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Oncogenic Signaling in Gastric Cancer

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1. Introduction

Gastric cancer is one of the most common and life-threatening cancers worldwide (for review see Power et al., 2010). The late diagnosis and high mortality of this disease reflects the reduced understanding of its etiological factors and pathogenesis model and the lack of effective treatments. This disease results from the complex interplay between genetic and environmental factors at the gastric mucosa level that deregulates cell potentially oncogenic signaling pathways, leading to gastric cancer development. It is known that more than 80% of gastric cancer cases can be attributed to deregulation of signaling pathways caused by *Helicobacter pylori* infection (Houghton & Wang, 2005). Some of these signaling pathways are important during gastric embryogenesis and during the normal lifetime of a gastric cell, but can be tumorigenic if deregulated and therefore their better understanding is crucial for the development of new therapeutic drugs. In this review we will summarize the most important intracellular signaling pathways that have been found to be deregulated in gastric carcinoma and we will include new data recently obtained in our laboratory, focused on MUC1 mucin-mediated signaling pathways.This new information is a relevant contribution for the understanding of the gastric oncogenic signaling scenario and opens new perspectives for the development of innovative therapeutic strategies against the disease.

2. Signaling pathways involved in gastric carcinogenesis

2.1 EGFR and the extracellular signal-regulated MAPK pathway

The mitogen-activated protein kinases (MAPKs) pathway is activated either by extracellular ligand binding or intracellular stimuli, and regulates a series of cell activities such as proliferation, differentiation and cell death. The extracellular signal-regulated kinase (ERK) MAPK pathway has been often found to be deregulated in cancers and consists of several kinases (Ras, Raf, MEK) that are activated by phosphorylation upon ligand binding to a membrane receptor, ending up in the activation of several proteins involved in processes of cell invasion, apoptosis, transcription, survival and drug resistance (for review see Kim EK & Choi E, 2010). Members of this cascade have been found to be deregulated in gastric cancers, such as RAS family members (Adjei, 2001; Velho et al., 2010). Ras/MAPK activation was found to be associated with cell proliferation in gastric carcinomas (Regalo et al., 2010). ERK1/2, the final effectors of this pathway, were also found to be activated in gastric cancers (Liang et al., 2005) and in *Helicobacter pylori* related gastric cancers (Hatakeyama ,

2006; Chen et al., 2006). In contrast, ERK2 activity was found to be reduced by nonsteroidal anti-inflammatory drugs NSAIDS, therefore inhibiting the proliferation of gastric carcinoma cells (Husain et al., 2001). All of these events were found in cell lines, but when examining human gastric carcinoma specimens, a decrease in the activation of ERK1/2 was found (Wu et al., 2008). One possible explanation for this fact is that gastric cells start expressing molecules that attenuate ERK-mediated signaling upon its activation, or on the other hand, the cells act by activating negative feedback mechanisms.

The epidermal growth factor receptor (EGFR) is a member of the growth factor family HER and works as a cell surface receptor of extracellular ligands. Ligand binding to EGFR extracellular domain leads to its activation, with subsequent homodimerization, leading to the phosphorylation of its intracellular tyrosine kinase domain. This will initiate a series of intracellular signals, including activation of the central Ras/Raf/mitogen activated protein kinase (MAPK) signaling pathway (Figure 1). This molecule modulates processes of cell , migration, adhesion and proliferation and it is known to provide tumor cells with growth and survival advantages (for review see Nicholson et al., 2001). EGFR expression was found to be deregulated in several types of cancers, including gastric cancer. High EGFR levels in gastric carcinoma have been associated with the disease prognosis (Kim et al., 2008) and presence of lymph node metastasis (Choi et al., 2009). Therapies against EGFR have been developed and are active in gastric cancer treatments (Pinto et al., 2007; Liu et al., 2011), although not completely effective. The EGFR/MAPK pathway has also been shown to be activated in gastric carcinomas with microsatellite instability (Corso et al., 2011).
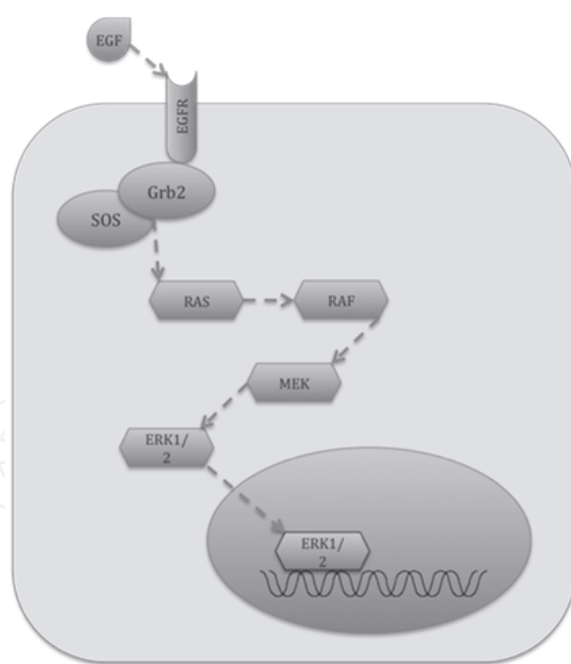

Fig. 1. EGFR/MAPK signaling pathway.

2.2 E-cadherin and Wnt/beta-catenin pathway

E-cadherin is a calcium-dependent cell-cell adhesion molecule that is essential for the maintenance of the normal epithelium architecture (for review see Van Roy & Berx , 2008). Loss of expression of this molecule has been found in gastric cancers, relating with tumor

dedifferentiation, invasiveness, metastasis and prognosis (Shino et al.,1995; Gabbert et al., 1996). Mutations of this molecule have been often found in familial gastric cancers (for review see Oliveira et al., 2006). The cytoplasmic domain of this molecule interacts with the molecule beta-catenin, forming strong cohesive nets between the actin cytoskeleton (Leckband & Sivasankar, 2000), essential for processes of cell-cell adhesion and cell shape, polarity, migration and invasion.

EGFR and E-cadherin were found to interact through the respectives extracellular domains and signaling mediated by EGFR was found to be inhibited by E-cadherin (Qian et al., 2004). EGFR was found to be hyper-activated in cells where the extracellular domain of E-cadherin is not present (Bremm et al., 2008). Therefore, it may be of therapeutic value to use EGFR inhibitors in the treatment of gastric cancers in which there is a deregulation of E-cadherin.

