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Review Article

Biomarkers Involved in Gastrointestinal Cancer

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Abstract

Objective: Analyze the participation of molecular biomarkers involved in gastrointestinal cancer (GIC).

Materials and Methods: A bibliographic selection of original and review articles reported in the last five years was conducted, which describe the role of biomarkers in the process of gastrointestinal cancer.

Results: The most frequently found biomarker in the different types of GIC is CXCR4; However, approximately 16 other biomolecules coexist and are involved in this pathology, including glycoproteins, proteoglycans, interleukins, claudins, and enzymes such as RHOA, RAC1, as well as transglutamines, fucosidases, and lactate dehydrogenases.

Conclusion: GIC is a multifactorial event resulting from the involvement of various biomarker molecules that play a significant role in progression and metastasis. Describing these mechanisms and their interactions allows for the development of potential therapeutic targets

Keywords: Biomarkers; Signaling; Gastrointestinal Cancer

Abbreviations

GIC Gastrointestinal Cancer; IARC: International Agency for Research on Cancer; RSPO: R-spondin; EMT: Epithelial-Mesenchymal Transition; PC: Pancreatic Cancer; HCC: Hepatocellular Carcinoma; GC: Gastric Cancer; ESCC: Esophageal Squamous Cell Carcinoma; PDAC: Pancreatic Ductal Adenocarcinoma; CRC: Colorectal Cancer; EGF: Epidermal Growth Factor; VEGF: Vascular Endothelial Growth Factor

Introduction

Cancer is currently a serious global problem, as it is the second leading cause of death after cardiovascular diseases. Gastrointestinal cancer (GIC) are all malignant lesions affecting the esophagus, stomach, liver and intrahepatic bile ducts, gallbladder, pancreas, and small and large intestine. According to data from the International Agency for Research on Cancer (IARC) presented for 2020, nearly 5.2 million new cases and more than 3.6 million deaths related to all GCCs were estimated worldwide in both sexes [1].

The increasing incidence of GCCs has led to the study of various molecules involved, which could be therapeutic targets. Among the biomarker molecules are receptors such as those rich in leucine residues, which have been detected as overexpressed in colon and pancreatic cancers. Additionally, the chemokine receptor promotes metastasis and tumor progression, triggering a more aggressive event. Similarly, tyrosine kinase receptors, such as the epidermal

growth factor receptor (EGFR), are present in 20-32% of adenocarcinoma cases. Other receptors involved in gastrointestinal cancers are erythropoietin-producing receptors, particularly the EphB2 receptor, which participates in monocyte adhesion and chemotaxis to endothelial cells, as well as contributing to angiogenesis and hepatic fibrogenesis. A group of molecules involved in the molecular mechanisms of hepatocellular carcinoma (HCC) are glycoproteins and proteoglycans. With this background, each of these families of molecules will be described, addressing in greater detail the mechanisms of action in which they participate.

Leucine-rich receptor

Leucine-rich G protein-coupled receptor 5 (LGR5)

It is a 7-transmembrane receptor characterized by an extracellular domain containing 17 leucine repeat sequences and the N-terminal peptide. Its respective ligand, R-spondin (RSPO), binds to its extracellular domain and acts in conjunction with the Frizzled (Fz) and LRP5/6 receptors to activate the Wnt/β-catenin signaling pathway [2,3].

This induces the appearance of the disheveled protein (Dvl), promoting the recruitment of the AXIN1 protein complex, glycogen synthase kinase 3β (GSK3β), casein kinase 1α (CK1α), and adenomatous polyposis coli (APC) tumor suppressor protein. Subsequently, inhibition of GSK3β, through phosphorylation, ensures an elevation of the cytosolic concentration of β-catenin [4].

Unphosphorylated β-catenin penetrates the nucleus and interacts with T cell transcription factors/lymphoid enhancer factor (TCF/LEF), for the production of Wnt signaling pathway target genes such as c-myc, cyclin D1, and CDKN1A, resulting in continuous cell proliferation, differentiation, migration, and invasion (figure 1) [5]. Particularly in colon cancer (CC), overexpression of LGR5 has been evidenced in 56.7% of the reviewed cases with a greater association in tumors on the left side and in tumor progression and metastasis through the process of epithelial-mesenchymal transition (EMT) by the cell signaling pathway described above [6]. On the other hand, low expression of LRG5 was described in patients with pancreatic cancer (PC), however, as in the case of CC, it is related to the promotion of EMT [7].

