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Quantum microRNA network analysis in gastric and esophageal cancers: Xenotropic plant microRNAs cure from cancerous paradox via *Helicobacter pylori* infection

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Abstract

Objective: We have previously shown the aetiology of cancer progression in breast, lung, pancreatic and colorectal cancers by the circulating microRNA (miRNA) panel using the miRNA entangling target sorter (METS) analysis with quantum miRNA language. It has been unveiled by the METS analysis that miRNA/miRNA quantum programming code would control oncogenesis via the hub miRNA in the miRNA biomarker panel. While the etiologic implication between gastric cancer and *Helicobacter pylori* (*H. pylori*) is still not cleared, many reports have statistically supported the efficacy of eradication of *H. pylori* to reduce the risk of gastric cancer.

Material and methods: To elucidate etiological significance of the biomarker miRNA panel in *H. pylori* infection, the data was firstly extracted from database to predict a feasible explanation for *H. pylori* pathogenicity upon cancer in the stomach. The aetiologies of gastric and oesophageal cancers, and *H. pylori* infection with or without vegetables and fruits were dynamically simulated by the computation using the quantum miRNA language with the METS. Statistical analysis was also performed by machine learning.

Results: In the quantum network, *H. pylori* infection showed proton pump inhibition, and insulin-like growth factor 1 receptor (IGF1R) expression was reduced as the common factor between gastric cancer stage I and *H. pylori* infection; however, both were pathogenic but not seriously oncogenic. Statistically, chronic *H. pylori* infection itself was not be significant upon oncogenic.

Conclusions: The environmental stress including mal-diets, such as long-term less fresh vegetable and fruit, would dysregulate miRNA expression, additionally it may contribute most for increasing risk of gastric cancer through enhancing glucose metabolic pathway on a paradox in Zen Buddhism riddle via IGF1R inhibition by *H. pylori* infection. Thus, xenotropic plant miRNAs (xenomiRNAs) from fresh vegetables and fruits may cure from paradoxical tumorigenesis with *H. pylori* infection.

Introduction

Gastric cancer and oesophageal squamous cell carcinoma (ESCC) have been the leading causes of cancer mortality in the world and the high incident rate in Asian with a total 5-years overall survival rate of 18-25% [1,2]. Risk factors of gastric cancer resemble those of ESCC, which are Tobacco, alcohol, chemical exposure, diet and obesity, etc. The other one of gastric cancer is associated with *Helicobacter pylor*i (*H. pylori*) infection but ESCC is not. Drs. Marshall B. and Warren R. were awarded the 2005 Nobel Prize for the discovery of *H. pylori*, which now is the dominant risk factor of gastric cancer; however, some people in Asia has persistently infected with *H. pylori* infection at high rates but do not suffer from high incident rates of gastric cancer because of availability of fresh fruits and vegetables all year round [3,4]. *H. pylori* infection reduces the risk of oesophageal inflammation and ESCC and shows to protect against cardia gastric cancer [5,6]. Thus, although the role of booster might be statistically shown in gastric cancer development under *H. pylori* infection, the relation of oncogenesis between *H. pylori* infection and host in gastric cancer is complex.

MicroRNA (miRNA) would be a quantum programming code device of lives because most of all protein genes are directly or indirectly tuned by miRNAs and it controls development, metabolism, cardiac system, neural system, immune system, infection and cancer. Highly dimensional quantum interaction of miRNA/miRNA has been correlated with context score of miRNA/mRNA the prediction tool, which is calculated by the sum of site-type specific, 3' UTR pairing, local A or U presence, and position contributions [7-9]. miRNA is circulated into the circulating system of human with stable extracellular form, such as in the exosomes, therefore, circulating miRNAs are now considered and clinically trialed as various disease biomarkers. Biomarker panel of miRNAs has been examined in diagnosis and prognosis of gastric cancer [10-13], oesophageal cancer [14-19] and *H. pylori* infection [10,20]. To elucidate a miRNA gene specific character of high dimension coherence in the RNA wave 2000, the ones for all and all for ones' relation between miRNAs and target mRNAs, we have previously shown the etiologic characters of Alzheimer's disease, and breast, pancreatic, lung and colorectal cancers by the miRNA memory package (MMP) from the circulating miRNA panel using the miRNA entangling target sorter (METS) analysis with quantum miRNA language [21, 22].