Beta-catenin is important in mediating the E-cadherin related cell adhesion and also by participating in Wnt signaling pathways. The Wnt signaling pathway regulates several processes during development, such as determination of cell fate, morphology, polarity, adhesion and growth. Wnt signaling can be divided into canonical and non-canonical pathways. In the canonical one, wnt signals (extracellular ligands, such as wnt-1) stabilize beta catenin, therefore activating gene transcription by interaction of beta-catenin with transcriptional factors (Figure 2).
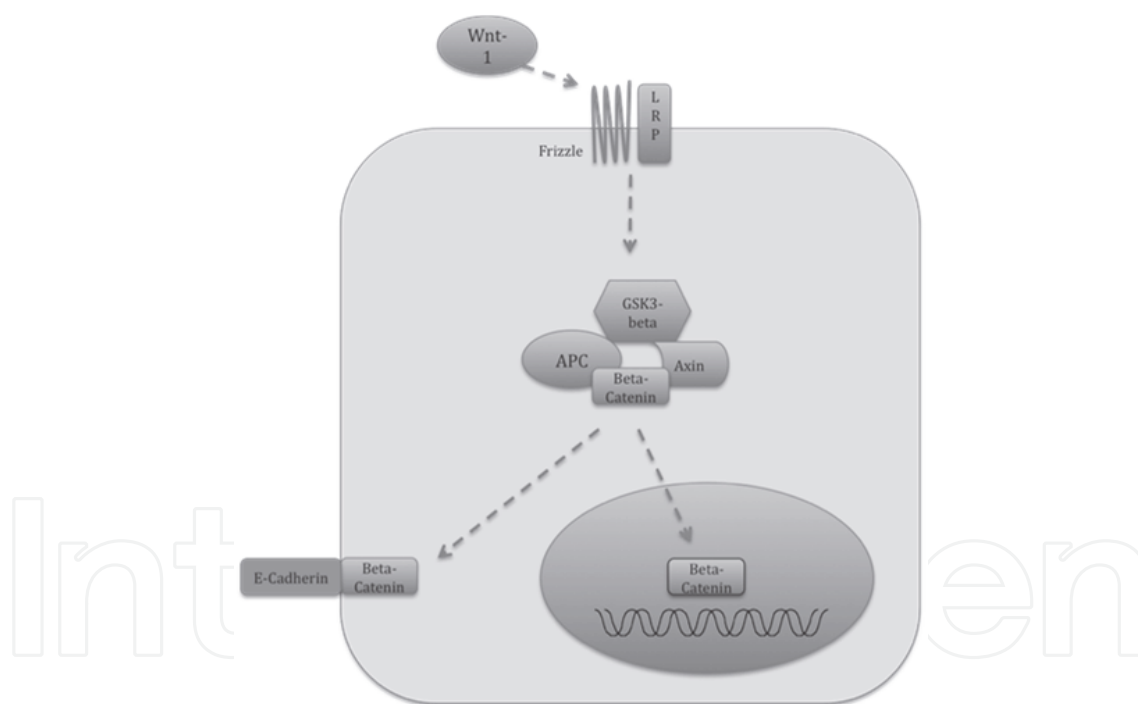

Fig. 2. Wnt signaling pathway (canonical).

This pathway was found to be deregulated in several cancers (for review see Polakis, 2007), including gastric carcinoma (Katoh et al., 2001; Clements et al., 2002; Nabais et al., 2003). The non canonical pathway is not related to beta-catenin and is involved in embryonic development and cell polarity and has also been linked to the development of gastric cancers (Kurayoshi et al., 2006; Gencer et al., 2010). This pathway seems to be repressed by Notch1 receptor in keratinocytes (Nicolas et al., 2003). Beta catenin was found to be activated by the bacterium *Helicobacter pylori* in gastric cancers (Franco et al., 2005).

In gastric cancer tissues, the expression of Wnt-1, beta-catenin and E-cadherin was found to be increased when compared to normal gastric tissue, as well as tumor size, tumor invasive depth, lymph node metastasis, pTNM stage, differentiation and five-year survival rate (Zhang & Xue , 2008). Therefore, these molecules are promising therapeutic targets for gastric carcinoma.

2.3 Hedgehog pathway

Hedgehog (Hh) signaling plays an important role during embryonic development and differentiation, proliferation and maintenance of adult tissues through the maintenance of stem cells population. Until now, three different members of the Hh family have been identified: Sonic Hedgehog (Shh), Indian Hedgehog (Ihh) and Desert Hedgehog (Dhh). All of them are secreted-type glycoproteins with a N-terminal signal peptide, a Hedgehog signaling domain and a Hint domain that signals through ligation to the hedgehog receptor Patched (Ptch), which usually acts by inhibiting the seven-span transmembrane receptor Smoothened (Smo) (Katoh and Katoh, 2005).

Of all Hh members, Shh is the most studied signaling pathway in vertebrates and plays a crucial role in stomach development. Shh protein expression is increased in parietal cells of the normal adult, gastric corpus and antrum (Saqui-Salces and Merchant, 2010). It is believed that Shh is important for regulation of gastric epithelial differentiation and its silencing causes gastric atrophy and subsequent disruption of glandular differentiation (Van den Brink, 2007). Recently, with the development of a mouse model expressing a parietal cell-specific Shh deletion, the function of this protein in adult stomach has been better clarified (Xiao et al., 2010).
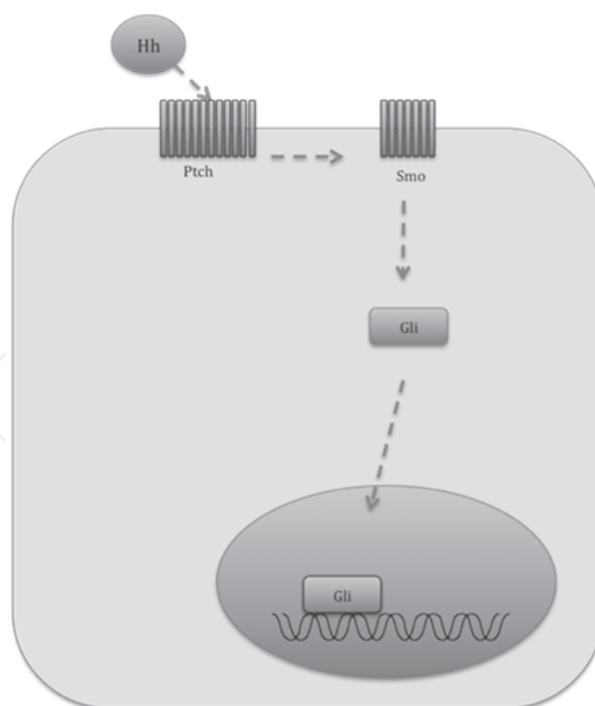

Fig. 3. Human Hedgehog signaling pathway.