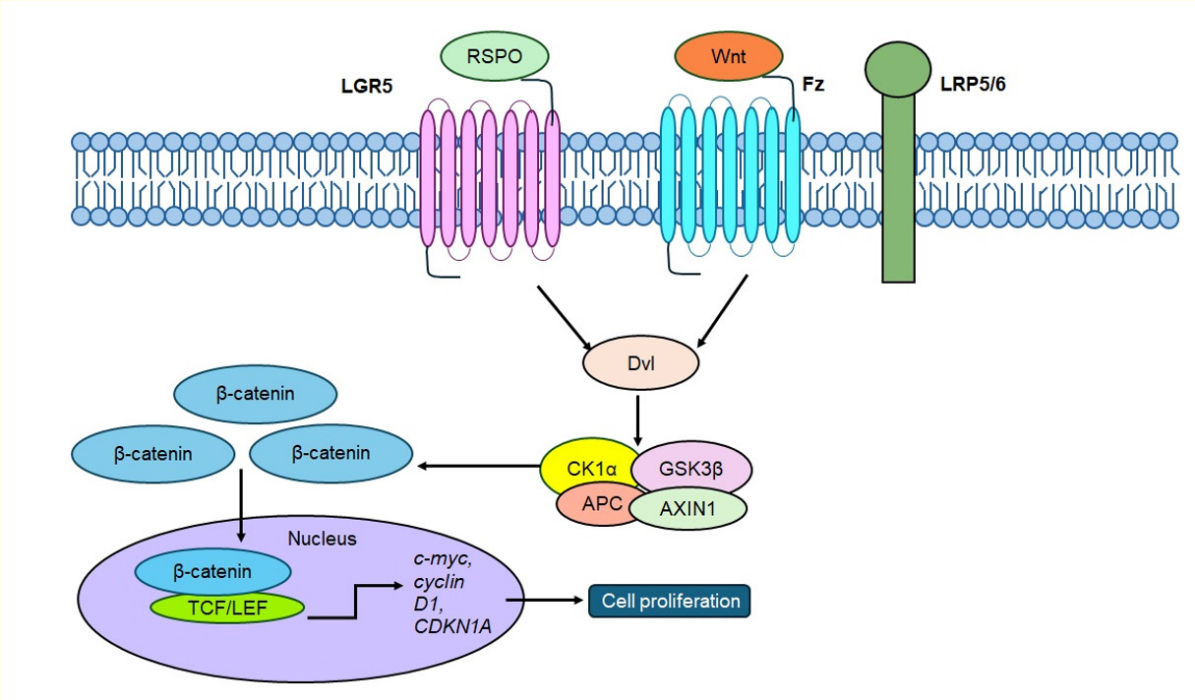

Figure 1: LGR5 promotes the Wnt/β-catenin signaling pathway. LGR5, through its ligand RSPO and together with the LRP5/6 and Fz receptors, induces the Dvl protein; in turn, the AXIN1, CK1α, GSK3β, and APC complex is formed, promoting an increase in cellular β-catenin concentration, penetration into the nucleus, and interaction with the TCF/LEF transcription factors for cell proliferation, differentiation, migration, and invasion.

Chemokine receptors

Chemokine receptor type 4 (CXCR4)

Also known as CD184, it is expressed on hematopoietic stem cells, immune cells, endothelial cells, and epithelial cells. Upon binding to chemokine 12 (CXCL12), it triggers signaling pathways distinct from LRG5, but produces the same response: cell proliferation and migration. Through mitogen-activated protein kinase (MEK/ERK) and phosphoinositide 3-kinase/serine-threonine kinase (PI3K/AKT) signaling pathways, it promotes the expression of the anti-apoptotic factor survivin, which promotes angiogenesis and drug resistance in several types of cancer, such as hepatocellular carcinoma (HCC) (figure 2). On the other hand, in PC, CXCL12 induces the activation of focal adhesion kinase (FAK), ERK and AKT, increasing the transcription of β-catenin [8]. This event could lead us to think that the negative regulation of LRG5 described in PC would be compensated because CXCL12 generates the expression of β-catenin. While in gastric cancer (GC) CXCR4 promotes metastasis and tumor progression, generating greater aggressiveness [9].

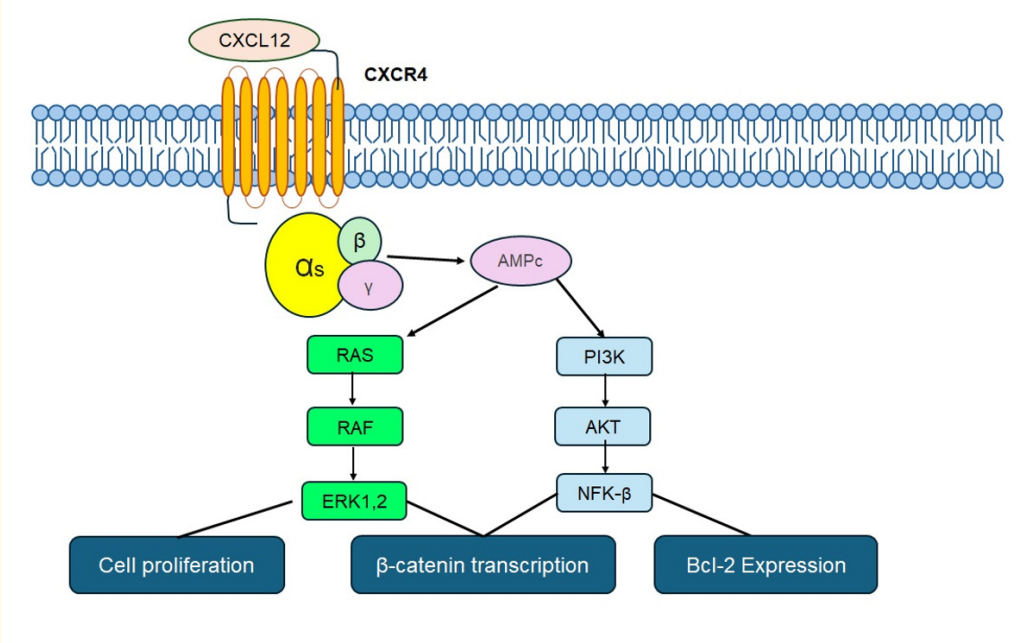

Figure 2: CXCR4 and its role in the progression of gastrointestinal cancer. This receptor produces different signaling cascades upon the dissociation of the G protein complex, such as PI3K/AKT, which promotes the production of Bcl-2, and RAS/ERK1-2, which promotes cell proliferation. Both pathways generate the transcription of the cytoplasmic protein β-catenin.

