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Gastric Cancer: Molecular and Clinical Dimensions

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Abstract

Gastric cancer (GC) imposes a significant health burden around the globe despite its declining incidence. GC is often diagnosed in advanced stages and carries a poor prognosis. In depth understanding of molecular underpinnings of GC has lagged behind many other cancers of its magnitude, as a result our knowledge base for identifying germline susceptibility traits for risk and somatic drivers of progression (to identify novel therapeutic targets) is limited. A few germline (*PLCE1*) and somatic (*ERBB2, ERBB3, PTEN, PI3K/AKT/mTOR, FGF, TP53, CDH1, and c-MET*) alterations are emerging and some are being pursued in the clinic. Novel somatic gene targets, *Arid1a, FAT4, and MLL/MLL3* are of interest. Clinically, variations in the therapeutic approaches for localized GC are evident by geographic regions. These are driven by preferences for the adjunctive strategies and the extent of surgery coupled with philosophical divides. However, there is a greater uniformity in approaches to metastatic cancer, an incurable condition. Having realized only modest successes, the momentum is building for carrying out more phase 3 comparative trials and some are using biomarker-based patient selection. Overall, rapid progress in biotechnology is improving our molecular understanding and can help with new drug discovery. The future prospects are excellent for defining biomarker-based subsets of patients and application of specific therapeutics. However, many challenges remain to be tackled. Here we review representative molecular and clinical dimensions of GC.

Review

The objective of this review is to adequately highlight advances in molecular and clinical arenas that reflect the current understanding and it is intentionally not encyclopedic. Details of preventive strategies, impact of new classifications, and nuances of surgery and radiation therapeutics are beyond the scope of this review.

1. Epidemiology

Globally, the incidence of GC ranks 4th in men and 5th in women, but its death rate is next to lung cancer.[1] In 2008, there were ~989,600 (8% of all cancers) new GC cases worldwide and 738,000 (10% of all cancer deaths) deaths. 70% of deaths occurred in the developing

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regions with China having ~40% of them.[1] The endemic regions are in Asia, Eastern Europe and South America. The incidence of GC has declined over time,[2] due to improving living standards.[2–5] The exemplary early detection strategy has reduced the GC death rate in Japan.[6] *Helicobacter pylori* (*HP*) infection as a risk factor is of importance for preventive strategies.[7]

2. Risk factors

Risk factors include old age, smoking, alcohol, above normal body weight, high salt and or fat consumption, low vegetables and fruits consumption, low economic status, pernicious anemia, other chronic gastric diseases, and *HP* infection.[5,8] Of these risk factors, the biology of *HP* is fascinating (Figure 1).

HP infection increases the risk 3–6 fold[9] and is more associated with distal GC and intestinal histologic phenotype.[10] Chronic active gastritis is an integral part of *HP*-related GC.[10,11] *HP*'s attachment to gastric epithelial cells leads to inflammation and an increase in the reactive oxygen or nitrogen species causing tissue damage.[12,13] CagA, an oncoprotein, producing *HP* species are carcinogenic.[11,14,15] CagA is encoded by *cag* PAI and is translocated by *HP* into the host epithelial cytosol.[14,16] Phosphorylated CagA (by Src and c-Abl kinases),[17,18] forms a complex with the SRC homology 2-domain (SH2)-containing tyrosine phosphatase SHP-2 in a phosphorylation-dependent manner, resulting in cytoskeletal reorganization that can induce cell transformation to GC.[19] CagA activates the ERK/MAP kinase cascade, resulting in Elk-1 phosphorylation and increased c-fos transcription.[20] In addition, CagA promotes invasion through activation of hepatocyte growth factor/scatter factor receptor c-MET.[21] Its induction of Toll-like receptors (TLRs) leads to proliferation.[22] CagA induces E-cadherin-mediated impairment of cell adhesion junctions leading to cytoplasmic and nuclear accumulations of β-catenin.[23] CagA binds Crk adaptor proteins (Crk-II, Crk-I, and Crk-L)[24] and kinase PAR1,[25] eliciting loss of cell polarity. CagA stimulates cytokines IL-8, IL-1 and TNF-alpha[26–28] through NF-kB in epithelium.[29] Pro-inflammatory IL-1 gene cluster polymorphisms (IL-1B, encoding IL-1B and IL-IRN, and its receptor antagonist) increase the risk of non-cardia GC.[30,31] CagA also upregulates cyclo-oxygenase-2 (COX-2)[26,32] that is overexpressed in GC. COX-2 induced prostaglandins are oncogenic.[33,34] *HP* alters the Fas-associated factor 1 (FAF1) that promotes apoptosis but it is reduced in GC.[35] *HP* also mediates increases in another oncoprotein, aquaporin 3 (AQP3).[36]

HP alters DNA methylation of E-cadherin (*CDH1*), an oncogenic event.[37,38] *HP* promotes methylation of tumor suppressor *TFF2*[39] and *RUNX3*[40] and likely 6 other tumor suppressors (*FLNc*, *HAND1*, *THBD*, *p41ARC*, *HRASLs* and *LOX*).[41] It would appear that *HP* is clearly carcinogenic but in susceptible individuals.

