Depression accelerates the development of gastric cancer through reactive oxygen species-activated ABL1 (Review)

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Abstract. Depression is a common symptom among gastric cancer (GC) patients and serves as a potential indication of poor prognosis and advanced cancer clinical stage. However, the molecular mechanism of depression-associated poor prognoses of GC patients remains unclear. Recent studies have revealed that GC patients with depression are under high levels of oxidative stress (OS) status that is accompanied by the dysfunction of numerous proto-oncogenes, including the ABL proto-oncogene 1 (ABL1), which is a non-receptor tyrosine kinase. Recent evidence indicates that ABL1 was dysregulated in both major depressive disorder (MDD) and cancer patients with depression, and high levels of reactive oxygen species (ROS) can lead to the activation of ABL1 in response to OS and that activated ABL1 subsequently contributes to development of GC via interactions with the downstream targets and corresponding signaling pathways. In this review, we examine the evidence to illuminate the molecular mechanism of ABL1 in the progression of GC patients with depression and identify out new and effective methods for the initial and long-term treatment of GC.

Contents

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1. Introduction

Despite the decline in the morbidity of gastric cancer (GC) in recent years, GC remains the fourth most common cancer and the second-leading cause of cancer-related death globally with >700,000 human deaths per year (1,2). The occurrence of depression challenges cancer treatment and acts as an underlying indicator of advanced stages and poor prognoses of cancer patients (3). Depression care for cancer patients can improve the clinical benefit, including the treatment response (4,5). Nevertheless, there are currently no clear theories to explain the molecular mechanism by which depression is associated with poor prognoses among cancer patients. As an insult to the human body, depression causes oxidative stress (OS) (6), which subsequently leads to the excessive generation of reactive oxygen species (ROS) (7). Gastric tissues are particularly vulnerable to ROS (8). Excessive ROS that exceed the scavenging ability of human body trigger carcinogenesis by activating diverse proto-oncogenes, including ABL proto-oncogene 1 (ABL1) (9,10).

ABL1 is a non-receptor tyrosine kinase that consists of the N-terminal Src homology 3 (SH3) domain, Src homology 2 (SH2) domain, kinase domains, and the C-terminal actin-binding domain (ABD) (11). ABL1 was upregulated in GC and colorectal cancer patients with depression, and patients with major depressive disorder (MDD) (12,13). Activated ABL1 can regulate nuclear factor (erythroid-derived 2)-like 2 (NRF2) to function in an adaptive manner to react to OS (14). Additionally, activated ABL1 can consequently lead to dysfunctions of its downstream targets and corresponding signaling pathways, e.g., the mitogen-activated protein kinase (MAPK) and mechanistic target of rapamycin (mTOR), which contributes to the promotion of the development of GC and results in poor prognosis (14-17). Therefore, we will collect the evidence that ROS-activated ABL1 is responsible for the poor prognoses of GC patients with depression. Because inhibitors of ABL1, such as vandetanib, are widely used in clinical tumor treatment, clearly understanding the ABL1 in the process of

GC will provide new methods to improve the prognoses of GC patients with depression.

2. Elevated levels of ROS are generated in GC patients with depression

Depression symptoms are common among GC patients both in Asia and the West (2,18-20). According to published reports, the prevalence of depression is ~50% among GC patients (2,21,22). The interaction of depression with cancer has long been a subject of investigation. The unambiguous mechanism responsible for the occurrence of depression among GC patients remains unknown. Inflammation is a crucial factor in gastric carcinogenesis (23). Due to inflammation, leukocytes release increased levels of cytokines and chemokines, e.g., TNF-α, IL-6, and chemokine (C-X-C motif) ligand 12 (CXCL12) (24-26). These cytokines and chemokines interact with the hypothalamic-pituitary-adrenal (HPA) axis, which may explain some of the mechanism of depression (27). Additionally, cancer diagnosis, post-diagnosis treatment, and cancer-related fatigue may also account for the occurrence of depression in GC (28). However, it is certain that depression is an indicator of poor prognosis among cancer patients, including patients with GC (4,29). In addition to other authors, we have suggested that depression is common among GC patients in our previous study (21). Compared with patients without depression, GC patients with depression exhibit shorter survival times. Furthermore, the prevalence of depression is positively correlated with the clinical stage of GC, i.e., GC patients with depression are susceptible to advanced stage cancer (22).