In esophageal cancer (EC), the CXCR4/CXCL12 complex generates matrix metalloproteinases (MMPs), facilitating tumor cell invasion by degrading the extracellular matrix (ECM) and EMT via the Wnt/β-catenin pathway, promoting cell proliferation [10]. Additionally, in esophageal squamous cell carcinoma (ESCC), CXCR4 plays an important role in its progression, as well as its correlation with invasion, metastasis, and a higher clinical stage [11].

On the other hand, overexpression of CXCR4 has been described in pancreatic ductal adenocarcinoma (PDAC). Using experimental models in BALB/c nu/nu mice [12], the CXCR4/CXCL12 axis was linked to the growth, spread, chemoresistance, and invasion of PDAC [13].

Meanwhile, in colorectal cancer (CRC), an increase in CXCL12 concentration has been detected, promoting the attraction of cells that present CXCR4 and thus favoring tumor progression through the secretion of proangiogenic and growth factors. Furthermore, lipopolysaccharides from bacteria that comprise the intestinal microbiota have been described to induce the expression of this receptor, favoring EMT and metastasis. Through the MAPK/ERK pathway, it inhibits cell apoptosis by inactivating the proapoptotic protein Bcl-2, causing an alteration in the cell cycle [14].

Receptor tyrosine kinases (RTKs)

RTKs encompass a wide variety of receptors that respond to growth factors, hormones, and cytokines, mediating a wide variety of cell activation pathways. Each of these receptors differ in the structure of their extracellular domain, while their intracellular domains are similar, with an α-helical structure and an enzymatic center that catalyzes the phosphorylation of tyrosine residues on target proteins using ATP. These residues function as docking sites for crucial effector proteins in cell activation pathways [15].

ERBB2 receptor

This receptor is part of the epidermal growth factor receptor (EGFR). EGFR through the cellular pathways Ras/mitogen-activated protein kinase (MAPK), PI3K/AKT and JAK-STAT are those that participate in carcinogenic processes through the epidermal growth factor (EGF) as their respective ligand (Figure 3). These receptors have 4 isoforms: ERBB 1-4 [15,16]. ERBB2 is a molecular biomarker that has been found in patients with GC [17]. The amplification of the ERBB2 gene generates a greater expression of said receptor, which induces a greater probability of developing CRC tumors in the left colon [18]. It has been described that in CRC there is a high prevalence of this with a great variety in the form of its expression, being able to be homogeneous or mosaic [19]. In turn, CG is overexpressed mainly in the upper third of the stomach, being well differentiated [20]. ERBB2 is present in approximately 20-32% of cases of gastroesophageal junction adenocarcinoma (AGE) [17].

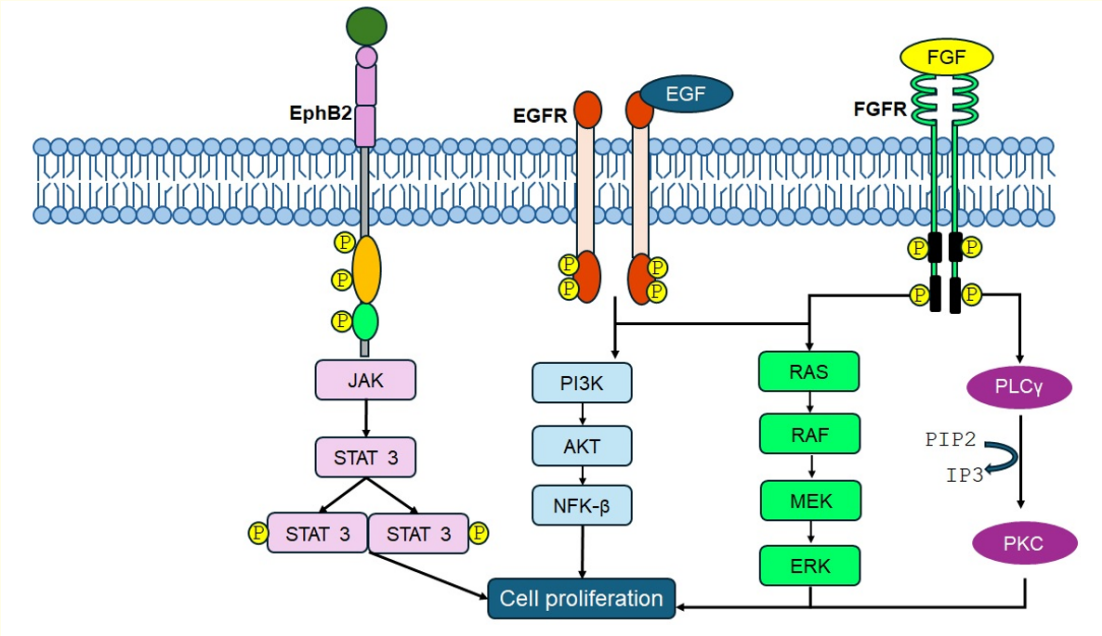

Figure 3: TRK receptors and their involvement in the gastrointestinal cancer process. Upon activation of EGFR and FGFR, the PI3K/AKT and RAS/ERK signaling pathways are activated, and PLCy/PKC is also activated in FGFRs. EphB2, on the other hand, generates the STAT 3 transcription factor, which targets cell proliferation and activation.

