (LGD – Low Grade Dysplasia) of inflammatory regenerative epithelium in patients with ulcerative colitis. Elevated plasma ATF6 titers are associated with reduced disease-free survival in patients with CRC. Experiments in nATF6IEC mice showed that sustained activation of ATF6 in the colon induced dysbiosis and microbiota-dependent tumourigenesis [60]. In addition, studies in germ-free mice demonstrated that UPR activation via ATF6 in the epithelium required the presence of intestinal microbiota for tumour development to occur. Although the diagnosis of LGD is important for the management of ulcerative colitis, it is sometimes difficult to distinguish LGD from inflammatory regenerative epithelium. There is accumulating evidence that ATF6 levels are elevated in lesions that have undergone typical preneoplastic histopathological changes in the context of CRC, with or without ulcerative colitis. Therefore, ATF6 may be useful as a promising biomarker to distinguish LGD from inflammatory regenerative epithelium in patients with ulcerative colitis [61].

**Diet, intestinal microbiota, and colorectal cancer.** The initiation, promotion, and progression stages of CRC are multifactorial. Evidences correlate CRC to socio-environmental aspects (predominantly consumed diet, sedentary lifestyle, and obesity), intestinal microbiota and innate or acquired genetic load. Epidemiological studies show that some specific types of diet can promote or protect humans from having CRC and dietary management can reduce its incidence, since diet composition has an important impact on intestinal arrangement and microbiota function, being more relevant for carcinogenesis than the individual’s own genetic load [62–63]. Figure 2 illustrates the main risk factors for CRC, demonstrating that there is an interrelation between them, and shows their individual percentages [64].

Liang et al. (2017) found that in patients with CRC and adenoma, the organization of the intestinal microbiota is disturbed, which is not the case in healthy patients. Switching from an African-derived diet (high in plant polysaccharides including fibre, and low in fat and processed meat) to a typical Western diet (low in plant polysaccharides/fiber and high in fat, processed meat, and sugar) has been found to lead to a rapid change in the composition and population density of the intestinal microbiota [65–66]. After the absorption of nutrients in the small intestine, waste products, which are basically complex carbohydrates (dietary fibre), protein residues and primary bile acids, secreted by the liver to digest fats, arrive in the colon. These waste products are critical for the composition and function of the gut microbiome, and play a delicate role in maintaining colonic health through fermentation. If the diet is balanced and healthy, the fermentation of dietary fibres will predominantly produce short-chain fatty acids (SCFAs). Butyrate, the most important representative of the SCFA family, performs several protective functions on colonocytes, including anti-inflammatory and antineoplastic properties, promoting microbiota homeostasis, and genetic and epigenetic immunomodulatory regulation. In contrast, an unbalanced Western diet promotes protein fermentation and bile acid deconjugation, which damage colonocytes through activation of pro-inflammatory and pro-carcinogenic pathways, and thereby increase the risk of developing CRC [64,67].

Dysbiosis is a phenomenon that occurs when there is an imbalance between the population of potentially pathogenic
intestinal bacteria and probiotic bacteria, those that promote the health of colon cells. The population increase of bacteria, such as colibactin-producing Escherichia coli, *Bacteroides fragilis*, *Fusobacterium nucleatum* and *Fusobacterium providencia*, are responsible for activating signaling pathways of colorectal carcinogenesis, while simultaneously there is a significant reduction of butyrate-producing bacteria, such as *Roseburia intestinalis* and *Faecalibacterium prausnitzii* [68]. *Fusobacterium nucleatum* adheres and invades colonocytes and promotes carcinogenesis through FadA, which binds to E-cadherin, activates β-catenin signaling and upregulates signaling pathways of inflammation and carcinogenesis [69].

**Enterotoxigenic fragile** bacteria produce fragilisin (BFT), a toxin that activates the Wnt/β-catenin and NF-κB signaling pathway and induces uncontrolled cell multiplication and inflammation [70]. BFT can trigger a multimodal pro-carcinogenic inflammatory cascade involving IL-17R, NF-κB and STAT3 signaling in colonocytes, and trigger myeloid cell-dependent oncogenesis in the distal colon [71]. The randomized clinical study conducted by Prizment et al. (2020), found that participants who used Aspirin at a daily dose of 325 mg had a decrease in the population of species from genus, *Prevotella*, *Akkermansia* and *Ruminococcaceae*, while there was increase in Bacteroides, Parabacteroides and Dorea species counts, a finding that was associated with reduced risk of CRC [72].

