Current development of molecular classifications of gastric cancer based on omics (Review)

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Abstract. Gastric cancer (GC) is a complex and heterogeneous disease with significant phenotypic and genetic variation. Traditional classification systems rely mainly on the evaluation of clinical pathological features and conventional biomarkers and might not capture the diverse clinical processes of individual GCs. The latest discoveries in omics technologies such as next-generation sequencing, proteomics and metabolomics have provided crucial insights into potential genetic alterations and biological events in GC. Clustering strategies for identifying subtypes of GC might offer new tools for improving GC treatment and clinical trial outcomes by enabling the development of therapies tailored to specific subtypes. However, the feasibility and therapeutic significance of implementing molecular classifications of GC in clinical practice need to addressed. The present review examines the current molecular classifications, delineates the prevailing landscape of clinically relevant molecular features, analyzes their correlations with traditional GC classifications, and discusses potential clinical applications.

Contents

1. Introduction

Gastric cancer (GC) stands as one of the most prevalent types of cancer worldwide. As outlined in the 2020 GLOBOCAN report, GC ranks fifth globally in incidence and fourth in mortality (1). Notably, East Asia, Eastern Europe and South America exhibit particularly elevated rates of both incidence and mortality associated with GC (2). As a highly heterogeneous disease, personalized treatment approaches are essential for GC (3). In the early stages of GC development, due to limitations in detection technologies, the most common classification systems were based on morphology; these included the World Health Organization (WHO) classification system (tubular, papillary, mucinous and poorly cohesive) (4), the Lauren classification system (diffuse, intestinal, and mixed) (5), and the Nakamura classification system (differentiated and undifferentiated) (6). Early-stage and advanced-stage GCs are characterized by extensive morphological differences, leading to an increasing number of classification systems (2). However,

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relying solely on histological classification is insufficient for effectively stratifying patients for individualized treatment and improving clinical outcomes (7).

In the late 1980s, the discovery of targeted molecules such as HER2 (8,9) and VEGF (10,11) played a significant role in GC treatment, marking the era of targeted therapy for GC (12). Individual gene typing, compared with morphological typing, is more precise and enables gene-targeted treatment with corresponding medications. However, with ongoing practice, it has become evident that targeting a single molecular pathway has limitations, including size of the application patient population, drug resistance and side effects. There is a pressing need to comprehensively clarify the molecular characteristics of GC to realize the potential of precision oncology and improve patient survival rates (13).

With technological advancements, omics techniques such as next-generation sequencing (NGS), metabolomics and proteomics have facilitated significant breakthroughs in the medical field, providing direct evidence at the microscopic level to understand the heterogeneity of GC. In 2011, Shah *et al* (14) differentiated GC subtypes with epidemiological and histological differences using gene expression data, demonstrating favorable consistency and enhancing understanding of tumor biology. In the same year, Tan *et al* (15) identified two major intrinsic subgroups of GC (G-INT and G-DIF) through gene expression analysis of 37 GC cell lines, laying a solid foundation for subsequent clinical genomic classification research. The use of various omics approaches contributes to a deeper understanding of the detailed biological characteristics of GC, providing a foundation for personalized treatment and drug development and improving the effectiveness of cancer treatment and patient survival rates. The present review summarizes the latest research on GC omics classification, elucidating its potential clinical applications in diagnosis, prognosis and treatment response prediction, and drug design.

2. Cluster-based molecular classification of GC

Research on the cluster-based classification of GC has gained significant momentum in the past decade. To date, 27 articles related to the cluster classification of GC patient samples have been published, 14 of which provided further validation of the studies (Table I). A milestone study was reported in 2014 by The Cancer Genome Atlas (TCGA) research network, which included the most comprehensive molecular characteristics of gastric adenocarcinoma at that time (16). Numerous subsequent cluster-based subtyping studies have been conducted based on the TCGA database (17-28). Apart from the TCGA research, a major gene expression profile study conducted by the Asian Cancer Research Group (ACRG) in 2015 revealed fresh expression subtypes of GC. This classification scheme is intricately linked to diverse molecular alterations, disease progression and prognosis patterns (29). An increasing number of countries and regions, such as Singapore (3,30), South Korea (29,31-33) and China (34-38), have started similar research. These studies commonly employ mainstream classification methods such as consensus clustering (3,18-20,33,34), K-value clustering (24,39) and non-negative matrix factorization (21,26,36,37,40), among others, to conduct cluster-based subtyping of GC patient samples. This finding not only correlates with different genomic alteration patterns but also with GC recurrence patterns, prognosis and drug sensitivity.

3. TCGA and ACRG classifications

The TCGA database categorizes gastric adenocarcinoma into four subtypes based on the following features: Epstein-Barr virus (EBV; 8.8%), microsatellite instability (MSI; 21.7%), genomically stable (GS; 19.7%) and chromosomal instability (CIN; 49.8%) (16). EBV-positive tumors exhibit recurrent mutations in phosphatidylinositol 3-kinase (PIK3CA) and AT-rich interactive domain-containing protein 1A (ARID1A), as well as extreme DNA hypermethylation and overexpression of programmed death-ligand 1/2 (PD-L1/2) (41). Amplifications of Janus-activated kinase 2 (JAK2) and Erb-B2 receptor tyrosine kinase 2 (ERBB2) (42) were also observed. MSI tumors, characterized by mismatch repair deficiency, were more common in elderly (median age 72 years) and female (56%) patients than in male (early) patients. MSI-high GC also had a high rate of PD-L1 expression. The GS subtype had low somatic copy number alterations (SCNAs), was rich in diffuse histological variations, and had mutations in Ras homolog family member A (RHOA) and E-cadherin (CDH1). CIN tumors were more common in the gastroesophageal junction/cardia and exhibited noticeable non-diploidy and focal amplification of receptor tyrosine kinase-Ras (RTK/Ras). There was also a high frequency of TP53 mutations in CIN tumors (Fig. 1).

Another major gene expression profile study conducted by the ACRG (29) reported four expression subtypes of GC, referred to as MSI (22.7%), microsatellite stable/epithelial-mesenchymal transition (MSS/EMT; 15.3%), microsatellite stable/epithelial/TP53 loss (MSS/TP53$^-$; 35.7%) and microsatellite stable/epithelial/TP53 intact (MSS/TP53$^+$; 26.3%). The MSI subtype predominantly occurred in the gastric antrum (75%) and typically presented as an intestinal subtype (>60%). The majority of cases of this type were diagnosed at an early stage (>50%) and exhibited a high frequency of loss of MLH1 RNA expression and elevated DNA methylation (43). This subtype was associated with hypermutation of genes including those in KRAS (23.3%), ARID1A (44.2%), the PI3K-PTEN-mTOR pathway (42%) and ALK (16.3%), as confirmed in multiple studies (44-48). Numerous research results have indicated a significant correlation between MSI and tumor-infiltrating lymphocytes (TILs) (49,50) and PD-L1 levels (51-53). The MSS/EMT subtype is often observed in cases in younger late-stage patients (III/IV), typically exhibiting a diffuse Lauren subtype (>80%); these cases include a significant number of signet ring cell carcinomas and exhibit loss of CDH1 expression (29). The MSS/TP53$^+$ subtype has a high rate of EBV infection (54), with higher mutation rates for PIK3CA, ARID1A, SMAD4, APC and KRAS than the other subtypes. The MSS/TP53-subtype had the highest TP53 mutation rate (60%) and showed enrichment of recurrent focal amplifications in ERBB2, epithelial growth factor receptor (EGFR), CCND1, MDM2, CCNE1, GATA6, ROBO2 and MYC. The MSI subtype is linked to a favorable prognosis, while MSS/EMT GC is associated with an unfavorable prognosis (Fig. 1).

The TCGA (16) and ACRG (29) classifications exhibit some similarities (Fig. 1). Both classifications include an MSI subtype, and the TCGA GS, EBV and CIN subtypes

Table I. Basic information on the molecular classifications of gastric cancer.