Fibroblast growth factor receptors (FGFRs)

These receptors have a specific binding affinity for fibroblast growth factors (FGFs). Upon engagement, they activate the Ras/MAPK, PI3K/AKT, and phospholipase C gamma (PLCγ) pathways. The purpose of these signaling pathways is to cause FGFR dimerization, leading to autophosphorylation of the intracellular kinase. Within this type of cellular receptor, four isoforms have been identified: FGFR1-4 [15]. Specifically speaking of GC, FGFR2 activates the MAPK and AKT pathways, promoting tumor progression. In some cases of GC, gene amplification (72%), activating mutation (13%), translocations (8.6%), and chromosomal fusions (6.3%) have been found to stimulate FGFRs in this cancer [21]. The FGFR2-IIIb isoform has been detected in the cytoplasm and cell membrane in diffuse-type GC [20].

Hepatocellular carcinoma (Eph) receptors

Erythropoietin-producing Eph receptors constitute a large subfamily of RTK receptors. They influence the actin cytoskeleton, cell binding, shape, motility, proliferation, survival, secretion, and differentiation through the interaction between Eph receptors and their ligands, ephrins. Based on their sequence, structure, and ligand-binding affinity, they are grouped into two subclasses: the EphA receptor (subtypes EphA1-10) and the EphB receptor (subtypes EphB1-6). The EphB2 receptor is a 117 kDa protein consisting of 1,055 amino acids (a.a.) involved in monocyte adhesion and chemotaxis to endothelial cells, T and B cell activation, autophagic cell death, platelet function, angiogenesis, and liver fibrosis. Through the TP53 and JAK-STAT signaling pathways, it promotes GC, while in CRC, it interacts with the transcription factors TCF/β-catenin, which appears to play an important role in CRC progression [22].

Similarly, overexpression of this receptor is found in PCa; However, silencing EphB2 has been shown to accelerate cell growth and promote cell proliferation through the G1/S phase transition of the cell cycle [23]. In HCC, T cell factor-1 (TCF1) regulates EphB2 expression through gene activation to form a Wnt/β-catenin positive feedback loop, thereby regulating cancer pluripotency through the TCF1/EphB2/β-catenin pathway [24].

EphA2, a 130 kDa transmembrane glycoprotein, promotes pluripotency in squamous cell carcinoma (SCC) cells by activating the ERK pathway, which facilitates the nuclear translocation of the YAP protein. This protein binds to TEA family protein 3 (TEAD3), activating the transcription factor KLF4 [25].

Glycoproteins

Leucine-rich α-2 glycoprotein 1 (LRG1)

It is a glycoprotein that is part of the leucine residue-rich (LRR) protein family [26]. It consists of a single polypeptide chain of 312 amino acid residues and 8 LRRs. Under physiological conditions, LRG1 is synthesized primarily by hepatocytes and neutrophils, but has also been found in the lung, skin, heart, testis, and kidney. The interleukin 6-STAT3 (IL-6/STAT3) complex is one of the main regulators of LRG1 transcription, as well as the Wnt/β-catenin axis. Its elevated expression has been associated with SCC, GC, and CRC. In the latter, it inhibits apoptosis and modulates cell EMT through the RUNX1 transcription factor [27].

In the case of PC, EGFR mediates the activity of this glycoprotein, which has been linked to angiogenesis, as well as migration, invasion, and synthesis of the vascular endothelial growth factor (VEGF) receptor, leading to cancer progression. In combination with carbohydrate antigen (CA19-9), these are diagnostic biomarkers in PDAC [28].

α-fetoprotein (AFP)

AFP, encoded by the AFP gene located on the Q arm of chromosome 4 (4q25), is a member of the albuminoid gene superfamily. It has a molecular weight of 70 kDa, is structurally similar to albumin, and is synthesized by fetal liver cells during pregnancy. AFP levels decrease rapidly after birth. However, in HCC, they can again increase dramatically in the patient's serum. It is the most widely used biomarker for HCC surveillance. In patients with HCC, a sharp rise in AFP indicates tumor recurrence or metastasis. An AFP >200 μg/L after surgery indicates incomplete HCC resection or metastasis. AFP-L3, an AFP isoform, helps identify patients at high risk for HCC who require ongoing monitoring. Several studies show that AFP-L3 exhibits better specificity but lower sensitivity for detecting HCC at an early stage compared to AFP [29,30].

Proteoglycans

Glypican 3 (GPC3)

It belongs to the GPC1-GPC6 family of heparan sulfate proteoglycans with similar structures. They contain a 60-70 kDa core protein, which is attached to the cell membrane surface by glycosylphosphatidylinositol (GPI), while the carboxyl terminus contains a heparan sulfate side chain. GPC3 has a molecular weight of 70 kDa and is physiologically expressed on various embryonic cell surfaces, including the liver. Under normal conditions, it is not found in the adult human liver; However, during HCC, it activates Wnt signaling by binding to Fz and acting as a recruiter of different signaling pathways [31]. Increased expression of this proteoglycan is a sign of HCC progression and is also used as a serum and histochemical marker for early diagnosis [29,32].