Emerging evidence suggests that OS works as primary crosslink between depression and GC. OS is primarily caused by the imbalance between oxidation and antioxidation *in vivo*. The recognized marker of OS 8-hydroxydeoxyguanosine (8-OHdG) is positively correlated with Hospital Anxiety and Depression Scale (HADS)-D scores (30). Under OS, ROS levels are particularly raised among patients with depression. Decreased antioxidants and elevated oxidants enhance the generation of ROS in patients with depression. Clinical studies have revealed that depressive patients exhibit decreased levels of antioxidants, including glutathione peroxidase (GPX), catalase and superoxide dismutase (SOD), and these antioxidants exhibit ROS scavenging activities (31-33). Patients with depression also exhibit elevated levels of oxidants, such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and xanthine oxidase (XO), which leads to the production of ROS (34-37). Indeed, antidepressant treatment has been reported to reduce MDA (6). Our team discovered that 8-OHdG is significantly elevated in the sera of cancer patients, including GC patients, with depression compared with those without depression (13,21). All of the above changes could lead to the excessive generation of ROS (Fig. 1).

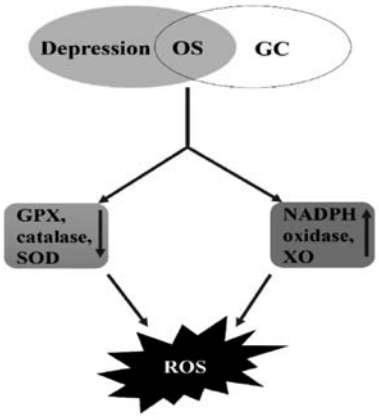

Figure 1. High levels of ROS in GC patients with depression. Decreased levels of antioxidants, including GPX, catalase and SOD, cooperate with increased levels of oxidants, including NADPH oxidase and XO, to promote the generation of ROS in GC patients with depression. ROS, reactive oxygen species; GC, gastric cancer; GPX, glutathione peroxidase; SOD, superoxide dismutase; NADPH, nicotinamide adenine dinucleotide phosphate; XO, xanthine oxidase.

3. ROS generated in GC lead to the activation of ABL1

ABL1 is well known for its characteristics related to chronic myelogenous leukemia (CML) in the form of BCR-ABL1, which mediates abnormal myeloproliferation and leads to the development of CML (38). As a non-receptor tyrosine kinase, ABL1 is expressed in the cytoplasm and the nucleus and is involved in the processes of cell differentiation, proliferation, adhesion, and stress responses (39). Similar to other protein kinases, ABL1 is activated by a ligand and functions through interactions with downstream targets. Vitally, the expression of ABL1 is context-dependent and is upregulated in response to OS and DNA damage (10,14,40). In diverse cancers with OS that are accompanied by DNA damage, including CML, acute lymphoblastic leukemia (ALL), kidney, breast, ovarian and colorectal cancers, as well as GC, ABL1 is highly expressed (14,38,41-45). Thus, this system is a perfect model to probe the activation and the activities of ABL1 in fumarate hydratase-deficient kidney cancer. Fumarate hydratase deficiency results in the accumulation of fumarate, which subsequently leads to elevated NADPH oxidase levels and enhanced generation of ROS (10,14). ROS levels are positively associated with the expression of ABL1. Hydrogen peroxide, a type of ROS, promotes ABL1 expression, and the ROS scavenger *N*-acetylcysteine (NAC) could inhibit ABL1 expression. Therefore, the metabolic maladjustment-associated accumulation of ROS is the primary cause of the activation of ABL1. Indeed, in some types of cancer, ABL1 has been found to be associated with the level of ROS. ABL1 expression in these cancers is ROS-dependent. OS and excessive ROS generation are well-documented contributors to carcinogenesis in GC (33,46). In GC, ABL1 and c-Src tyrosine kinase (CSK) kinases phosphorylate cytotoxin-associated gene A (CagA), which is vital in the initial and development of gastric carcinogenesis (47). The activity of ABL1 is enhanced in the GTL-16 cell line (48). Therefore, the ROS generated in GC development might lead to the activation of ABL1. ROS can regulate the expression of ABL1; however, the potential mechanism is unknown.