Time	Source/Country	Types of GC	Number	Clustering methods	Group name	Validation cohorts (N)	(Refs.)
2013	Singapore	GC (201)	201	CC	Mesenchymal, proliferative, metabolic	Melbourne Cancer Center (80)	(3)
2014	Singapore	GC (60)	60	RPMM	H, L	/	(30)
2014	United States, South Korea, Japan, Canada, Australia	GC (295)	295	UC	EBV, MSI, GS, CIN	/	(16)
2015	South Korea	GC (300)	300	PCA	MSI, MSS/EMT, MSS/TP53+, MSS/TP53-	TCGA cohort; GSE15459	(29)
2017	South Korea	GC (65)	65	HC	subtype 1-4	PMID: 24816253 (100)	(31)
2018	South Korea	GC (93)	93	UC	MP, EP	Yonsei University Severance Hospital (65); Kosin University College of Medicine (109); MDACC cohort (40); SMC cohort (432); ACRG cohort (300)	(32)
2018	China	DGC (84)	84	CC	PX1-3	/	(34)
2019	UK, Germany	AEG (107)	107	Mclust algorithm	Group1-3	OCCAMS cohort (158); BELFAST cohort (63); ACRG cohort (300); Singapore cohort (191)	(56)
2019	South Korea	EOGC (80)	80	CC	subtype 1-4	TCGA cohort (268); ACRG cohort (306); Singapore cohort (192)	(33)
2019	China	DGC (83)	83	CC	Ph1-3	/	(35)
2021	TCGA-STAD	GC (375)	375	HC	L1-3	/	(17)
2021	TCGA-STAD, ACRG-STAD, GSE84437	GC (1148)	1,148	CC	ImD, StE, ImE	/	(18)
2021	TCGA-STAD	GC (375)	375	CC	Cholesterogenic, Glycolytic, Mixed, Quiescent	/	(19)
2021	China	GC (70)	70	NMF	subtype1-4	Zhejiang University (23)	(36)
2021	TCGA-STAD	GC (243)	243	Ten classical clustering algorithms[a]	CS1-2	GSE62254; GSE26253; GSE15459; GSE84437	(28)
2021	TCGA-STAD	GC (375)	375	CC	C1-2	/	(20)
2021	TCGA-STAD	GC (371)	371	NMF	C1-2	GSE62254 (300); GSE15459 (192); GSE84437 (433); Tianjin (90)	(21)
2021	GSE84433	GC (357)	357	NMF	subtype1-3	GSE84426 (76)	(40)
2022	Germany	GC (362)	362	K-Means	T1-3; S1-3	VARIANZ cohort (42)	(39)
2022	TCGA-STAD, GSE13861, GSE26899, GSE26901, GSE57303, ACRG-STAD, GSE15459, GSE34942, GSE84426, GSE8443	GC (1673)	1,673	HC	hypoxiaCluster-high, hypoxiaCluster-medium, hypoxiaCluster-low	/	(22)

Table I. Continued.

Time	Source/Country	Types of GC	Number	Clustering methods	Group name	Validation cohorts (N)	(Refs.)
2022	TCGA-STAD, GSE84437, GSE62254	GC (996)	996	CC	IS1-3	/	(23)
2022	TCGA-STAD	GC (443)	443	K-Means	C1-3	GSE84437 (433); China (20)	(24)
2023	China	AEG (103)	103	NMF	S-I, S-II, S-III	/	(37)
2023	TCGA-STAD	GC (323)	323	CC	Group1 (ARID1A+ type), Group2 (TP53+ type), Group3 ($CDH1^+$ type)	GSE26253 (432); ACRG cohort (300); GSE26899 (93); GSE13861 (65); GSE26901 (109)	(25)
2023	TCGA-STAD	GC (348)	348	NMF	NMF1-3	GSE84437 (433); GSE26253 (432)	(26)
2023	China	GC (196)	196	CC	DGC clusters 1-3, IGC clusters 1-3/DGC TF clusters 1-2, IGC TF clusters 1-2/DGC phospho-proteomic clusters 1-3, IGC phospho-proteomic clusters 1-3	/	(38)
2023	TCGA-STAD	GC (350)	350	CC	cluster1-2	GSE62254; GSE15459; GSE57303; GSE34942; GSE84437; GSE26942; GSE29272; GSE28541; GSE13861	(27)

[a]The ten classical clustering algorithms used include iClusterBayes, moCluster, CIMLR, IntNMF, CC, COCA, NEMO, PINSPlus, SNF, and LRA. N, number; GC, gastric cancer; CC, consensus clustering; RPMM, recursively partitioned mixture model; UC, unsupervised clustering; HC, hierarchy clustering; TCGA, The Cancer Genome Atlas; EBV, Epstein-Barr virus; MSI, microsatellite instability; GS, genomically stable; CIN, chromosomal instability; PCA, principal component analysis; ACRG, Asian Cancer Research Group; MSS/EMT, microsatellite stable/epithelial-mesenchymal transition; MSS/TP53+, microsatellite stable/epithelial/TP53 intact; MSS/TP53-, microsatellite stable/epithelial/TP53 loss; MP, mesenchymal phenotype; EP, epithelial phenotype; DGC, diffuse-type gastric cancer; AEG, adenocarcinoma of the esophagogastric junction; ImD, immune-deprived; StE, stroma-enriched; ImE, immune-enriched; EOGC, early-onset gastric cancer; NMF, nonnegative matrix factorization; IGC, intestinal-type gastric cancer.

correspond to the ACRG MSS/EMT, $MSS/TP53^+$ and $MSS/TP53^-$ subtypes, respectively. However, there are also numerous differences, primarily in terms of molecular mechanisms, driver genes, and prognostic associations: i) Tumors classified as TCGA GS and CIN subtypes were included in all ACRG subtypes in the TCGA dataset; ii) RHOA and CDH1 mutations were common in the TCGA GS subgroup but not prevalent in the ACRG MSS/EMT subgroup, while RHOA mutations were more common in the ACRG $MSS/TP53^+$ and MSS/TP53-subtypes; and iii) the correlation between TCGA classification and prognosis is much weaker than the correlation between ACRG classification and prognosis.

4. Genomic/transcriptomic classifications

The rapid development of genomics and transcriptomics has been propelled by the widespread adoption of NGS technologies. This has significantly enhanced the understanding of GC biology, providing novel insights into the complex interactions among tumor cells, normal cells and their microenvironment (55). Genomic subtypes and transcriptomic subtypes are inherently interconnected. The research on genomic/transcriptomic clustering subtypes encompasses a total of 16 studies (Table II), with four studies (3,18,19,32) characterizing the subtypes descriptively. These studies cover various aspects but primarily focus on EMT (3,18,21,22,32), metabolic characteristics (3,19,20,26,27,56), and immune features (18,20-24,27,40,56). The following is a summary of these aspects.

In total, five articles discussed the differences in the EMT pathways among subtypes, with two articles providing characteristic names for them (3,32). In 2013, Lei *et al* (3) classified gastric adenocarcinoma patients into three main subtypes, with the mesenchymal subtype exhibiting high activity in

