Oncogenes Orchestrate Immunosuppressive Stroma in Gastric Adenocarcinoma

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Abstract

Gastric adenocarcinoma (GAC) is among the three most common cancers in the world. The majority of GAC patients are diagnosed in an advanced stage and have a median survival of ~9 months. There are limited effective therapeutic strategies available in the clinic and currently U.S. Food and Drug Administration (FDA) approved immune therapy is programmed death-1 (PD-1) antibodies (e.g. pembrolizumab) but only a few patients seem to benefit. Transformation to cancer occurs when multiple genes and cellular pathways are dysregulated in multi-cellular organisms. Mounting evidence supports that oncogenes orchestrate tumor immune suppressive stroma to foster tumor favoring microenvironmental niche. Thus, deeper understanding of the immunosuppressive mechanisms in tumor stroma especially orchestrated by notable oncogenes can allow exploration of novel avenues that may have an impact on patient outcome. In this review, we summarize current progress of notable oncogenes and pathways including Ras/Myc, EGFR/HER2, PI3K/mTOR, Wnt/β-catenin, and Hippo/YAP pathways focusing on the interplay between these oncogenic pathways and...
immunosuppressive stroma. Future potential novel targets and immune checkpoint blockage are discussed.

**Keywords**
Gastric adenocarcinoma; oncogenes; immune cells; immunosuppression; stroma; TME

1. Introduction

Cancer occurs, in multicellular organisms, when multiple oncogenes are activated along with simultaneous or sequential loss of function of tumor suppressor genes leading to multiple cellular pathways being deregulated. This process is driven by accumulated genetic abnormalities. According to the World Health Organization (WHO), cancer is the second leading cause of death globally and is a generic term for a large group of diseases that can affect any part of the body, other terms are malignant tumors and neoplasms. Gastric adenocarcinoma (GAC) is among the 3 most common causes of cancer deaths in the world (https://who.int/cancer). An oncogene literally is a cancer-causing gene, which is often mutated (gain-of-function mutation) or highly amplified. The normal functional proto-oncogenes are involved in the regulation of cell growth and proliferation, differentiation, and inhibition of apoptosis. Mutated proto-oncogenes become activated by a variety of genetic mechanisms including insertion/deletional mutagenesis, amplification, point mutations, and chromosomal translocations [1]. Here we summarize current research progress of selected notable oncogenes in GAC including Ras/Myc, epidermal growth factor receptor (EGFR)/HER2, PI3K/mTOR, Wnt/β-catenin, and Hippo/YAP1.

2. Notable Oncogenes in Cancers

2.1 Oncogenes Activated by Viruses

A comprehensive book [2] in 2017 detailed all the major discoveries of viruses associated in human cancers from 1911 till now. Oncogene Myc (also as c-myc or MYC) was first identified in an avian myelocytoma virus and the other Ras gene was first identified in rat sarcoma virus long before they became associated with human malignancies [3]. The first confirmed oncogene SRC (proto-oncogene c-SRC, a non-receptor tyrosine kinase) was a homolog of previous avian sarcoma virus v-SRC gene and transmitted by a chicken retrovirus Rous sarcoma virus (RSV) that acted as an oncogene upon infection [4], even though human genome has the RSV homolog in place. Table 1 briefly lists viral infections turned on oncogenes or mutated tumor suppressors, leading to cancer, some of them are marked as milestones in cancer molecular biology.

For GAC, The Cancer Genome Atlas (TCGA) analysis identified one of four molecular subtypes of GAC is Epstein-Barr virus+ (EBV+) tumors, in which detected PIK3CA mutations, CDKN2A silencing, JAK2 amplification and programmed death-ligand-1 (PD-L1) and PD-L2 amplifications [5].
| Viruses                                | Host Oncogenes /Tumor suppressors                        | Cancers                                | Notes                                                                 | References |
|----------------------------------------|----------------------------------------------------------|----------------------------------------|----------------------------------------------------------------------|------------|
| Rat sarcoma virus                      | Activated Ras                                            | Rat sarcoma                            |                                                                       | [3, 4]     |
| Epstein-Barr virus (EBV)               | Sstr1 methylated; Bcl-2 overexpression; viral miR-Bart3-3p induces RasG12V, PIK3CA mutations | Gastric Cancer                         | One of four molecular subtypes of GAC                                | [6-9]      |
| Human herpesvirus 8 (HHV-8)            | Induced FAK and SRC; Induced ERK1/2, NFKB and NRF2        | Kaposi’s sarcoma                       |                                                                       | [10, 11]   |
| Avian myelocytoma virus                | Activated Myc                                            | Avian myelocytoma                      |                                                                       | [3, 4]     |
| Epstein-Barr virus (EBV)               | Myc translocation and activation                          | Burkitt lymphoma                       | First human tumor virus in 1964                                      | [12]       |
| Rous sarcoma virus (RSV)               | Transforming SRC                                          | Chicken Rous sarcoma                    | First discovered oncogene transmitted by a virus                     | [2, 4]     |
| Epstein-Barr virus (EBV)               | NFkB activation and/or activated PI3K/mTOR/AKT            | Nasopharyngeal carcinoma (NPC)          |                                                                       | [13]       |
| Hepatitis B virus (HBV)                | HBV-human fusion transcript lncRNA (HBx) binds & impairs p53 | Hepatocellular carcinoma               | Oncogenic lncRNA                                                      | [14]       |
| Human papillomavirus (HPV)             | Viral E6 destabilizes p53; viral E7 degrades pRB         | Cancer in cervix, vagina, and vulva and oropharyngeal, anal, penile, and cutaneous carcinomas. Tumors in rabbits |                                                                       | [2]        |
| Human T-cell leukemia virus type 1 (HTLV-1) | Viral Tax gene activates/ modifies NFkB/Rel family    | Adult T-cell leukemia (ATL)             | First retrovirus discovered                                           | [2, 15]    |
| Lentiviruses (HIV, SIV)                | Vpr gene product arrests human cells in G2. Viral integrase hijacks LEDGF/p75 | Human HIV                              |                                                                       | [16, 17]   |
| Polyoma virus and simian virus 40 (SV40)| Viral proteins bind p53 and pRB; Loss-of function p53 and pRB | Murine polyoma                         |                                                                       | [4, 18]    |
2.2 Oncogenes Activated by Bacteria