Shh ligand is expressed as a 45-kDa precursor that is cleaved autocatalytically to yield a 19kDa amino terminal fragment, that contains all the signaling functions and a 26-kDa

carboxy-terminal fragment (ShhC), that acts as a cholesterol transferase (Goetz et al., 2006; Zavros et al., 2007). This activation process depends on the acid-activated protease pepsin A. Gastrin increases acid secretion in parietal cells leading to conversion of pepsinogen A to pepsin A, mediating Shh processing (Zavros et al., 2007). In the stomach, Shh binds directly to Ptch receptor but not to Smo being the activity of Smo controlled indirectly by Ptch (Figure 3). In Shh absence Ptch supresses Smo activity. The binding of Shh to Ptch results in loss of Ptc activity and consequently Smo activation. Smo activation triggers Hh signal into the cytoplasm by triggering activation of Glioblastoma family transcription factors (Gli1, Gli2 and Gli3) that induce transcription of signaling targets like Wnt and the zinc finger transcription factor, Snail (Martin et al., 2010). Gli 1 induces the transcription of Snail that inhibits E-cadherin transcription. The inhibition of E-cadherin, a protein that plays an important role in cell adhesion, is associated with an increase in nuclear beta-catenin, triggering the activation of Wnt pathway targets like CD44, c-Myc and cyclin D1 (Li et al., 2006; Medici et al., 2008; Tanaka et al., 2002).

Alterations in Hh signaling pathway activation are related to different types of cancer such as gastric cancer, breast cancer, small-cell lung cancer, skin and pancreatic cancer (Kubo et al., 2004; Thayer et al., 2003; Watkins et al., 2003; Yang et al., 2010). The expression of Hh ligands, Ptch1, Smo and the three Gli transcription factors (Gli1, Gli2 and Gli3) has been related with more than two-thirds of primary gastric cancers and correlated with poorly differentiated and more aggressive tumors (Fukaya et al., 2006; Lee et al., 2007). Hh signaling activation is triggered by expression of hedgehog ligands like Shh and Ihh or an increased Ptch receptor expression (Wu et al., 2010; Zavros, 2008). Inhibition of Shh signaling pathway using Smo or antagonists like cyclopamine or Hedgehog neutralizing antibody 5E1 causes growth inhibition and regression of xenograft tumors in vivo (Berman et al., 2003). However, in the presence of precancerous lesions such as gastric atrophy (loss of parietal cells) or intestinal metaplasia, Shh protein expression is reduced or totally lost (Shiotani et al., 2005; Suzuki et al., 2005; van den Brink et al., 2001). This observation is associated with *Helicobacter pylori* infection, which is directly linked to the development of gastric cancer (Correa et al., 1975; Uemura et al., 2001). Taken together, these evidences may indicate that the inactivation of Hh signaling mediates in part the precancerous tissue alterations induced by *Helicobacter pylori* infection while its re-activation confers survival advantages in later stages of gastric carcinogenesis.

2.4 Notch pathway

Notch signaling pathway is evolutionary conserved and plays a role in many important and fundamental processes in cell and tissues such as proliferation, differentiation, apoptosis, cell fate determination, and maintenance of stem cells (Koch and Radtke, 2007; Leong and Karsan, 2006; Radtke and Raj, 2003). Notch signaling is activated during cell-to-cell contact through four receptors (Notch1-4) that can interact with ligands of the Delta (Dll-1, Dll-3, Dll-4) and Jagged (Jagged-1 and Jagged-2) family (Bray, 2006). Notch-ligand binding induces the cleavage of Notch receptor through a cascade of proteolytic cleavages by the metalloprotease tumor necrosis factor-α-converting enzyme (TACE) and γ-secretase, releasing the intracellular domain of Notch (NICD) (Katoh, 2007a; Wang et al., 2009). The NICD is translocated into the nucleus to associate with CSL transcription factor triggering the activation of Notch target genes (Androutsellis-Theotokis et al., 2006; Miele, 2006). Until now, few Notch target genes have been identified in different cellular and developmental contexts (Borggrefe and Oswald, 2009), such as Hes-1 (Hairy enhance of split-1), Cyclin D1, Nuclear factor-κB (NF-κB) and c-myc (Miele, 2006) (Figure 4).
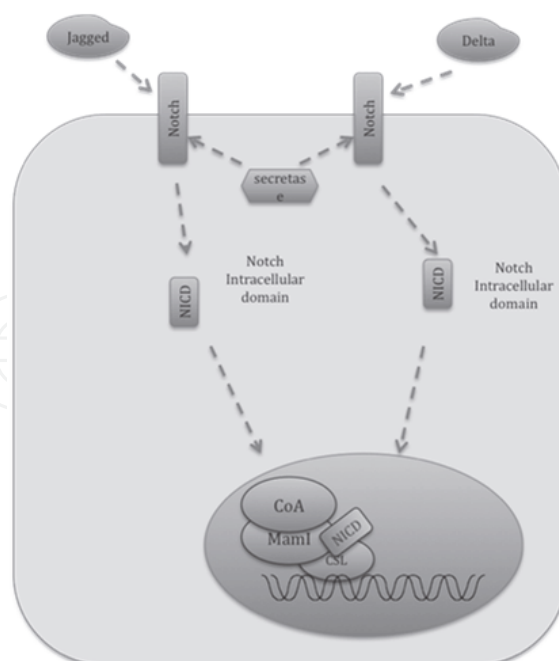
Fig. 4. Notch signaling pathway.