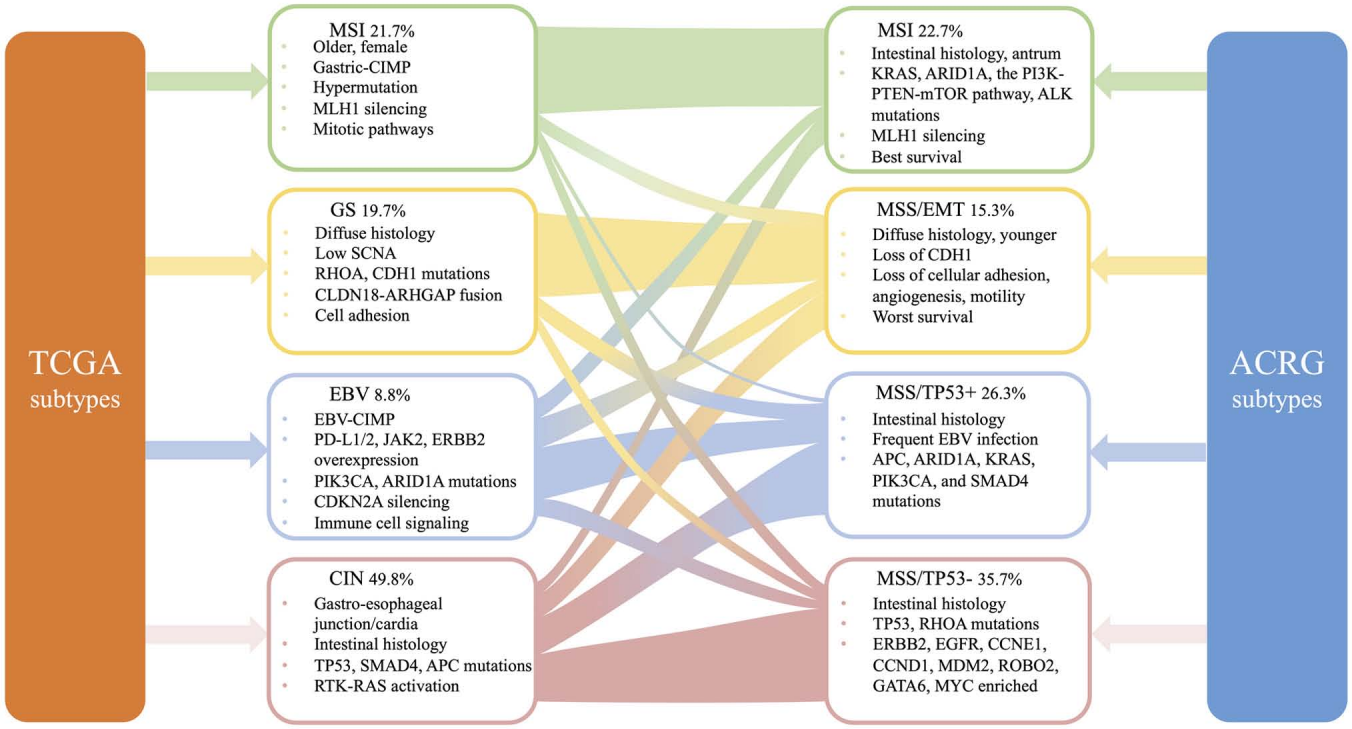

Figure 1. Key features of TCGA and ACRG gastric cancer subtypes. Diagram shows some significant features associated with each of the eight cluster subtypes of GC in the TCGA and ACRG studies. The connecting lines depict the distribution of TCGA gastric dataset tumors according to ACRG subtypes compared with TCGA GC subtypes. TCGA, The Cancer Genome Atlas; ACRG, Asian Cancer Research Group; EBV, Epstein-Barr virus; GS, genomically stable; CIN, chromosomal instability; MSI, microsatellite instability; MSS/EMT, microsatellite stable/epithelial-mesenchymal transition; MSS/TP53^{+}, microsatellite stable/epithelial/TP53 intact; MSS/TP53-, microsatellite stable/epithelial/TP53 loss.

the cancer stem cell pathway. Oh *et al* (32) suggested that the mesenchymal phenotype (MP) subtype within the intrinsic subtypes exhibits clinical and molecular features akin to those of the Genomic Diffuse (G-DIF) tumors classified by Tan *et al* (15). The ACRG research also reached a similar conclusion. Furthermore, the MSS/EMT subtype (ACRG classification) (29) was considered a subset of the MP subtype, and both were suggested to be linked with an unfavorable prognosis (18,21,22). Li *et al* (18) reported that the stroma-enriched (StE) subtype shares similar characteristics with Oh *et al*'s MP subtype (32), including high genomic stability, prominent EMT features, resistance to standard chemotherapy and poor prognosis. Ning *et al* (22) suggested that high hypoxia status is positively correlated with high m6A methylation in tumors of the MSS/EMT subtype (ACRG classification) (29). Previous research has indicated that EMT significantly enhances the movement and spreading of cancer cells, playing a central role in tumor progression (57-59). Additionally, Oh *et al* (32) reported high activation of the insulin-like growth factor 1 (IGF1)/IGF1 receptor (IGF1R) pathway in patients in the MP group, and this pathway is considered a crucial therapeutic target for numerous cancers (60-62). Several studies have identified immune suppression features in groups with enrichment of EMT characteristics (18,21,22). Previous studies reported that the activation of EMT and TGF-related signaling pathways led to weakened transport of T cells to tumors, reducing the cytotoxicity of tumor cells (63-65).

Disruption of cellular energy metabolism stands as one of the core hallmarks of cancer cells (66). Lei *et al* (3) reported a significant correlation between the metabolic subtype classified in their study and a pathway associated with spasmolytic polypeptide-expressing metaplasia (5), considered an intermediate step in gastric adenocarcinoma development (67). Bornschein *et al* (56) classified gastroesophageal junction (GEJ) adenocarcinoma into three groups based on differentially expressed genes and revealed enrichment of fatty acid metabolism pathways in the stroma-enhanced and poor prognosis subgroups (Group 1). Previous research has suggested that adipose tissue can create a proinflammatory microenvironment in obese patients, contributing to stromal activation associated with more aggressive tumor behavior and an unfavorable prognosis (68-70). The presence of Barrett's esophagus was strongly correlated with a Group 1 designation. Group 2 was characterized by metabolic pathways, which are typically active in the intestinal and hepatobiliary systems. A total of four studies (19,20,26,27) conducted analyses on the TCGA dataset, classifying subtypes based on metabolism-related genes. Zhu *et al* (19) classified the TCGA samples into four subtypes based on the express of glycolysis-related genes and cholesterol-related genes and identified abnormal amplification of MYC and TP53 in the cholesterol subtype. Upregulated MYC expression is linked to a more invasive phenotype in GC cell lines. MYC amplification represents a common mechanism of MYC mutation in cancer (71). MYC amplification has been reported in plasma samples from patients with GC (72). The glycolysis subgroup had increased expression of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and PDCD1. Li *et al* (20) reported that the C2 subtype, which has a high TP53 mutation rate, was enriched in bile acid metabolism. Tao *et al* (27) reported that cluster

Table II. Features of gastric cancer subtypes based on genomic/transcriptomic clustering studies.

Sequencing type (Basis)	Group name (N)	Survival	Histology	TCGA	Clinical/Immune	Molecular findings	(Refs.)
Transcriptome (DEGs)	Mesenchymal (60)		Diffuse (58.2)			High CD44 and low CD24 expression	(3)
	Proliferative (93)		Intestinal (73.6)			Characterized by gene sets related to the cell cycle High GI, TP53 mutations DNA hypomethylation	
	Metabolic (48)		Intestinal (53.6)			SPEM	
Transcriptome (DEGs)	Subtype 1 (11)					miR-202/CACNA1E/type II diabetes mellitus	(31)
	Subtype 2 (29)					miR-338/CCL21/NF-κB signaling	
	Subtype 3 (13)					miR-146B/PSMD3/proteasome	
	Subtype 4 (12)					miR-34A (C)/VCL/focal adhesion	
Transcriptome (DEGs)	Mesenchymal Phenotype/MP (27)	Poor	Diffuse (61.9)			High genomic integrity; MSS Intact MLH1 activity High Signaling pathways driving EMT and the IGF1/IGF1R pathway activation	(33)
	Epithelial Phenotype/EP (66)	Good				Low genomic integrity Uniform downregulation of all SFRPs	
Transcriptome (DEGs)	Group 1 (28)	Poor				Enriched in pathways involved in cell turnover High CTSE and membranous CLDN18 scores	(56)
	Group 2 (39)					Enriched in metabolic processes	
	Group 3 (40)	Good				Enriched in immune-response pathways High IDO1 positive immune cells and IP10 expression	
Transcriptome (tumor-specific lncRNAs)	L1 (171)	Good	Intestinal	MSI		High LINC01614 expression Mutations in ARID1A, PIK3CA, KMT2B, KRAS, and FBXW7	(17)
	L2 (104)		Diffuse	EBV; GS		Mutations in CDH1	
	L3 (100)	Poor	Intestinal	CIN		Presence of TP53 mutations Low methylation Overexpression of oncogenic lncRNAs	
Transcriptome (15 pathways associated with immune, DNA repair, oncogenic, and stromal signatures)	Immunity-deprived/ ImD		Intestinal	CIN	Low immune infiltration	High DNA damage repair activity, high tumor aneuploidy level, high ITH, high TMB, and frequent TP53 mutations	(18)

Table II. Continued.

Sequencing type (Basis)	Group name (N)	Survival	Histology	TCGA	Clinical/Immune	Molecular findings	(Refs.)
	Stroma-enriched/StE	Poor	Diffuse	GS	Higher proportion of advanced tumors; high stromal signatures	Low DNA damage repair activity Low ITH High EMT	
	Immunity-enriched/ImE	Good	Intestinal	MSI; EBV	High immune infiltration	High DNA damage repair activity; high TMB High PD-L1 expression; mutations in ARID1A	
Transcriptome (23 GLYCOLYSIS genes and 20 CHOLESTEROL genes)	Cholesterogenic (53) Glycolytic (47) Mixed (110) Quiescent (122)	Poor				Abnormal amplification of TP53 and MYC High PDCD1 and CTLA4 expression High MPC1/2 expression	(19)
Exome (Based on mutational signature, copy number variation, neoantigen, clonality, and essential genomic alterations)	Subtype 1 (22)		Intestinal (72.7)	CIN (90.9)	Liver metastasis tendency	Recurrent TP53 mutation and ERBB2 amplification High TMB/TNB; intratumoral heterogeneity	(36)
	Subtype 2 (16)		Intestinal (62.5)	CIN (50); GS (50)	Elderly patients	Frequent TP53, LRP1B, and SYNE1 mutations High TMB/TNB	
	Subtype 3 (12)		Diffuse/Mixed (66.7)	GS	Peritoneal metastasis tendency	Frequent deletion of ARID1A	
	Subtype 4 (20)	Good	Diffuse/Mixed (70)	GS	Peritoneal metastasis tendency	Frequent deletion of ARID1A Mutational signature 1 dominant	
Transcriptome (metabolism-related lncRNA regulators)	C1 (299)			EBV; MSI	High immune infiltration	Enriched in interferon-gamma response, interferon-alpha response, and inflammatory response Mutations in ARID1A, AHNAK2, PIK3CA, and ZBTB20	(20)
	C2 (67)					Enriched in bile acid metabolism; mutations in TP53 High CNV	
Transcriptome (Immune DEGs)	C1 (175)	Poor	Diffuse		Elderly patients; immune resting	Enriched in epithelial mesenchymal transition, Angiogenesis, and UV response Mutations in BNC2, CDH1, and CTNNB1	(21)
	C2 (196)	Good	Intestinal			Enriched in MYC Target, oxidative phosphorylation, and E2F target; high TMB Mutations in APC, NBEA, PIC3CA, XIRP2, RNF43, SMAD4, TP53, KRAS, and BNCA	

Table II. Continued.