Bacteria are normally not considered as agents that cause cancers, but research has found more connections. Common bacteria *Staphylococci pneumoniae* infection was reported to be associated with leukemia, lymphoma, or myeloma; *Staphylococci bovis* infection was speculated to be associated with colorectal cancer in a case study in 1951; *Salmonella typhimurium* was reported to be associated with gallbladder cancer, etc. [19]. Persistent *Mycoplasma penetrans* infection in immunodeficient mice demonstrated lower expression of tumor suppressors p53 and p21 and higher expression of oncogenes HRas, nuclear factor-κB (NFκB-p65) and B-cell lymphoma 2 (Bcl-2), which are associated malignant transformation [20].

For GAC, a book chapter detailed bacterial infections causing cancers, such as *Helicobactor pylori* causes GAC and mucosa-associated lymphoid tissue (MALT) lymphoma [19]. *H. pylori* is the most important risk factor for GAC, which is found in 90% of GAC (especially in Asia). This bacterium has 3 virulence factors: cytotoxin-associated gene A (CagA), CagA pathogenicity island (Cag PAI) and vacuolating cytotoxin A (VacA) [5, 21]. In gastric epithelium, oncogenic CagA activates oncogenes β-catenin, MET (also as c-Met or cMet), EGFR, PI3K and AKT, results in loss of function of tumor suppressor genes RUNX1, CDH1 (E-cadherin) and TFF1, and suppresses the immune milieu by recruiting tumor-associated macrophages [TAMs] and alter the microRNA (miRNA) profile [5]. *H. pylori* is the most important risk factor and carcinogen for GAC. Long-term infection leads to chronic atrophic gastritis and pre-cancerous changes [6].

*H. pylori* virulence factors CagA and VacA activate multiple pathways including Ras/Myc, MAPK, NFκB, activating protein (AP), Wnt/β-catenin, PI3K in stomach epithelial cells into production of inflammatory cytokines, such as IL-1β, IL-6, IL-8, necrosis factor alpha (TNFα), INF-γ and MCP1, resulting in an inflammatory response, mucosal damage and eventually gastric carcinogenesis [22].

2.3 Tumorigenesis Sustained by Activated Oncogene and Dysregulated Protooncogenes

A single mutated or dysregulated oncogene (a gene fusion) can lead to cancer but that is not common. In most cancers, multiple oncogenes drive cells in the context of loss-of-function tumor suppressor genes. Such a complex process can take years before a fit clone emerges as established cancer. In GACs, promoter CpG island hypermethylation (CIMP) is frequently found, high levels of CIMP are associated with poor prognosis in younger patients and are associated with mutated oncogenes β-catenin, HER2, KRas, and PIK3CA [5].

In the transgenic mouse models with inducible oncogenes under the control of regulated promoters, oncogenes are turned on and tumors can emerge, extinction of expression often leads to rapid disappearance of the tumor, and those genes with tumor maintenance include KRas, HRas, Myc, Neu (HER2), Wnt, EGFR, fusion gene Bcr-Abl (breakpoint cluster region-Tyrosine-protein kinase Abl1), and MET, etc. [23]. Oncogene MDM-2 is overexpressed as much as 100-fold in as many as one-third of human sarcomas [16]. The first identified human oncogene was by R. Weinberg in 1982 and later was identified as a mutated allele of HRas [24]. Myc proto-oncogene coordinates genes essential to cellular programs required for normal as well as neoplastic cellular growth and proliferation. With Myc inactivation, cancer cells undergo proliferation arrest, which induces immune activation, angiogenesis arrest, cell senescence, and apoptosis [25].
3. Interplay Between Oncogenes and the Immunosuppressive Stroma in the Tumor Microenvironment (TME)

3.1 Innate, Adaptive Immune Cells and Immunomarkers

A comprehensive review of immunology in GAC peritoneal carcinomatosis (PC) was recently reviewed by our group [26]. Macrophages (Mφ), neutrophils, dendritic cells (DCs), and natural killer (NK) cells are part of innate immunity and directly defend against invading pathogens and cancer cells and convene adaptive immune systems by T and B lymphocytes. Innate immunity, adaptive immunity, cytokines, chemokines, immune checkpoints proteins are parts of cell immunity. Cytokines are regulators of the innate and adaptive immune systems, which control proliferation, differentiation, effector functions, and survival of leukocytes [27]. Chemokines are small, secreted proteins/peptides being the largest subfamily of cytokines that mediate immune cell trafficking and lymphoid tissue development. In TME, chemokines can be expressed and produced by tumor cells and other cells including immune cells and stromal cells [28]. For tumor proliferation, cancer cells upregulate vascular endothelial growth factor (VEGF), MMPs, immunosuppressive IL-10, transforming growth factor-beta (TGF-β), and epithelial-mesenchymal transition (EMT). For metastases, cancer cells downregulate NK ligands to become disseminated tumor cells (DTCs), recruit immunosuppressive macrophages, and increasing neutrophil extracellular traps (NETs). Notable oncogenes can orchestrate an interplay between tumor cells and immune suppressive stroma as stated below.