Recently, it has been described an association between Notch signaling and progression of gastric cancer. Three Notch receptors (Notch1-Notch3) and Notch ligand Jagged1 are expressed in human gastric cancer (Katoh, 2006; Sander and Powell, 2004; Sekine et al., 2006) and Notch signaling pathway is activated after infection with *Helicobacter pylori* in gastric cancer (Katoh, 2007b). Gastric cancer patients with Jagged1 expression in tumor tissues have more aggressive tumors and poor survival, suggesting an important role of this pathway in gastric cancer progression (Yeh et al., 2009). This aggressiveness seems to be correlated with the interaction between Notch signaling pathway and COX-2, an independent prognostic factor of gastric cancer (Shi et al., 2003). Notch signaling induces Cox-2 expression by directly binding to it through the intracellular domain of Notch1 receptor producing a stimulatory effect on cancer growth and invasion (Yeh et al., 2009). Nuclear factor-κB is also involved in Notch signaling and mediates COX-2 expression to regulate cell proliferation of human gastric cancer cells (Espinosa et al., 2003). Therefore, COX-2 inhibitors may be a new strategy to be used for treatment of gastric cancer in the future.

Twist, another transcription factor regulated by Notch signaling, was also shown to regulate cell motility and invasion in gastric cancer cell lines, probably through N-cadherin and fibronectin (Yang et al., 2007). Possibly, these EMT mediators induced by NICD could lead to an increased expression of COX-2. Whether N1ICD induces expression of COX-2 to modulate metastasis in gastric cancer through EMT mediators remains unknown.

Furthermore, activation of Notch signal pathway is involved in epithelial-mesenchymal transition (EMT), during development and tumorigenesis. Notch signaling increases Snail-1 expression and elevates EMT in cardiac development, kidney tubular cell differentiation, and hypoxia (Sahlgren et al., 2008; Timmerman et al., 2004; Zavadil et al., 2004). The Jagged1-activated Notch signaling also promotes EMT through E-cadherin repression by Slug (Leong et al., 2007). Jagged1 and Hey1, a target gene of Notch signal pathway, are also involved in mediating transforming growth factor-β–induced EMT (Zavadil et al., 2004). All these findings together indicate that Notch signaling plays a multitude of important roles in gastric carcinogenesis.

2.5 COX-2/PGE2 pathway

The regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with a reduced risk of cancer development in the gastrointestinal tract (Thun et al., 1993; Farrow et al., 1998; Oshima et al., 2009). The major target of NSAIDs is cyclooxygenases (COXs), such as COX-2, which is a rate-limiting enzyme responsible for the conversion of arachidonic acid to prostaglandins (PGs) (Chan et al., 2007; Williams et al., 1999). The anticancer effect of these agents is thought to be caused by the inhibition of COX-2 and, consequently the reduction of PG synthesis (Wu et al., 2010). Regular use of NSAIDs is associated with a decreased incidence of gastric cancer (Oshima et al., 2009, as cited in Thun et al, 1993; Zaridze et al., 1999).

The over-expression of COX-2 was reported in several common human malignancies, such as in lung, colon, pancreas, bladder, head and neck cancers, being its main expression in gastrointestinal tract (Pereira et al., 2009, as cited by Fujimura et al., 2006 and van Rees & Ristimaki, 2001; Schuller et al., 2006). Several studies have shown that the treatment with NSAIDs or COX-2 selective inhibitors (COXIBs) suppressed chemically induced tumor formation and xenografted tumor growth, so these results show that the COX-2 pathway plays an essential role in cancer development (Oshima & Taketo, 2002; Oshima et al., 2009).

The inducible enzyme, COX-2 is responsible for catalyzing the biosynthesis of prostaglandin (PG) H2, which is further converted to PGE2 by microsomal PGE synthase-1 (mPGES-1), a PGE2 converting enzyme that is functionally coupled with COX-2 (Murakami et al., 2000; Seno et al, 2002). Cox-2-derived PGE2, a stable prostanoid synthesized by prostaglandin E synthase (PGES) can modulate inflammation (Huang & Chen, 2011, as cited in Harizi et al., 2000), relax vascular smooth muscles (Huang & Chen, 2011, as cited in Smyth et al., 2009) and act as a promoter of cancer progression (Huang & Chen, 2011, as cited in Iniguez, 2008). This molecule also has the ability to stimulate tumor-associated angiogenesis (formation of new blood vessels that supply oxygen and nutrients), promote cellular proliferation, inhibit apoptosis and enhance cellular invasiveness, facilitating the progression of cancers (Gross et al, 2005). Among the COX-2 downstream prostanoids, PGE2 is the one that is better studied, concerning its potential role in tumor progression (Huang & Chen, 2011) and mediates most, if not all, of the oncogenic effect of COX-2 in gastric cancer (Muller-Decker & Furstenberger, 2007). Such as for COX-2, an up-regulation of PGE2 in most of the gastrointestinal cancers also occurs (Huang & Chen, 2011). Therefore, it is crucial for gastric carcinogenesis an increased level of PGE2 through the induction of COX-2 and mPGES-1. Simultaneous induction of COX-2 and mPGES-1 is observed in gastric cancer tissues, which suggests the induction of PGE2 pathway in gastric tumors (Oshima et al., 2006). Several studies using mouse models have elucidated the roles of the PGE2 pathway in gastric tumorigenesis in the Wnt-activated and BMP-suppressed gastric mucosa (Oshima et al., 2009).

It is known that *Helicobacter pylori* infection causes chronic gastritis, as well as an over-expression of COX-2 and mPGES-1(Oshima et al., 2009). Concordantly, after eradication of *H. pylori*, COX-2 expression is suppressed (McCarthy et al., 1999), with correlation with decreased levels of mPGES-1, indicating that *H. pylori* infection induces the PGE2 pathway through induction of both COX-2 and mPGES-1. Several studies have found over-expression of COX-2 in gastric precancerous lesions and in gastric cancer (Tatsuguchi et al., 2000; Wambura et al., 2002). The molecular mechanism for COX-2 induction in tumors has not been totally elucidated, however there is a possibility that *H. pylori* can stimulate Toll-like receptors (TLRs) leading to the activation of the nuclear factor-κB (NF-κB) pathway that in turn induces the expression of COX-2. Another possibility is that the cytokine network can

be activated by infection and, as a result, an induction of COX-2 expression occurs (Chang et al., 2004; Smith et al., 2003). Transgenic mice over-expressing COX-2 and mPGES-1 simultaneously develop intestinal metaplasia and hyperplastic tumors in the glandular stomach, which is associated with macrophage infiltration, so these results suggest that increased levels of PGE2 enhance infiltration of macrophages, whose activation by *H. pylori* may enhance gastric carcinogenesis (Oshima et al., 2004; Wu et al., 2010).