The regulation of gene expression is a complex process, and only one report has discussed expression of ABL1 in GC as a target of miR-203. Epigenetically silenced miR-203 releases the expression of ABL1 to promote gastric lymphomagenesis (45). Furthermore, the increased expression of ABL1 by epigenetically silenced miR-203 has also been confirmed in CML (49,50). In *Helicobacter pylori* (Hp)-induced GC,

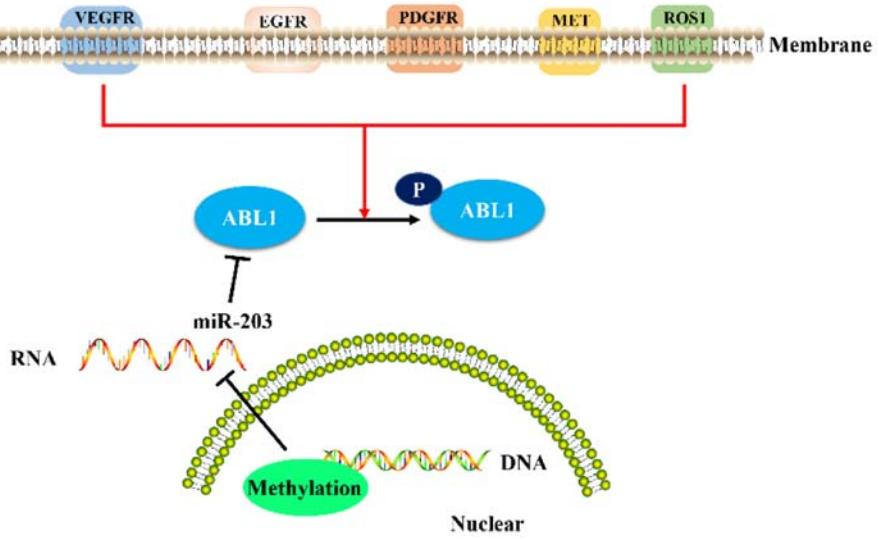

Figure 2. Expression and activation of ABL1 in GC. miR-203 and methylation can regulate the expression of ABL1 at the gene level. RTKs, including EGFR, PDGFR, VEGFR, MET, and ROS1 can activate ABL1. ABL1, ABL proto-oncogene 1; GC, gastric cancer; RTKs, receptor tyrosine kinases; EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

