

REVIEW

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Genetic and molecular biology of gastric cancer among Iranian patients: an update

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Abstract

Background: There is a declining trend of gastric cancer (GC) incidence in the world during recent years that is related to the development of novel diagnostic methods. However, there is still a high ratio of GC mortality among the Iranian population that can be associated with late diagnosis. Despite various reports about the novel diagnostic markers, there is not any general and standard diagnostic panel marker for Iranian GC patients. Therefore, it is required to determine an efficient and general panel of molecular markers for early detection.

Main body of the abstract: In the present review, we summarized all of the reported markers until now among Iranian GC patients to pave the way for the determination of a population-based diagnostic panel of markers. In this regard, we categorized these markers in different groups based on their involved processes to know which molecular process is more frequent during the GC progression among Iranians.

Conclusion: We observed that the non-coding RNAs are the main factors involved in GC tumorigenesis in this population.

Keywords: Gastric cancer, Incidence, Risk factor, Genetic, Marker, Iran

Background

Gastric cancer (GC) is one of the leading causes of cancer-related deaths in Iran with a mortality rate of 8,000 cases per year [1]. GC incidence has a noticeable declining trend during the recent decades in the world; however, it has still a high incidence among the Iranian population. Despite novel therapeutic modalities, it has still a poor prognosis and low survival rate [2]. GC is more frequent in males compared with females [3]. East Asia, East Europe, and South America are the hotspots of GC incidences in the world [4]. Ethnic is also the other important determining factor involved in incidence variation in different populations [5]. Different genetic and environmental factors are involved in tumor progression [6]. It has been shown that *Helicobacter pylori* (*H.pylori*) infection and smoking are the main environmental risk

factors of GC in Iran. Although management of such environmental risk factors is the main way to reduce the GC incidence, early detection can improve the overall survival rates [7]. GC is mainly diagnosed in advanced tumor stages with a high chemoresistance [8, 9]. GC has a poor prognosis in advanced stage patients; however, gastrectomy can be effective following the early diagnosis that improves the patients survival [10, 11]. The majority of GC patients have not any access to the endoscopy as a screening method because of the high cost [12]. Therefore, the introduction of molecular mechanisms involved in early tumor stages will be helpful to design novel diagnostic methods for the early detection of GC. In the present review, we have summarized all of the significant reported molecular factors among Iranian GC patients (Table 1). We categorized all of the reported factors based on their involved molecular processes (Fig. 1) to know more about the molecular biology of GC among Iranian patients.

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Table 1 All of the involved markers in gastric cancer susceptibility among the Iranian patients

References	Gene	population	Results
Cell cycle, DNA repair, and apoptosis			
Abbaszadegan [15]	P16	52 patients 50 controls	Hyper methylation was correlated with malignant tumors
Moghbeli [17]	hMLH1	51 N/T*	Hyper methylation was correlated with advanced stages
Azarhoush [18]	P53	111 patients	Over-expression was correlated with tumor type
Rezaei [20]	SRBC	40 N/T 20 controls	Hyper methylation was correlated with age
Kordafshari [23]	AdipoR1 and AdipoR2	42 patients 52 controls	Over-expression
MicroRNAs and long non coding RNAs			
Ranjbar [31]	miR-19, miR-21	120 patients 102 controls	Over-expression
Ranjbar [31]	miR-146, miR-375, Let-7	120 patients 102 controls	Under-expression
Adami [32]	miR-146a	100 tumors 44 normal	Over-expression
Emami [35]	miR-21, miR-222	30 patients 30 controls	Over-expression
Larki [38]	miR-21, miR-25, miR-93, miR-106b	39 tumors 29 normal	Over-expression
Ziasarabi [39]	miR-17, miR-25, miR-133b	120 patients 102 controls	Increased serum levels of miR-17 and miR-25 reduced levels of miR-133b
Zare [40]	miR-155-5p, miR-15a, miR-186	39 tumors 29 normal	Under-expression
Parvaei [41]	miR107, miR-194, miR-210	50 patients 50 controls	Under-expression
Zare [42]	miR-124-3p, miR-218-5p, miR-484	40 tumors 31 normal	Under-expression
Ebrahimi Ghahnavieh [44]	miR-584	26 patients 11 controls	Over-expression was correlated with h. pylori infection, stage, and lymph node metastasis
Baratieh [54]	PlncRNA-1	35 N/T	Over-expression was correlated with sex and poor prognosis
Salavaty [55]	RAB6C-AS1	30 N/T	Correlation with differentiation
Kangarlouei [59]	ANRIL, ANRASSF1	39 N/T	Over-expression
Behzadi [60]	BC032913	80 N/T	Under-expression
Signaling pathways and transcriptional regulation			
Kosari-Monfared [64]	CTNBP1	58 N/T	Under-expression was correlated with sex and grade
jafari [69]	NOTCH1 and GATA6	24 N/T	NOTCH1 under-expression was correlated with distant metastasis
Ghadami [72]	CYLD	53 N/T	Under-expression was correlated with sex, grade, and age
Pilehchian Langroudi [76]	FAT4	30 N/T	FAT4 expression was inversely correlated with grade
Nasrollahzadeh-Khakiani [80]	CEBPA, UCA1	40 N/T	Over-expression
Moghbeli [81]	ERBB1, ERBB3	50 N/T	EGFR and ERBB3 co-overexpression was correlated with age and tumor size
Ayatollahi [83]	KRAS	120 patients	Mutation
Dokhaee [86]	GKN1	27 patients	Under-expression
Behroozi [88]	ADAR	42 N/T	Over-expression was significantly correlated with stage, poor prognosis, and tumor size
Abbaszadegan [90]	MAEL	80 N/T	MAEL had higher levels of expression in primary-stage tumors
Soleymani Fard [92]	AR	60 N/T 50 controls	Over-expression was positively correlated with increased lymph node involvement, tumor size, higher distant metastasis, and advanced stages
Inflammation			
Mohammadian Amiri [97]	NOD1, NOD2	39 patients 52 controls	Over-expression