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In this paper, for further understanding of the etiologic implication under quantum miRNA language between miRNA/miRNA program and mRNA targets, *H. pylori* pathogenicity concerning foods was investigated by METS analysis in gastric and oesophageal cancers.

Materials and methods

Data base usage

To review the validated data for miRNAs and cancers, PubMed (www.ncbi.nlm.gov/pubmed/) and Google Scholar (https://scholar.google.co.jp) were used. Total information content was 1,060, 2,822 and 256 in oesophageal and gastric cancers, and *H. pylori* infection, respectively. The gene function of protein was searched by GeneCards (www.genecards.org). Protein ontology was investigated by GO enrichment analysis powered by PANTHER in Geneontology (geneontology.org).

Data mining

About data mining, biomarker miRNAs were selected by; 1) data from serum or plasma, 2) showed in two or more references, 3) cleared in expression levels of up- and down-regulation (Table 1).

METS simulation

The physicochemical interaction has been calculated by METS between miRNA/miRNAs using the quantum miRNA language [21]. Data of the multi-targets of the microRNA memory package (MMP) were extracted from TargetScan Human 7.2 (www.targetscan.org/vert_72/) and miRTarBase Ver. 8.0 (mirtarbase.cuhk.edu.cn/php/search.php). Target protein/protein interaction and cluster were searched by String Ver. 11.0 (https://string-db.org/cgi/input.pl). The hub of miRNAs in cancers and *H. pylori* infection was selected by the clusters of functional protein/protein interaction (Table 1).

Food miRNA functionally analogy analysis

The functional analogy of miRNAs was performed as previously described data processing between human miRNAs and human immunodeficiency virus type 1 *nef*/3' LTR miRNA [9,21,23]. The plant miRNAs were homologically compared with human miRNAs data in miRbase Ver. 22.1 (miRbase.org) by MirCompare (160.80.35.140/MirCompare/). The secondary structure of plant miRNAs to the target regions were computed by mfold (mfold.rit.albany.edu) and CentroidFold (rtools.cbrc.jp/centroidfold).

Statistic tools

The valuation of statistical significance for carcinogenic pathology in the METS simulation was performed by the area under the curve (AUC) in receiver operating characteristic (ROC) or the χ^2-based Cochran's Q test using BellCurve for Excel (Social Survey Research Information Co. Ltd., Tokyo, Japan). Accuracy and precision of the miRNAs' relation with ESCC and gastric cancer were computed by machine learning using Prediction One Ver. 05.09.19 (Sony Network Communications Inc., Tokyo, Japan).

Results and discussion

Distribution of quantum energy in gastric and oesophageal cancers

In oesophageal and gastric cancers (ESCC and GC), the frequency and total amount of double nexus score (DNS) on each layer of quantum core region (QCR) were calculated and compared with those in previously described colorectal cancer (CRC) (Figure 1) [24].

Quantum energy frequency of stage I-IV oesophageal, gastric or colorectal cancers was widely spread among layers (Figure 1, red bars). DNS amounts of the hub miRNA in stage I-IV oesophageal and