**Anticarcinogenic potentials targeting ER stress via Activation of unfolded protein response**

**Fucoidan.** Fucoidan (a drug prepared with Cladosiphon okamuranus, an edible seaweed from Okinawa, and with Fucus evanescens, an Arctic seaweed) negatively regulated GRP78 in HCT116 colon cancer metastatic cells. Fucoidan triggered eIF2α pro-apoptotic signaling pathways resulting in CHOP activation and inhibited IRE-1α/XBP-1s pro-survival signaling pathways [73].

**DPE (2-(3,4-dihydroxyphenyl ethanol).** The antioxidant phenol extracted from olive oil, 2-(3,4-dihydroxyphenyl) ethanol (DPE), promoted tumour growth arrest and apoptosis in HT-29 cells of human colon carcinoma. This compound caused prolonged endoplasmic reticulum stress and activated the two main branches of the UPR, including the IRE-1α/XBP-1/GRP78 and PERK/eIF2α pathways. DPE treatment induced over-expression of the pro-apoptotic factors CHOP/GADD153 and sustained activation of the Jun-NH2-terminal kinase/activator protein-1 signaling pathway [33].

**PERK 42215 inhibitor.** Potent anti-carcinogenic action was discovered in the 42.215 molecule. Research has shown that the PERK 42215 inhibitor has selective action on human colon adenocarcinoma neoplastic cells CCD 841 com. In *vitro* treatment of tumour cells nullified their viability in a dose and time-dependent manner and induced apoptosis and cell cycle arrest in G2/M. In addition, the substance caused significant inhibition of eIF2α phosphorylation in HT-29 CRC cells [74].

**Resveratrol.** Resveratrol (3,4',5 trihydroxystilbene), a polyphenolic compound found in large amounts in grapes and red wine, has been shown to have anti-proliferative and pro-apoptotic activity in human cancer cell lines. It was observed that treatment of HT-29 human colon cancer cells with Resveratrol induced the expression of several ER stress markers, such as eIF-2α, XBP1s CHOP. Furthermore, Resveratrol activated the positive modulation of GRP78, confirming the induction of ER stress [75].

**Piperine.** A piperidine alkaloid present in black pepper, increased the expression of proteins linked to endoplasmic reticulum stress in HT-29 cells, such as IRE1α, CHOP, C-Jun and p38 mitogen-activated protein kinase. Other experiments demonstrated that Piperine promoted ER stress-mediated tumour cell apoptosis due to mitochondrial dysfunction induced by ROS generation [76].

**Curcumin.** One of the main bioactives isolated from the root of Curcuma longa, inhibited the growth of HT-29 colon carcinoma cells in a dose-dependent manner. Curcumin cytotoxicity was determined by ERE, induction of mitochondrial dysfunction verified by CHOP upregulation, JNK phosphorylation and SERCA2 ATPase downregulation, Cytochrome-c release, Bcl-2 decrease and reduction of mitochondrial membrane potential inducing cells HT-29 to suicide. It was also observed that HT-29 cells treated with Curcumin showed over-expression of bax, total JNK, phospho-FADD and total FADD. In addition to these mechanisms, it was shown that Curcumin induced a reduction in cytoplasmic and ER Ca2+, but increased mitochondrial Ca2+, activating the DR5 protein and causing tumour apoptosis [77].

**Treatment of BRAF mutation-type CRC with CFZ/ACY-1215.** Colonic cells carrying BRAFV600E mutations induce tumour aggressiveness and a low survival rate in CRC patients. The BRAF oncogene activates the ERE and triggers the activation of UPR signaling pathways through MEK/ERK. In this study, it was demonstrated that BRAF mutant cells are more dependent on GRP78 than wild-type cells. The proteasomal inhibitor Carfilzomib (CFZ) and the aggressive inhibitor Ricolinostat (ACY-1215 – A selective histone deacetylase inhibitor) are drugs with potential use for CRC with BRAF mutation. Treatment of BRAF mutation-type CRC with CFZ/ACY-1215 combined, resulted in a better outcome compared to the effect of each drug alone. Research also revealed that combined CFZ/ACY-1215 treatment resulted in significantly increased expression of eIF2α/ATF4/CHOP and IRE1α/JNK [78].