Table 1 (continued)

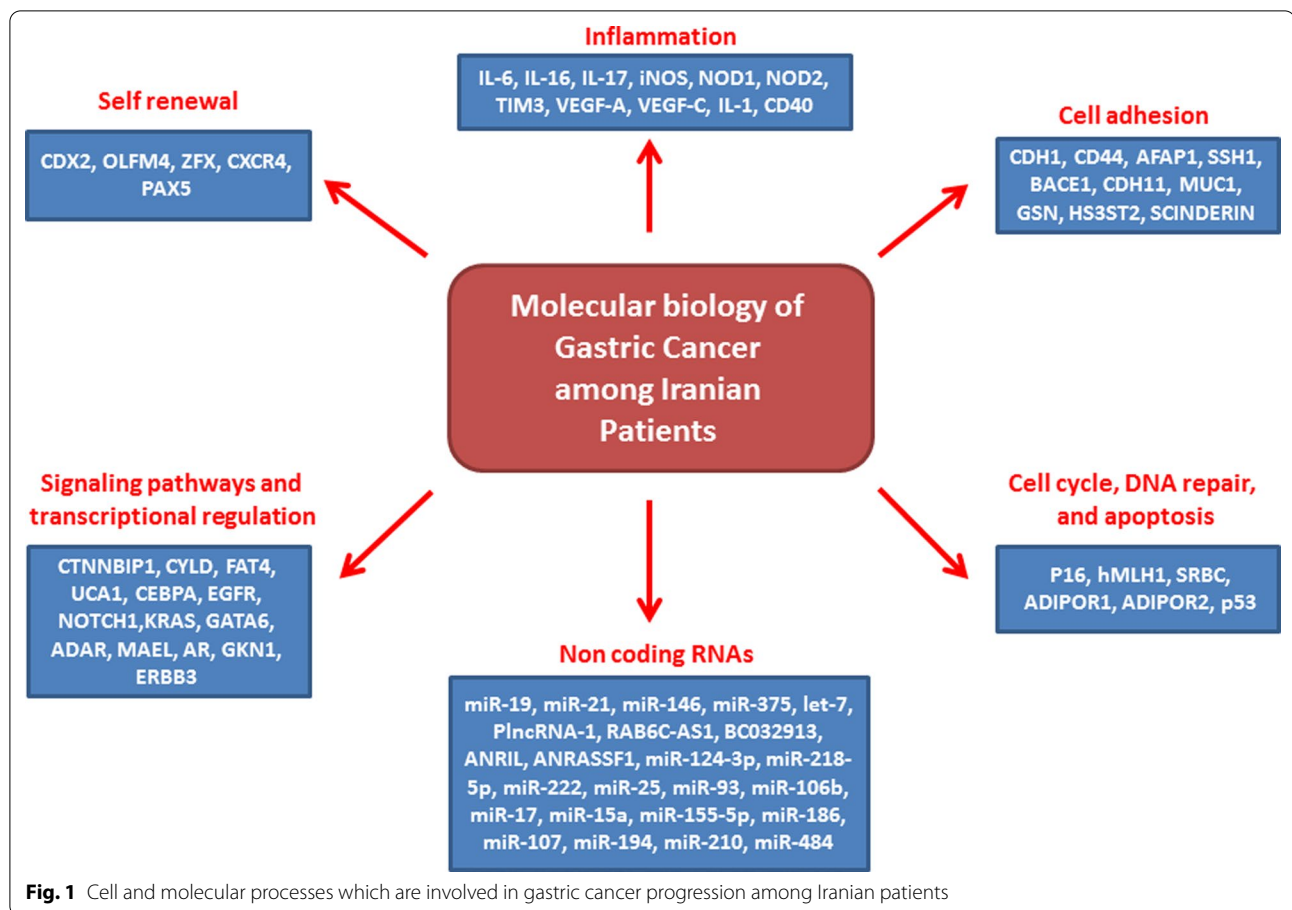
References	Gene	population	Results
Naghavi-Alhosseini [101]	TIM-3	43 patients 42 controls	Over-expression
Attar [105]	IL-6	100 patients 361 controls	Polymorphism was correlated with GC
Taghizadeh [109]	VEGF-C	38 patients 52 controls	Over-expression
Kashfi [113]	IL-16	256 patients 300 controls	Polymorphism was correlated with GC
Rafiei [116]	IL-17	161 patients 171 controls	Polymorphism was correlated with stage
Rafiei [120]	iNOS	159 patients 170 controls	Polymorphism was correlated with GC
Abbasian [122]	IL-1	35 patients 97 controls	Polymorphism was correlated with GC
Amini [123]	CD40	25 N/T	Hyper methylation
Stemness and self-renewal			
Samadani [127]	CDX2	–	Hypo methylation
Dabiri [129]	OLFM4	25 patients 10 controls	Over-expression
Nikpour [131]	ZFX	30 N/T	ZFX expression was correlated with grade
Rahmati [132]	ZFX	30 N/T	Over-expression was correlated with grade and size
Nikkhoo [134]	CXCR4	43 patients	CXCR4 expression was correlated with survival
Haghverdi [136]	PAX5	35 patients 35 controls	Under-expression
Cell adhesion and structural factors			
Menbari [139]	CDH1	50 patients 54 controls	Polymorphism was correlated with survival
Eyvazi [141]	CDH11 and HS3ST2	40 patients 40 controls	Hyper methylation
Bitaraf [144]	CD44	150 patients 150 controls	Polymorphism was correlated with survival
Mokhtarian [145]	CD44	86 patients 96 controls	Polymorphism was correlated with GC
Alikhani [147]	MUC1	99 patients 96 controls	Polymorphism was correlated with GC
Esfandi [150]	AFAP1	30 N/T	Under-expression
Daryabari [155]	SSH1	40 N/T	Over-expression
Esfandi [159]	BACE1	30 N/T	Under-expression
Tavabe Ghavami [162]	Gelsolin and Scinderin	41 patients	Gelsolin downregulation and Scinderin upregulation were associated with lymph node involvement