Sequencing type (Basis)	Group name (N)	Survival	Histology	TCGA	Clinical/Immune	Molecular findings	(Refs.)
Transcriptome (significant genes)	Subtype 1 (171)					High HLADQA1, HLA-DPA1, and TRIM22 expression	(40)
	Subtype 2 (103)	Poor			High stromal signatures	High SPARC, COL3A1, and CCN expression	
	Subtype 3 (83)	Good			High immune infiltration	High FGL2 and DLGAP1-AS5 expression	
Transcriptome (m6A-related hypoxia pathway DEGs)	HypoxiaCluster-high (279)	Poor			High immune Higher proportion of advanced tumors infiltration	Enriched in stromal and metastatic activation pathways, such as EMT, angiogenesis, myogenesis, hedgehog signaling, and TNFa signaling via NFkB	(22)
	HypoxiaCluster-medium (657)						
	HypoxiaCluster-low (378)	Good				Enriched in signaling pathways associated with MYC targets V2, MYC targets V1, E2F targets, and the G2 M checkpoint	
Transcriptome (TIME-associated signature genes)	IS1 (369)	Poor				High Notch, Hippo, Wnt, TGF-beta, and PI3K expression	(23)
	IS2 (324)					Enriched in the cell cycle pathway	
	IS3 (303)	Good			High immune infiltration	Enriched in immunity-related oncogenic pathways	
Transcriptome (prognostic aging-relevant genes)	C1 (143)	Good		EBV; MSI		High TMB	(24)
	C2 (117)			GS	High immune infiltration	Low TMB and SCNA Upregulation of immune activation pathways and stromal activation pathways High MHC molecules and most chemokines (receptors) expression	
	C3 (91)			CIN		High SCNA	
Transcriptome (metabolism-associated genes)	NMF1 (135)	Good				High TMB; Mutations in TTN, MUC16, and TP53 High incidence of chain mutation and unique mutations	(26)
	NMF2 (98)					Mutations in TTN, TP53, and LRP1B	
	NMF3 (115)	Poor				Mutations in TP53, TTN, and MUC16 Driver gene: CNBD1	

Table II. Continued.

Sequencing type (Basis)	Group name (N)	Survival	Histology	TCGA	Clinical/Immune	Molecular findings	(Refs.)
Transcriptome (metabolism-associated genes)	Cluster1 (164)	Poor		GS	High immune infiltration	Hypomethylation; activation of multiple intercellular communication-related signaling pathways	(27)
	Cluster 2 (186)	Good		MSI		High metabolic features; high TMB; activation of nucleotide processing and repair-related pathways	

N, number; TCGA, The Cancer Genome Atlas; DEGs, differentially expressed genes; GI, genomic instability; SPEM, spasmolytic polypeptide-expressing metaplasia; miR, miRNA; CACNA1E, calcium voltage-gated channel subunit α1; CCL21, C-C motif chemokine ligand 21; PSMD3, proteasome 26S subunit, non-ATPase 3; VCL, vinculin; MSS, microsatellite stability; IGF1, insulin-like growth factor 1; EBV, Epstein-Barr virus; GS, genomically stable; CIN, chromosomal instability; MSI, microsatellite instability; ITH, intratumor heterogeneity; EMT, epithelial-mesenchymal transition; TMB, tumor mutation burden; MPC1/2, mitochondrial pyruvate carriers 1 and 2; TNB, tumor neoantigen burden; CNV, copy number variation; TIME, tumor immune microenvironment; SCNA, somatic copy number alteration.

2, which presented activation of numerous metabolic pathways, also exhibited activation of nucleotide processing and repair-related pathways and a higher tumor mutation burden (TMB). This was associated with an improved prognosis for patients with GC (26,27).

Tumor tissues and cells undergo varying degrees of metabolic dysregulation and immune dysfunction (73). Li *et al* (18) classified patients with GC not only into the StE subgroup but also into the immune-deprived (ImD) and immune-enriched (ImE) subtypes. The ImD and ImE subtypes share several common features with Oh *et al*'s epithelial phenotype (EP) (32), such as high genomic instability, elevated DNA damage repair activity and sensitivity to standard chemotherapy. However, Li *et al*'s classification (18) could capture the intratumoral heterogeneity within the EP, including significantly different tumor immune microenvironments, somatic cell mutations and SCNA patterns, responses to chemotherapy and immunotherapy and clinical outcomes. Both ImD and ImE subtypes had high TMB, but their levels of immune infiltration vary significantly. The primary reason might be that ImD exhibits a high frequency of SCNAs that suppress antitumor immune responses (74). Similarly, Wu *et al* (21) used the TCGA dataset to classify major classes based on immune-related genes: C1 and C2. The C1 subtype exhibited immune quiescence, EMT and angiogenesis pathway activity. By contrast, the C2 subtype primarily exhibited enrichment of MYC targets, oxidative phosphorylation and the E2F target pathway, along with a higher TMB. TMB could serve as an indicator for predicting immunotherapy response, and patients with high TMB had improved clinical outcomes (75-77). Several studies have reported that high TMB is associated with a favorable prognosis in patients with GC (24,26,27,78,79). Interestingly, cluster 1, classified by Tao *et al* (27), had a poor prognosis despite the enrichment of immune cells, conflicting with previous research results (18,21,23,40,56). Tao *et al* (27) suggested that this difference might be due to the innate immune and memory cell status of immune cells in cluster 1, as well as the presence of various immune cells with immunosuppressive effects.

Additionally, numerous classification studies have focused simultaneously on the correlation between their own molecular classification and the traditional Lauren classification (3,17,18,21,29,32,36), as well as the classical TCGA classification (17,18,20,24,27,29,36). It was found that the diffuse subtype according to Lauren classification was mostly associated with EMT features (18,21,29), genomic stability (17,18,36) and late-stage GC (18,21). The intestinal subtype is often found in patients with MSI (18,29), TP53 mutations (3,17,18,36), or high TMB (18,21,36).

5. Proteomic classifications

Proteomic technologies, predominantly reliant on liquid chromatography coupled to tandem mass spectrometry, are gaining traction in cancer research. They are utilized to identify and quantify proteins and post-translational modifications that undergo modulation in cancer. These technologies also help elucidate their associations with copy number variations, epigenetic silencing and alterations in microRNA (miRNA)

expression (80). In recent years, several proteomic studies on various cancers have rediscovered numerous of the same subtypes identified through gene expression and proposed new disease classifications (81-85).