miR-203 has been confirmed to be downregulated. Therefore, miR-203 may be a reason for the high level of ABL1 in GC. As mentioned above, the expression of ABL1 is ROS-dependent, and ROS can influence methylation status by sustaining the stability of hypoxia-inducible factor 1α (HIF-1α) (51), which increases the expression of the DNMT enzymes DNMT1 and DNMT3B, which keep gene silenced by hyper-methylation (52). Interestingly, HIF-1α can also result in the hypo-methylation of genes by regulating the MAT1A/MAT2A switch (53). Given the role of ROS in the epigenetic regulation of gene expression, the expression of ABL1 may be mediated by the ROS-related hyper-methylation of miR-203. Moreover, although the methylation of ABL1 in GC has not been clarified, in CML, dynamic methylation changes in the ABL1 promoter have been clearly identified (54,55). ROS might supervise the expression of ABL1 by directly influencing the methylation status of ABL1. Additionally, the activity of ABL1 can be triggered by receptor tyrosine kinases (RTKs), including epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), erb-b2 receptor tyrosine kinase 2 (ERBB2), vascular endothelial growth factor receptor (VEGFR), MET, c-ros oncogene 1, and receptor tyrosine kinase (ROS1), and their substrates (9,19,20). Importantly, EGFR, PDGFR, VEGFR, MET, and ROS1 have been proven to be elevated in GC (56-60). Moreover, some RTKs, such as EGFR, are regulated by ROS, and MET has been confirmed to interact with ABL1 (48,61). Therefore, ROS may affect the expression of ABL1 through a combination of a variety of mechanisms (Fig. 2). Additional studies should be designed to identify the detailed mechanism of the regulation of the expression of ABL1 by ROS in GC.

4. ABL1 contributes to cancer development in GC patients with depression

The function of ABL1 most strongly depends on its biological structure. As a tyrosine kinase, the N-terminal SH2 regulates

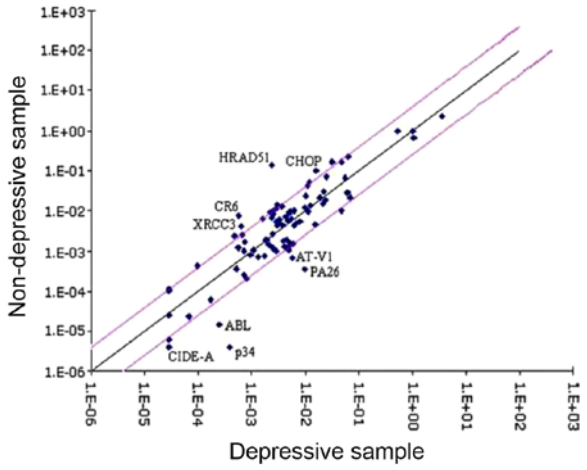

Figure 3. ABL1 was significantly increased in colorectal carcinoma patients with depression. ABL1, ABL proto-oncogene 1.

the activation of kinase domains via contact with the SH2/N-lobe interface (62,63). The N-terminal SH3 is regulated by Ras and Rab interactor 1 (RIN1) and also influences the activation of ABL1 (64), and the kinase domain is involved its major activities. Based on its structure, ABL1 activates its substrates and associated signaling pathway to promote gastric tumorigenesis.

Both the expression and the activity of ABL1 are increased in GC (48,65). Our preliminary study confirmed that genes involved in DNA-damage signaling pathways were markedly dysregulation by gene chips in GC and colorectal carcinoma, including ABL1. ABL1 was significantly increased in GC patients with depression compared with that without depression (Table I, and unpublished data). Similarly, in colorectal carcinoma, we also concluded that ABL1 was significantly increased (Fig. 3) (13). Vitally, with whole-genome cRNA microarrays, Yi *et al* screened 30 differently expressed genes

Table I. Different expressions of genes involved in DNA-damage signaling pathways in GC patients without and with depression.