*Tumor tissues and normal margins

Main text**Cell cycle, DNA repair, and apoptosis**

Cell cycle deregulation triggers the aberrant cell proliferation that results in genetic instability in tumor cells. DNA-repair and cell-cycle checkpoints are the pivotal cellular processes that enable the cells to deal with DNA damages. Neoplastic transformation is due to the genetic changes which are facilitated in tumor cells through deregulation of DNA repair and replication. Both checkpoint controls and DNA repair systems have pivotal

roles in genome stability. Cell cycle progression is regulated by multiple checkpoints which evaluate the growth signals, DNA integrity, and cell size. Cyclin-dependent kinases (CDKs) and cyclin-dependent kinase inhibitors (CKIs) are the positive and negative regulators of cell cycle progression, respectively. Therefore, CDKs activation or CKIs suppression triggers tumorigenesis [13]. P16 is a tumor suppressor that induces cell cycle arrest through the inhibition of CDK4 and CDK6. Moreover, it suppresses the pRb phosphorylation and subsequent



transcription factors which are involved in G1 checkpoint transition [14]. The methylation status of p16 promoter sequence was evaluated in a group of Iranian GC patients. Promoter hyper methylation was observed in 44.2% of tissues and 26.9% of sera in patients. Regarding the lower ratio of methylation in well-differentiated tumors, p16 hyper methylation is probably correlated with malignant tumors. P16 was introduced as an efficient serum marker for the early detection of GC among Iranian patients [15].

Microsatellite instability is directly related to the mismatch repair system [16]. The role of hMLH1 promoter methylation as one of the components of MMR system was assessed among a subpopulation of Iranian GC cases. There was a significant correlation between methylation status of hMLH1 and tumor stages, in which the majority of hyper-methylated tumors were in advanced stages. Therefore, hMLH1 hyper methylation results in lower GC progression among Iranian patients compared with other countries [17]. Beyond the different checkpoint controls, cell cycle regulators, and DNA repair, there is also another barrier for the tumorigenesis in which the cells will be forced to undergo programmed cell death

(apoptosis). P53 as a tumor suppressor gene is associated with cell-cycle arrest and apoptosis. It has been reported that there was a high frequency of p53 protein upregulation in cardia compared with the antrum adenocarcinoma in a subpopulation of Iranian GC cases [18].

SRBC is also a tumor suppressor involved in apoptosis induction through TNF α [19]. It has been reported that there was SRBC hyper methylation in Iranian GC tissues compared with normal margins which was significantly correlated with the age of patients [20]. Adiponectin is a tumor suppressor that regulates apoptosis by the caspases and BCL2 activations [21, 22]. It has been observed that there were significantly higher expression levels of adiponectin receptors (AdipoR1 and AdipoR2) in a subpopulation of Iranian GC patients [23].