Four studies classified GC molecularly based on proteomic subtyping, all of which were conducted on Chinese cohorts (Table III) (34). Based on gene products significantly differentially expressed between tumor and normal tissues, Ge *et al* (34) classified 84 patients with diffuse-type GC (DGC) from the Beijing Cancer Hospital into PX1-3 subtypes. PX1 and PX2 subtypes exhibited dysregulation throughout the cell cycle, and the PX2 subtype also displayed promotion of EMT. The PX3 subtype was enriched in immune-related proteins and drug-target proteins such as TMEM173 (STING), CD276, CD40, FCGR1A, ARG1, SIRPA, NT5E and IDO1 (86-88). DNA mutations in the PI3K-AKT, CXCR4, and focal adhesion pathways were enriched in the PX3 subtype. According to the prognostic analysis of advanced GC, patients with PX1 GC had the best prognosis, while patients with PX3 GC had the worst prognosis, which might be related to the abnormal enrichment of immune-regulating proteins. Subsequently, this institution conducted a proteomics analysis of phosphorylated proteins (35), which classified 83 patients with DGC into the Ph1-3 subtypes. The Ph1 subtype had the best prognosis and was enriched in TILs and stromal cells. Elevated levels of intratumoral and stromal TILs have been confirmed to correlate with improved prognosis in various cancers (89-92). The Ph1 subtype also showed upregulation of rRNA processing and RNA polymerase II promoter activity. The Ph2 subtype mainly presented upregulation of DNA metabolism and repair processes with loss of essential functions of the stomach, including gastric acid secretion. The Ph3 subtype presented upregulation of chromosome segregation with loss of cell-to-cell interactions and communication. Additionally, compared with the previous proteomic subtypes, the Ph1 subgroup included some patients assigned to the PX2 and PX3 groups, but these patients had improved overall survival (OS) than those in the original PX2 and PX3 groups, indicating that subtyping based on phosphorylated proteomic data may be more accurate (35).

Shi *et al* (38) reported that ARID1A mutations have opposite prognostic implications for DGC and intestinal-type GC (IGC). The prognosis is worse in DGC but improved in IGC. Therefore, comparing DGC and IGC based on multilevel proteomic data is highly important. Shi *et al* (38) molecularly classified 196 Chinese patients with DGC and IGC based on proteomics, phosphorylated proteomics, transcription factor (TF) activity profiling, and the relative abundance of different cell types in the tumor microenvironment (Table III). Clustering analysis of the differentially upregulated proteins revealed that DGC cluster 1 and IGC cluster 3 were characterized by enrichment of cell cycle-related proteins (such as CDK6 and CDK1/2) and DNA replication-related proteins (such as AHCTF1 and ORCS3). Numerous immune response-related proteins (such as IDO1, ICAM1 and CD163) as well as proteins regulating neutrophil degranulation and complement cascades (such as C5, IL 16 and FCER1G) were overexpressed in DGC cluster 3 and IGC cluster 1. DGC cluster 1 had a favorable prognosis but was insensitive to chemotherapy, while IGC cluster 3 had a poor prognosis but was sensitive to chemotherapy, indicating significant differences in clinical outcomes between the two groups with similar protein expression profiles. ATM/ATR are key kinases involved in DNA mismatch repair and may be potential targets for DGC treatment (93). The potential target for IGC was CDK4/6. It has been previously shown that CDK4/6 inhibitors not only induce tumor cell cycle arrest but also enhance antitumor immunity (94). Subtypes based on TF activity demonstrated the importance of the TFs SMARCC1 and NFKB1 in DGC and IGC. Patients with high SMARCC1 activity in IGC or low NFKB1 activity in DGC who received adjuvant chemotherapy had a favorable prognosis. The NFKB complex has been reported to play a crucial role in the immune response (95), cell proliferation/death and inflammation (96), among other functions (97). Conversely, the SWI/SNF complex was implicated in translation and cell cycle progression in IGC TF cluster 2, while it was involved in RNA splicing and DNA replication in DGC TF cluster 1. There was a correlation between the phosphorylated proteomic subtype and the proteomic subtype. According to the subtyping of the relative abundance of different cell types in the tumor microenvironment, the difference in prognosis between DGC and IGC was reversed in immune cluster 3, which was enriched in matrix components.

The incidence of adenocarcinoma of the esophagogastric junction (AEG) has been increasing annually (98,99), and the prognosis has been poor (100). Li *et al* (37) classified 103 AEG tumor samples based on proteomic clustering. The S-I subtype was more abundant in Siewert type II patients, while the S-III subtype was more common in Siewert type III patients. The S-III subgroup had the best prognosis, followed by the S-II subgroup, and the S-I subgroup had the worst prognosis. The most common leptin receptor (LEPR) and significant co-occurrence of the CSMD1 and ANKRD36C genes were found in the S-I subtype. LEPR is a receptor for leptin, a protein hormone mainly secreted by adipose tissue (101). LEPR genotypes have been found to be associated with the risk of various cancers, including esophageal squamous cell carcinoma (102), breast cancer (103) and GC (104). RYR2 and TTN mutations found in the S-III subtype were mutually exclusive, and the FAT4 and PRKDC genes exhibited a significant co-mutation relationship. The RYR2 gene plays a crucial role in steroid metabolism and could reduce the risk of breast cancer (105). In the S-II subtype, specific cooccurring mutations in the MUC4 and CPED1 genes were identified, with NCKAP1 mutations being the most common. In addition, in the S-I and S-III subtypes, there was a significant correlation between CDK1/2 and their phosphorylated substrates. Moreover, CSNK2A1 was found to be significantly correlated with the phosphorylation of Occludin S408 in the S-II subtype, and CSNK2A1 may be a target for the S-II subtype. Moreover, CSNK2A1 has been shown to participate in tumorigenesis by phosphorylating various proteins, including SIRTs (106,107). Li *et al* (37) found and validated that the characteristic protein of the S-II subtype (FBXO44) could promote tumor progression and metastasis *in vitro* and *in vivo*. Recent research has indicated that FBXO44 serves as a crucial inhibitor of DNA replication-coupled repeat elements in human cancer (108).

Table III. Features of gastric cancer subtypes based on proteomic clustering studies.

Sequencing type (Basis)	Group name (N)	Survival	Clinical/Immune	Molecular findings	(Refs.)
Proteome (DEPs)	PX1 (16)	Good		Enriched in cell cycle-related proteins	(34)
	PX2 (34)			Enriched in cell cycle-related and the EMT process proteins	
	PX3 (34)	Poor		Enriched in immune response proteins Mutations in the CXCR4, PI3K-AKT, and focal adhesion pathways High TMEM173 (STING), ARG1, NT5E, CD40, IDO1, SIRPA, CD276, and FCGR1A expression	
Phosphoproteome (Differentially expressed phosphorylation sites)	Ph1 (22)	Good	Younger (<50); early-stage (stage II) enriched in higher intratumoral TILs and mesenchymal cells	Upregulated rRNA processing and RNA polymerase II promoter activity	(35)
	Ph2 (33)		Older (>50); advanced stage (stage III-IV)	Upregulated DNA metabolic process and DNA repair while losing the basic function of the stomach including gastric acid secretion	
	Ph3 (28)		Older (>50); advanced stage (stage III-IV)	Upregulated chromosome segregation and mainly lost cell-cell interaction and communications	
Proteome, phosphoproteome, and TF activity	DGC (83)	Poor (ARID1A mutation)	High immune infiltration	Enriched in immune system, complement cascade, ECM organization, and cell migration proteins Potential targets: CDK4/6	(38)
	IGC (102)	Good (ARID1A mutation)		Enriched in DNA damage, ERBB signaling, metabolism, and VEGF signaling pathway proteins Potential targets: ATM/ATR	
Proteome (Differentially expressed upregulated proteins)	DGC cluster 1 (23)	Good		Characterized by the cell cycle and DNA replication Upregulated S phase signature proteins	
	DGC cluster 2 (28)			Characterized by ECM organization, collagen formation and biosynthesis	
	DGC cluster 3 (28)			Overexpression of numerous immune response-related proteins and proteins regulating neutrophil degranulation and complement cascade	
	IGC cluster 1 (18)	Good		Overexpression of numerous immune response-related proteins and proteins regulating neutrophil degranulation and complement cascade	
	IGC cluster 2 (49)			Characterized by ECM organization, collagen formation and biosynthesis; high stroma score	
	IGC cluster 3 (25)	Poor		Characterized by the cell cycle and DNA replication Upregulated G2M phase transition signature proteins	
TF activity (Detected in >50% of patients)	DGC TF cluster 1 (40)	Good		Master TFs: MLX and SMARCC1; the SWI/SNF complex involved in RNA splicing and DNA replication	

Table III. Continued.