2.6 NF-$_\kappa$B pathway

NF-κB (Nuclear Factor kappa B) is a critical regulator of genes involved in cell survival and proliferation, cellular stress response, innate immunity and inflammation (Baeuerle & Baltimore, 1996; Barnes & Karin, 1997). The NF-κB family is composed by five closely related DNA binding proteins: RelA (p65), RelB, c-Rel, NF-κB1/p50 and NF-κB2/p52, which function as various homodimers and heterodimers. All share a highly conserved domain called the Rel homology domain (RHD), responsible for their dimerization, nuclear translocation, DNA binding and also interaction with the inhibitors of NF-κB (IκBs) (Gilmore, 2006). This family can be subdivided according to differences in synthesis and C-terminal sequences. While members of the "Rel subfamily" (RelA, RelB and c-Rel) have a transactivation domain (TAD) at their C-termini and are synthesized directly as mature forms, p50 and p52 from "NF-κB subfamily" are generated from large precursor proteins, p105 and p100, respectively, by limited proteolysis or arrested translation. Although lacking a TAD, the precursors of the second subfamily contain a C-terminal with multiple copies of ankyrin repeats - ankyrin repeat domain (ARD) - the typical domain of IκBs. Characteristic NF-κB dimmers usually involve one member from each subfamily, although all NF-κB members may form various homo- or heterodimers. p50 or p52 homodimers inhibit NF-κB target gene expression due to lack of a TAD, therefore, members of the NF-κB subfamily are generally not activators of transcription but function as IκB-like inhibitors of NF-κB, except when they form heterodimers with members of the Rel subfamily, participating in target gene transactivation (Li & Verma, 2002).

NF-κB is essencial in cellular response regulation being an example of transcription factors that are present in cells in an inactive state and do not require new protein synthesis to be activated. The activation of NF-κB requires phosphorylation of IκBs, resulting in their ubiquitin-dependent degradation. Therefore, NF-κB can enter the nucleus and activate the genes in response to certain stimuli, including reactive oxygen species (ROS), tumor necrosis factor alpha (TNFα), interleukin 1-beta (IL-1β) and bacterial lipopolysaccharides (LPS) - a component of the outer membrane of Gram-negative bacteria including *H. pylori* (Thanos & Maniatis, 1995). In unstimulated cells, the NF-κB dimers are sequestered in the cytoplasm by IκBs. There are two pathways leading to NF-κB activation: the canonical/classical and non-canonical/alternative. The canonical pathway can be activated by several stimuli including inflammation cytokines and antigens that induce the phosphorylation and activation of an IκB kinase (IKK) complex, consisting of catalytic kinase subunits (IKKα and/or IKKβ) and a scaffold, sensing protein termed NF-κB essential modulator (NEMO). The activated IKK promotes phosphorylation of IκBα and its ubiquitin-dependent degradation by the proteasome. The released NF-κB is able to enter the nucleus and regulate the expression of a wide range of genes including activation of its own repressor, IκBα (Nelson et al., 2004) (Figure 5).
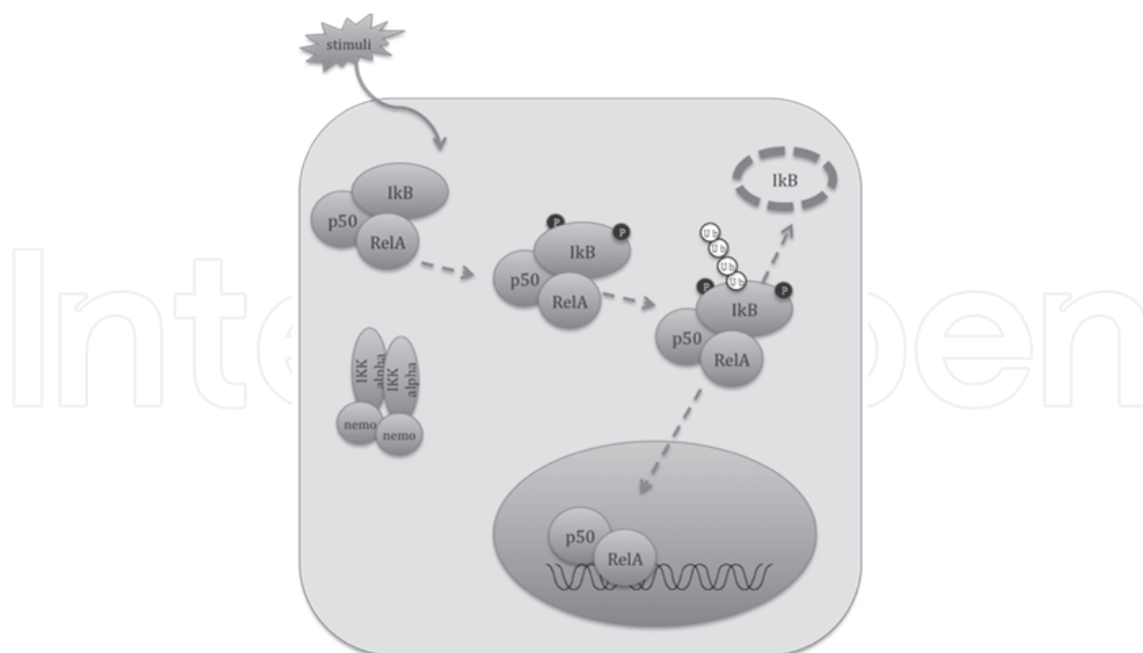
Fig. 5. NF-kB signaling pathway (canonical activation).