Micro RNAs and Long non-coding RNAs

MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are the most popular non-coding RNAs associated with tumorigenesis. MicroRNAs negatively regulate the mRNAs through binding with three untranslated regions [24]. These non-coding RNAs are involved in cell proliferation and migration through a post-transcriptional

regulation of target mRNAs. MiR-21 is associated with cell growth, angiogenesis, and metastasis by targeting PTEN, APAF1, and TGF- β [25, 26]. MiR-146a is upregulated by inflammatory cytokines such as IL-1 and TNF α [27]. STAT1, CCL8, and TLR4 are also the targets of miR-146a [28–30]. It has been shown that there were miR-19 and miR-21 over-expressions and miR-146, miR-375, and let-7 under-expressions in a subpopulation of Iranian GC patients [31]. Another report has been also shown the miR-146a upregulation in primary stages of GC tumors among a group of Iranian cases [32]. PTEN and RECK tumor suppressors are the targets of miR-222 [33, 34]. It has been observed that there were significantly increased miR-21 and miR-222 plasma levels in a sample of Iranian GC patients compared with controls. Therefore, these markers can be introduced as a minimally invasive diagnostic method for GC [35]. FOXO3 transcription factor is one of the main miR-25 target genes which regulates cell cycle progression and apoptosis [36]. MiR-106b/miR-93 functions as an oncogenic cluster through the regulation of p21 and BIM tumor suppressors [37]. It has been observed that there were increased levels of miR-21, miR-25, miR-93, and miR-106b expressions in GC compared with normal samples among a group of Iranian cases. Except for the miR-93, over-expression of three other markers were significantly correlated with stage, *H. pylori* infection, and lymph node involvement. Since there were significant different miR-25 expressions between dysplasia and tumor tissues, the miR-25 can be introduced as a diagnostic marker for the early detection of GC [38]. It has been also observed that there were significantly increased serum levels of miR-17 and miR-25, whereas the reduced levels of miR-133b expression among a subpopulation of Iranian GC patients compared with controls. MiR-17 and miR-25 were introduced as diagnostic markers of early tumor stages [39]. Another group has been reported that there were significant decreased expression of miR-155-5p, miR-15a, and miR-186 in GC compared with controls among a group of Iranian cases. The *H. pylori*-positive GC tissues had lower levels of miR-155 in comparison with the infection-free samples. Moreover, the tumors with metastatic lymph nodes had significantly lower levels of miR-155 and miR-186 expressions [40]. MiR-194 functions as a tumor suppressor via the regulation of NFAT5 and RAC1. MiR-210 is also another tumor suppressor which can inhibit the E2F3 expression. It has been shown that there were significantly lower levels of plasma miR-107, miR-194, and miR-210 expressions in a sample of Iranian intestinal-type GC cases compared with the control group [41]. As a tumor suppressor, miR-124-3p targets the FRA2 and DN3B. MiR-218-5p is also associated with CD44-ROCK signaling inhibition. Moreover,

miR-484 suppresses cell proliferation and EMT process through downregulation of ZEB1 and SMAD2. It has been observed that there were miR-124-3p, miR-218-5p, and miR-484 downregulations in a group of Iranian GC cases. There was a significant correlation between miR-218 downregulation and advanced tumor grade. MiR-484 was correlated with malignant tumors in which advanced stage tumors had reduced levels of miR-484 expression [42]. MiR-584 induces the EMT process through FOXA1 targeting [43]. There was a significant miR-584 upregulation in gastric tumor tissues compared with normal margins among Iranian GC patients. There was a direct correlation between miR-584 upregulation and *H. pylori* infection. Moreover, miR-584 expression was inversely associated with higher stages and lymph node involvement [44].

LncRNAs are a class of non-coding RNAs with greater than 200 nucleotides in length [45, 46]. They have fundamental roles in cell differentiation, immune responses, and tumor progression through transcriptional and post-transcriptional mechanisms [47–50]. Since ncRNAs deregulations are associated with tumor progression, they can be used as diagnostic tumor markers [51]. PlncRNA-1 is an lncRNA encoded by the CBR3 antisense, which is upregulated in different solid tumors [52, 53]. PlncRNA-1 upregulation was reported in a subpopulation of Iranian GC cases. There were significant correlations between PlncRNA-1 upregulation and sex, N-classification, and poor prognosis. PlncRNA-1 was introduced as a marker of GC progression among Iranian patients [54]. RAB6C-AS1 expression was also assessed in a sample of Iranian GC patients that showed a probable association between RAB6C-AS1 and cell dedifferentiation during GC progression [55]. ANRIL is an lncRNA associated with polycomb repressive components such as CBX7 and SU12. ANRIL downregulates the p16 and p15 through PRC1 and PRC2 [56, 57]. ANRASSF1 is a lincRNA transcribed from the opposite strand of RASSF1A gene which inhibits the RASSF1 expression through SUZ12 to promote cell proliferation [58]. It has been reported that there were significant ANRIL and ANRASSF1 upregulations in a sample of Iranian GC patients [59]. BC032913 is an lncRNA transcribed from the antisense strand of DPP10 which functions through recruitment of PRC2 complex. It has been observed that there was BC032913 downregulation in a sample of Iranian GC patients [60].