**Berberine (BBR).** A natural vegetable triterpenoid, interfered negatively in the expression of GRP78, inhibited the proliferation and migration of tumour cells, and induced apoptosis of colonic neoplastic cells SW480. In addition, BBR inhibited the expression of Bax, Bcl-2, c-Myc and Vimentin, positively modulating cyokeratin expression in SW480 cells [79].

**Mung bean trypsin inhibitor (mTI).** The mTI has anti-tumour activity attributed to targeted suppression of GRP78. It was shown that mTI significantly inhibited growth and induced apoptosis in colorectal cancer cells, but not in normal cells. From a biomolecular point of view, these antineoplastic effects were attributed to the induction of cell cycle arrest in the G1 phase and activation of multiple apoptosis-promoting pathways [80].
**Epigallocatechin gallate (EGCG).** The main bioactive isolated from green tea (Camellia sinensis). This catechin has the potential to reduce tumour growth and increase drug sensitivity in several types of cancer. Current research shows that EGCG acts as an activator of the GRP78/NF-κB/miR-155–5p/MDR1 pathways, and plays a crucial role in increasing CRC sensitivity to treatment with the chemotherapeutic 5-Fluorouracil [81].

**Bortezomib.** The proteasome inhibitor which is able to amplify the load of protein misfolding in tumour cells, conferring a chemo-sensitizing effect on Cisplatin, Doxorubicin or Camptothecin in several types of tumours, including CRC [46].

**Paclitaxel.** Paclitaxel induces varying degrees of apoptosis in human CRC cells and activates signaling pathways of the endoplasmic reticulum stress response, including upregulation of GRP78 and IRE1α. Inhibition of the MEKP/ERK pathway sensitizes colorectal cancer cells to undergo Paclitaxel-induced apoptosis. Thus, combining GRP78 inhibitor molecules may represent a new approach to improve the effectiveness of Paclitaxel in the treatment of CRC [82].

**Chloroquine and Propranolol.** In an *in vitro* study, the incubation of CT26, HCT116 and HT29 cell lines in a solution containing Chloroquine (CQ) and Propranolol (P), at a dose of 2.5 µM of Chloroquine and 2.5 µM of Propranolol, triggered the apoptosis and impaired CRC cell migration. When tested alone, neither Chloroquine nor Propranolol demonstrated the effects obtained with the combined use of the drugs. In the same study, the combination of CQ + P administered to hairless mice that received a subcutaneous injection of HCT116 or CT26 cells, decreased tumour growth and the development of metastases [83].

**Serum biomarkers for CRC and their effect on local invasion and metastasis.** A study by GAO et al. (2018) evaluated the sensitivity, reliability, and ratio of single or multiple serum markers for the diagnosis of CRC in 279 patients with colorectal cancer. Carcinoembryonic Glycoprotein Antigen (CEA) has been observed to have the highest sensitivity among single markers in the following order: CEA > Cancer Antigen 72–4 (CA72–4) > Cancer Antigen 19–9 (CA19–9) > Ferritin > Cancer Antigen 125 (CA125), while the most sensitive combined markers for association between two and five were: CEA + CA72–4; CEA + CA72–4 + CA125; CEA + CA19–9 + CA72–4 + CA125; and CEA + CA19–9 + CA72–4 + CA125 + Ferritin, respectively. Patients with positive pre-operative sera CEA, CA19–9 or CA72–4, were more likely to have lymph node invasion, positive CA125 were prone to vascular invasion, and positive CEA or CA125 were correlated with perineural Invasion. Furthermore, patients with positive CA19–9, CA72–4 or CA125 were associated with poorly differentiated tumours, whereas those with elevated levels of CEA, CA19–9, CA72–4 and CA125 were positively correlated with pathological stages of tumour-nodule-metastasis [84].

**Recent findings and prospects for tumour markers in CRC.** A huge opportunity opens in the face of techniques capable of identifying and determining predictive biomarkers and opportune prognoses for the risk stratification of patients with CRC. Circulating tumour DNA (ctDNA) has emerged as a promising and possibly predictive diagnostic marker in the personalized treatment of patients with CRC. This pathology is essentially appropriate for an investigation based on liquid biopsy, since there is a large amount of tumour fragments circulating in the peripheral blood (cells, DNA, methylation markers, etc.). ctDNA has been shown to have several potential uses, including detection of minimal residual disease (MRD), early recurrence monitoring, molecular profiling, and prediction of therapeutic response [85–86]. A prospective study, lasting 3 – 4 years which included 184 patients with stage II or III CRC, confirmed the importance of ctDNA as a risk factor for tumour recurrence before surgery, and as a marker of minimal residual disease after surgery, which may include predicting recurrence several months before it can be detected by imaging techniques [87].