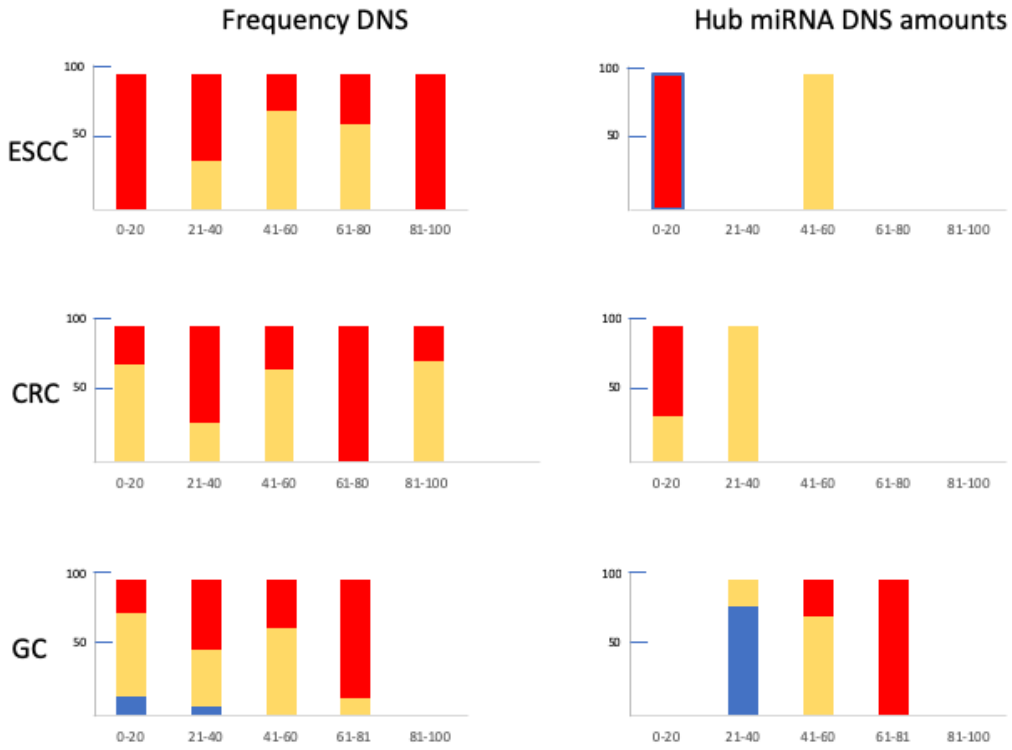


Figure 1. Distribution of quantum energy in gastric and oesophageal cancers. Frequency of DNS and DNS amounts in the miRNA hub were calculated in each layer (5 QCRs) in METS analysis of oesophageal cancer (ESCC), colorectal cancer (CRC) and gastric cancer (GC).

Table 1. miRNA biomarkers in gastric cancer and ESCC

Cancer and infection		miRNA information		
	Stage	miRNA*	Level	SNS
GC	I	**miR-21-5p**	up	5
		miR-223-5p	up	6
		miR-218-1-3p	down	6
		miR-16-5p	up	9
		miR-25-5p	up	9
		miR-92a-1-5p	up	9
		miR-451a	up	6
		miR-486-5p	up	6
GC	I-IV	miR-17-5p	up	7
		miR-106a/b-5p	up	7
		miR-21-5p	up	5
		let-7a-5p	down	8
		miR-19a-5p	up	4
		miR-92a-1-5p	up	9
ESCC	0-I	miR-21-5p	up	5
		miR-223-5p	up	6
		miR-25-5p	up	9
		miR-375	down	7
		miR-106a-5p	up	7
		miR-18a-5p	up	7
		miR-20b-5p	up	7
		miR-486-5p	up	6
		miR-584-5p	up	8
ESCC	IV	miR-16-5p	up	6
		miR-451a	up	3
		miR-574-5p	up	11
		miR-21-5p	up	5
		miR-25-5p	up	9
		miR-145-5p	up	4
		miR-129-5p	up	7
		miR-29c-5p	down	5
		miR-205-5p	down	4
H. pylori infection		miR-28-3p	up	6
		miR-143-3p	up	6
		miR-151a-3p	up	6
		miR-148a-3p	up	4
		miR-223-5p	up	6