		$2^{-\Delta\Delta Ct}$		Relative expression
Symbol	Gene name	Group A	Group B	Group A/group B
ABL1	ABL/JTK7	4.50E-04	7.20E-05	6.32
APEX1	APE/APE1	4.10E-01	1.50E-01	2.69
ATM	AT1/ATA	9.00E-03	1.20E-02	-1.29
ATR	FRP1/MEC1	6.30E-03	1.20E-02	-1.95
ATRX	ATR2/MRXS3	1.50E-02	2.00E-02	-1.3
BRCA1	BRCAI/BRCC1	2.00E-03	1.50E-03	1.34
BTG2	PC3/TIS21	9.20E-03	4.20E-03	2.16
CCNH	CAK/p34	2.10E-04	5.00E-04	-2.35
CDK7	CAK1/CDKN7	1.20E-02	7.80E-03	1.51
CHEK1	CHK1	3.80E-02	2.40E-02	1.6
CHEK2	CDS1/CHK2	1.50E-02	8.10E-03	1.8
CIB1	CALMYRIN/CIB	3.00E-01	4.20E-01	-1.42
CIDEA	CIDE-A	1.10E-04	4.90E-05	2.31
CRY1	PHLL1	3.70E-02	2.10E-02	1.77
DDB1	DDBA/UV-DDB1	1.20E-01	8.00E-02	1.54
DDIT3	CEBPZ/CHOP	3.20E-02	1.10E-01	-3.34
DMC1	DMC1H/HsLim15	3.70E-04	8.10E-04	-2.17
ERCC1	UV20	5.60E-02	6.30E-02	-1.13
ERCC2	EM9/XPD	1.90E-02	3.10E-02	-1.62
EXO1	HEX1/hExoI	2.10E-02	1.30E-02	1.68
FANCG	FAG/XRCC9	2.40E-02	2.00E-02	1.23
FEN1	FEN-1/MF1	3.60E-02	1.00E-02	3.58
XRCC6	CTC75/CTCBF	2.40E-01	2.30E-01	1.06
GADD45A	DDIT1/GADD45	6.80E-03	1.30E-02	-1.91
GADD45G	CR6/DDIT2	4.60E-03	2.20E-02	-4.82
GML	LY6DL	3.10E-05	4.90E-05	-1.56
GTF2H1	BTF2/TFIIH	3.50E-02	2.00E-02	1.82
GTF2H2	BTF2/BTF2P44	8.50E-03	2.00E-02	-2.3
GTSE1	B99	3.80E-02	7.50E-02	-1.99
HUS1	Hus1	3.50E-02	4.80E-02	-1.38
IGHMBP2	CATF1/HCSA	1.20E-02	3.30E-02	-2.75
IHPK3	INSP6K3/IP6K3	6.10E-05	5.70E-03	-93.05
XRCC6BP1	KUB3	2.50E-02	1.10E-02	2.25
LIG1	MGC117397	2.30E-02	6.20E-02	-2.69
MAP2K6	MAPKK6/MEK6	1.00E-02	3.30E-03	3.12
MAPK12	ERK3/ERK6	3.00E-03	2.50E-03	1.19
MBD4	MED1	6.20E-02	9.40E-02	-1.53
MLH1	COCA2/FCC2	1.80E-02	1.10E-02	1.74
MLH3	HNPCC/HNPCC7	3.60E-02	4.70E-02	-1.31
MNAT1	MAT1/RNF66	1.10E-02	1.70E-02	-1.57
MPG	AAG/APNG	1.50E-01	1.50E-01	-1
MRE11A	ATLD/HNGS1	2.50E-02	4.50E-02	-1.78
MSH2	COCA1/FCC1	2.10E-02	1.40E-02	1.49
MSH3	MSH3	8.60E-03	1.70E-02	-2.03
MUTYH	MYH/MYHβ	7.70E-02	1.90E-01	-2.46
N4BP2	B3BP	2.40E-03	5.30E-03	-2.17
NBN	AT-V1/AT-V2	6.70E-02	2.00E-02	3.43
NTHL1	NTH1/OCTS3	5.10E-02	1.30E-01	-2.48
OGG1	HMMH/HOGG1	3.40E-02	3.00E-02	1.15
PCBP4	LIP4/MCG10	2.60E-04	2.30E-03	-8.69
PCNA	MGC8367	6.10E-01	1.30E-01	4.82

Table I. Continued.