3.2 Ras and Myc

KRas (also known as K-ras, KRAS) is a small GTPase that mediates downstream signaling from growth factor receptors which binds guanosine triphosphate and diphosphate nucleotides. KRas is the most frequently mutated oncogene. The mutated and activated KRas binds and activates kinases sequentially in an axis of KRas-RAF1/BRAF/ARAF-MEK1/MEK2-ERK1/ERK2/transcription factors ELK1/c-JUN, leading to cell proliferation [29]. In pancreatic cancer, mutated KRas, together with mutated tumor suppressor CDKN2A (P16), TP53 and SMAD4 accounted for more than 90% of tumors [30]. Pancreatic intraepithelial neoplasia (PanIN) grading of 4 types are based on KRas, and loss-of-function CDKN2A, TP53, BRCA1 and 2 [29]. In GAC, KRas has a relatively low mutation/amplification frequency in the range of 7–20% [31]. Myc was first identified in an avian myelocytoma virus v-myc long before it becomes associated with human malignancies [3]. Myc is a family of transcription factors, including the human gene c-myc (Myc), l-myc (MYCL), and n-myc (MYCN). In cancer, Myc is often persistently expressed, leading to the expression of many other oncogenes, which are involved in cell proliferation, contributing to the formation of cancer [32].

3.2.1 Interplay Between Ras/Myc and Other Oncogenic Signaling.

In GAC transformation, *Mycoplasma penetrans* infection in immunodeficient mice showed lower expression of tumor suppressors p53 and p21 and higher expression of oncogenes HRas (also as transforming protein p21), NFkB-p65 subunit and Bcl-2 indicating that coordination among oncogenes in malignant transformation [20]. In five GAC cell lines, MET activation as well as mutations in KRas and CDH1 was associated with cetuximab resistance [33]. By administration of
rapamycin and CPT-11, embryonic stem cell-expressed Ras (ERas) was upregulated in GAC cells, which induces a cascade of oncogenes of AKT, mTOR, and the nuclear factor (NFkB) in conferring chemoresistance [34]. These studies indicate that oncogenes EGFR, MET, and KRas, AKT, NFkB interplay and lead to resistance to therapies. Tanshinone IIA (Tan-IIA) extracted from an herb inhibits GAC AGS cells by decreasing VEGFR, HER2, Ras, RAF, MEK, and ERK expression [35]. An interplay between Ras/Myc, other oncogenes and their elements of immunosuppression is illustrated in Figure 1A.

3.2.2 Interplay Between Ras/Myc and the Immune Microenvironments

The first direct evidence of KRas mediated inflammation and immune microenvironments reported by Okumura et al. (2010) that conditional expression of oncogenic KRas mutation in K19-expressing putative gastric epithelial progenitor cells induced gastric atrophy, metaplasia, and dysplasia by activating inflammatory pathways and displaying recruitment of BMDCs (bone marrow-derived cells) to the TME. Most importantly, they found that oncogenic KRas mutation in gastric epithelial cells upregulated cytokine and chemokine expression including IL-1, IL-6, CXCL1, and CXCL5 which create a tumor favoring TME that facilitates tumorigenesis of GAC [36]. In a mouse lung model of KRasG12D-driven adenomas, co-activation of Myc drives the immediate transition to highly proliferative and invasive adenocarcinomas marked by highly inflammatory, angiogenic, and immune-suppressed stroma. Epithelial-derived CCL9 and IL-23 were identified as the principal instructing signals and orchestrate recruitment of macrophages, angiogenesis, and PD-L1-dependent expulsion of T and B cells for a tumor immune suppressive environments [37]. Casey et al. (2016) reported that Myc regulates the expression of two immune checkpoint proteins on the tumor cell surface: the innate immune regulator CD47 (cluster of differentiation 47) and the adaptive immune checkpoint PD-L1. Suppression of Myc in mouse tumors and human tumor cells reduced levels of CD47 and PD-L1 expression. Myc inactivation in mouse tumors down-regulated CD47, PD-L1 expression, and enhanced the antitumor immune response [38].

In GAC, PD-L1 expression was associated with loss-of-function ARID1A mutation. The study found in 3 MSI-H (MSI-high, microsatellite instability-high) tumors showing highest expression of PD-L1 had simultaneous KRas mutation and loss of ARID1A. Loss of ARID1A triggers upregulation of PD-L1 through PI3K/AKT signaling pathway. KRas mutation boosts PD-L1 expression in MSI-H GACs, suggesting a possible synergistic role boosting PD-L1 [39].

3.3 EGFR/HER2

The epidermal growth factor receptor (EGFR) family is composed of four closely-related members: ErbB-1 (HER1 or EGFR), ErbB-2 (HER2, or c-erbB-2), ErbB-3 (HER3), and ErbB-4 (HER4), all of which play a critical role in regulating cell growth, proliferation, and migration of tumor cells. GACs overexpress this gene family in a heterogeneous pattern, especially EGFR and HER2. Improved survival from the use of trastuzumab (Herceptin) has paved the way for ErbB receptor family-targeted treatments in GAC [40]. Among GAC patients, ~15% show HER2 overexpression and/or amplification, and this percentage increases somewhat in gastroesophageal junction (GEJ) adenocarcinomas [41].
3.3.1 EGFR/HER2 and Mechanisms of Target Resistance

Study of EGFR-directed antibody cetuximab in GAC cell lines revealed that high EGFR expression and low levels of receptor activation were associated with cetuximab responsiveness, however, MET activation and mutations of KRas and CDH1 was associated with cetuximab resistance [33]. In one study, evaluation of HER2 status in 97 GAC patients showed that HER2 3+ (highest) expression are likely to benefit the most from trastuzumab [42]. Two GAC cell lines with HER2 amplification, one sensitive (NCI-N87) and other one insensitive (MKN-7) to trastuzumab, inhibition of the mTOR/S6K using everolimus was the key in enhancing fluorouracil-induced apoptosis specifically in GAC cells. mTOR inhibitors may be attractive alternative drugs in GACs with HER2 amplification/over-expression [43]. Inhibition of checkpoint kinase 1 (Chk1) phosphorylation enhanced HER2-targeting lapatinib sensitivity of HER2-positive MKN-7 cells, which was shown by potentiated anti-proliferative effect [44].