The non-canonical pathway is induced by certain receptor signals like B-cell activating factor (BAFF), Lymphotoxin β (LTβ), CD40 ligand, TNF-like weak inducer of apoptosis (TWEAK) and receptor activator of NF-κB ligand (RANKL) (Xiao et al., 2006). It is a slow process that depends on NF-κB-inducing kinase (NIK) protein synthesis. Despite the fact that its mRNA expression is abundant, protein levels are usually low due to its constitutive degradation by a TRAF3-dependent mechanism (Qing et al., 2005). When non-canonical NF-κB stimuli occur, the key components of this mechanism are degraded by the proteasome and NIK is activated and then able to activate an IKKα complex (an homodimer lacking NEMO), that consequentially phosphorylates p100, leading to its partial proteolysis (in the proteasome) and formation of p52. The p52/RelB complex then translocates into the nucleus to modulate gene expression (Zarnegar et al., 2008) (Figure 6).

There is evidence that NF-κB is constitutively activated in gastric cancer tissues, with higher levels in gastric carcinoma cells in comparison to normal adjacent epithelial cells (Sasaki et al., 2001) although it is RelA and not NF-κB that is used as a prognostic indicator of gastric carcinoma. It has also been reported that patients with highly activated NF-κB levels in cancer cells would have a lower survival potential when compared to those with low NF-κB activation (Yamanaka et al., 2004). In gastric cancer, abnormal NF-κB activation has been shown to lead to enhanced proliferation, evasion of apoptosis, genomic instability, increased rate of glycolysis and drug resistance (Cho et al., 2008; Kang et al., 2008; X. Liu et al., 2010).

Regarding drug resistance, a study has been performed in order to evaluate the effect of 5-Fluorouracil (5-FU) and irinotecan (CPT-11) in NF-κB activation. It led to the conclusion that these components are inducing two different pathways: apoptosis through direct effect on nucleic acids, and inhibition of apoptosis through activation of NF-κB. Moreover, the same authors used an inhibitor of NF-κB and predicted that its combination with 5-FU and CPT-11 may be a more effective treatment option instead of chemotherapy alone for gastric cancer (Camp et al., 2004).
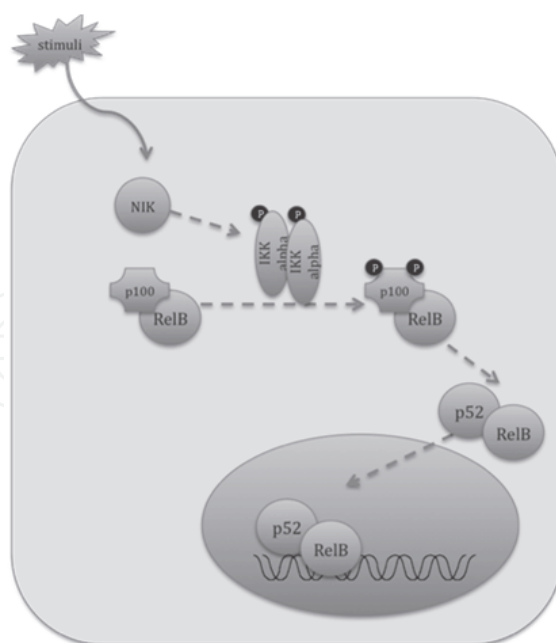
Fig. 6. NF-kB signaling pathway (non-canonical activation).

Since the discovery that blocking NF-κB can cause tumor cells to stop proliferating, to die, or enhance their sensitivity to the action of anti-tumor agents NF-κB has been widely used as a target for anti-cancer therapy (Escarcega et al., 2007). HIF-1α, one of the components of hypoxia-inducible factor 1 (HIF-1), has been directly implicated in tumorigenesis including angiogenesis, tumor cell proliferation, metastasis, as well as chemo- and radiotherapy response, particularly in gastric cancer (Liu et al., 2008; Weidemann & Johnson, 2008). Interestingly, a recent study showed that NF-κB inhibition in gastric cancer suppressed hypoxia-induced HIF-1α protein expression (but not at the mRNA level), suggesting that this protein is a downstream molecule of NF-κB in the angiogenesis pathway in gastric cancer. Also, NF-κB seems to be activated by hypoxia leading to HIF-1α protein accumulation at the translational level, but not at the transcriptional or post-translational levels. Thus, NF-κB/HIF-1α pathway may be a fitter candidate target for inhibition in gastric carcinoma therapy (Nam et al., 2011).

Using a different approach, other investigators described a new mechanism in gastric tumor cells associated with NF-κB inhibition responsible for impairment of cell proliferation and induction of apoptosis of cancer cells. By blocking NF-κB (with a RelA inhibitor, SN50) they achieved an increase in p53 expression, which led to the induction of pro-apoptotic and autophagic proteins. Thus, p53 contributes to NF-κB inhibitor-induced apoptosis of cancer cells by activation of autophagic mechanisms (Zhu et al., 2011).

2.7 Transforming growth factor- β, bone morphogenic protein pathway

Transforming growth factor (TGF)-β is a multifunctional cytokine that controls differentiation, apoptosis, cell growth and immune reactions (Roberts, 2002; Shi & Massagué, 2003). TGF-β1, -β2, and -β3 are three isoforms of TGF-β that are present in mammals. In most types of cells, TGF-β is a potent growth inhibitor, so alterations on TGF-β signaling lead to tumor progression by the induction of angiogenesis, extracellular matrix accumulation and immunosuppression (Blobe et al., 2000; Derynck et al., 2001; Wakefield & Roberts, 2002).