*Boldface miRNA: hub miRNA

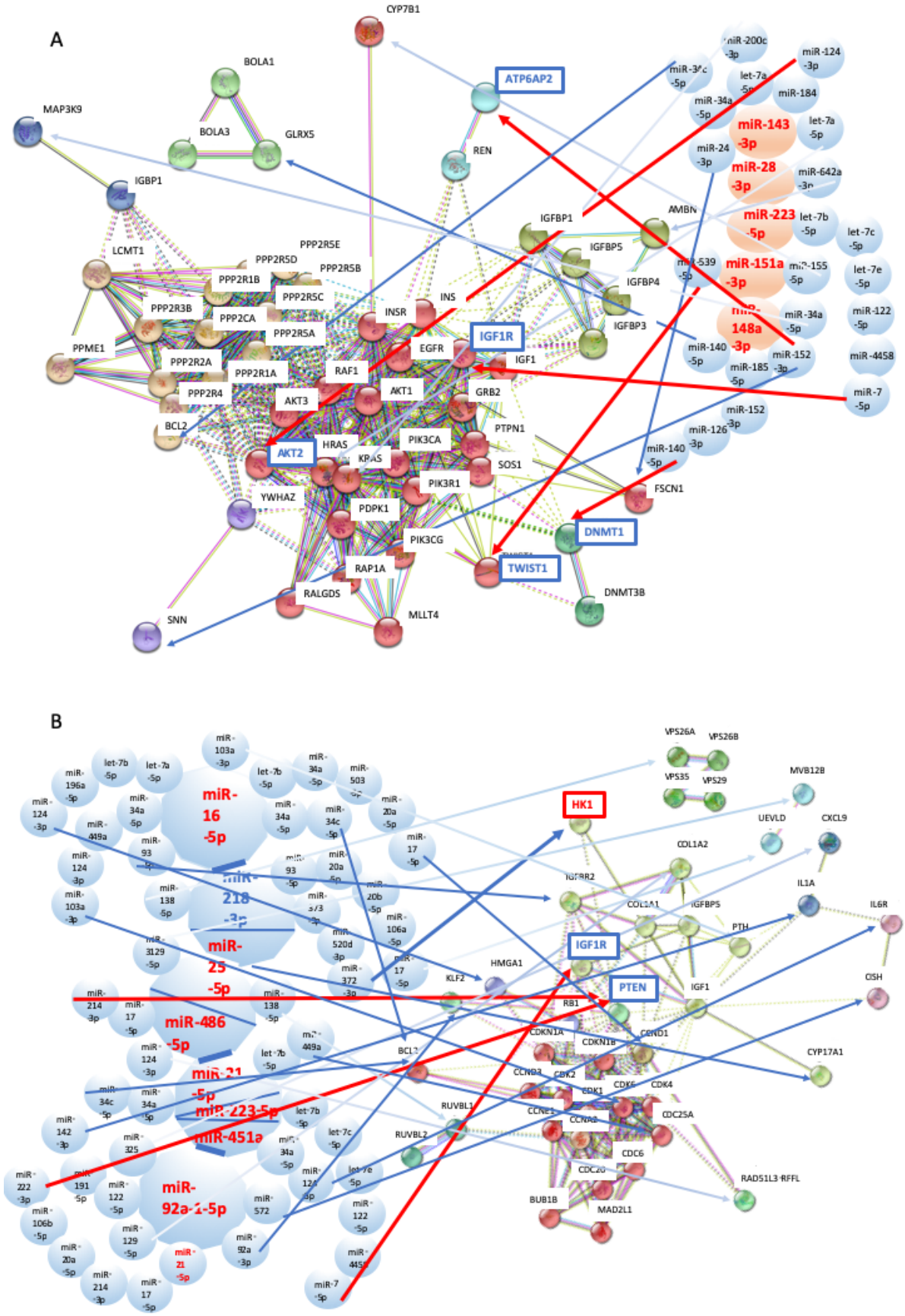
colorectal cancers were located into a narrow and lowest QCR layer, 0-20, and hub miRNA expression was downregulated in oesophageal cancer's QCR (Figure 1, a red plus blue border bar). On the other hand, the frequency DNS and DNS amounts of hub miRNA in stage I and stage I-IV gastric cancer were gradually pushed to the upstream of QCR layers, 41-81 (beige and red bars) by additional quantum energy, 0-40 QCR of *H. pylori* infection (blue bars). The data clearly suggest that quantum energy level in gastric cancer was increased by a dopant factor of *H. pylori* infection, and oesophageal cancer was not at all. Thus, gastric cancer biomarker miRNAs might have been associated to some panel miRNAs in *H. pylori* infection as the dopant donor when compared with oesophageal cancer. Finally, the hub miRNA layer was selected from the total layer through the cluster of protein/protein interactions as described previously (Figures 2-4) [25].