Maron and Catenacci (2017) listed oncogene HER2, VEGFR2, EGFR, MET, and FGFR2 (fibroblast growth factor type 2) for targeted therapies for esophagogastric cancer (only Her2 and FGFR2 may remain useful targets) [45]. Cancers that overexpress EGFR, HER2, and HER3 are uniquely sensitive to agents that disrupt HER2 and EGFR protein folding. Disruption of disulfide bond formation by disulfide disrupting agents (DDAs) kill HER2/EGFR overexpressing cells. Interference with proline isomerization in HER2/EGFR overexpressing cells also induces cancer cell death. The peptidyl-prolyl isomerase inhibitor cyclosporine A (CsA) selectively kills EGFR+ or HER2+ breast cancer cells in vitro by activating caspase-dependent apoptotic pathways. Further, CsA synergizes with the DDA to kill HER2+ tumor cells in vivo, which may apply to EGFR/HER2 overexpressed esophageal and GACs [46]. Tanshinone IIA (Tan-IIA) extracted from a herb inhibits GAC AGS cells by upregulating expression of PARP and caspase-3 but decreased VEGFR, HER2, Ras, Raf, MEK, and ERK, suggesting all those oncogenes together facilitate the proliferation and survival of cancers [35].

3.3.2 Interplay Between EGFR/Her2 and the Immunosuppressive TME

Through tumor-derived exosomes (TEXs), cancer cells are able to transfer activated EGFR to host macrophages and thereby suppress innate antiviral immunity assessed by measuring interferon-β (IFNβ). EGFR is required for TEX-mediated immunosuppression, kinase MEKK2 is identified in macrophages as an effecter of TEX-delivered EGFR that negatively regulates the antiviral immune responses [47]. Macrophage inhibitory cytokine-1 (MIC-1) in the TME can inhibit the secretion of TNF-α, reducing tumor killing of macrophages [48]. MIC-1 induced transactivation of HER2 in breast cancer and GAC cells, and induced significant phosphorylation of AKT and ERK-1/2. siRNA-mediated downregulation of HER2 significantly reduced not only phosphorylation of AKT and ERK-1/2 but also invasiveness of cells induced by MIC-1. MIC-1 induced expression of HIF-1α and its target VEGF, via the activation of the mTOR signaling. Thus, MIC-1 may participate in the malignant progression of cancer cells that overexpress HER2 [49].

Trastuzumab has been the mainstay of therapy for HER2+ breast cancer and GAC through antibody-dependent cellular phagocytosis (ADCP) [50, 51]. It was unexpectedly realized that after ADCP macrophages inhibited NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC) and T cell-mediated cytotoxicity in breast cancers and lymphomas. Combined treatment with anti-HER2 antibody and inhibitors of PD-L1 and IDO (indoleamine 2,3-dioxygenase) enhanced antitumor immunity and anti-HER2 therapeutic efficacy in the mouse models. Trastuzumab therapy has
significantly upregulated PD-L1 and IDO in the TAMs of HER2+ breast cancer samples, correlating with poor trastuzumab response. It is unveiled a deleterious role of ADCP macrophages in cancer immunosuppression and suggested that oncogene-directed antibody plus immune checkpoint blockade may provide synergistic effects against cancer [51].

It was reported that the endosomal sorting complexes required for transport (ESCRT)-associated protein ALIX as a regulator of both EGFR activity and PD-L1 surface presentation in basal-like breast cancer (BLBC) cells. ALIX-deficient tumors were larger and showed an increased immunosuppressive environment by induced EGFR activity and redistribution of PDL-1 to the cell surface [52]. VEGF-, HER2- and EGFR-targeted agents are sometimes used to treat gastric, esophageal, and colorectal cancers. However, treatment outcomes are poor in most gastrointestinal (GI) cancers, antibodies such as targeting immune checkpoints anti- PD-1 (nivolumab and pembrolizumab) and PD-L1 (atezolizumab) therapies have not done well in general [53]. Interplay between oncogenes EGFR/HER2 and their immunosuppression is illustrated in Figure 1B.

3.4 PI3K/mTOR

The PI3K/mTOR pathway is an intracellular signaling pathway important in regulating the cell cycle involving AKT and PI3K which phosphorylates and activates their downstream signaling. The mammalian target of rapamycin (mTOR), a mechanistic target of rapamycin, is a kinase, which has core component of two distinct protein complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) which regulate different cellular processes. mTOR regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, autophagy, and transcription.

3.4.1 PI3K/mTOR and Target Strategies

As previously mentioned, activation of PI3K/mTOR mediated resistance of trastuzumab in GAC cell lines with HER2 amplification/over-expression. Thus, inhibition of mTOR/S6K using everolimus may be attractive alternative [43]. In gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs), PKI-587 is a highly potent, novel dual inhibitor of PI3K and mTORC1/C2, with dose-dependent inhibition of proliferation. In all cell lines treated with PKI-587, all led to cell cycle arrest and induction of apoptosis and successfully suppressed activity of mTORC1 target 4E-BP1, a crucial factor for tumorigenesis. PI3K/mTOR dual targeting showed promising new therapeutic approach in neuroendocrine tumor [54].

Inhibition of mTORC1 with mTOR inhibitor rapamycin may lead to an induction of AKT phosphorylation in cancer cells via mTORC2 activation paradoxically. A study found that rapamycin additionally up-regulated both insulin-like growth factor 1 receptor (IGF-IR) and HER2 expression. mTORC2 inhibition reduced the phosphorylation of GSK-3 and NFkB, and significantly impaired cancer cell motility. Inhibition of mTORC2 may abrogate unfavorable signaling effects of mTOR inhibitors [55]. Rapamycin-insensitive companion of mTOR (RICTOR) amplification defines a subset of advanced GAC and is sensitive to AZD2014-mediated mTORC1/2 inhibition. Treatment of RICTOR amplified patient-derived cells with selective drugs targeting AKT, mTORC1/2 demonstrated preferential sensitivity to the mTORC1/2 inhibitor (AZD2014). Knockdown of RICTOR reversed patient-derived cells’ sensitivity to AZD2014, validating the importance of RICTOR amplification in solid tumors including GAC [56]. Activation of IGF-IR signaling is implicated in tumor cell mobility of various cancers, including GAC [57].
3.4.2 Interplay Between PI3K/mTOR and the Immunosuppressive TME