3. Single nucleotide polymorphisms (SNP) and Genome-wide association studies (GWAS)

Genetic susceptibility can be critical, for example, all endemic areas have high prevalence of *HP* but have few GC cases.[42] Rare germline mutations in *CDH-1* lead to familial GC.[43,44] SNPs can facilitate GC but one adverse allele may be a weak contributor, however, multiple adverse alleles can increase the risk.[45] Prior SNP investigation have focused on genes involved in mucosal protection against *HP* (e.g., *IL1B*, *IL1RN*, and *TNF-α*), carcinogen metabolism (e.g., *CYP2E1* and *GSTM1*), deoxynucleotide synthesis, DNA repair (e.g., *MTHFR* and *XRCC1*), and tumor suppressors (e.g., *TP53* and *CDH1*). However, these have had limited yield and none can be used clinically.

GWAS can scan the whole genome for implicating SNPs. A Japanese group documented that *PSCA* was associated with diffuse GC.[46] They genotyped 188 cases and 752 controls

for 85,576 SNPs and then replicated in 749 cases and 750 controls for 2,753 SNPs. The intronic rs2976392 SNP in *PSCA* was identified as the risk allele and the SNP was in diseuilibrium with rs2294008 located in exon 1. The second study included 1,077 esophageal cancer cases and 1,733 controls leading to 18 hits that were validated in 2,766 cases of cardia GC and *PLCE1*rs2274223 and *C20orf54* rs1304295 SNPs were associated with GC risk.[47] The third study included 2,240 GC cases and 3,302 controls and identified the *PLCE1*rs2274223 SNP as a risk allele for cardia GC.[48] *PLCE1* SNPs were associated with GC risk,[49,50] and prognosis of Chinese patients[51] but not Caucasian patients.[52] The fourth GWAS in China included 1,006 cases and 2,273 controls and replicated in 3,288 cases and 3,069 controls; SNP rs13361707 located between *PTGER4* and *PRKAA1* and the *ZBTB20* rs9841504SNP were associated with risk.[53] Table 1 sumerizes the current GWAS results. Clearly, we have a long way to go.

GWASs have identified previously unknown genes, for example, the *PLCE1* is not known to be involved in GC, but its oncogenic role in skin and intestine is reported.[47]

4. Gastric cancer stem cells (GCSCs) and Aberrant signaling pathways (Figure 2)

Gastric carcinogenesis is complex and not fully characterized.[54] Although, intestinal GC (IGC) develops after systematic progression from the pre-neoplastic stages, diffuse GC (DGC) is thought to arise *de novo* as the result of downregulation (mutation or promoter methylation) of *CDH1*,[55,56] thereby permitting tumorigenesis and progression. Nevertheless, accumulated genetic alterations (mutations, amplifications, insertions, deletions, and or recombinations) lead to GC.[57,58] More alterations accumulate as GC progresses. Cancer is hierarchically organized with ample plasticity. There is increasing evidence for the existence of GCSC to initiate tumor by self-renewal and differentiation. The origin of human GCSCs is still unclear, but may be the mesenchymal stem cells in bone marrow.[59,60]

CSCs can undergo epithelial mesenchymal transition (EMT), activate oncogenic pathways[61] and embryogenesis signaling pathways[62] essential for self renewal and maintenance. The combination of EMT, CSC, and drug resistance forms the axis of evil.[63] EMT leads to the CSC-like phenotype.[64] CSCs depend on the Wnt, Notch, and Hedgehog (Hh) pathways.[65] Four pleiotropic transcriptional factors (Snail, Slug, Twist, and Zeb1/2) orchestrate the EMT and related processes.[66] c-MET and TGF-β signaling can be critical for EMT. c-MET activation can induce the reprogramming transcription factors known to support embryonic stem cells and induce differentiated cells to form the pluripotent stem (iPS) cells.[67]

TGFβ can be pro-oncogenic by inducing matrix deposition, immunosuppression, and EMT.[68–70] TGF-β signaling drives EMT and CSC self-renewal mediated by targeting microRNAs,[66] upregulating Snail family members, and repression of E-cadherin.[63] Downstream of c-MET and TGF-β receptor, PI3K/Akt/mTOR signaling conveys pro-survival messages for CSC expansion and maintenance.[71] There has been interest in targeting mTOR with metformin to inhibit CSCs.[72] Ras and Hh help maintain CSCs.[73,74] GCSCs express CD133, CD44, ALDH1 (aldehyde dehydrogenase 1) and ABCG2 (ATP-binding cassette sub-family G member 2); CD44 and ALDH are associated with therapy resistance and can be exploited therapeutically upon understanding the underlying mechanisms.[75]

Members of the human epidermal receptor (HER) family have been of interest.[76] Oncogenic properties are conferred through the RAS/MEK/MAPK and PI3K/Akt/mTOR pathways.[77,78]. Overexpression of HER2 is due to *HER2* amplification and this is more prevalent in IGC than DGC. [79,80]

HER2 interacts with EGFR, HER3[81], and IGF1R.[82] These genes are amplified and/or overexpressed[83,84] or acquire activating mutations.[85–87]