Signaling pathways and transcriptional regulation

There are various intra-extra cellular signaling networks that are involved in the biology of cells. These signaling pathways are the regulators of various cellular functions such as cell division, proliferation, apoptosis, and

differentiation. Therefore, it is required for the normal cells to regulate the signaling pathways. Indeed, every aberration can result in deregulation of cellular homeostasis and neoplastic transformation. WNT signaling pathway regulates different developmental processes such as cell proliferation and migration [61]. Therefore, deregulation of WNT pathway induces tumor progression through excessive cell proliferation [62]. Catenin beta interacting protein 1 (CTNNBIP1) is an antagonist of β -catenin to bind with TCF/LEF complex [63]. It has been reported that there was a significant CTNNBIP1 downregulation in tumors compared with normal margins among a sample of Iranian GC patients. Moreover, there was a significant correlation between the levels of CTNNBIP1 expression and sex in which the females had lower levels of CTNNBIP1 expression in comparison with males. A significant CTNNBIP1 under-expression was also observed in well-differentiated tumors that suggested the CTNNBIP1 as a tumor suppressor during tumor initiation [64].

Notch is a developmental signaling pathway involved in cell proliferation, differentiation, apoptosis, and self-renewal. It can be triggered by four Notch receptors (Notch1-4) following the ligand–receptor binding which results in cleavage of Notch intracellular domain (NICD) and nucleus translocation where it regulates the expression of target genes [65, 66]. GATA is a developmental transcription factor that activates canonical WNT signaling pathway during tumor progression [67]. CDX2 is also a critical transcription factor involved in intestinal epithelial cells differentiation and proliferation [68]. It has been reported that downregulation of Notch1 was correlated with distant metastases in a sample of Iranian GC patients. There was also a significant GATA6 downregulation in tumor samples compared with normal margins. A significant positive association was also observed between the levels of CTNNB1 and GATA6 expressions in GC tissues [69].

The cylindromatosis (CYLD) is a negative regulator of several signaling pathways such as WNT, SHH, and NOTCH, which have critical roles in apoptosis and cell cycle regulation. Therefore, CYLD aberration can be correlated with tumor progression [70, 71]. CYLD promoter methylation was assessed and showed that there was a significant correlation between CYLD under-expression and high-grade tumors, age, and sex. Moreover, CYLD under-expression was significantly correlated with lack of lymph node metastasis in Iranian GC cases [72].

The Hippo signaling pathway is involved in regulation of the cell proliferation and organ size [73]. FAT4 belongs to the E-cadherin protein family and is also a member of Hippo signaling pathway which is involved in organ size. The (YAP/TAZ) transcriptional coactivator is the

main component of hippo pathway to regulate cell proliferation [74, 75]. It has been observed that there was an inverse correlation between FAT4 expression and tumor grade among Iranian GC patients [76].

PI3K/AKT signaling pathway is also the regulator of different cellular processes that can be suppressed by PTEN. More than 30 AKT substrates have been reported that mediate the AKT functions in cell proliferation, differentiation, and migration. Therefore, aberrant PI3K/PTEN/AKT pathway can be observed in neoplastic transformation [77]. UCA1 functions as a mediator of AKT pathway in activation of CREB transcription factor during tumorigenesis [78]. UCA1 also upregulates the cyclin D1 which induces cell cycle progression in GC [79]. Extra coding CEBPA (ecCEBPA) is an lncRNA that is involved in DNA methylation through interaction with DNA methyltransferase 1. Patterns of UCA1 and ecCEBPA expressions were assessed in a subpopulation of Iranian GC patients that showed ecCEBPA and UCA1 over-expressions in tumor tissues compared with normal margins. Moreover, the levels of UCA1 expressions were significantly correlated with tumor type and grade. Therefore, UCA1 and ecCEBPA were involved in GC and introduced as efficient diagnostic/prognostic markers in Iranian patients [80].

EGFR family of tyrosine kinase receptors is comprised of ERBB1-4 which are associated with cell proliferation, differentiation, and migration. EGFR activation triggers PI3K/AKT signaling pathway. The correlation between EGFR and ERBB3 expressions were assessed among a sample of Iranian GC cases which showed that the EGFR and ERBB3 co-overexpression was a poor prognostic marker. EGFR and ERBB3 co-overexpression was correlated with age and tumor size. It was concluded that the ERBB1/3 had a key role in the early stages of GC and can be suggested as diagnostic markers for the early detection of aggressive gastric tumors in this population [81]. K-RAS is a G-protein member of RAS family involved in EGFR signaling pathway [82]. A mutational analysis was performed to assess the frequency of KRAS codon 12 and 13 mutations in a sample of Iranian GC patients compared with the general population. Point mutations were observed among 30% of GC subjects. There was also a significant correlation between KRAS mutation and tumor location in which the majority of KRAS mutation codon 13 were in fundus [83].