Sequencing type (Basis)	Group name (N)	Survival	Clinical/Immune	Molecular findings	(Refs.)
	DGC TF cluster 2 (43)	Poor	Lymphovascular invasion (75.6) Antrum (46.7)	Master TFs: NFKB1, RELA, and IRF2; the NFKB complex involved in immune response, CAMs translation, and cell migration	
	IGC TF cluster 1 (42)	Good	Early-stage	Master TFs: NFKB2; the NFKB complex involved in Rho protein signal transduction and platelet activation	
	IGC TF cluster 2 (60)	Poor		Master TFs: SMARCE1 and TFAP4; the SWI/SNF complex involved in translation and cell cycle progression	
Phosphoproteome (Detected in >50% of patients)	DGC phospho-proteomic cluster 1 (27)			Characterized by RNA splicing, cell cycle, DNA repair and RHO GTPase cycle	
	DGC phospho-proteomic cluster 2 (37)			Characterized by cytoskeleton organization	
	DGC phospho-proteomic cluster 3 (16)			Characterized by cadherin binding and cell adhesion molecule binding	
	IGC phospho-proteomic cluster 1 (27)			Characterized by cytoskeleton organization and actin cytoskeleton organization	
	IGC phospho-proteomic cluster 2 (26)			Characterized by RNA splicing and DNA repair	
	IGC phospho-proteomic cluster 3 (30)			Characterized by cell cycle	
Proteome (DEPs)	S-I (40)	Poor	Older (75%≥65); Siewert type II	Mutation in LEPR; CSMD1 and ANKRD36C genes showed significant mutation co-occurrence Enrichment of IKBKB and PRKDC kinases	(37)
	S-II (23)		Low immune infiltration	Mutation in NCKAP1; characteristic protein: FBXO44; MUC4 and CPED1 genes showed significant mutation co-occurrence Enrichment of HIPK2 kinase Protein kinase target: CSNK2A1	
	S-III (40)	Good	Siewert type III	Mutation in WIZ; mutually exclusive mutations in RYR2 and TTN FAT4 and PRKDC genes showed significant mutation co-occurrence Enrichment of CHEK2 and AURKB kinases High integrated protein abundance of the 'G2M checkpoint' hallmark Low integrated protein abundance of the 'pancreas beta cells'	

N, number; EMT, epithelial-mesenchymal transition; TILs, tumor-infiltrating lymphocytes; DGC, diffuse-type gastric cancer; IGC, intestinal-type gastric cancer; TF, transcription factor; DEPs, differentially expressed proteins; CSNK2A1, casein kinase II subunit α

6. DNA methylation, metabolomic and multi-omic classifications

Since the discovery of 5-methylcytosine in bacteria in 1925 (109), research on DNA methylation has gradually progressed. DNA methylation profiling, as an emerging tool, serves as an adjunctive means to enhance the accuracy of pathological diagnosis (110). In 2014, Lei *et al* (3) classified patients into low methylation (L) and high methylation (H) subgroups based on the methylation status of 1421 CpG sites in 768 cancer-related genes. High methylation in females was correlated with MSI in GC. CpG sites with high methylation in the H group were more frequently located on CpG islands and marked with polycomb occupancy.

Metabolomics involves examining metabolites present in biological fluids, cells and tissues, and is widely utilized for the identification of biomarkers (111). Wang *et al* (39) conducted spatial metabolomic studies on 362 patients with GC and identified three tumor (T1-3)- and three stroma (S1-3)-specific subtypes with distinct tissue metabolism patterns. The tumor-specific T1 subtype exhibited positive correlations with CD3, CD8, FOXP3, MIB1 and HER2 expression, while displaying negative correlations with MMR status. The T1 subtype exhibited 45 significantly upregulated metabolic pathways, including 13 associated with carbohydrate metabolism and 10 associated with amino acid metabolism. Notably, nucleotide metabolism, as well as ascorbic acid and citric acid metabolism, was upregulated only in T1. In a recent study on psoriasis, the upregulation of ascorbic acid and citric acid metabolism was shown to enhance the immunosuppression of Tregs (112). Conversely, the tumor-specific subtype T2 exhibited downregulation HER2, MIB1, CD3 and FOXP3 but a high rate of MMR status. Additionally, 17 notably upregulated metabolic pathways were identified, comprising 7 associated with carbohydrate metabolism and 4 associated with amino acid metabolism. Additionally, this subtype is associated with an unfavorable prognosis. The tumor-specific subtype T3 was shown to be associated with biotin metabolism and cytoplasmic DNA sensing pathways. The cGAS-STING pathway was identified as a vital DNA-sensing mechanism in innate immunity and viral defense. The cGAS-STING signaling pathway also functions in promoting tumor metastasis, and chronic activation of this pathway can paradoxically induce immunosuppressive tumor microenvironments (113). Subtype similarities were observed between T1 and S3, T2 and S2, and T3 and S1.

Integrated single-cell genomics, epigenomics, transcriptomics, proteomics, and/or metabolomics analyses are reshaping our understanding of cellular biology in health and disease (114). Molecular classification based on multi-omics data has been conducted for various cancers (115-117). Hu *et al* (28) subtyped GC samples into CS1 and CS2 subtypes based on data for mRNAs, long non-coding RNAs, miRNAs and DNA methylation CpG sites associated with prognosis. The main pathways enriched in the CS1 subtype, which has a favorable prognosis, were involved in the activation of extracellular-related biological processes, including EMT, cell adhesion tissue, response to growth factors and cell-matrix adhesion pathways. SMOC2, which promotes EMT, was significantly upregulated in the CS1 subtype (118). The CS2 subtype, which has an unfavorable prognosis, was primarily enriched in pathways related to the cell cycle, including the G1/S-specific transcription, G2M checkpoint, E2F targets, DNA replication and repair biological processes. Patients in the CS2 subgroup exhibited activated programmed death-1 (PD-1) signaling, which is associated with most EBV and MSI subtypes found in CS2 patients.

Mun *et al* (33) conducted a proteogenomic analysis on paired tumor and adjacent normal tissues from 80 cases of early-onset GC (EOGC), classifying them into four subtypes (subtypes 1-4). Each subtype exhibited distinct genetic and protein characteristics. Subtype 1 was primarily involved in processes related to cell proliferation; Subtype 2 was mainly associated with immune response processes; Subtype 3 was primarily engaged in metabolism-related processes; Subtype 4 was mainly involved in invasion-related processes. Notably, the more favorable prognosis subtype 2 demonstrated that mutations in CXCR5 and its downstream G-proteins (GNAI3, GNB3-5 and GNG4) could modulate phagosome activity in antigen-presenting cells and TCR signaling in T cells through their interactions with phosphorylated proteins in these pathways (NCF2/4 and CYBA/B in phagosomes, and CD8A, CD247, LCK and PLCG in T cell signaling). Conversely, the poorer prognosis subtype 4 revealed that the activity of the actin cytoskeleton, primarily regulated by RHOA and RAC1 signaling, could be influenced by mutations in two genes, PLK4 and NEK3, in their upstream pathways via their associations with phosphorylated proteins involved in actin cytoskeleton regulation (MSN, PPP1R12B/C, MYLK, ACTN4, VCL, PXN, PAK4 and ARHGEF7 in RHOA or RAC1 signaling).

Li *et al* (25) used a multivariate Cox regression model to identify crucial features from mRNA, miRNA and DNA methylation datasets, dividing patients into three subtypes. Tumors of subtypes 1 and 3 were located mainly in the gastric antrum, while tumors of subtype 2 were located predominantly in the cardia. Features of subtype 1 ($ARID1A^+$ type) included high ARID1A and PIK3CA mutations, which are correlated with a favorable prognosis and mainly correspond to previously reported EBV, MSI, and EP subtypes (16,32). ARID1A plays a crucial role in multiple regulatory processes (119), including the modulation of the PI3K/AKT/mTOR pathway, steroid receptor regulation, DNA damage checkpoints, and regulation of p53 and KRAS targets, contributing significantly to the regulation of oncogenic or tumor-suppressive gene expression. Tumors of subtype 2 ($TP53^+$ type) had highly recurrent TP53 mutations, which are linked to an unfavorable prognosis, and mainly corresponded to the previously reported CIN and EP subtypes (83%) (16,32). Tumors of subtype 3 ($CDH1^+$ type) had high CDH1 and apolipoprotein (APO) A1 mutations and was associated with an unfavorable prognosis; this type mainly corresponded to the previously reported GS and MP subtypes (72%) (16,32). CDH1 is the basis of hereditary diffuse GC syndrome (120). APO A1 is the major apolipoprotein among plasma high-density lipoproteins and has therapeutic potential for various diseases (121). Detailed information is included in Table IV.

7. Personalized treatment based on molecular classifications

GC is one of the most prevalent malignant tumors of the digestive system, exhibiting notable heterogeneity and complex

Table IV. Features of gastric cancer subtypes based on DNA methylation/metabolomic/multiomics clustering studies.