Constitutive activation of c-MET triggers proliferation and anti-apoptotic signals.[88] Amplification/overexpression of c-MET rather than mutated gene can activate receptor tyrosine kinase.[89,90] c-MET overexpression/amplification is more common in IGC[91,92] but its amplification has been reported in DGC cells.[93]. Amplified c-MET cross talk can activate EGFR, HER2, and HER3 to establish a signaling network leading to constitutive PI3K/AKT signaling.[94–96] GCs with c-MET overexpression coexpress EGFR, HER-3, or both;[97] clinically relevant for the dual inhibition strategies.[93,96,97]

PI3K/AKT/mTOR pathway is frequently altered as a results of amplification or overexpression (PIK3CA, Akt1), activating mutations (*PIK3CA*)[55,98] of components, or loss of *PTEN*.[99] Overexpression of phospho-mTOR can occur in DGC.[55] HER3 and FGFR amplification in DGC is another mechanism for PI3K/Akt activation.[100,101]

TGFβ is overexpressed in DGC[102] and it stimulates collagen synthesis and subsequent fibrosis. TGFβ can be anti-apoptotic through transactivation of EGFR.[103] The bone morphogenetic proteins (BMPs), members of TGF-β superfamily activate PI3K/Akt.[104] There has been considerable interest in the inhibition of angiogenesis. In that regard, VEGF and VEGFR overexpression is common in IGC through activation of NFκB by *HP*. [105,106]

While *HERs, c-MET, PI3K/AKT/mTOR, VEGFRs, VEGF* have been targeted, *TGFβ* and *CDH1* are not targetable. There are also several novel targets worth mentioning. Chromatin modifiers such as *ARID1A, MLL3, MLL*, and *FAT4* (cell adhesion) are of increasing interest and importance.[107,108]

While some efforts have been made to genotype IGC and DGC (and identify novel subtypes)[109–120], clinically relevant and robust molecular subtypes have yet to emerge. IGC and DGC genotypes in one study[121] resulted in homogeneity in response to therapy than did the phenotypes.

5. MicroRNAs

miRNAs play a role in tumorigenesis, tumor progression, and metastasis. Here we update (Figure 3) our recent review.[122] Oncogenic miRNAs (oncoMIRs): OncoMIRs are overexpressed and inhibit tumor suppressors leading to cell proliferation, invasion, and reduced apoptosis. For example, overexpression of miR-296-5p in GC cells increased cell proliferation and inhibition of apoptosis by repression of tumor suppressor *CDX1*.[123] Overexpressed miR-301a directly targets tumor suppressor *RUNX3*.[124] miR-17-5p/20a targets p21 and p53-induced nuclear protein 1 (*TP53INP1*).[125] miR-18a levels were correlated with those of survivin, Bcl-xL, and c-Myc (downstream targets of *STAT3* and negatively regulated by *PIAS3*; thus, miR-18a acts as an oncoMIR by negatively regulating *PIAS3*.[126] microRNA-372 is oncogenic as it targets *TNFAIP1* and modulates NFkB signaling in GC cells.[127] *IRX1*, a newly identified tumor suppressor gene, is inactivated by miR-544.[128] miR-10b is highly expressed in IGC is associated with the depth of invasion, lymph node, and metastatic progression.[129] Tumor suppressor miRNAs (TsMIRs): TsMIRs are downregulated miRNAs, thus facilitating activity of target oncogenes. miR-195 and miR-378 are downregulated in GC and GC cells and their target oncogenes are *CDK6* and *VEGF*.[130] miR-133b's oncogene target is *FGFR1* often amplified in DGC.[131] miR-29c's oncogene target is *Mcl-1* and activation of miR-29c by celecoxib represses *Mcl-1* and promotes apoptosis of GC cells.[132] miR-34a is downregulated in GC cells and its oncogene target is *survivin*.[133] miR-145 suppresses v-ets erythroblastosis virus E26 oncogene homolog 1 (*Ets1*) by binding to 3′-UTR and reducing the oncogenic processes.[134] Let-7i is

frequently downregulated in most tumors and is prognostic of lymphatic invasion, nodal metastasis, and poor pathologic in GC.[135] *ZFX* has a role the maintenance of CSCs and it is the target of miR-144 in GC.[136] miR-101 targets the 3′-UTR of *COX-2* mRNA and its downregulation in GC correlates with COX-2 overexpression and proliferation.[137] microRNA-146a inhibits NF-kappaB by targeting *CARD10* and *COPS8* in GC.[138]

miRNAs as biomarkers: miRNAs are stable in serum, plasma, gastric juice, and other body fluids.[139] miR-21 and miR-106a were overexpressed in GC and gastric juice compared to normal controls.[140] Additionally, miR-421 in gastric juice of GC patients was higher than in controls ($P < 0.001$) and it resulted in early diagnosis of GC compared by serum carcinoembryonic antigen.[141] Plasma miR-106b, miR-20a, and miR-221 levels were elevated in GC patients than in healthy controls ($P < 0.05$).[142] Plasma levels of miRNA-199a-3p was associated with tumor invasion, malignant node, and metastases.[143] Circulating miR-17-5p and miR-20a (miR-17-5p/20a) have been detected in GC patients and both miRs correlated with clinical variables.[144] The miR-200c expression level in blood in GC patients were significantly higher than in normal controls ($p = 0.018$). Clearly, research on several miRs needs to be fully developed and holds promise.