Quantification of ctDNAs has a promising future as a circulating biomarker for the diagnosis, prognosis and prediction of CRC. These biomarkers which are detectable in plasma can help us to improve the early detection of CRC, the post-operative follow-up, and surveillance of patients undergoing treatment; however, their validation requires large-scale clinical trials. This minimally invasive liquid biopsy biomarker still requires optimization and standardization of blood collection, refinement of ctDNA isolation and quantification, and performance evaluation to support its extensive use in clinical practice [85–86].

**Relationship between alcohol consumption and colorectal cancer.** A meta-analysis which included 57 studies (1986–2010) on the incidence of CRC and alcohol intake, showed that alcohol consumption – an intake greater than 1 drink per day (> 12.5 g/day of ethanol) – was associated with an increased risk of CRC, Therefore, public health recommendations aimed at preventing CRC include limiting the intake of alcoholic beverages [88]. A European study followed 478,732 people without CRC from 1992–2000. The cohort had a median duration of 6.2 years, during which time 1,833 cases of CRC were observed. The study demonstrated a positive and statistically significant association between high alcohol consumption (> 30 grams/day) and the risk of CRC. The relationship was maintained even after statistical adjustments for several confounding factors, including diet and lifestyle [89]. A meta-analysis including 16 studies concluded that people who did not drink and those who consumed up to 1 gram of alcohol/day had a reduced risk of CRC (p=0.005). Those who consumed 2–3 drinks/day did not have a significant association with CRC risk (p=0.08). However, heavy drinkers (more than 3 drinks/day) were associated with a significantly increased risk of CRC (p<0.001) [90].

**Chemopreventive drugs for colorectal cancer**

**Aspirin.** Aspirin (acetylsalicylic acid) is the drug that has the greatest amount of evidence in favour of chemoprevention of CRC. Aspirin is an irreversible inhibitor of cyclooxygenase (COX) 1 and COX2. Although there are disagreements about the exact chemo-preventive mechanism, aspirin inhibits several CRC-related signaling pathways, including platelet activation, prostaglandin production, inflammation, and Wnt signaling for β-catenin [91–92]. Several systematic reviews were analyzed, and it was observed that aspirin reduced the incidence of CRC and mortality in populations that made its use the primary prevention for cardiovascular disease. These
effects were only reported in those participants who used aspirin uninterruptedly for more than 10 days [93]. A meta-analysis of 4 randomized, placebo-controlled clinical trials, studied 2,967 participants who received placebo or aspirin at doses ranging from 81–325 mg/day, with the aim of assessing the secondary preventive potential of colorectal adenomas. The average follow-up of the participants was 33 months, with 60% of them being male and average age of 58 years. A total of 2,698 people underwent serial colonoscopy and were included in the post-randomization analysis of the occurrence of adenoma and advanced lesions. The study concluded that aspirin is modestly effective in preventing colorectal adenomas in people with a history of these lesions. [72].

**Non-Steroidal Anti-Inflammatory Drugs Non-Aspirin.** A meta-analysis including 23 studies involving more than 1 million people observed significant protective effects of Non-Aspirin Non-Steroidal Anti-Inflammatory Drugs (NA-NSAIDs) use in women (19% risk reduction), at higher doses (19% risk reduction 18%), in distal CRC (22% risk reduction), and in Caucasian participants (31% – 41% risk reduction). From these data, it is concluded that the use of NA-NSAIDs, at higher doses, can reduce the risk of colorectal cancer in specific subgroups of the population [94].

**Metformin.** A meta-analysis including 21 studies (12 cohorts, 7 case-controls and 1 randomized-controlled trial) investigated the incidence of colorectal adenomas or CRC. Metformin is shown to be associated with a reduced incidence of colorectal adenomas (p=0.0002). When the analyzed data were adjusted, statistics showed that there was a 25% decrease in the risk of adenomas among drug users (p=0.03). A significant reduction in the risk of CRC was also observed (p=0.0002), and when the analyzed data were adjusted, the risk of CRC was reduced by 22% for those receiving metformin compared to those not receiving it (p<0.00001) [95].