Gastrokine 1 and 2 (GKN1 and 2) are mainly expressed in normal gastric epithelium and preserve the integrity of gastric mucosa [84]. GKN1 induces apoptosis and reduces cell proliferation and epigenetic modification through the suppression of DNMT1, EZH2, and DNMT1. GKN2 inhibits the JAK2/STAT3 signaling pathway which results in reduced cell proliferation and apoptosis

induction via upregulation of Bax and downregulation of Bcl-2 and Cyclin D1 [85]. It has been reported that there was GKN1 downregulation in a sample of Iranian GC tissues [86].

RNA editing is a critical post-transcriptional process catalyzed by adenosine deaminase (ADAR) to change RNA molecules through adenosine deamination [87]. It has been shown that there was significant ADAR over-expression in a sample of Iranian GC tumors which was significantly correlated with stage, poor prognosis, and tumor size. Tumors in stage IV had higher levels of ADAR expression compared with stage III [88]. Piwi proteins are pivotal factors in genetic stability during spermatogenesis through suppression of retrotransposon. MAEL is a cancer testis and PIWI-interacting protein involved in transcriptional regulation of transposable elements and DNA damage [89]. It has been reported that there was a correlation between MAEL expression and tumor sizes in Iranian GC patients. Higher levels of MAEL expression were observed in *H. pylori* positive in comparison with negative tumors. MAEL had higher levels of expression in primary-stage tumors which was directly correlated with lymph node metastasis [90]. Androgen receptor (AR) belongs to the nuclear receptor family [91]. There was AR over-expression in the majority of Iranian GC patients compared with normal cases which was positively correlated with increased lymph node involvement, tumor size, higher distant metastasis, and advanced stages [92].

Inflammation

The inflammatory cytokines are important components of the tumor microenvironment. Local inflammatory condition is prerequisite for the neoplastic transformation in some tumor types, whereas in other types the tumor cells change their local inflammatory condition to promote tumor progression. Therefore, identification of new molecular cancer-related inflammatory pathways prepares novel diagnostic modalities [93]. NOD1 and NOD2 are members of NOD-like receptors (NLRs) family which are involved in gram-negative bacteria detection and chronic inflammatory response [94, 95]. They also stimulate the tumor progression through several transcription factors such as (NF)- κ B and STAT1 [96]. It has been shown that the Iranian GC cases had higher levels of NOD1 expression compared with the peptic ulcer disease (PUD) and non-ulcer dyspepsia (NUD) cases independent of *H. pylori* infection. PUD cases had also higher levels of NOD1 in comparison with the NUD cases. However, *H. pylori*-positive GC patients had higher levels of NOD2 expression compared with NUD and PUD groups [97].

Tim-3 is a regulator of anti-tumor immunity which is mainly expressed on Th1 cells, cytotoxic T-cells, and innate immune cells [98, 99]. Tim-3 expression in tumor infiltrating lymphocytes is correlated with TNF- α , IL-2, and IFN- γ aberration [100]. Levels of Tim-3 mRNA and protein expressions were assessed in a subpopulation of Iranian GC and PUD cases. There was a significant Tim-3 upregulation among GC and PUD subjects in comparison with the controls. A probable role of Tim-3 was suggested in immunoregulatory mechanisms during the primary steps of GC or PUD progression [101].

IL-6 is a pro-inflammatory cytokine involved in the differentiation of immune system, bone metabolism, CRP synthesis, and tumor progression [102–104]. Role of IL-6 -174 G/C polymorphism in GC susceptibility was also evaluated among a subpopulation of Iranian patients. It was observed that there was a significant difference in G allele frequency between the controls and patients. Moreover, IL-6 -174 C/G polymorphism had a probable influence on GC susceptibility among the Iranian population [105].

VEGF family including VEGF-A to F are glycoproteins that are involved in tumor metastasis and angiogenesis [106]. VEGF-A and B have key functions in blood vessels, whereas VEGF-C and D are involved in growth of lymphatic vessels [107, 108]. Inflammatory cytokines such as IL-1, IL-6, and TNF- α induce the VEGF that is responsible for tumor angiogenesis. Increased levels of VEGF-A and C expressions were observed among PUD or GC in comparison with NUD cases. Moreover, *H. pylori* positive PUD or GC cases had higher levels of VEGF-A and VEGF-C expressions compared with the negative cases. Therefore, VEGF-C over-expression following the inflammation can be resulted in neoplastic transformation of gastric mucosa into GC among Iranian patients [109].