6. Mechanisms of resistance using HER2 as an example

The major reason for treatment failure in patients is the occurrence of primary and or secondary resistance. We focus on secondary resistance and use her2 inhibition as an example. The predominant mechanism is the compensatory signaling by other cell surface receptors.[145] HER2 overexpressing cells when inhibited reprogram other oncogenes, including *IGF-IR* and *c-MET*, growth differentiation factor 15 (*GDF15*), and other members of the *ERBB* family.[146] The IGF-IR-mediated resistance involves the PI3K pathway, leading to enhanced degradation of $p27^{Kip1}$.[82,147,148] While activated MET mediates resistance in GC cells[149,150] by restoring shared downstream signaling in the MAPK and AKT pathways.[149] Increased levels of EGFR and HER3 ligands can overcome HER2 inhibition.[63,100,146] Constitutively activated p95HER2, truncated HER2 receptor, is the most intriguing mechanism of resistance in response to the blockade of the extracellular domain of HER2.[151] Membrane mucins such as Muc4 interact with HER2 in HER2-overexpressing breast cancer cells resulting in epitope masking that blocks trastuzumab binding.[152] Other proteins that confer resistance include focal adhesion kinase (FAK), and Src, as well as alterations in cell cycle regulators.[153] Constitutive activation of PI3K due to activating *PIK3CA* mutations,[57] reduced PTEN expression,[154] or deregulated signaling can induce resistance to HER2 inhibition.[57,155,156] Finally, *STAT3* activation can mediate resistance as a result of production of IL-6.[157] All this suggests that cancer cells have many redundant mechanisms to overcome therapy resistance and we have considerable work ahead of us. Including exploring drug conjugates and immune modulation.

7. Clinical Dimensions

7.1 Regional differences—The epidemiology and location of the primary GC varies geographically[158] due to variations in genetic susceptibilities, predominance of certain histologic phenotypes (e.g., IGC is frequent in the endemic areas), and carcinogenic forces including *HP*. [159] Cardiac GC is more common in the West and non-cardia GC is more common in the endemic regions. Besides these differences, surgical approach is more comprehensive in Asia where a D2 dissection is a routine[160] than in the West where it is D0 or D1. Other regional differences are in the adjunctive strategy for localized GC (LGC). Many of these factors may account for differences in survival of patients in different regions.[159]

7.2 Localized GC—Localized GC (LGC) can be cT1 or higher with or without regional nodes. Once a patient is diagnosed with LGC, a multidisciplinary evaluation (by medical oncologists, surgical oncologists, surgeons, gastroenterologists, pathologists, radiation oncologists, geneticists [if appropriate], and nutritionists) is highly recommended prior to initiating any therapy.[161] Endoscopic therapy for a T1 lesion, when feasible, is recommended. For those GCs not amenable to effective endoscopic therapy, surgery should be considered. However, adjunctive therapies have contributed to the higher (~10%) cure rates than those obtained by surgery.[162–165]

Adjunctive Strategies: In North America and Europe, results from the INT-0116[165] and MAGIC [166] trials have established specific strategies. The postoperative adjuvant chemotherapy strategy has been established in Asia.[167,168]

Post-operative adjuvant chemoradiation: Although, the safety of INT-0116, a phase III trial that compared observation after surgery with adjuvant chemoradiation after surgery, has been a concern; chemoradiation improved the 5-year cure rate by ~10%.[165] This advantage prevailed with a longer follow-up.[169] A follow-up trial coordinated by CALGB[170] produced negative results as it investigated the adjuvant chemotherapy strategy that has failed many times in the West. Similarly, the ARTIST trial that used the INT-0116 strategy, but differed in two aspects: (1) the control group was treated with chemotherapy and (2) all patients had a D2 gastrectomy, failed to demonstrate benefit for chemoradiation.[171] Thus the ARTIST trial raises more questions than the answers.

Postoperative Chemotherapy: The benefits of adjuvant chemotherapy after D2 gastrectomy was first established in Japan using S-1 as the adjuvant.[167] The Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC)[167] randomized 1,059 patients to one year of S-1 or observation. The primary analysis demonstrated a 33% improvement in overall survival (OS) for the S-1 group. The results prevailed after a longer follow-up.[172] Second Asian study, the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC trial) randomized 1,035 patients post D2 gastrectomy to capecitabine plus oxaliplatin for 6 months or observation,[168] and documented benefit for chemotherapy for the endpoint of disease-free survival (at 3 years; HR 0.56, 95% CI, 0.44–0.72; $P < .0001$). A meta-analysis based on data from 3,710 patients showed 7% improvement in OS for FU-based postoperative chemotherapy when compared to surgery[164] but this evidence is soft.