**CONCLUSIONS**

Despite providing useful new insights for the prevention, diagnosis and treatment of CRC, current evidence on the role of ERE/UPR in CRC still lacks robust information to support the use of drugs and natural products in the prevention and treatment of CRC, especially when used in synergy with currently available chemotherapeutics. Meanwhile, there are no solid grounds to categorically state that currently available drugs for ERE/UPR targets are safe to use as monotherapy in CRC. Using currently available drugs or compounds to treat CRC by modulating only specific ERE/UPR targets, is still a challenge, as it implies directing their antitumour effects only to cancer cells, sparing normal ones, reducing systemic side-effects, such as those presented by current chemotherapeutics.

New studies focused on the target-specific molecular biology of ERE/UPR and its signals, especially those that appropriate knowledge of genetic engineering and handling of monoclonal antibodies, are necessary to clarify the still unknown gaps in the pathophysiology and chemoresistance of CRC. It is believed that the correct interpretation of isolated or combined serum markers can be used to diagnose early, define the status of a tumour, guide the treatment, evaluate the curative effect, and estimate the prognosis of patients with suspected or confirmed diagnosis of CRC.

With the well-established correlation between ERE/UPR and CRC, this study serves to alert patients who have the potential to develop CRC, which may prove useful in the prevention of patients with risk factors, not only with normal colonoscopies, but with positive plasma markers. In such cases, these patients could be advised to change their lifestyle habits, especially their diet, well before the appearance of tumours, and their physicians would have important tools for monitoring and early diagnostic search. The cooperative work between scholars in this line of research, the pharmaceutical industry and specialists in bioinformatics, by using artificial intelligence will be able to access and manipulate robust databases of molecules, and to develop new target-specific drugs in a much shorter time than would be spent if the efforts worked independently.

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**Conflict of Interest.** The authors have no conflicts of interest to disclose.

**TERMINOLOGY**

**ACY-1215** – Ricolinostat; **AMPK** – AMP-Activated Protein Kinase; **ARE** – Antioxidant Response Element; **ASK1** – Apoptosis Signal-Regulating Kinase 1; **ATF4** – Transcription Factor 4; **ATF6** – Activating Transcription Factor 6; **ATF6p50** – 50-kDa bZIP Transcription Factor; **ATP** – Adenosine TriPhosphate; **BRR** – Berberine; **BCL-2** – B2 cell Lymphoma; **BFA** – Brefeldin-A; **BiP** – Binding Protein; **BMDC** – Myeloid Cells Like Dendritic Cells; **BRAF** – v-Raf Murine Sarcoma Viral Oncogene Homolog B1; **Ca2+** – Calcium Ion; **Cdc48** – Cell Division Control protein 48; **CFZ** – Carfilzomib; **CHOP** – C/EBP Homologous Protein Gene; **CRC** – Colorectal Cancer; **CREB/ATF bZIP** – CREB/ATF bZIP Transcription Factor; **Cue1** – Ubiquitin Conjugation to ER Degradation Protein 1; **Doa10** – Ubiquitin Ligase Doa10; **DPE** – 2-(3,4-dihydroxyphenyl) ethanol; **DR5** – Death Receptor 5; **ECM** – Extracellular Matrix; **EGCG** – Epigallocatechin Gallate; **eIF2α** – Eukaryotic Initiation Factor 2 Alpha; **EMT** – Epithelial Mesenchymal Transition; **ER** – Endoplasmic Reticulum; **ERAD** – Endoplasmic-Reticulum-Associated Protein Degradation; **ERE** – Endoplasmic Reticulum Stress; **ERK** – Extracellular Signal-Regulated Kinases; **ERODa1** – Endoplasmic Reticulum Oxido-reductin-1 Alpha; **ERQC** – Endoplasmic Reticulum Quality Control; **FADD** – Fas Associated Via Death Domain; **F-FDG** – Fluorodeoxyglucose (18F); **FOXO** – Forkhead Box O; **GADD153** – CHOP induces DNA Damage 34; **GRP75** – Glucose-Regulated Protein 75; **GRP78** – Glucose-Regulated Protein 78 (BiP); **GRP94** – Glucose-Regulated Protein 94; **H2O2** – Hydrogen Peroxide; **HCT116** – Cell line was isolated from the colon of an adult male with colon cancer; **Hd1** – E3 Ubiquitin-Protein Ligase; **HSP** – Heat Shock Proteins; **HSP110** – Heat Shock Proteins 110 KDa; **HSP27** – Heat Shock Proteins 27 KDa; **HSP40** – Heat Shock Proteins 40 KDa; **HSP60** – Heat Shock Proteins
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