Symbol	Gene name	$2^{-\Delta\Delta Ct}$		Relative expression
		Group A	Group B	Group A/group B
PDCD8	AIF	6.70E-02	1.10E-01	-1.64
PMS1	DKFZp781M0253/HNPCC3	1.60E-02	2.10E-02	-1.27
PMS2	HNPCC4/PMS2CL	2.50E-02	4.50E-02	-1.78
PMS2L3	PMS2L9/PMS5	1.30E-02	4.40E-02	-3.39
PNKP	PNK	3.00E-02	6.30E-02	-2.13
PPP1R15A	GADD34	4.70E-03	5.50E-03	-1.17
PRKDC	DNAPK/DNPK1	2.70E-02	3.60E-02	-1.31
RAD1	HRAD1/REC1	8.60E-03	1.10E-02	-1.26
RAD17	CCYC/HRAD17	1.90E-02	3.90E-02	-2.07
RAD18	RNF73	7.90E-03	1.20E-02	-1.48
RAD21	HR21/HRAD21	5.10E-01	9.50E-02	5.31
RAD50	RAD50-2/hRad50	1.20E-02	1.00E-02	1.14
RAD51	BRCC5/HRAD51	7.70E-03	1.90E-03	4.03
RAD51L1	R51H2/RAD51B	1.90E-03	2.90E-03	-1.53
RAD9A	RAD9	9.40E-06	4.90E-05	-5.21
RBBP8	CTIP/RIM	7.80E-02	5.70E-02	1.38
REV1L	REV1	2.00E-02	4.40E-02	-2.2
RPA1	HSSB/REPA1	4.00E-02	3.90E-02	1.02
SEMA4A	SEMAB/SEMB	2.10E-03	1.50E-03	1.37
SESN1	PA26/SEST1	7.40E-02	1.00E-02	7.36
SMC1L1	DKFZp686L19178/DXS423E	6.00E-02	8.30E-02	-1.38
SUMO1	GMP1/PIC1	2.70E-01	2.60E-01	1.05
TP53	LFS1/TRP53	2.80E-02	1.20E-02	2.39
TP73	P73	1.30E-03	3.50E-03	-2.81
TREX1	ATRIP/DKFZp434J0310	4.70E-03	8.90E-03	-1.91
UNG	DGU/DKFZp781L1143	3.20E-02	1.00E-02	3.12
XPA	XP1/XPAC	9.50E-02	4.50E-02	2.1
XPC	XP3/XPCC	1.10E-02	3.00E-02	-2.68
XRCC1	RCC	2.80E-02	5.90E-02	-2.07
XRCC2	DKFZp781P0919	7.30E-03	3.60E-03	2.04
XRCC3	XRCC3	1.70E-02	1.00E-02	1.62
ZAK	AZK/MLK7	3.60E-02	2.40E-02	1.52

Group A represents GC patients with depression; group B represents GC patients without depression. GC, gastric cancer; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase.

in patients with MDD, including ABL1 (12). In response to OS, ABL1 is the first to induce an adaptive pathway to protect the cell from ROS injury. ABL1 can upregulate nuclear respiratory factor 2 (NRF2), and NRF2 leads to high levels of antioxidant response elements (AREs), including NAD(P)H:quinone oxidoreductase 1 (NQO1) and aldo-keto reductase 1C1 (AKR1C1), which antagonize the DNA damage and the generation of ROS (66,67). Nevertheless, the function of NRF2 can be blocked by silent mating-type information regulation 2 homologue 1 (SIRT1), which is a gene that is related to MDD and influences the poor prognosis of GC (68-70). Thus, in GC patients with depression, the dysfunction of the protection system induced by SIRT1 may explain part of the mechanism responsible for the poor prognosis.