Perioperative or Preoperative Chemotherapy: The MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) trial (that randomized 504 patients) established the evidence for perioperative chemotherapy for GC patients in the West.[166] A second trial, although with differing tumor type composition (and terminated early because of the lack of interest), demonstrated benefit for preoperative chemotherapy.[163] Several trials using a variety of adjunctive strategies are currently ongoing (MAGIC-B: NCT00450203, CRITICS: NCT00407186, TOPGEAR and PRODIGY: NCT01515748.[173] (Table 3)

7.3 Advanced Gastric Cancer (AGC)

First line therapy: Level 1-evidence for an advantage in OS is available for only a few therapeutic agents (docetaxel,[174] cisplatin,[175] and trastuzumab[176]). Most trials have been disappointing with the exception of the trastuzumab trial investigating a biomarker-based enriched population.[176] However, the longer follow up has reduced the HR for OS to 0.8 (http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm230418.htm;), suggesting that only a few patients benefit. Notable among trials with disappointing results are two randomized studies investigating the value of EGFR inhibition (REAL-3; NCT00824785 and EXPAND; NCT00678535; these references will be

updated). Two other studies are worth mentioning: (1) The AVAGAST trial was conducted in 774 patients, randomized to chemotherapy with or without bevacizumab and it did not meet its primary endpoint of OS[177] and (2) the First line Advanced Gastric Cancer Study (FLAGS) conducted in >1,000 patients randomized to S-1 plus cisplatin versus 5-FU plus cisplatin also failed to meet its primary endpoint of OS advantage.[178]

Second line therapy: A phase III AIO trial In 40 patients randomized patients to irinotecan with best supportive care (BSC) or BSC. The OS was significantly longer for the irinotecan/BSC arm but the has only 40 patients.[179] The GRANITE-1 study (NCT00879333) that randomized >600 patients to everolimus or placebo in second or third line setting also did not achieve its primary endpoint of survival (will update reference). However, the REGARD trial (NCT00917384) that compared BSC with or without ramucirumab in 345 patients has demonstrated a borderline improvement in OS for ramucirumab.[180] More impressively, the Cougar-02 trial randomizing approximately 186 patients to BSC or docetaxel plus BSC demonstrated a significant prolongation of OS in the docetaxel/BSC arm.[181]

Lapatinib, a dual inhibitor of HER2 and EGFR was investigated in a phase III study (TYTAN) of 300+ patients randomized to lapatinib versus placebo but the primary endpoint of prolongation of OS was not achieved.[182]

Targeting c-MET pathway is of interest. In a small study with crizotinib, 2 of 4 patients with MET copy number gain >=5 had a prolonged response.[183] Rilotumumab (AMG 102), a fully human monoclonal antibody, demonstrated longer OS for patients having tumors with high total c-MET expression.[184] Table 3 lists representative completed studies and important ongoing studies.

Conclusions

Considerable advances in biotechnology have improved our understanding of cancer, nevertheless immense complexities confront us. Although, GC lags behind many other tumor types, more progress is anticipated. Greater understanding of pathogenesis o IGC by *HP* is poised to help with more sophisticated preventive strategies. Germline susceptibility investigations have uncovered novel genes but clinical implementations have proven problematic and more work is needed. Clinically, progress has been slow but adjunctive strategies are now frequently employed for LGC around the world and this is an advance. The future progressed will be propelled by further improvements in biotechnologies that will produce better biomarkers and drugs.

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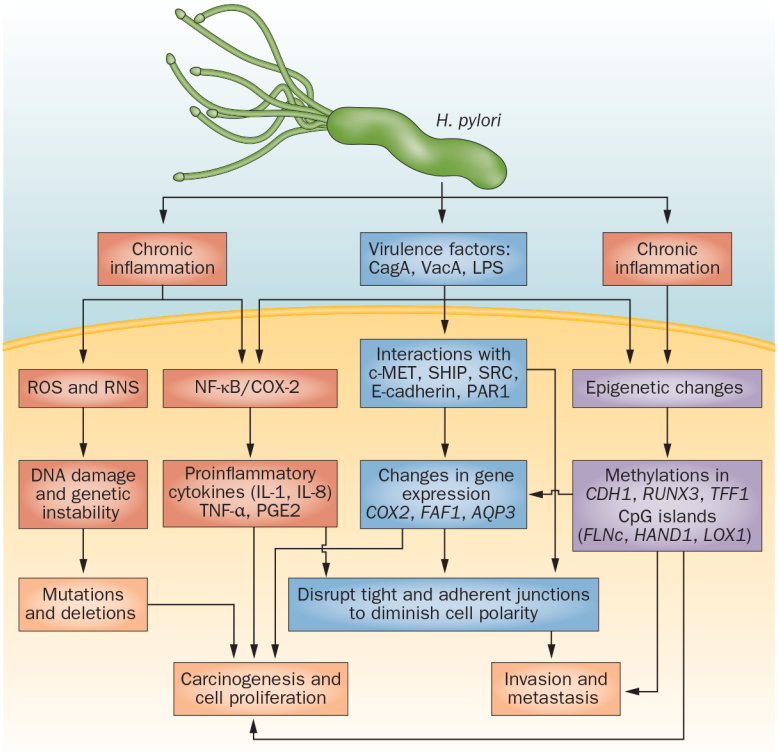

Figure 1. Molecular carcinogenesis of *Helicobacter pylori* in gastric cancer

H. pylori and its several virulence factors, such as CagA, interact with gastric epithelial cells to induce chronic inflammation, mucosal damage and multiple alterations in gene expression and genetic and epigenetic changes, eventually leading to gastric carcinogenesis.