Tumor associated macrophages (TAMs) are the main regulatory cell type in the TME. The fatty acid enriched tumor environment itself was sufficient to induce the regulatory phenotype of TAMs, including the up-regulation of classical markers like CD206, IL-6, VEGFα, MMP9 or Arg1. mTORC2 activation played a critical role in the generation of the suppressive myeloid cell phenotype. Cell-specific inhibition of DGAT1 and 2 prevented oleate-induced polarization into immunosuppressive TAMs [58]. GAC mesenchymal stem cells (MSCs) derived IL-8 induced PD-L1 expression in GAC cells via STAT3/mTOR-Myc signal axis. MSCs exerted broad immunosuppressive potential, modulating the activity of cells either in the innate or adaptive immune system to promote tumor progression. MSCs enhanced PD-L1 expression in GAC cells resulting in resistance of GAC cells to CD8+ T cells cytotoxicity. The study proved that IL-8 derived from MSCs induced PD-L1 expression in GAC cells via Myc regulated by STAT3 and mTOR signaling pathways [59].

Chemokine CXCL12 is a small protein that functions in normal hematopoietic stem cell homing in addition to repair of damaged tissues through its receptor CXCR4. CXCR4 plays an important role in metastatic progression and destination. CXCL12 activation induced phosphorylation of AKT, and then phosphorylated mTOR (pS6K and 4E-BP1) in disseminated GAC cells [60]. CXCL12/CXCR4 activated the PI3K/AKT/mTOR pathway in GAC line MKN-45. Rapamycin inhibited secretion/expression of CXCL12/CXCR4. The mTOR pathway played an important role in CXCL12/CXCR4-mediated cell migration, and drugs targeting the mTOR pathway can be used for therapy of GAC expressing high levels of CXCL12 [61]. Binding of CXCL12 to CXCR4 led to activation P13K/mTOR and MEK/ERK while binding to CXCR7 leads to β-arrestin mediated signaling, leading to anti-apoptotic signaling Bcl-2 and survivin upregulation, and promoting the EMT. A CXCR4 antagonist AMD3100 (plerixafor or Mozobil), is the most frequently used drug targeting the CXCL12-CXCR4/CXCR7 axis for GI cancers. Thus, the CXCL12-CXCR4/CXCR7 axis acts as a mechanism of immune resistance in GI cancers. [62]. GI cancers are frequently associated with chronic inflammation and excessive secretion of IL-6 family cytokines, which promote tumorigenesis through persistent activation of the GP130/JAK/STAT3 pathway. A parallel pathway that activated excessive mTORC1 alongside STAT3 in human intestinal-type GACs. Activation of GP130-dependent mTORC1 is required for inflammation-associated GI tumorigenesis [63]. The interplay between PI3K/mTOR signaling and TME is shown in Figure 1C.
Figure 1 Interplay between oncogenes and their immunosuppressive TME. A. Ras/Myc mediated interplay. Bacterial virulence factors CagA/VacA turn on a plethora of oncogenes Ras, Wnt/β-catenin, Myc, NFkB, PI3K/mTOR, MAPK, elicit multiple pro-inflammatory cytokines IL-1β, IL-6, IL-8, TNFα, INFγ1, MCP1 to cause epithelial mucosa inflammation and mucosal damage, with persistent bacterial infection and oncogenic KRas and Myc driving and cytokine CCL9, IL-23 secretion, tumorigenesis and cancer proliferation proceed. Other factors, such as cancer stem cell associated Eras, tumor-associated PD-L1 with help of mutated ARID1 and KRas and MSI-H, all drive GC tumorigenesis and proliferation. B. EGFR/HER2 mediated interplay. Tumor-associated M2 Mφ secreted cytokine MIC-1 and turned on many oncogenes, HER2, HIF1, VEGF, mTOR, AKT and ERK, to cause tumorigenesis. By ADCP, M2 Mφ induced cell checkpoint ligand PD-L1/IDO and secrets IL-1β that results in cancer immunosuppression. Exosome TEXs recruit M2 Mφ and turn on EGFR/MEEK2 to promote tumor cells self-renewal, tumorigenesis and proliferation, suppressing innate antiviral immunity. C. PI3K/mTOR pathways: bacterial virulence factor CagA turned on PI3K and AKT. PI3K and its direct target mTOR (including components mTORC1/2) interact a host of other oncogenes STAT3, Myc, VEGFα, HER2, MMP9, Arg1, NFkB, AKT to promote gastric tumorigenesis and proliferation. AKT was proved to regulate mTOR. Second, rapamycin inhibits mTOR, thus suppresses gastric cancer progression, but rapamycin induces IGF-IR and HER2 paradoxically, impairs cancer cell motility. Third, gastric cancer MSC stem cells-derived IL-8 inducing PD-L1 modulates the activity of cells either in innate or adaptive immune system to promote tumor progress. ERas expressed in human GC exert chemoresistance. TAMs in tumor stroma upregulated many oncogenes.
3.5 Wnt/β-catenin

Wnt proteins are cysteine-rich glycoproteins that bind to the extracellular domain of frizzled receptor and lipoprotein receptor-related protein. Wnt/β-catenin signaling is an evolutionarily conserved pathway that is known to be involved in embryonic development and tissue homeostasis. An aberrant activation of this pathway with accumulation of β-catenin, a core protein, in the nucleus promotes the transcription of many oncogenes [64].