Secondly, GC cells exhibit features of the enduring activation of the Kirsten rat sarcoma viral oncogene homolog (K-ras)/extracellular signal-regulated kinase (ERK) signaling pathway (71). The ERK signaling pathway can directly induce the proliferation of cancer cell (72). Additionally, ERK also mediates the expression of miR-21, and increased in miR-21 decrease programmed cell death 4 (PDCD4) levels, which subsequently leads to anti-apoptosis and transformation effect on GC cells (73,74). Additionally, PTEN is also a target of miR-21, and decreased levels of PTEN account for the proliferation of GC cells (75). Indeed, studies have revealed that ABL1 can directly interact with RAS and activate the RAS/ERK signaling pathway to promote carcinogenesis of GC (76). Hence, ROS-dependent ABL1 triggers the RAS/ERK

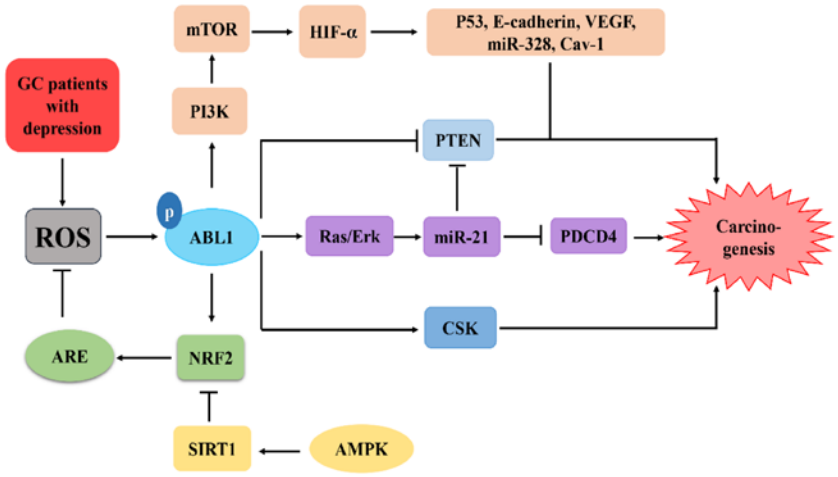

Figure 4. The ABL1-related signaling pathway in cancer development in GC patients with depression. High levels of ROS in GC patients with depression lead to the activation of ABL1, and ABL1 then induces NRF2 to protect cell from ROS injury. ABL1 results in tumorigenesis in GC by phosphorylating its substrates PI3K, Ras, and CSK and the associated signaling pathways. ABL1, ABL proto-oncogene 1; GC, gastric cancer; ROS, reactive oxygen species; NRF2, nuclear factor (erythroid-derived 2)-like 2; PI3K, phosphatidylinositol 3-kinase; CSK, c-Src tyrosine kinase.

signaling pathway to promote the proliferation of GC cells directly or by affecting miR-21.

Third, in GC, hypoxia leads to the generation of ROS that prevent the degradation of HIF-1α (51). As a transcription factor, the accumulation of HIF-1α can modulate the expression of genes that are important in gastric tumorigenesis. For example, HIF-1α attenuates caveolin-1 (Cav-1) and leads to the epithelial-mesenchymal transition (EMT) in GC by regulating E-cadherin (77). HIF-1α activates the vascular endothelial growth factor (VEGF) pathway to enhance angiogenesis in GC (78). Crosstalk between HIF-1α and the tumor suppressor gene p53 has also been discovered, and the expressions of both of these factors are correlated with ROS (79,80). HIF-1α also induces miR-328 to inhibit the activity of PTEN, which then releases the suppression of the mTOR signaling pathway to promote GC cell survival (81). Notably, ROS-dependent ABL1 directly communicates with p53 in the GC cell line GTL-16 to promote gastric tumorigenesis (48). Moreover, there is also evidence that ABL1 can enhance the activity of HIF-1α via the mTOR signaling pathway (14). Therefore, ABL1 participates in parts of the mechanism of gastric carcinogenesis by affecting HIF-1α.

Finally, as discussed above, ABL1 can be activated by RTK, and RTK can be activated and act as a substrate of ABL1. One thoroughly investigated factor in GC is CSK (82). Humar *et al* found that CSK was activated in mesenchyme-like cancer cells and that CSK activation is a central event that is required for the development of early diffuse GC. More importantly, the activation of CSK is mediated by ABL1 via the activation of the Src homology 2 domain-containing 1 (SHC1) of CSK (15). Phosphatidylinositol 3-kinase (PI3K) is also a substrate of ABL1, and the induction of PI3K can trigger the PI3K/v-akt murine thymoma viral oncogene homolog 1 (AKt)/mTOR signaling pathway, which can result in the development of GC (1,15).