Abbreviations: COX-2, cyclooxygenase-2; CpG island, areas of cytosine and guanine repeats; LPS, lipopolysaccharide; RNS, reactive nitrogen species; ROS, reactive oxygen species; VacA, vacuolating cytoxin A.

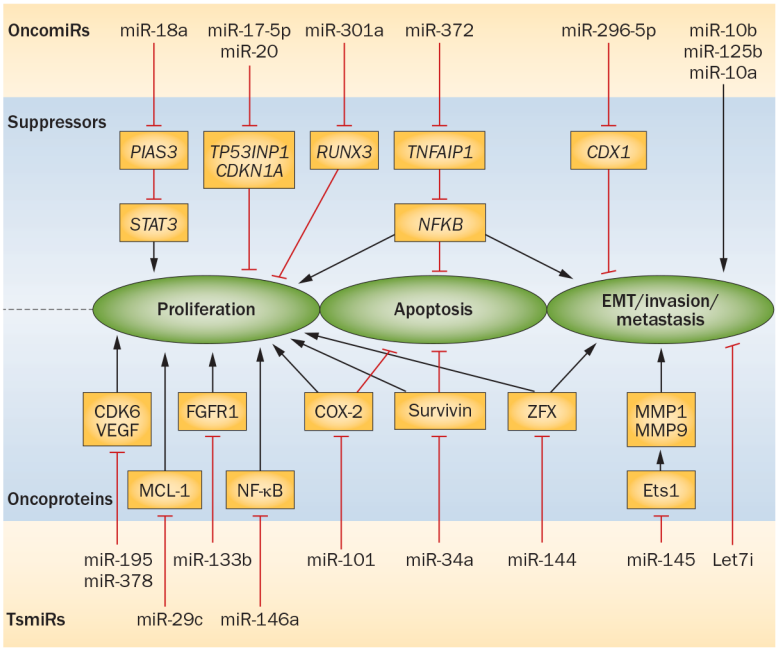

Figure 2. microRNA targets and functions in gastric cancer

Some oncomiRs are overexpressed in tumours and inhibit tumour suppressors, leading to cell proliferation, invasion and reduced apoptosis. By contrast, tsmiRs normally target oncogenes that are downregulated in tumours and facilitate the activity of their target oncogenes. Abbreviations: EMT, epithelial–mesenchymal transition; miR, microRNA; oncomiRs, oncogenic microRNAs; tsmiRs, tumour-suppressor microRNAs.