3.5.1 Wnt/β-catenin and Oncogenic Interplay

In GAC, two signaling pathways, Wnt/β-catenin and NFκB, are dysregulated in 70% of GAC patients. H. pylori’s virulence factor CagA interacts with E-cadherin, leading to β-catenin accumulation in cytoplasm and nucleus. The overexpression of Wnt2 is correlated with cytoplasmic/nuclear β-catenin accumulation in GAC in Chinese patients. The expression of Wnt2 was positively correlated with lymph node metastases [6]. Activation of Wnt/β-catenin signaling has been important in GI tumorigenesis. It has been suggested that the promotion of Wnt/β-catenin activity beyond the threshold is important for carcinogenesis [65]. As core protein, nuclear β-catenin in Wnt pathway activates many oncogenes such as Myc and CyclinD1 [64]. Figure 2A illustrates the interplay among Wnt/β-catenin signaling, other oncogenes, and related immunosuppressive stroma.

3.5.2 Interplay Between Wnt/β-catenin and the Immunosuppressive Stroma

Macrophages promote Wnt/β-catenin activity in gastric tumorigenesis in mouse stomach and GAC cells [65]. Macrophage-derived TNFα activates Wnt/β-Catenin during GI cancer development, mutated tumor suppressor APC (APCΔ716) sustains Wnt/β-catenin expression. With other factors such as H. pylori infection, macrophages produce TNFα, promotes nuclear accumulation of β-catenin via AKT and GSK3β in neoplastic epithelial cells. This process can be exasperated by production of Wnt ligands by stromal cells that bind frizzled receptors, leading to inhibition of the β-catenin degradation complex (APC, AXIN, GSK3b) [66]. A drug lupeol does not exhibit toxicity to normal cells and tissues but was noted to inhibit the proliferation of GAC cells in a dose-dependent manner and induced proliferation of NK cells in GAC cell lines. The possible mechanism is that lupeol might increase expression of PFP, IFNγ, and CD107a via activation of PI3K/AKT and Wnt/β-catenin signaling [67]. In a study, β-catenin demonstrated its immunosuppressive role in GAC through a β-catenin-CCL28-Treg cell axis, clarifying an important mechanism for immunosuppression. Expression of β-catenin directly activated its target CCL28 which recruited Tregs. In a clinically relevant mouse GC model established by bacterium H. felis infection and N-methyl-N-nitrosourea (MNU) treatment, inhibition of β-catenin/TCF activity suppressed CCL28 expression and Treg cell infiltration in the stomach, and anti-CCL28 antibody attenuated Treg cell infiltration and tumor progression. Diphtheria toxin-induced Treg cell ablation restrained GAC progression in mice, clarifying the tumor-promoting role of Tregs [68].

Early studies proved TNFα as an immune regulator in GAC. One study revealed that TNFα induced up-regulation of Wnt10A in GAC cell lines in the same fashion as H. pylori [69]; Wnt10B is up-regulated by TNFα in human GAC cell line MKN45 [70]; Expression and regulation of Wnt5A by TNFα in MKN45 Cells was reported [71]. H. pylori’s CagA dysregulates and activates Wnt/β-catenin [6], the active CagA activates multiple pathways including Wnt/β-catenin among others in stomach
epithelial cells into production of inflammatory cytokines, such as IL-1β, IL-6, IL-8, TNFα, INF-γ and MCP-1 [22]. A mouse study used steroid analog for osteoporosis, bazedoxifene, to suppress GP130-dependent tumor growth of the GI epithelium, where tumors arose through excessive GP130/STAT3 signaling in response to cytokine IL-11 [72]. Using conditionally replicating adenoviral vectors (CRAds) which integrated an adenoviral E1A gene and apoptosis-inducing gene IL-24 inhibited proliferation and tumor growth in mouse GAC xenografts, which were with β-catenin mutation status or aberrant Wnt signaling [73]. IL-24 is unusual in that a cytokine exhibits tumor suppressor property.

Bone morphogenetic protein and activin membrane-bound inhibitor (BAMBI) has been confirmed as a transmembrane glycoprotein and is a member of immune checkpoint TGF-β family. Knockdown of BAMBI in aggressive GAC cell lines significantly inhibited cell invasion and proliferation. β-catenin expression was downregulated as a result of BAMBI knockdown, and TGF-β was downregulated in a similar manner [74]. TGF-β1 works with immunity Treg to promote cancer stem marker leucine-rich repeat containing G protein-coupled receptor 5 (Lgr5), leading to Wnt/β-catenin upregulation in GAC [75].

3.5.3 Wnt/β-catenin, Cancer Stem Cells (CSC) and Immunosuppression

*H. pylori’s* VacA induces Wnt/β-catenin signaling, promotes CSC properties in GAC cells and cell proliferating [6]. Cancer cell stemness together with oncogenic Wnt/β-catenin expression sustained GAC progression and drug resistance. SALL4, an embryonic stem cell marker, has a direct interaction with Wnt signaling, its overexpression is correlated with lymph node metastases in GAC [6]. A study demonstrated expression of transglutaminase-1 (TGM1) was upregulated in GAC, and that TGM1 expression levels were correlated with patient survival, which promotes stemness and chemoresistance in GAC cells by regulating Wnt/β-catenin signaling [76]. In another study, Lgr5 was examined in 180 GACs by immunohistochemistry (IHC), and in 80 pairs of GACs for analysis of Th1/Th2 (T helper cells) cytokines. Lgr5 expression was up-regulated in GAC cells co-cultured with Tregs or treated with exogenous TGF-β1. This up-regulation was partially inhibited by the TGF-β1 neutralizing antibody, or TGF-β1 receptor antagonist. β-catenin was up-regulated with high Lgr5 expression induced by exogenous TGF-β1, and this up-regulation was inhibited by TGF-β1 receptor antagonist. Thus, Tregs and TGF-β1 promoted CSC marker Lgr5, led to Wnt/β-catenin upregulation, all interplayed and conferred poor prognosis [75].