For GC patients, excessive ROS are produced due to low levels of antioxidants and high levels of oxidants (83). Moreover, the occurrence of depression among GC patients enhances the production of ROS via a similar mechanism (13,84). ROS act to directly increase the expression of ABL1 (9,14,85). Additionally, ROS also trigger tyrosine kinase inhibitor (TKI) to increase the activity of ABL1 (34,61). Importantly, in Hp infection-associated GC, ABL1 functions as a proto-oncogene by phosphorylating CagA to promote tumorigenesis (47,86). Taken together, these findings indicate that ABL1 contributes to the protection of cells from ROS by inducing NRF2 and enhancing the activity of HIF-1α to catalyze its substrate and corresponding substrates to promote carcinogenesis of GC patients with depression (Fig. 4).

5. Conclusions

ABL1 regulates cell proliferation in Hp-induced gastric B-cell lymphomas in mucosa-associated lymphoid tissue (MALT) lymphoma, and blocking the activity of ABL1 with imatinib can inhibit cell proliferation (45). GTL16 is a subclone of MKN45 that is characterized as 'Met-addicted' (87). In GTL16, ABL1 has been proven to be activated by Met, and the activation of ABL1 then mediates the phosphorylation of p53 by p38-MAPKs, which results in the overexpression of MDM2, which in turn promotes cell proliferation. Similarly, the effect of ABL1 in GTL16 can be interfered with by imatinib and shRNA interference (48). As discussed above, GC patients with depression have high levels of ROS, and ABL1 may be directly regulated by ROS-related methylation or miR-203, or the ROS-activated ligands of ABL1 may act to indirectly promote the activation of ABL1. Therefore, treatments with TKIs may be clinically beneficial for GC patients with depression.

6. Perspective

Collectively, considering the above clinical results, depression is a world-class problem and is frequent among cancer patients. Depression in GC patients is associated with shorter survival times. Worse, there are no ideal drugs for clinical depression. Therefore, the probing of the underlying molecular changes associated with depression in cancer patients represents a new option. We focus our studies on the role of OS and its product ROS in GC and depression and conclude that ROS serve as

a crosslink for both; i.e., ROS mediate a mutual promotion process for depression and GC. In this review, we elucidated the molecular mechanism of the poor prognosis of GC patients with depression and found that ABL1, which is a non-receptor tyrosine kinase, may function as a crucial factor in the development of GC and the poor prognoses of GC patients with depression. High ROS levels in GC patients lead to the activation of ABL1, and ABL1 then induces NRF2 to protect the cells from ROS injury. ABL1 results in tumorigenesis in GC by phosphorylating its substrates and activating signaling pathways. Considering that inhibitors of ABL1 have been widely used in the treatment of CML, it is possible to assess the value of ABL1 in the treatment of GC patients with depression.

However, because ABL1 is widely expressed in the human body and is required for the maintenance of normal physiological functions, e.g., tissue development and immune function, it is difficult to avoid the side-effects of ABL1 inhibitors that are related to these physiological functions. Furthermore, the activity of ABL1 is tissue-specific and context-dependent; thus, future explorations of ABL1 should primarily concentrate on research into the biological processes in which ABL1 functions rather than employing old gene-centric styles. Nevertheless, probing the mediation of the ABL1-dependent phosphorylation of GC should elucidate some of the reasons for GC-related cell death. Given the accumulated evidence, the FDA-approved status of TKIs, and the experience of patients with other cancers, including CML, AML, lung and breast cancer, following exposure to these drugs, ABL represents a prospective target for future treatments for GC patients with depression.

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