H. pylori infection and cancer

H. pylori is a Gram-negative bacterium and colonizes on the gastric mucosa, and it is believed that *H. pylori* infection directly or indirectly contributes to gastritis and gastric cancer development [26]. The *cagA* gene is presented in approximate 60% of *H. pylori* strains and the *cagA* encodes a 120-140 kDa CagA protein. *H. pylori* could inject CagA protein into the host epithelium via the type IV secretion system, which induces morphologic alteration of the host cells. CagA protein antibody-positive patients infected with *H. pylori* have shown 5.8-fold higher risk than uninfected people to develop gastric cancer [27]; however, CagA negative ones with *H. pylori* has also been 2.2-fold risk compared with uninfected control. Therefore, it is not clear whether CagA is absolute virulence factor for gastric cancer development or not. In addition, the purified VacA protein of *H. pylori* also had little effect on the viability of gastric epithelial cells [28].

In *H. pylori* infection miRNA biomarkers were selected as follows; upregulation of miR-28-3p, miR-143-3p, miR-151a-3p, miR-148a-3p and miR-223-5p in plasma specimens [10,20]. An infectious virulence factor, *H. pylori* CagA induced miR-223-3p expression [29]. Involving in pre-miRNA of miR-223, miR-223-5p has also been increased in both *H. pylori*-infected normal fixed tissues and fixed cancer ones of the human stomach [30], however, miR-223-5p was a tumor suppressor in lung cancer, colon cancer, breast cancer and oesophageal cancer cells [31-33]. Oncomir expression was not changed by *H. pylori* eradication in gastric cancer tissues when the *H. pylori* negative and positive ones were compared, whereas miR-223-5p was decreased and let-7 was increased by *H. pylori* eradication [34]. Further, miR-223-5p suppressed inflammatory pathway in *H. pylori*-infected macrophages [35]. The data suggested that the implication among *H. pylori* CagA and miR-223 may be anti-tumour and anti-inflammation. Although the specific miRNA panel have been identified in *H. pylori*-infected patients' plasma [10,20] and *H. pylori*-positive patients' tissue of gastric cancer [36], gastric cancer progression has been also clinically reported to be implicated in *H. pylori* infection [37,38]. Wang et al. [39] showed difference of the miRNA expression profile between *H. pylori*-positive and *H. pylori*-negative groups in tissues fixed and cultured cells of gastric cancer. miR-143-3p significantly increased in *H. pylori*-positive tissue samples and RAC-alpha serine/threonine-protein kinase (AKT) expression was reduced by miR-143-3p in gastric cancer cells, that is similar with a diagnostic panel of miRNA upon *H. pylori* infection [20]. As shown in Figure 2 (the total layer) and 3A (the miRNA hub), miRNA-143-3p upregulation suppressed AKT2 with miR-124-3p and miR-184 in *H. pylori* infection. On the contrary, AKT activation is reviewed by *H. pylori*-induced chronic gastritis [38] and activation of AKT was described in early gastric cancer tissues fixed [40,41]. Further, phosphorylation of AKT was increased by *H. pylori* infection and Polo-like kinase 1 (PLK1) expression was significantly high, which would be related with the downstream of PI3K/AKT pathway. However, AKT2 suppression by miR-143-3p upregulation in the *bona fide* plasma might be involved in *H. pylori*-infectious gastric epithelial cells. Although AKT is oncogene in general [42], our data suggested that host cell reaction would be anti-tumour by *H. pylori* infection.

AKT has AKT1 and AKT2 isoforms, and two isoforms have different biological functions, and both AKT1 and AKT2 amplifications were observed in gastric cancer and hepatocellular or colorectal cancers, respectively [43,44]. But AKT2 is specifically implicated in glucose metabolism and in the upstream of insulin-like growth factor 1 receptor (IGF1R) [45], which was suppressed by upregulation of miR-223-5p with let-7b-5p, let-7c-5p, let-7e-5p, miR-122-5p, miR-4458 and miR-7-5p (Figure 3A). It is well known that insulin-like growth factor 1 (IGF1) and IGF2 bind to IGF1R and IGF1R as a tyrosine kinase triggers phosphorylation of insulin receptor substrates (IRS-1 to -4) and Src-homology collagen (Shc), and then their signaling permits downstream mitogen-activated protein kinase (MAPK) and phosphatidylinositol