By generating mouse GAC cell line and comparing its metastatic variant, stem cells antigen-1 (Sca-1) was identified as a cell surface marker, which was mostly upregulated in metastatic variant, Sca-1-high mouse GAC cells demonstrated increased tumorigenicity. Sca-1 expression was downregulated by TGF-β pathway activation and Wnt/β-catenin pathway inhibition. A chromatin immunoprecipitation (ChIP) analysis demonstrated that Sca-1 was a β-catenin/LEF1 target gene. Sca-1-high allografts were more resistant to cisplatin/fluorouracil chemotherapy and overexpressed Bcl-xL. Sca-1 is a novel CSC enrichment marker that mediates TGF-β and Wnt/β-catenin signaling [77].

A study proved that human GAC cells subvert gene expression and cytokine production by reprogramming of "naive" MSCs into specialized tumor associated MSC equipped with a tumor-promoting phenotype for the MSC-mediated support of cancer stemness in GAC. CSC properties are sustained *in vivo* through an interplay between GAC and tumor associated MSC by activating the R-
spondin/Lgr5 axis and Wnt/β-catenin signaling pathway. β-Catenin+ cell clusters show β-catenin nuclear localization, indicating the activation of the Wnt/β-catenin signaling pathway in these cells [78].

3.6 Hippo/YAP1

The Hippo pathway and its coactivator YAP1 is an essential pathway that regulates cell proliferation, apoptosis, organ growth, and homeostasis of the GI tissues. This pathway is highly conserved in mammals [79]. Dysregulation of Hippo pathway is associated with initiation, development, and distant metastases [6, 80-84]. YAP1 is frequently elevated in a number of cancer types such as lung, colorectal, ovarian, liver, and prostate cancers, where it acts as a powerful tumor promoter for tumor progression [85].

3.6.1 Hippo/YAP1 and Oncogenic Interplay

An early study by using integrative genomic analyses of Wnt5A revealed that Snail, CD44, G3BP2 and YAP1 are Wnt5A target genes [86]. Fat4 functions as a Hippo signaling regulator, loss of Fat4 due to gene mutation was detected in a variety of tumors including GAC, thus Fat4 was recognized as a tumor suppressor. By silencing Fat4 using shRNA in GAC cells, Fat4 suppression led to the increase in phosphorylated YAP1 (p-YAP) and YAP1 nuclear accumulation. Transfection of a full-length Fat4 downregulated p-YAP1 and inhibition of the cell cycle progression. Intriguingly, Fat4 reduction also leads to accumulation of cytoplasmic β-catenin. Fat4-silenced cells treated with 5-FU, cisplatin, oxaliplatin and paclitaxel individually demonstrated less sensitivities to these drugs. IHC analysis revealed that Fat4 expression was significantly reduced in GAC tissues [87]. Large tumor suppressor 1 (LATS1) being part of the Hippo pathway plays important role for cellular homeostasis. Loss of LATS1 promotes growth and metastases of GAC cells through YAP1 upregulation. Overexpression of LATS1 decreased GAC cell proliferation and invasion in vitro and inhibited tumor growth and liver metastases in mice; depletion of LATS1 expression restored the invasive phenotype. The Hippo/YAP pathway was required for LATS1-induced inhibition of cell growth and invasion, and LATS1 abated nuclear transfer of YAP1, downregulated YAP1, PCNA, CTGF, MMP-2, MMP-9, Bcl-2 and CyclinD1 expression and upregulated p-YAP and Bax expression. The finding proved that LATS1 is a tumor suppressor and inhibits the growth and metastases of GAC cells through YAP1 downregulation [88]. A drug verteporfin impaired YAP1 and TEAD interaction to suppress the expression of downstream targets in pancreatic cancer [89]. Figure 2B illustrates the interplay among Hippo/YAP1, other oncogenes and the immunosuppressive microenvironment.

3.6.2 Hippo/YAP1 and Cancer Stem Cells

ALDH1 is a CSC marker in many different tumor tissues. Inducible YAP1 expression in esophageal cancer cells increased ALDH1+ cells, double (ALDH1+/CD44+) positive cells, and greatly increased tumor-sphere numbers and size; conversely, YAP1 knockdown decreased ALDH1+ cells and double (ALDH1+/CD44+) positive cells, leading to significant reduction of tumor-sphere size and number, which indicated that YAP1 in esophageal cancer cells endowed tumor cells with CSC properties [83]. YAP1 was highly upregulated in peritoneal carcinomatosis (PC cells or malignant ascites), conferred CSC properties and appeared to be a metastatic driver. YAP1 expression significantly correlates with
CSC genes such as Sox9, Hes1, Prom1 (CD133) and Itga6 (CD49f) [84]. Sox9 is a CSC marker in GI tract and a YAP1 target gene that controls CSC features in esophageal cancer [83]. Hes1, a Notch signaling target, has been reported to regulate CSC features in the GI tract. CD133 and CD49f are reported CSC markers in many tumor types. YAP1 expression is correlated with the proportion of ALDH1+ cells in PC specimens. CyTOF (mass cytometry by time of flight) analyses further revealed that YAP1 expression is highly associated with ALDH1, Hes1, CD133, and CD49f suggesting that high expression of YAP1 correlates with a CSC signature in PC [84].

3.6.3 Interplay Between Hippo/YAP1 and the Immunosuppressive Stroma

An innate antiviral immunity gene, the interferon regulatory transcription factor 3 (IRF3) is essential for innate immunity against viral infection and cancer, its expression is positively correlated with YAP1 and its target genes in GAC. IRF3 interacts with both YAP1 and TEAD4 by co-binding in the nucleus to enhance their interaction, promoting nuclear translocation, and activation of YAP1. Knockdown or pharmacological targeting of IRF3 by amlexanox, a drug used clinically for anti-inflammatory treatment, inhibits GAC growth in a YAP-dependent manner. Therefore, IRF3 is identified as a positive regulator for YAP1 [90] Shibata et al. (2018) presented review of the Hippo/YAP1 pathway on tumorigenesis and immunosuppression in TME [79]. YAP1 and its paralog TAZ act as transcriptional coactivators with TEADs to mediate this pathway. YAP1 in cancer cells upregulates cytokines and chemokines TNFα, IL6, CSF1-3, CXCL5, CCL2, CSF1 that are associated with recruitment of M2 Mφ, Tregs and MDSCs (myeloid-derived suppressor cells) and inhibition of NK cells [79]. Tregs suppress antitumor immunity and can be induced by malignant cells [91].