Interleukins

Interleukin 6 (IL-6)

This is a proinflammatory cytokine that promotes tumor spread through JAK/STAT3 signaling pathways, while also inducing the transcription and secretion of C-reactive protein (CRP) in hepatocytes [33,34]. (Figure 4). It plays a central role in the development of CRC, with its significantly elevated expression. On the other hand, cancer-associated fibroblasts (CAF) induce IL-6 and, through the JAK1-STAT3 pathway, promotion in the GC [35]. In a study conducted in patients with stage III CRC [36], high serum levels of IL-6 and overexpression of the soluble tumor necrosis factor α receptor 2 (sTNF-αR2) were evidenced, these data are associated with a higher risk of recurrence and mortality [10].

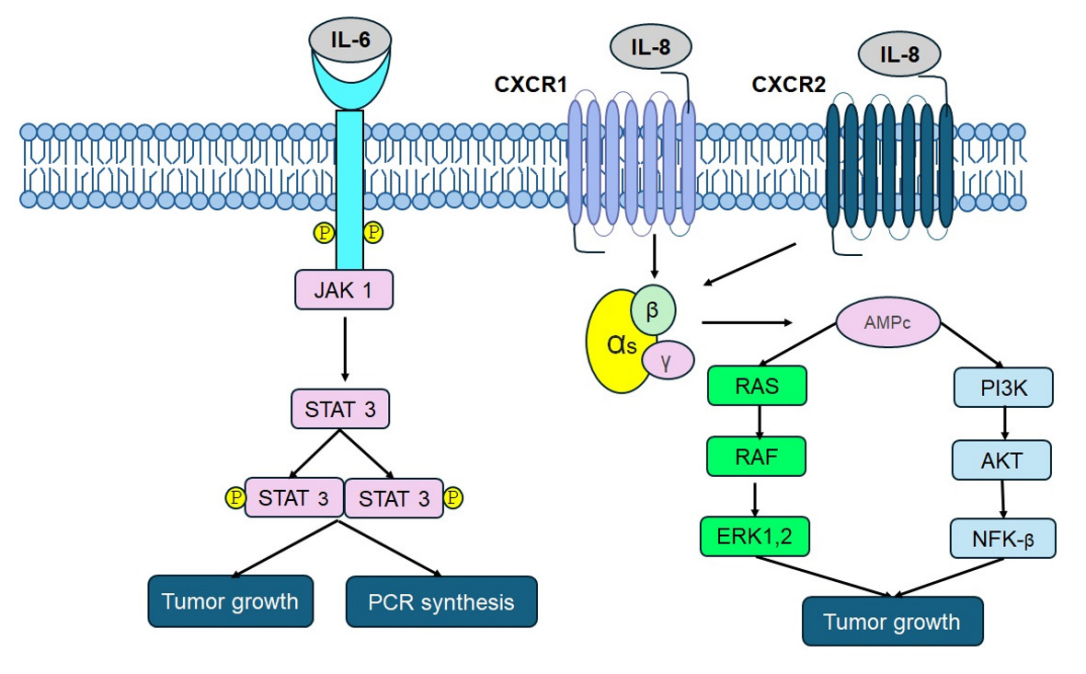

Figure 4: Mechanism of action of interleukins in gastrointestinal cancer. Both interleukins play an important role in cell progression mediated by CXCR1-2 receptors in the case of IL-8 and its receptor, IL-6. Furthermore, IL-6 synthesizes CRP in hepatocytes, establishing a pro-inflammatory state.

Interleukin 8 (IL-8)

It is a chemokine that belongs to the CXC cytokine family. It binds to the cell surface of the CXCR1 and CXCR2 receptors and can activate several intracellular signaling pathways. It is an important proinflammatory cytokine that is upregulated in various malignancies. In the case of CRC, it induces the migration and proliferation of cancer cells through the ADAM- and disintegrin-dependent pathway, where EGF, which binds to heparin, acts as the main ligand. By binding to IL-8/CXCR2, its autocrine properties facilitate the intrinsic mechanism of tumor cells to prevent stress-induced apoptosis [35].

On the other hand, in the case of PC, serum IL-8 levels appear to be a more accurate diagnostic marker compared to classic tumor markers such as CA 19-9 or carcinoembryonic antigen (CEA) [37]. This interleukin has also been found in CRC, being useful for its early detection and prognosis [38].

Additionally, elevated expressions have been evidenced in HCC, promoting greater macrovascular invasion, increasing tumor size, and generating an advanced stage. Furthermore, this interleukin has been reported to promote β3 integrin expression and cancer cell invasion in HCC via the PI3K/AKT pathway [39].

Claudins (CLDN)

They are a group of transmembrane proteins measuring 20-30 kDa that form complexes between cell tight junctions, promoting cell adhesion, maintaining membrane polarity, and selective paracellular permeability. Disruption of these proteins facilitates EMT, metastasis, and infiltration of cancerous processes. CLDN are classified as classical (1-10, 14, 15, 17, and 19) and nonclassical (11-13, 16, 18, and 20-24) [10].

CLDN 18 is encoded by the CLDN18 gene, which has two isoforms: CLDN18.1 and CLDN18.2. The latter is expressed under physiological conditions in epithelial cells of the gastric mucosa, regulating the Na^{2+} and H^{+} permeability of gastric acid. In GIC, this permeability is decreased, being identified in 58% of cases [40]. Furthermore, it is also overexpressed in HCC, PC, and cholangiocarcinoma [41].