IL-16 is a proinflammatory cytokine involved in immune system homeostasis, cell differentiation, and tumorigenesis [110, 111]. This factor can induce tumor-related cytokines such as TNF- α , IL-1 β , IL-6, and IL-15 [112]. It has been found that there was a significant correlation between rs1131445 T/C and rs4072111 T/C polymorphisms of IL-16 and GC susceptibility among Iranian population [113]. IL-17 is a pro-inflammatory cytokine that is mainly produced by Th17 cells and is involved in innate and adaptive immune responses [114, 115]. Role of the IL-17 G-197A promoter polymorphism was assessed among a subpopulation of Iranian GC cases. There was a significantly higher frequency of G-197A polymorphism in GC compared with control subjects. There was also a significant correlation between -197A allele and tumor stages of I/II [116].

H. pylori is one of the most important factors in GC progression and activates pro-inflammatory cytokines

[117, 118]. NO is a tumor-related proinflammatory factor which is upregulated following the *H. pylori* infection [119]. It has been observed that there was a significant correlation between *H. pylori* infection and iNOS C150T polymorphism among Iranian GC patients in which, CT or TT iNOS genotypes increased the risk of GC progression in *H. Pylori* positive cases [120].

IL-1 is involved in chronic intestinal inflammation and tumor progression [121]. It has been reported that there were significantly different frequencies of A1/A2 genotypes in IL-1RN VNTR polymorphism between tumor and control groups among a subpopulation of Iranian GC patients. Moreover, the ILRN *2/*2 genotype was correlated with high risk of GC in this population [122]. CD40 belongs to the tumor necrosis factor protein family that functions in B cells maturation and maturation of antigen-presenting cells (APCs) for anti-tumor immunity. CD40/CD40L interaction inhibits tumor cell growth and induces apoptosis. It has been reported that there was CD40 hyper methylation in precancerous samples compared with normal tissues among Iranian GC patients which was associated with longer survival [123].

Stemness and self-renewal

Stemness and self-renewal are the ability of a cell to generate its lineage and differentiated cells which are observed in somatic and cancer stem cells (CSCs). CSCs are a subpopulation of tumor cells with self-renewal ability and resistance toward the chemotherapeutic treatments [124]. CDX2 is a member of Homeobox transcription factors which is associated with cell differentiation, embryogenesis, tumorigenesis, and digestive disorders [125, 126]. CDX2 methylation status was evaluated in a subpopulation of Iranian GC cases that showed a significantly reduced CDX2 methylation in tumors compared with normal tissues [127]. Olfactomedin 4 (OLFM4) is an important factor in neural crest development, cell cycle regulation, and tumorigenesis [113]. NFκ B and AP-1 are the upstream regulators of OLFM4 expression [128]. OLFM4 over-expression has been observed in tumor tissues in comparison with the normal margins. Therefore, OLFM4 was suggested as an early diagnostic and stage-dependent prognostic marker among the Iranian GC patients [129]. ZFX is a zinc-finger developmental transcriptional regulator [130]. Levels of ZFX mRNA expression were assessed in a group of Iranian GC patients. It was shown that there were significantly different expression levels between different tumor types and grades, in which diffused types and advanced grade (III) tissues had higher levels of ZFX expressions [131]. Another report evaluated the correlation between clinicopathological features and ZFX isoform 3/variant 5 expressions in Iranian GC samples.

Although there was a heterogeneous pattern of expression among the patients, the majority of overexpressed cases were high-grade and diffuse-type. Moreover, there was a direct correlation between size of tumor and ZFX isoform 3/variant 5 mRNA expressions [132]. CXCR4 as a G-coupled receptor has a key function in hematopoietic stem cells maintenance inside the bone marrow [133]. Although, normal solid tissues have low levels of CXCR4 or lack of its expression, the majority of primary GC tissues had cytoplasmic and nucleus CXCR4 expressions. There was a correlation between CXCR4 expression and survival, in which the Iranian GC patients with positive CXCR4 nucleus expression had higher survival rates [134]. PAX genes are tissue-specific transcription factors associated with developmental programs and cell differentiation [135]. It has been shown that there was a lower level of circulating PAX5 expression in a subpopulation of Iranian GC patients compared with controls. Since 28% of patients were methylated and there was not any methylated sample among the normal cases, reduced levels of expression can be associated with PAX5 promoter methylation. Moreover, there were significant associations between PAX5 expression, age, and methylation status [136].

Cell adhesion and structural factors

Cell adhesion is a pivotal cellular process involved in cell polarity and tissue homeostasis. Reduced adhesive properties of tumor cells and subsequent signaling pathways are associated with tumor progression. Lack of cell-cell connections results in tumor metastasis. Cadherin-1 (CDH1) as a trans-membrane glycoprotein and tumor suppressor plays important roles in intercellular adhesion and normal-neoplastic morphogenesis [137, 138]. It was shown that there was not any correlation between CDH1 -160(C/A) polymorphism and GC susceptibility; however, CC genotype carriers had higher survival rates in comparison with the cases with CA genotype. Therefore, the CC genotype of CDH1 was suggested as a good prognostic marker among a subpopulation of Iranian GC patients [139].