A study reported that YAP1 is essential for Treg-mediated suppression of antitumor immunity. FOXP3 is a transcription factor expressed in Tregs that is required for its function. It was discovered that YAP1 upregulates activin signaling, and amplifies TGF-β/SMAD activation, bolsters FOXP3 expression and Treg function. YAP1 deficiency resulted in dysfunctional Tregs unable to suppress antitumor immunity or promote tumor growth in mice. Chemical YAP1 antagonism and knockout or blockade of the YAP1-regulated activin receptor similarly improved antitumor immunity. It was concluded that YAP1 as an unexpected amplifier of Treg-reinforcing pathway with significant potential being an anticancer immunotherapeutic target [85].

Another study revealed that YAP1 displays nuclear translocation and works with TEAD to activate transcription of the crucial inflammatory cytokine IL-1β in GACs infected with H. pylori. As IL-1β accounts for inflammation-associated tumorigenesis, this process leads to gastric carcinogenesis. YAP1 plays a major role in inflammation amplification by activating inflammatory cytokine genes, YAP1’s coactivator TEAD binds to IL-1β promoter thus directly regulates IL-1β transcription. Deleting IL-1β by siRNA partially neutralized YAP’s ability to promote proliferation [92]. It has been identified hyperactivated Hippo/YAP1 drives CXCL5 upregulation in cancer cells through YAP/TEAD complex and promoting MDSC recruitment, and the latter is via heterotypic CXCL5-CXCR2 signaling [93]. Studies in glioblastoma multiforme (GBM) models established that PTEN deficiency activates YAP1, which directly upregulates lysyl oxidase (LOX) expression. LOX functions as a potent macrophage chemoattractant. These infiltrating macrophages secrete SPP1 and then sustains glioma cell survival and stimulates angiogenesis. This symbiotic glioma-macrophage interplay provides potential therapeutic targets [94].
Figure 2 Interplay between oncogenes and the tumor-immune interactions mediated by Wnt/β-catenin and Hippo/YAP1 signaling. A. Interplay mediated by Wnt/β-catenin signaling. Bacterial CagA/VacA turn on β-catenin and suppress CDH-1, driving β-catenin/LEF/TCF axis signals, like Wnt5A/10A/10B turned on β-catenin. M2 Mφ secretes TNFα and with help of mutated APC turns on Wnt/β-catenin, resulting in neoplastic epithelial cells. Second, cancer stem cell associated SALL4 acts through Wnt/β-catenin to cause lymph node metastasis. Cancer stem cell associated TGM1 and activated Sca1 promote gastric tumor self-renewal and proliferation. Ligand Lgr5 in Treg cells secreted CCL28 promoted Treg cells self-renewal and Wnt/β-catenin activation. TGF-β1 and chemokine CCL28 works with Tregs to promote cancer stem marker Lgr5. Notably tumor stromal cells block β-catenin degradation complex that increases β-catenin and promotes gastric tumorigenesis. B. Crosstalk of Hippo/YAP pathway and TME. Tumor suppressors FAT1/4 and LATS1/2 keeps delicate balance in suppressing YAP1 activation. YAP1 binds co-transactivators Tead1/2/3/4 to turn on some oncogenic genes, Sox6, Cyr61, CTGF, Birc5 etc., some of which act as stem cell markers, such as Sox9, ALDH1 and CD44, which recruit tumor cells-associated M2 Mφ and Tregs to amplify those CSC markers. Tumor secretes cytokines CCL2 and CSF1 to stimulate M2 Mφ, that autocrine feedback augments the process of tumorigenesis and cancer proliferation. Again H. pylori’s CagA induces YAP1, and Tead binds IL-1β promoter, which turns on IL-1β transcription in a positive feedback, exacerbating gastric cancerogenesis.
4. Conclusions

Cancers in multicellular organisms are believed to be caused by accumulated genetic alterations with activated oncogenes and/or inactivated tumor suppressor genes. Mutated or highly expressed oncogenes derived from normal functional proto-oncogenes are literally the cancer-causing genes. Oncogenes are activated either by viruses or bacteria or other environmental factors, epigenetics and cross-talks with other oncogenic pathways and interplay with cancer stroma to play immunosuppressive functions to further facilitate tumor growth and metastases. In this review, we illustrated the key oncogenes including Ras/Myc, EGFR/HER2, PI3K/mTOR, Wnt/β-catenin and Hippo/YAP1 focusing on their interactions with each other and their immunosuppressive stroma to promote tumorigenesis, proliferation and cancer metastases, focusing on GAC. New therapeutic strategies should target both oncogenes and the immune suppressive stroma activated as mentioned in this review.

Abbreviations

CSC: cancer stem cell; EMT: epithelial-mesenchymal transition; FDA: U.S. Food and Drug Administration; GC: gastric cancer; GAC: gastric adenocarcinoma; GEC: gastroesophageal cancer; GI: gastrointestinal; HGFR: hepatocyte growth factor receptor; IHC: immunohistochemistry; IL: interleukin; IncRNA: long noncoding RNA; MALT: mucosa-associated lymphoid tissue lymphoma; MDSC: myeloid-derived suppressor cells; MSI: Microsatellite instability; NK cell: natural killer cell; PC: peritoneal carcinomatosis; TME: tumor microenvironment; Treg: regulatory T-cell; NRF2: nuclear factor E2-related factor 2; LEDGF: transcriptional co-activator lens epithelium-derived growth factor; TAM: Tumor associated macrophage.

Author Contributions

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Competing Interests

No potential conflicts of interest were disclosed by all authors.
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