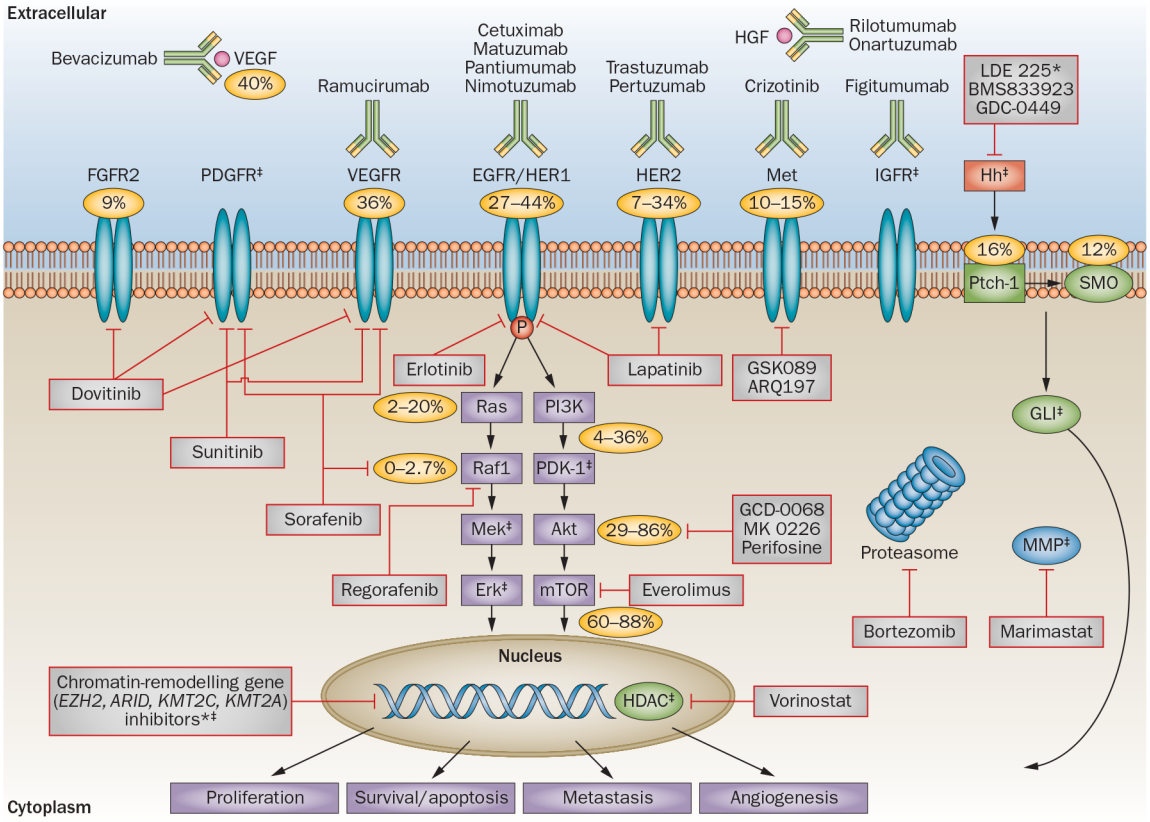

Figure 3. Targeted therapy in gastric cancer

Percentages signify the overall molecular characteristics in the disease: FGFR2 amplification (9%), VEGF/VEGFR overexpression (36–40%), EGFR amplification and overexpression (27–44%), HER-2 amplification and overexpression (7–34%), c-MET amplification (10–15%), kRAS mutation (2–20%), Raf mutation (0–3%), PI3K mutation (4–36%), phospho-Akt expression (29–86%), phospho-mTOR expression (60–88%), PTCH1 overexpression (16%), SMO overexpression (12%) and HER3 mutations (10%, not shown). *No clinical trials of these agents have yet been reported in gastric cancer. ‡No known numbers or percentages for these genes and pathways. Abbreviations: EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; GLI, glioma-associated oncogene family zinc finger 1; HDAC, histone deacetylase; HER, human epidermal growth factor receptor; HGF, hepatocyte growth factor; Hh, Hedgehog; IGFR, insulin-like growth factor receptor; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; Ptch-1, protein patched homolog 1; Smo, smoothened; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Table 1

Representative GWAS studies in gastric cancer

Type of gastric cancer	Genes	Chr no.	Significant SNP identified by GWAS	Ref no.	Confirmed by other studies	Ref no.
Non-cardia Diffuse	*PSCA*	8q24.3	rs2976392A>G rs2294008	46	Yes	53,185–189
Diffuse	*MUC1*	1q22	rs2070803G>A	46l	Yes	52,190
Cardia, non-cardia	*PLCE1*	10q23	rs2274223A>G	47,48	Yes	49,186,191
Cardia, non-cardia	*C20orf54*	20p13	rs1304295	47	No	52
Non-cardia	*PTGER4* or *PRKAA1*	5p13.1	rs13361707T>C	53	Yes	189
Non-cardia	*ZBTB20*	3q13.3	rs9841504C>G	53	No	

Table 2

Comparison of molecular characteristics between intestinal and diffuse subtypes of gastric cancer.

	Intestinal	Reference	Diffuse	Reference
Amplification/overexpression	HER2	76	c-MET	183
	EGFR	84	TGFβ	102
			SHH/Ptch/SMO	192
	VEGF	105	HER3	102
	Notch1	193	FGFR2	101194
	p-mTOR(47–60%)		p-mTOR (58–64%)	195196
			PIK3CA	55
	MMP -1, -7(32–70%)		MMP -1, -7(62–90%)	197,198
Activating mutations	EGFR	199	PIK3CA	55
			c-MET	96
Loss of function mutations			E-cadherin	200
	p53(*-overall 40%)		p53(* -overall 40%)	89,201,202
	PTEN(*)		PTEN(*)	203
Loss of expression	E-cadherin (69%)		E-cadherin (89%)	197
	p53(*)		P53(*)	204
	PTEN(*)		PTEN(*)	98

*NS: No statistical correlation with pathological features. Other molecular alterations implicated in GC but has not been assigned to subtypes include amplification of IGF-IR [205], Ki-Ras [206].

HER2-, EGFR-, MET- and VEGF-related signaling are predominantly implicated in the intestinal subtype, while loss of E-cadherin, FGFR2-, mTOR-, HER3- and MMP-related pathways are more frequently involved in the diffuse subtype.

Table 3

Major Phase III trials for gastric cancer

Table 3a: Localized gastric cancer trials				
Trials	**Treatment Arms**	**N**	**Hazard Ratio for OS; P**	**Primary end point comparison in months (survival rates in %)**
INT-116[165]	Surgery + CTRT (45Gy + 5FU) vs. Surgery	556	1.32; 0.004	OS (36 vs. 27)
MAGIC[166]	ECF/Surgery/ECF vs. Surgery	503	0.75; 0.009	5-year OS (36.3% vs. 23%)
CALGB-80101[207]	FU/CTRT-FU/FU vs. ECF/CTRT-FU/ECF	546	1.03; 0.80	OS (37 vs. 38)
ARTIST[171]	Surgery/XP vs. Surgery/XP/XRT/XP	458	0.0862	3-year DFS (74.2% vs 78.2%)
ACTS-GC[167]	Surgery vs. Surgery/*S*-1	1,059	0.68; 0.003	3-year OS (70.1% vs. 80.1%) RFS (65.4% vs. 53.1%)
CLASSIC[168]	XELOX and Surgery vs. Surgery	1,035	0.56; <0.0001	3-year DFS (74% vs. 59%)
FNLCC [163]	Perioperative Chemotherapy vs. Surgery	224	0.69; 0.003	5-year OS (38% vs. 24%)
SAMIT*[208]	Surgery/UFT vs. Surgery/S1 vs. Surgery/Paclitaxel/UFT vs. Surgery/Paclitaxel/S1	1,495	NR	
ARTIST-II*	Surgery/XP vs. Surgery/XP/XRT/XP	1,000	NR	
MAGIC-B* NCT00450203	ECX + Bevacizumab vs ECX	1,100	NR	
TOPGEAR*[209]	Preoperative CT vs. Preoperative CTRT	752	NR	
CRITICS*[173]	ECX/Surgery/ECX vs. ECX/Surgery/CX-CTRT	788	NR	