Sequencing type (Basis)	Group name (N)	Survival	TCGA	Clinical/Immune	Molecular findings	(Refs.)
DNA methylation profiling (Tumor-specific CpG methylation sites)	L/low methylation (17) H/high methylation (43)			Female (36%)	CpG sites that were hypermethylated were more frequently located in CpG islands and marked for polycomb occupancy SEZ6L, FLT4 and ALK CpG sites with the greatest differences	(3)
Spatial metabolomics (Differentially metabolized products in tumor/stromal regions)	T1/HER2+MIB+CD3+ (161)/S3/HER2+MIB+ CD3+FOXP3+ (164)	Good		Early pathological UICC stage High TILs	Positively correlated with HER2, MIB1, DEFA-1, CD3, CD8, FOXP3, but negatively correlated with MMR and pEGFR; enriched nucleotide metabolism Upregulated nucleotide metabolism and ascorbate and aldarate metabolism	(39)
	T2/HER2+ MIB+CD3+ (55)/S2/HER2-MIB-CD3- (50)	Poor		Late pathological UICC stage Low TILs	Negatively correlated with HER2, MIB1, CD3, FOXP3, but positively correlated with MMR	
	T3/pEGFR+ (131)/S1/FOXP3- (125)				Positively correlated with pEGFR Related to biotin metabolism and cytosolic DNA sensing pathway	
Transcriptome, DNA methylation (OS-associated mRNA, LncRNA, miRNA, DNA methylation CpG sites, and mutant genes)	CS1 (131)	Poor	CIN (71.5)	White patients; Younger	Enriched in the activation of extracellular associated biological processes, including EMT, cell adhesion tissue, cell component morphogenesis, response to growth factors, and cell-matrix adhesion pathways High SMOC2 expression	(28)
	CS2 (112)	Good	EBV; MSI		Enriched in the cell cycle, including G2M checkpoint, cell cycle, E2F targets, G1/S-specific transcription, DNA replication, and repair biological processes High TMB; High immune activation feature score Mutations in TTN, MUC16, and ARID1A	
Proteome, Genome (mRNA)	Subtype 1				Cell proliferation-related processes: cell cycle and DNA replication, RNA processing, translation, and protein degradation	(33)
	Subtype 2	Good	EBV; MSI		Immune response-related processes: antigen presentation, BCR/TNF/Toll-like receptor signaling, TCR signaling, and phagosome; phagocytosis and antigen presentation; TCR signaling	
	Subtype 3				Metabolism-related processes: oxidative phosphorylation, fatty acid β-oxidation, and citrate cycle	
	Subtype 4	Poor	GS		Invasion-related processes: actin cytoskeleton, MAPK, PI3K-AKT, WNT, RHOA, and cadherin signaling; RHOA	

Table IV. Continued.

Sequencing type (Basis)	Group name (N)	Survival	TCGA	Clinical/Immune	Molecular findings	(Refs.)
Genome, transcriptome, DNA methylation (the important features of mRNA, microRNA, and DNA methylation data selected by the multivariate Cox regression model)	Subtype 1/ARID1A+ type (151)	Good	EBV; MSI		Mutations in ARID1A and PIK3CA Cosmic signature: SBS6 GSVA gene sets: KRAS_SIGNALING_DN, CDC73_TARGET_GENES, STK33_SKM_DN Diver genes: ORC1, EZH2, CDC7, ASF1B, CENPU, CDCA7, MAPK4 and DUSP26	(25)
	Subtype 2/TP53+ type (94)		CIN		Mutations in TP53; Cosmic signature: SBS17b GSVA gene sets: ANDROGEN_RESPONSE, MYCMAX_03, STK33_SKM_UP Diver genes: DKK1, IGFBP1, MATN3	
	Subtype 3/CDH1^{+} type (78)		GS		Mutations in CDH1 and APOA1; Cosmic signature: SBS1 GSVA gene sets: TGF_BETA_SIGNALING, AHRARNT_01, CAHOY_ASTROGLIAL Diver genes: APOA1	

N, number; TCGA, The Cancer Genome Atlas; MMR, mismatch repair; HER2, epidermal growth factor receptor 2; p-EGFR, phospho-epidermal growth factor receptor; MIB1, E3 ubiquitin-protein ligase; CD3, cluster of differentiation 3; CD8, cluster of differentiation 8; FOXP3, forkhead box the P3; EMT, epithelial-mesenchymal transition; EBV, Epstein-Barr virus; MSI, microsatellite instability; GS, genomically stable; CIN, chromosomal instability; TMB, tumor mutation burden.

molecular features (122). Historically, targeted therapies focused on single genes have shown promise in prolonging survival and improving quality of life compared with treatment based on pathological or morphological classifications. Claudin 18.2, due to its unique biological behaviour-being almost exclusively expressed in the gastric mucosa and appearing on the tumour cell surface during malignant transformation-has emerged as a promising target for GC therapy (123). In several international multicentre phase II/III clinical trials, zolbetuximab (an anti-claudin 18.2 monoclonal antibody) demonstrated the ability to improve OS and progression-free survival in previously untreated patients with GC with high levels of claudin 18.2 when used in combination with chemotherapy (124-127). A recent systematic review has detailed the biological behaviour of claudin 18.2 and the clinical efficacy of its targeted therapies (123). However, these approaches have limitations, including limited therapeutic efficacy and severe side effects. With the advent of the era of precision medicine in GC, personalized treatments involving multigene clustering are gradually demonstrating their advantages, as they effectively address the suboptimal outcomes associated with the high heterogeneity of GC (128). Among 27 studies on GC molecular subtyping, 10 described suitable treatment options based on their own molecular subtyping results (Fig. 2).

Adjuvant chemotherapy, primarily based on fluoropyrimidine, includes single-agent treatment with S1 (a combination of tegafur, gimeracil and oteracil) or combination therapy with capecitabine and oxaliplatin or S1 and docetaxel (129,130). Adjuvant chemotherapy has shown favorable survival benefits in East Asian countries (2). Lei *et al* (3) reported that the metabolic subtype of GC was more sensitive to 5-fluorouracil (5-FU) than were the other two subtypes, possibly due to the significantly reduced expression of dihydropyrimidine dehydrogenase and thymidylate synthase (TS) (131,132). Additionally, sensitivity to 5-FU in a specific molecular subtype was also identified in three other studies (23,27,28). A prospective study suggested that MSI (dMMR) patients with GC may not benefit from 5-FU adjuvant chemotherapy (133). Li *et al* (18) investigated the response rates to four different chemotherapies (cisplatin, capecitabine, oxaliplatin and doxorubicin) among GC subtypes. They found that almost all drugs followed the same sensitivity pattern: ImE > StE > ImD. Cisplatin had the highest efficacy in treating ImD (ImD: 73%; StE: 46%; ImE: 67%). This may be due to the high prevalence of homologous recombination defects in ImD, which might increase the sensitivity to cisplatin chemotherapy (134,135), a phenomenon extensively studied in BRCA1/2-negative triple-negative breast cancer (136-138). Cisplatin was also effective in Tao *et al*'s (27) cluster 1 and Zhu *et al*'s (23) subtype IS3. A previous study revealed that patients with CIN GC with a high level of fractional allelic loss were more likely to benefit from neoadjuvant chemotherapy based on cisplatin (139). Shi *et al* (38) discovered that patients with elevated SMARCC1 activity in IGC and reduced NFKB1 activity in DGC may derive benefits from chemotherapy. Notably, NFKB1 has been linked to chemotherapy resistance in breast cancer (140,141). SMARCC1 is the core subunit of the switching or sucrose non-fermentable (SWI/SNF) complex (142). Multiple pieces of evidence suggest that SWI/SNF complex alterations can serve as biomarkers for the efficacy of cancer immunotherapy (143,144). Abnormal expression of the SWI/SNF complex was identified as an independent adverse prognostic factor in patients with GS GC (based on TCGA classification). Detecting abnormalities in the SWI/SNF complex might help identify patients likely to benefit from novel treatment approaches (145). A clinical study revealed that SMARCC1-positive patients benefit from gemcitabine treatment after recurrence, as SMARCC1 can regulate cancer cell resistance to gemcitabine (146). Regarding gemcitabine, Li *et al* (20) reported that the C1 subtype was more sensitive than the C2 subtype was.

Oh *et al* (32) suggested that 5-FU-based chemotherapy could improve the prognosis of EP-subtype tumor patients but that this chemotherapy regimen did not benefit patients with MP-subtype tumors. MP-subtype GC cells were more sensitive to an inhibitor of the IGF1/IGF1R pathway (linsitinib). Lei *et al* (3) found that cell lines of the mesenchymal subtype were particularly sensitive to targeted phosphoinositide 3-kinase (PI3K)-AKT-mTOR pathway (PAM) inhibition. Previous studies have indicated that excessive activation of the PAM pathway promotes EMT and metastasis by significantly affecting cell migration (147,148). Although some inhibitors of this pathway have received approval from the U.S. Food and Drug Administration, concerns remain about resistance and toxicities, and sensitivity markers are still needed (149).