HS3ST2 is involved in heparan sulfate biosynthesis via modification of glycosaminoglycan chains [140]. It has been reported that there were CDH11 and HS3ST2 promoters hyper methylation in a sample of Iranian GC patients compared with controls [141]. CD44 is one of the main factors in cellular connections, migration, and proliferation [142]. CD44 activation increases cell proliferation and maintenance through PI3K/AKT signaling pathway [143]. CD44 interaction with hyaluronan initiates tumorigenesis via regulation of cell growth, differentiation, and migration. It has been reported that there was a correlation between CD44 rs187116

polymorphism and survival of Iranian GC patients. CD44 polymorphisms can be used in early detection of patients with a high risk for tumor relapse [144]. Another study showed a correlation between rs8193 C allele of CD44 and higher risk of GC among Iranian cases. The rs8193 C allele was also associated with increased lymph node involvement [145].

Mucin 1 (MUC1) is a membrane-bound glycoprotein involved in the protection of gastrointestinal epithelium toward microorganisms and enzymes [146]. It has been reported that there was a significant correlation between rs4072037 AG genotype of MUC1 and reduced risk of GC among Iranian patients [147].

Actin filament-associated protein 1 (AFAP1) regulates the function of actin filaments which is associated with cell migration and metastasis [148]. The AFAP1-antisense RNA 1 (AS1) is also an lncRNA transcribed from the antisense strand of AFAP1 [149]. The AFAP1 and AFAP1-AS1 downregulations were observed in a subpopulation of Iranian GC subjects. There were also significant correlations between the levels of AFAP1 and AFAP1-AS1 expressions and tumor location in which the cardia tumors had decreased levels of expressions. Moreover, the younger patients and high-grade tumors had lower levels of AFAP1 expressions compared with older patients and low-grade tumors, respectively [150].

Actin is the basic factor of cellular motility during tumor progression and metastasis which is regulated by CFL1 [151]. CFL1 induces the cell mobility through actin depolymerization [152]. It is also activated through slingshot diphosphatase (SSH) [153]. Therefore, SSH1 has a critical role in the regulation of cell migration [154]. It has been reported that there was a significant correlation between SSH1 expression and cancerous nature of tumors which can be suggested as an efficient diagnostic marker of GC in Iranian population [155].

Beta-secretase 1 (BACE1) is a protease involved in myelin sheaths construction and amyloid- β peptides production [156, 157]. The BACE1 inhibitors reduce endothelial cell proliferation and tumor growth [158]. It has been shown that there was significant BACE1 downregulation in a sample of Iranian GC patients which was associated with cardia region [159]. Gelsolin (GSN) and Scinderin are important regulators of actin reorganization, cell motility, and morphology [160, 161]. It has been observed that there was a significant correlation between grade, age, and the levels of Gelsolin expression. A significant correlation was also between the levels of Scinderin expression and tumor size. Moreover, Gelsolin downregulation and Scinderin upregulation were associated with lymph node involvement among a sample of Iranian GC patients [162].

Conclusions

In the present review, we summarized all of the reported markers until now among Iranian GC patients. Regarding the different categories, it seems that the epigenetic modifications through non-coding RNAs are the main molecular processes involved in tumor initiation and progression among Iranian GC patients. Aberrant immune responses and inflammatory reactions had also pivotal roles in GC progression in this population. Indeed this review paves the way for introducing a specific panel of diagnostic markers for the Iranian population.

Abbreviations

AS1: AFAP1-antisense RNA 1; AFAP1: Actin filament-associated protein 1; ADAR: Adenosine deaminase; APCs: Antigen-presenting cells; BACE1: Beta-secretase 1; CDH1: Cadherin-1; CSCs: Cancer stem cells; CTNNBIP1: Catenin beta interacting protein 1; CKIs: Cyclin-dependent kinase inhibitors; CDKs: Cyclin-dependent kinases; CYLD: Cyldromatosis; eCCEBPA: Extra coding CEBPA; GC: Gastric cancer; GKN1 and 2: Gastrokine 1 and 2; GSN: Gelsolin; lncRNAs: Long non-coding RNAs; miRNAs: MicroRNAs; MUC1: Mucin 1; NLRs: NOD-like receptors; NUD: Non-ulcer dyspepsia; OLFM4: Olfactomedin 4; PUD: Peptic ulcer disease.

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MRA, HRR, and MMOjarrad were involved in search strategy and drafting. MMoghbeli supervised the project and revised and edited the manuscript. All authors read and approved the final manuscript.

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Declarations

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Competing interests

The authors declare that they have no competing interests.

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