Table 3b: Advanced/Metastatic gastric cancer trials-First-line				
Trials	**Treatment Arms**	**N**	**Hazard Ratio for OS; P**	**Primary end point comparison in months (survival rates in %)**
ToGA[176]@	CX/CF +trastuzumab vs. CX/CF	584	0.74, 0.0046	OS (13.8 vs 11.1)
AVAGAST[177]	Cisplatin/Fluoropyrimidine vs. Cisplatin/ Fluoropyrimidine+ Bevacizumab	774	0.87, 0.1002	OS (10.1 vs 12.2) PFS (5.3 vs 6.7)
EXPAND [210] NCT00678535	CX vs. CX+ Cetuximab	904	1.004, 0.9547	OS (10.7 vs 9.4)
REAL-3 [211]	EOC vs. mEOC–P	574	1.37, 0.013	OS (11.3 vs 8.8)
V325[174]	DCF vs. CF	457	1.47,<0.001	TTP (5.6 vs 3.7)
SPIRITS[175]	S-1 + Cisplatin vs. S-1	305	0.77, 0.04	OS (13.0 vs 11.0)
FLAGS[178]	cisplatin/S-1 vs. cisplatin/5-FU	1,053	0.92, 0.20	OS (8.6 vs. 7.9)
LOGIC* NCT00680901	CapeOx plus Lapatinib vs. CapeOx plus Placebo	545	NR	

Table 3c: Advanced/Metastatic gastric cancer trials-Second-line				
Trials	**Treatment Arms**	**N**	**Hazard Ratio for OS; P**	**Primary end point comparison in months (survival rates in %)**
GRANITE-1 NCT00879333	BSC Placebo vs everolimus	648	0.90, 0.1244	OS (4.3 vs 5.4)
REGARD[180] NCT00917384	BSC with Ramicirumab vs. BSC	355	0.776, 0.0473	OS (5.2 vs 3.8)
TYTAN[182]	Lapatinib + paclitaxel vs. paclitaxel	261	0.2441	OS (11.0 versus 8.9)
Kang et al [212]	BSC vs. docetaxel or irinotecan	202	0.657, 0.007	OS (3.8 vs 5.3)
AIO[179]	Irinotecan/BSC vs. BSC	40	0.48; 0.012	OS (4.0 vs 2.4)
COUGAR-02[181] (Trial 13366390)	Docetaxel/ASC vs. ASC	168	0.67, 0.01	OS (5.2 vs 3.6)

*=Ongoing Trials, NR=Not Reported yet

N: Total Sample Size; P=P-value; CTRT: Chemoradiotherapy; OS: Overall Survival; RFS: Relapse Free Survival; PFS: Progression free survival; DFS: Disease free Survival; HR: Hazard Ratio; ECF: Epirubicin, Cisplatin, 5-FU; ECX: epirubicin, cisplatin capecitabine; XP, capecitabine/cisplatin, XRT: XP+ Radiotherapy; XELOX: Capecitabine plus Oxaliplatin; EOC: epirubicin, oxaliplatin and capecitabine; mEOC–P: mEOC + panitumumab; CX: cisplatin and capecitabine; CF: cisplatin, fluorouracil; D: Docetaxel; UFT: Tegafur and Uracil; CapeOx: Capecitabine, Oxaliplatin; BSC: best supportive care; ASC: Active Symptom Control; TTP=time to progression.

INT: US Intergroup Study; CALGB: Cancer and Leukemia Group B ; MAGIC: Medical Research Council Adjuvant Gastric Cancer Infusion Chemotherapy; ACTS-GC: Adjuvant Chemotherapy Trial of S1 in Gastric Cancer; CRITICS: ChemoRadiotherapy after Induction chemo Therapy in Cancer of the Stomach; ARTIST: Adjuvant Chemoradiation Therapy in Stomach Cancer; CLASSIC: Capecitabine and Oxaliplatin Adjuvant study in stomach cancer; REAL-3: Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 3; AVAGAST: Avastin in Gastric Cancer; EXPAND: Erbitux in Combination with Xeloda and Cisplatin in Advanced Esophagogastric Cancer; GRANITE-1:Safety and efficacy of RAD001 (Everolimus) Monotherapy plus Best Supportive care in Patients with Advanced Gastric Cancer; ToGA: Trastuzumab for Gastric Cancer; LOGIC: Lapatinib Optimization Study in HER-2 Positive Gastric Cancer; SAMIT: Stomach Cancer Adjuvant Multi-institutional Trial.

@the hazard ration is reduced to 0.8 on a follow up analysis ((http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm230418.htm;)