Additionally, in patients with HER2 (also known as ERBB2) overexpression or amplification, trastuzumab should be added to first-line cytotoxic chemotherapy (39,128). Immunotherapy has proven to be an effective treatment for various cancers (150). PD-1 and CTLA-4, belonging to the immunoglobulin-related receptor family, play diverse roles in regulating T-cell immune responses (151). Subtypes enriched in immune cells, such as Li *et al*'s (18) ImE subtype, Zhu *et al*'s (19) glycolysis subtype, and Zhu *et al*'s (23) IS3 subtype, are more likely to benefit from immunotherapy than other subtypes. The MSI and EBV subtypes (based on TCGA classification) have been largely confirmed to be sensitive to immunotherapy (18,28). MSI subtype GC, identified in several studies, might not benefit from chemotherapy, possibly because of elevated TS levels (152,153). Patients with MSI subtype GC exhibit increased reactivity to immunotherapy due to elevated PD-L1 expression (153-156). Patients with MSI subtype GC with high mutation rates in the PAM pathway often exhibit lower TIL numbers and primary resistance to immune checkpoint inhibitors, suggesting that immunotherapy could be used as a stratification approach in patients with advanced MSI-H GC (48,157). Similarly, EBV-positive GC might also respond to immune checkpoint therapy (158), but its efficacy awaits verification. High CTLA-4 levels and lower TILs might have impacted the effectiveness of anti-PD-1 monoclonal antibodies in patients with EBV GC (156,159). Ge *et al* (34) reported that the PX3 subtype of DGC, which exhibits high expression of IDO1 and ARG1, might benefit from IDO1 and ARG1 inhibitors. Various IDO1 and ARG1 inhibitors have been evaluated in clinical trials (160,161).

8. Conclusions and outlook

GC, characterized by strong heterogeneity, is a complex malignancy of the digestive system with unique epidemiological, histological and molecular differences (13).

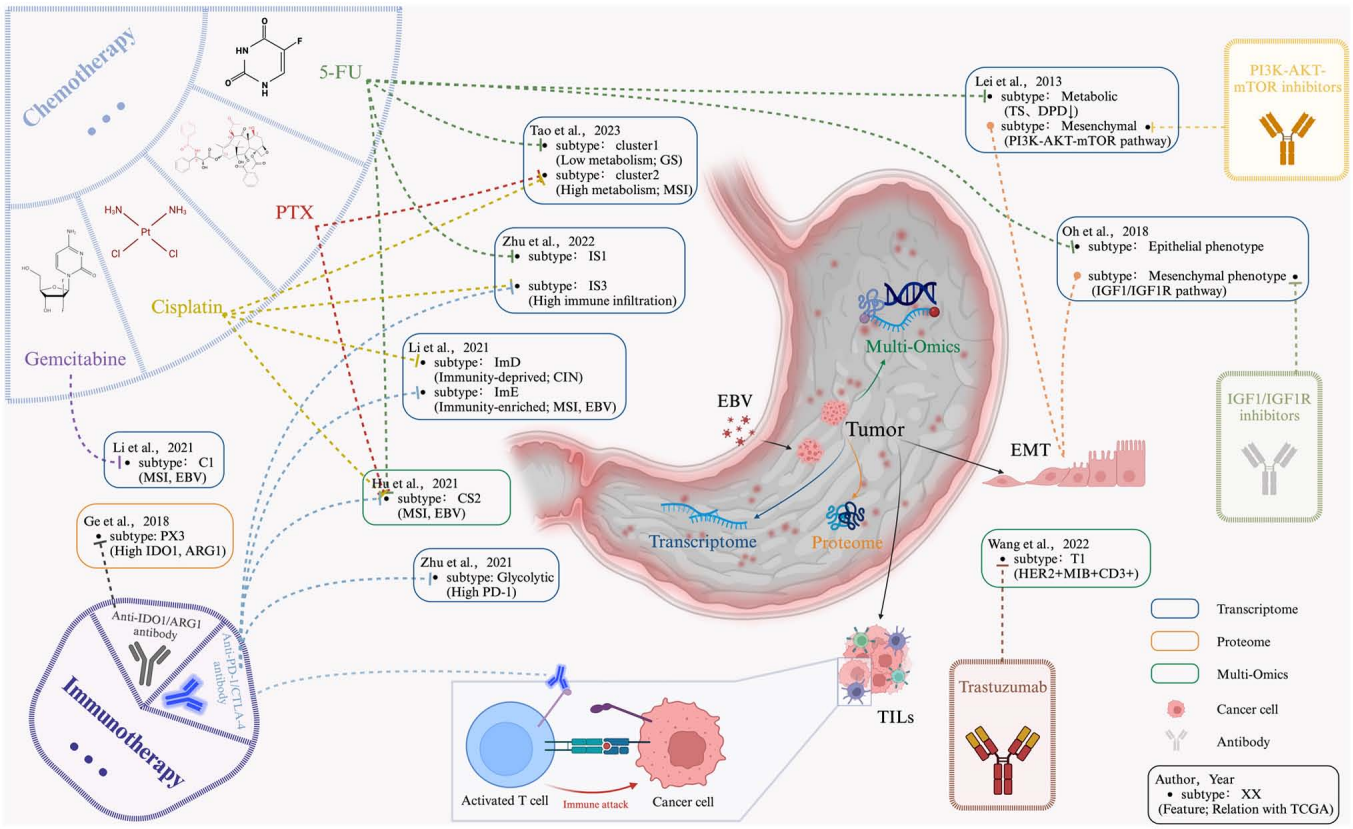

Figure 2. Therapeutic landscape of gastric cancer cluster subtypes. The diagram illustrates the effective drug treatment choices corresponding to subtypes mentioned in the 10 cluster classification studies. Below each subtype, information related to treatment and TCGA subtypes is provided. The bottom right corner of the diagram includes a legend for reference. Created with BioRender.com. TCGA, The Cancer Genome Atlas; EBV, Epstein-Barr virus; GS, genomically stable; CIN, chromosomal instability; MSI, microsatellite instability; IGF1, insulin-like growth factor 1; EMT, epithelial-mesenchymal transition; TILs, tumor-infiltrating lymphocytes; TS, thymidylate synthase; DPD, dihydropyrimidine dehydrogenase; PTX, paclitaxel; 5-FU, fluorouracil; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; PD-1, programmed death-1.

Cluster-based subtyping has great value in GC research. Unlike traditional molecular classification methods, cluster classification methods allow for the subdivision of GC into subgroups with distinct molecular characteristics, tumor biological features and clinical presentations. This approach forms the basis for personalized treatment, optimized clinical trial designs and improved patient management, driving medical advancements.

Immunohistochemistry, *in situ* hybridization, or reverse transcription-quantitative polymerase chain reaction analyses, which assess protein and mRNA expression, could serve as valuable and cost-effective tools for stratifying GC in clinical practice (162). However, in clinical application, the selection of appropriate biomarkers or gene sets, the adoption of standardized experimental procedures, and the integration of clinical data for comprehensive analysis are indispensable to ensure the reliability and reproducibility of the results.

Although cluster-based subtyping of GC provides crucial information for clinical diagnosis and treatment, there are still limitations: i) Most research findings are derived from bioinformatic analyses in basic research, and unlike conventional pathological classifications or single-gene classifications, they have not been widely used in clinical settings. This may be the focus of the next step in GC genomic subtype research; ii) the current genomic subtyping system for GC, although diverse, has not been validated in large cohorts (n>1,000), and simultaneous comparisons in large cohorts to explore the most adaptive genomic subtype are needed for precise application; iii) with the development of GC, molecular changes are dynamic, therefore identifying stable molecules to establish a consistent classification system is crucial; and iv) GC often exhibits both inter-tumor and intratumor heterogeneity, thus further exploration of the role of spatial genomics, single-cell technologies and other new techniques in GC cluster classification is needed.

In conclusion, GC should not be treated as a single disease. Cluster-based molecular classifications could aid in GC research, allowing us to delve deeper into the biological characteristics of different subtypes of GC, laying the foundation for personalized treatment and precision medicine. Additionally, utilizing new information from clustering subtypes will help in the design of more accurate and targeted clinical trials, enhancing the effectiveness and credibility of related research. This approach is expected to accelerate the discovery of new treatment methods, providing more effective treatment options for patients with GC and propelling medical research toward more rational and individualized treatment.

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Availability of data and materials

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Authors' contributions

YM and ZJ wrote and revised the manuscript. ZJ, LY and ZL conceived and designed the review. YM, ZJ, YZ, LP and RX performed the literature review. LP and LY revised the manuscript. ZL and LY acquired funding. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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