This pathway is considered to be a tumor suppressor pathway that negatively regulates cell growth and promotes apoptosis of epithelial cells (Siegel & Massagué, 2003). In early stages of cancer, TGF- β signaling acts as a tumor-suppressor and in later stages promotes invasion and metastasis (Wu et al., 2010). TGF-β signaling pathway is composed of two distinct receptors with intrinsic serine/threonine kinase activity, TGF-β type I and type II receptors (TbRI and TbRII) and Smad proteins. The binding of TGF-β to TbRII leads to recruitment and transphosphorylation of TbRI (heteromeric complex). Cytoplasmatic Smad2 and Smad3 are then phosphorylated by activated TbRI kinase, allowing them to form a heteromeric complex with Smad4, that is translocated into the nucleus acting as transcription factors. (Massagué, 1998; Miyazono et al., 2000; Miyazono et al., 2003) (Figure 7).
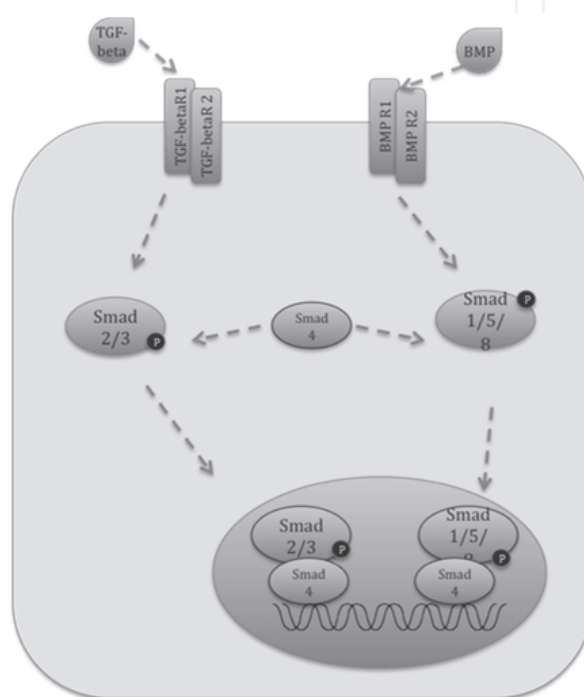

Fig. 7. Wnt signaling pathway (canonical).

Several studies demonstrated that the over-expression of TGF-β, in gastric cancer, is correlated with lymph node metastasis and poor prognosis (Maehara et al., 1999; Saito et al., 2000), as well as promotion of invasion and metastasis (via Smad3-, ERK- and JNK-dependent signal pathways) (Fu et al., 2009; Wang et al., 2006; Yoo et al., 2008). TGF-β induces RUNX3, a transcription factor that is involved in the formation of a variety of cancers (Ito, 2004). RUNX3 is expressed in glandular stomach epithelial cells, however, the loss of expression of this gene is associated with the progression, differentiation, metastasis and poor prognosis of gastric cancer (Li et al., 2002; Sugiura et al., 2008; Wei et al., 2005). Vogiatzi and colleagues (2006) demonstrated that RUNX3 interacts with FoxO3a /FKHRL1 to activate Bim and induce apoptosis in gastric cancer cells. *H. pylori* causes methylation of RUNX3 gene and its loss of expression in gastric epithelial cells (Katayama et al., 2009). Moreover, RUNX3, Smad4 inactivation has been documented in gastric cancer (Wu et al., 2010 as cited in Powell et al., 1997). Another study carried out by Shinto and colleagues (2011) demonstrated that the expression of p-Smad2 is associated with malignant phenotype and poor prognosis in patients with advanced gastric carcinoma.

Bone morphogenetic proteins (BMPs) are members of the TGF-β superfamily (von Bubnoff & Cho, 2001). They were originally identified as osteoinductive cytokines that regulate bone and cartilage formation (Balemans & Van Hul, 2002; Chen et al., 2004; Hogan, 1996). The BMPs mediate their effects by binding to type I and II serine–threonine kinase receptors (BMPR), leading to the phosphorylation of Smad1, Smad5 and Smad8. These phosphorylated Smads heterodimerize with Smad4 and this complex is translocated to the nucleus to activate the transcription of downstreams targets (Derynck et al., 1998; Kretzschmar et al., 1997; Heldin et al., 1997). Several studies have demonstrated that BMPs play important roles in the regulation of cell motility, proliferation, apoptosis, differentiation, self-renewal of embryonic stem cells and remodeling of the extracellular matrix (Hardwick et al., 2004; Hogan, 1996; Li et al., 1996; Massagué, 1996; Nissinen et al., 1997; Von Bubnoff, 2001). BMP proteins are expressed in adult stomach (Peek & Blaser, 2002; van den Brink et al., 2001).

BMP signaling in the stomach is down-regulated in cancer and upregulated during inflammation (Wu et al., 2010). *H. pylori* infection leads to an increase in BMP expression, mainly caused by an influx of BMP2-producing cells. The influx correlates with an increase in the activity of the BMP pathway (Bleumeing et al., 2006). A study carried out by Wen and colleagues (2004) demonstrated that BMP-2, a BMPR ligand, caused cell cycle arrest in the G1-phase in MKN74 and OUMS37 cells, and that this growth inhibitory action may be mediated by p21$^{Waf1/Cip1}$ (BMP-2 suppresses gastric cancer cells proliferation). Moreover, this BMP is suppressed by tumor methylation in gastric cancer cells (Wen et al., 2006). Taken together, these results suggest that the inhibition of BMP signaling contributes to gastric tumorigenesis through the suppression of differentiation. (Oshima et al., 2009). However, recent studies have discovered that BMP-2 can accelerate the migration and invasiveness of gastric cancer cells and may correlate with disease progression (Kang et al., 2010; Park et al., 2010).

3. MUC1 mucin-mediated signaling pathways in gastric cancer

The stomach is continuously subjected to a harsh acidic environment and several external aggressions. The mucus layer produced by the gastric epithelium has a crucial protective role against these adverse conditions. Three major heavily glycosylated proteins (mucins) line the stomach epithelium under normal conditions: one membrane associated mucin, MUC1, and two secreted mucins, MUC5AC and MUC6. They all contribute to the formation and maintenance of a cohesive "mucin net" that covers the entire epithelium, working as an efficient barrier. Abnormal expression and glycosylation have been described for these highly polymorphic mucins in gastric carcinoma and pre-neoplastic lesions (Reis et al., 1999; Teixeira et al., 2002). MUC1 polymorphism defines different susceptibility backgrounds associated with the development of conditions that precede gastric carcinoma: chronic atrophic gastritis and intestinal metaplasia (Silva et al., 2001).