CLDN1 has been identified under normal conditions in the intestine, spleen, brain, liver, kidney, and testis. Its expression is significantly increased in cases of CRC, GC, PDAC, and HCC. In HCC, it is involved in tumor formation and metastasis, as well as in EMT and MMP-2 production. Similarly, overexpression has been detected in CRC, which is attributed to its role in cell invasion and change. While CLDN decreases E-cadherin expression by activating the ZEB-1 repressor, which causes cell proliferation [42].

CLDN4 is increased in precancerous PC lesions, and K-ras mutations can increase this expression and thus increase the likelihood of developing PC [43].

RHO GTPase enzymes

Rho GTPases are a family of G proteins, the most studied subfamily being RHO (subtypes RHOA, RHOB, and RHOC), RAC (subtypes RAC1, RAC2, RAC3, and RHOG), and CDC42 (subtypes RHOQ and RHOJ). They regulate cell dynamics, cytoskeletal mechanisms, morphology, polarity, motility, vesicle trafficking, cell cycle progression, survival, growth, differentiation, and expression of new genes [44]. They are activated when bound to guanosine triphosphate (GTP) and inactive when bound to guanosine diphosphate (GDP), and they cycle between these two states regulated by two opposing families of proteins: guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs). These are essential for dissociating tightly bound GDP from GTPases and promoting GTP hydrolysis, respectively. Multiple GEFs/GAPs can act on a single GTPase, while a single GEF/GAP can activate multiple GTPases [45].

RHOA enzyme

The bacterium *Helicobacter pylori* (*H. pylori*), through the cytotoxin A-associated gene (cagA), encodes a highly immunoreactive, high-molecular-weight protein of 120-140 kDa present in approximately 60% of H. pylori strains. The cagA gene is part of a pathogenicity island of approximately 40 kDa, which contains 31 genes, whose products are involved in the stimulation of chemokines and the activation of MAP kinases, a family of proteins capable of phos-

phorylating their substrate and involved in numerous cells signaling pathways, and the subsequent induction of proinflammatory factors. In GC, cytotoxin A activates the RHOA enzyme, triggering the Raf/MEK/ERK signaling cascade, which is involved in GC propagation. Growth factors can also induce GC cell invasion and migration through TGFβ1 signaling, which activates RHOA, leading to GC cell migration through the EMT [45].

RAC1 enzyme

In CRC, RAC1 overexpression induces cell migration, invasion, and metastasis with downregulation of E-cadherin and upregulation of N-cadherin, vimentin, and SNAI-1, while RAC1 inhibition impairs oncogenic function. p21-activated kinase 1 (PAK1), a serine/threonine protein kinase, is activated upon binding to RAC1, leading to tumor promotion and metastasis [46].

Transglutaminases (TG)

They are multifunctional Ca^{2+}-dependent enzymes. The most common function of TG is to catalyze the formation of isopeptide bonds between the carboxamide moieties of protein-bound glutamine residues and the ε-amino group of protein-bound lysine residues. The TGM1 type has been found to promote pluripotency and chemoresistance in GC cells by regulating Wnt/β-catenin signaling. The TGM2 type is involved in several biological functions, including, but not limited to, apoptosis, ECM formation, cell adhesion, and migration. Its overexpression is associated with advanced tumor stages, distant metastasis, and chemoresistance in GIC [47].

α-L fucosidase (AFU)

The AFU enzyme, which consists of two isoforms, AFU1 and AFU2, are encoded by the FUCA1 and FUCA2 genes, respectively. It is a lysosomal enzyme that clears the terminal residues of α-L fucose from glycoproteins. AFU is involved in the metabolism of glycoproteins, glycolipids, and oligosaccharides, and is widely distributed in human tissues and blood. Serum AFU levels remain low under normal circumstances. Although serum AFU levels rise rapidly as tumors invade the body, their levels are closely related to tumor stage and size. AFU has been shown to be one of the most valuable biomarkers for HCC detection, with a sensitivity of 85% and a specificity of 91%. The combination of AFU and AFP biomarkers is used in the diagnosis of HCC, improving diagnostic specificity [30].

Lactate dehydrogenase (LDH)

LDH is an enzyme that catalyzes the reversible reaction of lactate to pyruvate by reducing NAD+ to NADH. It consists of two isoforms, LDHA and LDHB. LDHA plays a key role in the glycolytic pathway due to its greater affinity for pyruvate and catalyzes the conversion of pyruvate to lactate by oxidizing NADH to NAD+. Factors such as the oncogene c-Myc and hypoxia-inducible factor (HIF-1α) stimulate its transcription. LDHA-mediated aerobic glycolysis influences the EMT process during PCa, due to the increased expression of the forkhead box Q1 (FOXQ1) transcription factor, glucose metabolism, and lactate synthesis. In contrast, LDHB exhibits a greater affinity for lactate and converts lactate into pyruvate by reducing NAD+ to NADH, allowing cancer cells to obtain more energy and biosynthetic precursors more efficiently, which is essential for their growth and survival [48,49].

To date, several biomarker molecules have been described that are directly involved in the mechanisms of action in different types of gastrointestinal cancer (Figure 5). All these molecules can be overexpressed in different body compartments.