A
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BOLA3
GLRX5
MAP3K9
IGBP1
ATP6AP2
REN
IGFBP1
AMBN
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IGFBP3
LCMT1
PPP2R5E
PPP2R5D
PPP2R5B
PPP2R1B
PPP2R5C
PPP2R3B
PPP2CA
PPP2R5A
PPME1
PPP2R2A
PPP2R1A
PPP2R4
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INSR
IGF1R
EGFR
IGF1
RAF1
AKT1
AKT3
GRB2
BCL2
AKT2
HRAS
KRAS
PIK3CA
PIK3R1
PTPN1
SOS1
YWHAZ
PDPK1
PIK3CG
RAP1A
RALGDS
SNN
MLLT4
TWIST1
DNMT1
DNMT3B
FSCN1
miR-200c -3p
miR-124 -3p
let-7a -5p
miR-184
miR-34a -5p
miR-143 -3p
let-7a -5p
miR-24 -3p
miR-28 -3p
miR-642a -3p
miR-223 -5p
let-7b -5p
let-7c -5p
miR-539 -5p
miR-151a -3p
miR-155 -5p
let-7e -5p
miR-148a -3p
miR-34a -5p
miR-122 -5p
miR-140 -5p
miR-152 -3p
miR-185 -5p
miR-4458
miR-7 -5p
miR-126 -3p
miR-140 -5p
B
miR-16 -5p
miR-218 -3p
miR-25 -5p
miR-486 -5p
miR-21 -5p
miR-223-5p
miR-451a
miR-92a-1-5p
HK1
IGF1R
PTEN
HMGA1
KLF2
RB1
CDKN1A
CDKN1B
CCND1
CCND2
CDK2
CDK6
CDK4
CCNE1
CCNA2
CDC25A
CDC6
CDC20
BUB1B
MAD2L1
RUVBL1
RUVBL2
BCL2
VPS26A
VPS26B
VPS35
VPS29
MVB12B
UEVLD
CXCL9
COL1A2
COL1A1
IGFBP5
IGFBP2
IL1A
IL6R
PTH
IGF1
OSH
CYP17A1
RAD51L3-RFFL