MUC1 and MUC4 have been recently identified as participating in intracellular signaling pathways, by their cytoplasmic domains (Carraway et al., 2003; Hollingsworth and Swanson, 2004). The phosphorylation of MUC1 cytoplasmic domain (MUC1-CD) has been found to modulate its interaction with several molecules, such as EGFR, β-catenin, p53, ER-α, ICAM-1, among other molecules (for review see Singh & Hollingsworth , 2006). These interactions have been mainly found for breast, pancreatic and lung cancer cells and so far the data about MUC1-mediated signaling pathways or MUC1 signaling partners in gastric

carcinoma cells is limited. MUC1-CD is known to interact with beta-catenin and upregulate the Wnt signaling pathway in CagA *Helicobacter pylori*-infected gastric carcinoma (Udhayakumar et al., 2007).

Our group has been studying the MUC1-dependent signaling pathways in gastric cancer cells. We have stably down-regulated MUC1 expression in MKN45 gastric carcinoma cell line by shRNA and we evaluated MUC1 down-regulation impact in potential MUC1-mediated signaling pathways. We observed that MUC1-downregulation leads to abnormal expression levels of ERK1/2 proteins and an increased phosphorylation of these kinases. We further characterized the association between MUC1 and ERK1/2 and we showed by proximity ligation assays that MUC1-CD directly interacts with ERK1/2 kinases in these cells. The impact of MUC1 in the transcription and stability of these kinases and the interaction with other signaling partners (e.g. EGFR) are being currently evaluated, nonethless this clearly suggests that MUC1-CD is involved at different levels in the regulation of the MAPK signaling pathway in gastric carcinoma cells (Figure 8).
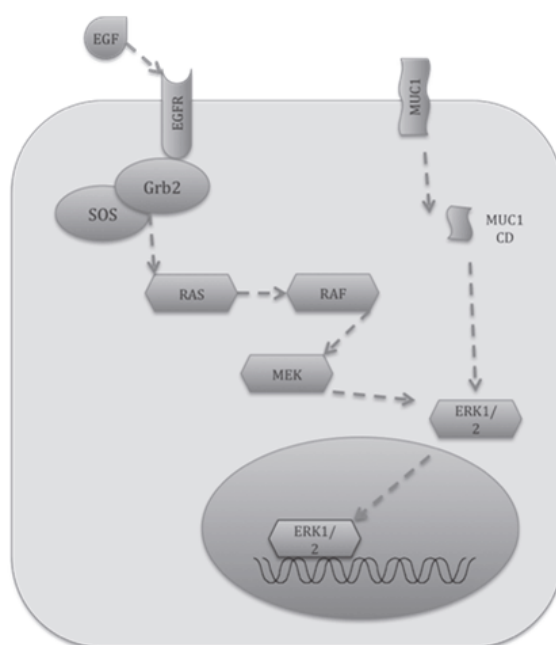

Fig. 8. MUC1 and EGFR/MAPK signaling pathway.

The kinases of EGFR/MAPK signaling pathway are crucial effectors responsible for cell proliferation and oncogenic transformation. Recent data from other tumor models further reinforce the relevance of MUC1 as a key player in cell-cell (microenvironment) signaling contexts (Behrens et al., 2010). Therefore, it assumes critical relevance an extensive characterization of MUC1-mediated signaling events in this pathway and their impact in gastric carcinoma phenotype. These results suggest MUC1 as a new and promising candidate to be targeted by therapies against gastric cancer.

4. Conclusions

Gastric cancer is a leading cause of cancer-related death worldwide. Given the limited options currently available for gastric cancer therapy and prevention, it becomes urgent to better understand the oncogenic signaling pathways beyond the emergence of the disease.

There is an increased knowledge about the alterations occurring in multiple signaling pathways and the acquisition of gastric cancer phenotype. The complex interplay between environmental factors and oncogenic signaling pathways involving cell proliferation, differentiation, apoptosis and invasion, remains however elusive. Emerging evidence in other models has brought new evidences on the complex interaction among different oncogenic signaling pathways. Whether such phenomena occur in gastric cancer, remains unclear.

The elucidation of individual interactions is thus required to develop a more consistent understanding of the gastric oncogenic signaling networks and will help to identify novel targets for anticancer drug development. The reviewed signaling pathways are relevant contributors for gastric carcinogenesis and encompass a multitude of potential therapeutic targets. In addition to these signaling-related targets we included new data on MUC1 mucin, previously described as being involved in gastric cancer susceptibility phenotype. The characterization of the complete spectrum of MUC1-dependent oncogenic signaling interactions in gastric cancer cells, will offer the molecular basis for the development of innovative therapies using MUC1 as an elective target. Furthermore an integrative perspective, of these MUC1-mediated signaling pathways, will be critical to design therapeutic strategies that inhibit multiple signaling pathways enhancing the efficacy of gastric cancer therapies and probably prevent the development of drug resistance phenotype.

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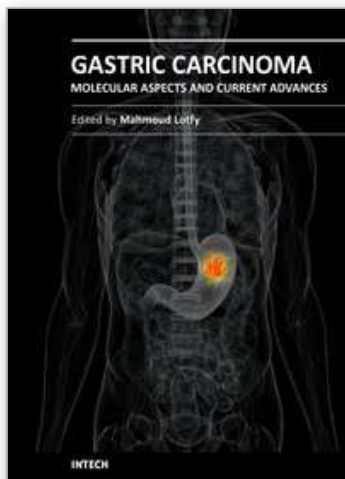
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Gastric cancer is one of the most common tumors worldwide. It has a heterogeneous milieu, where the genetic background, tumor immunology, oxidative stress, and microbial infections are key players in the multiple stages of tumorigenesis. These diverse factors are linked to the prognosis of the gastric cancer and the survival of gastric cancer patients. This book is appropriate for scientists and students in the field of oncology, gastroenterology, molecular biology, immunology, cell biology, biology, biochemistry, and pathology. This authoritative text carefully explains the fundamentals, providing a general overview of the principles followed by more detailed explanations of these recent topics efficiently. The topics presented herein contain the most recent knowledge in gastric cancer concerning the oncogenic signaling, genetic instability, the epigenetic aspect, molecular features and their clinical implications, miRNAs, integrin and E-cadherin, carbohydrate-associated-transferases, free radicals, immune cell responses, mucins, Helicobacter-pylori, neoadjuvant and adjuvant therapy, prophylactic strategy for peritoneal recurrence, and hepatic metastasis.

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