Predictive biomarkers and targeted therapy

Currently, one of the goals of modern molecular biology is to understand the behavior of tumor and normal cells. In recent decades, significant advances have been reported regarding cancer pathogenesis, where mutagenic processes that modify cellular integrity lead to unchecked proliferation mechanisms, self-sufficiency in cell signaling, and apoptotic and antiproliferative resistance. Although intracellular signaling mechanisms are complex, some predictive markers that serve as therapeutic targets have been identified.

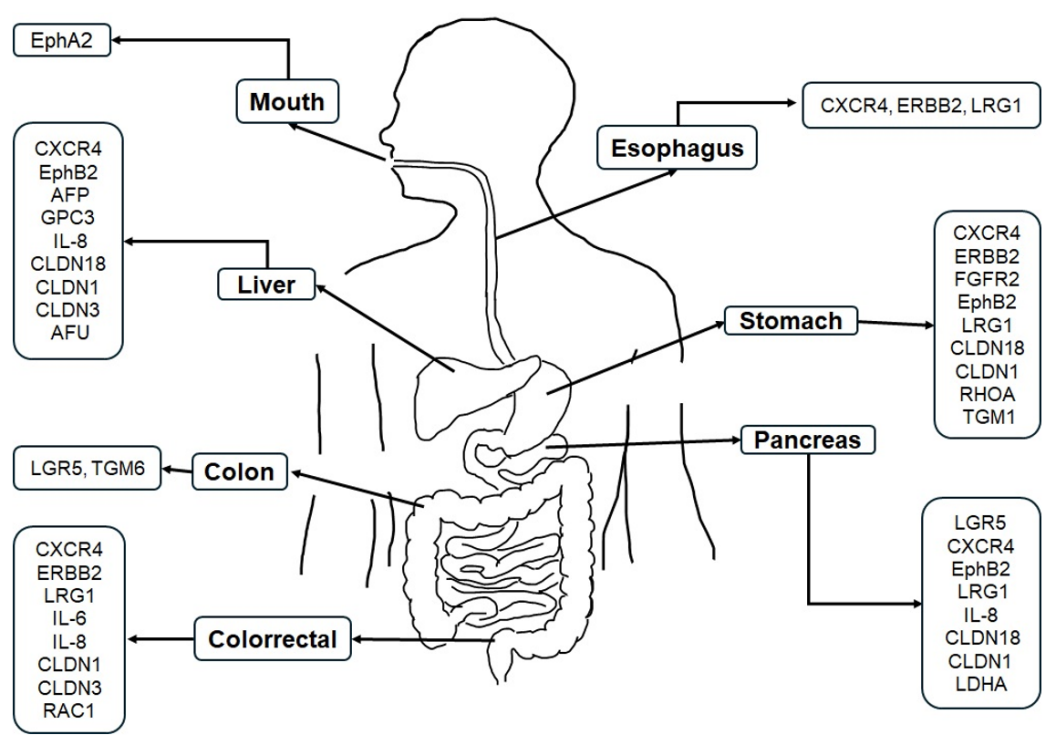

Figure 5: Molecular biomarkers for cancer expressed in the gastrointestinal tract.

HER2 tyrosine kinase receptor

The combination of trastuzumab and fluoropyrimidine with cisplatin chemotherapy has been shown to improve survival in patients with advanced, HER2-positive gastroesophageal junction adenocarcinoma. Similarly, HER2-targeted immunotherapy with pembrolizumab has shown increased survival in patients with GAC [50].

Claudin 18.2

This component of gastric epithelial intercellular junctions has become an ideal target for monoclonal antibodies, such as zolbetuximab, which binds to claudin 18.2 and induces cell death. Furthermore, it has been shown to optimize disease-free survival and overall survival when combined with first-line chemotherapy in patients with gastric abscess [51].

FGFR2

The irreversible FGFR1-4 inhibitor futibatinib is being tested in a phase II trial involving patients with advanced-stage solid tumors harboring FGFR alterations. Bemarituzumab is an antibody against the FGFR2b splicing variant that is frequently overexpressed in FGFR2-amplified GACs; its use has shown promising results to date [51].

cirRNA-7

This is a member of the circular RNAs, which are a subtype of non-coding RNAs. This circRNA is located on chromosome Xq27.1 and plays a crucial role in regulating DNA damage, RNA transcription, gene expression, and protein production. A cirRNA-7 positive status in patients with advanced digestive tract tumors may benefit anti-CIRS-7 therapy and, in turn, may predict survival response to trastuzumab treatment [52].

Tropomyosin tyrosine kinase (TRK) receptors

The FDA has authorized the use of targeted therapies with TRK inhibitors, such as larotrectinib or entrectinib, in patients with solid tumors that exhibit a positive gene fusion in NTRK. This has been tested in patients with digestive tract cancers who have not responded to conventional treatments, but for whom it has been possible to perform tests to identify these drug fusions [52].

Toothless ubiquitin ligase (DTL) homolog of E3

It is a regulator of DNA replication, the cell cycle, and the DNA damage response. DTL has been found to be overexpressed in various types of gastrointestinal tract cancers. This protein has been proposed as a diagnostic and prognostic biomarker for several cancers, as well as for its relationship with immune cell infiltration in hepatocellular and gastric cancers. Similarly, it can be used as a therapeutic target through DTL inhibitors as an alternative therapy option [53].

A biomarker as an indicator of treatment response

Serum Cystatin S (CST4)

CST4 is a protein that prevents the degradation of the extracellular matrix and alters the tumor microenvironment by inhibiting cysteine protease enzymes. This allows the infiltration of immune cells, such as helper T cells and CD8+ T cells, resulting in the adhesion, proliferation, and migration of tumor cells. Increased CST4 expression in patients with gastric cancer (GC) correlates with decreased overall survival and disease-free survival, making it a prognostic biomarker for GC survival. Furthermore, in post-surgical patients, CST4 levels are significantly reduced and are associated with complete and partial responses, suggesting that this biomarker serves as an indicator of treatment response and tumor progression. In a study by Zhou D., *et al.* (2024), CST4 was incorporated alongside other tumor markers (AFP, CEA, CA199, CA153, and CA274) for the diagnosis of malignant tumors of the digestive system. The study demonstrated improved sensitivity and suggests that CST4 is important in screening for gastrointestinal malignancies, as well as in differentiating between gastrointestinal polyps and malignant tumors. Therefore, serum testing for this biomarker is suggested as a promising and convenient diagnostic tool [54].

Diagnostic biomarkers

Threonine tyrosine kinase (TTK)

This enzyme is essential at the spindle assembly checkpoint, which regulates tumor cell growth. Several studies have shown that TTK expression is increased in pancreatic cancer and hepatocellular carcinoma.

Suppression of TTK in pancreatic ductal adenocarcinoma cell lines significantly reduces cell migration and increases cell death by inducing apoptosis, indicating its significant role in pancreatic carcinogenesis [52].

Centrosome protein 55 (CEP55)

Plays an important role in cytokinesis during cell division, regulating the physical separation of daughter cells. Its overexpression or dysfunction can lead to failure of this process, resulting in chromosomal instability, aneuploidy, and the formation of multinucleated cells. Another important function of CEP55 is the regulation of the AKT/PI3K signaling pathway, which can cause uncontrolled cell survival in tumor processes. Its importance as a biomarker stems from its overexpression in colorectal and liver cancer, which is associated with larger tumor size and advanced stage [52].

Aurora kinase A (AURKA)

Is a serine/threonine kinase that regulates centrosome duplication, spindle assembly, and chromosome segregation. Numerous studies report its overexpression in various types of cancer, including pancreatic cancer, where it contributes to tumor development by promoting chromosomal instability and activating oncogenic pathways such as p53 degradation, MYC stabilization, and EMT induction [52].

CA19-9

Serum levels of this marker are elevated in pancreatic, gallbladder, and gastric cancers, as well as liver and colorectal cancers. Detection of CA19-9 in serum is one of the best reference indicators for the diagnosis of pancreatic cancer, the prediction of metastasis and recurrence, and the monitoring of the curative effect [52].

CA242

The content in normal cells is very low, and when malignant hyperplasia occurs, its content increases significantly, especially in tumors of the digestive tract, where it is significantly higher than in benign diseases [52].

Gastric cancer antigen MG-AGS

This novel tumor antigen exhibits high specificity for CG, showing low expression in normal tissues and high expression in gastric tumor tissues, thus conferring significant diagnostic value. Immunohistochemical studies have demonstrated that its histological positivity rate exceeds 90%. Furthermore, when detected in serum by PCR for MG-AGS in patients with CG, the positivity rate can reach 70%, approximately 15% higher than that of other commonly used methods. Screening in high-risk populations has indicated that this antigen allows for the identification of gastric cancer in individuals with high titers or positive serum MG-AGS, including some early-stage gastric cancers [52].

Colorectal cancer alterations

Additionally, a wide variety of molecular markers have been described and studied as prognostic or predictive factors in colorectal cancer; however, these patients have shown a high probability of developing Lynch syndrome [55]. One marker with predictive capacity is the RAS gene, which predicts the lack of efficacy of antibodies directed against EGFR. It is currently suggested that in patients with colorectal carcinoma, the RASm gene should be analyzed, including codons 12 and 13 of KRAS and NRAS in exon 2; 59 and 61 of exon 3; and 117 and 146 of exon 4, to consider targeted therapy. Another marker that can be determined is alterations in the BRAF gene [56].

Furthermore, the presence of lymphocytes infiltrating the tumor is further evidence, since a high density of CD8+ T cells and CD45RO+ cells is associated with the pathological absence of early metastatic invasion, early stage, and improved patient survival [56, 57].

Conclusion

This review describes the existence of a variety of molecules that can be considered biomarkers, like CXCR4 being the biomarker that is found most frequently in the different types of GIC. It is also highlighted that some molecules, share expression sites, as well as cell signaling pathways like leucine-rich receptor, chemokine receptors and receptor tyrosine kinases. As a result, continuous proliferation and metastasis are promoted, thus conditioning an important factor in the development of this disease. In addition, several biomarker molecules play an important role in triggering, progression and metastasis processes such as glycoproteins, proteoglycans, interleukins, claudins, and enzymes like RHOA, RAC1, as well as transglutaminases, fucosidases, and lactate dehydrogenases. Understanding the role of each of the biomarkers is crucial, as it allows for the identification of new therapeutic targets and, therefore, the modification of GIC progression. It is essential to emphasize the need for basic biomedical research to describe these processes in detail.

Declaration of Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the information presented in this study.

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