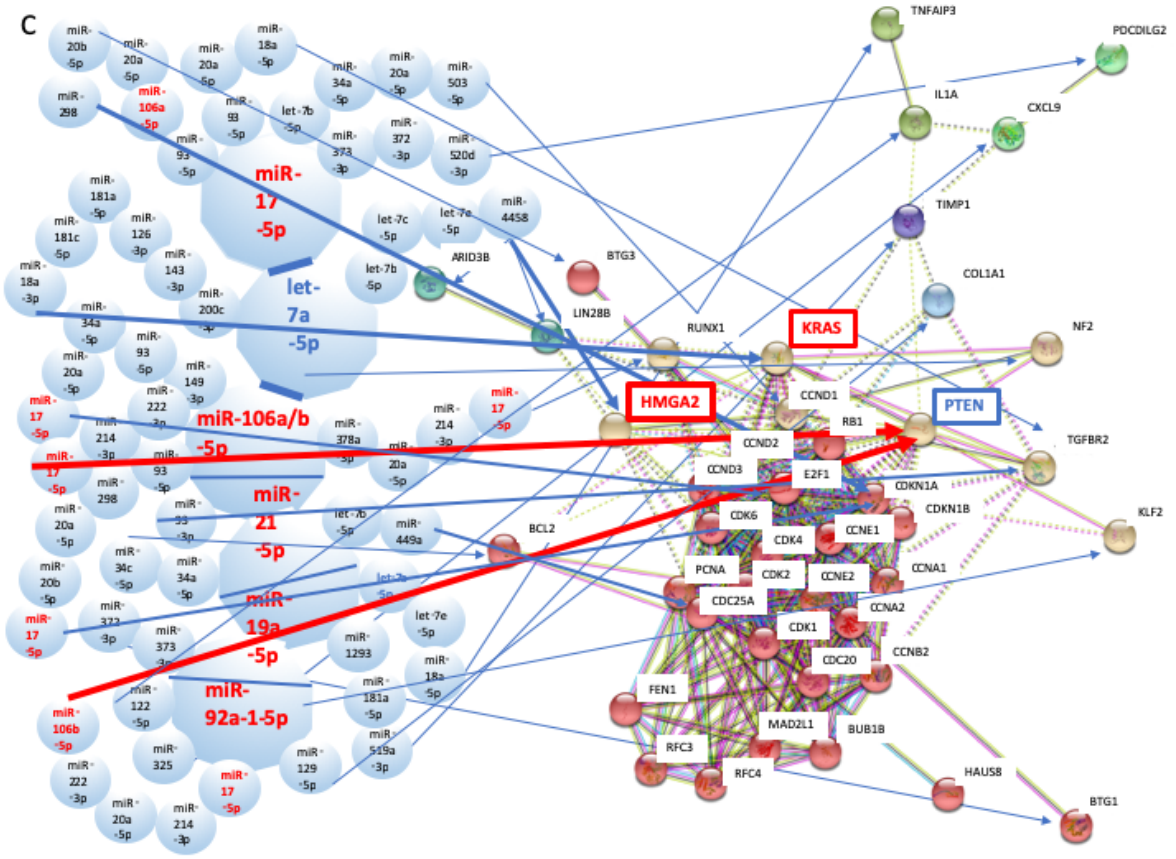
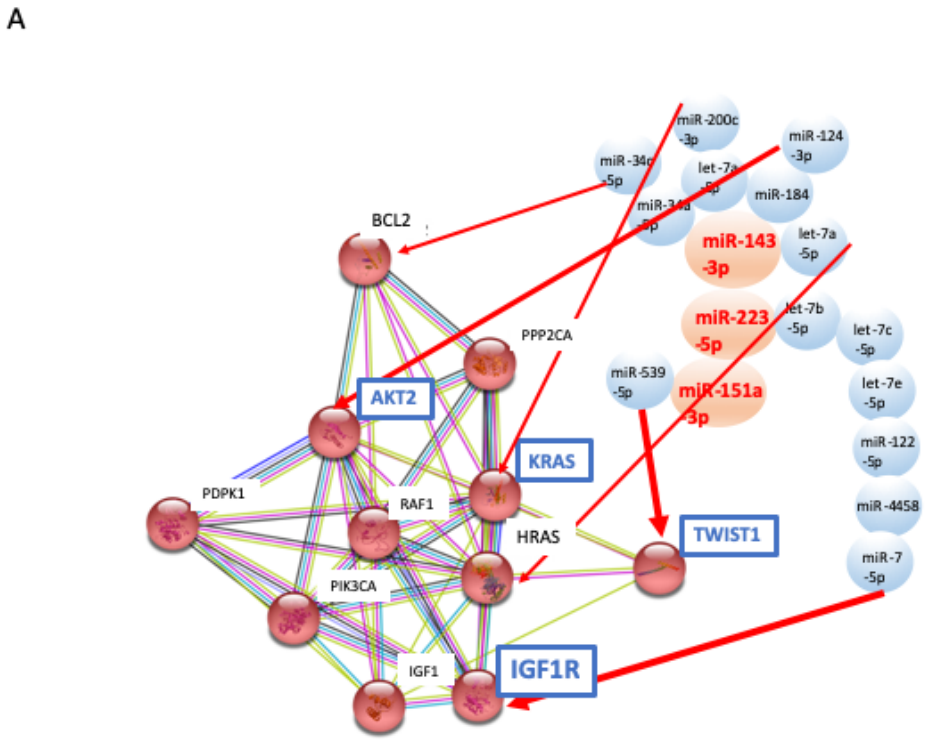


Figure 2. METS simulation of gastric cancer and *H. pylori* infection in all QCRs. After data mining, miRNA biomarker panels were selected and METS simulation was performed in *H. pylori* infection (A), gastric cancer in the stage I (B) and gastric cancer in the stage I-IV (C) on all QCRs. miRNAs: upregulation, red; downregulation, blue. Proteins: augmentation, red; suppression, blue.



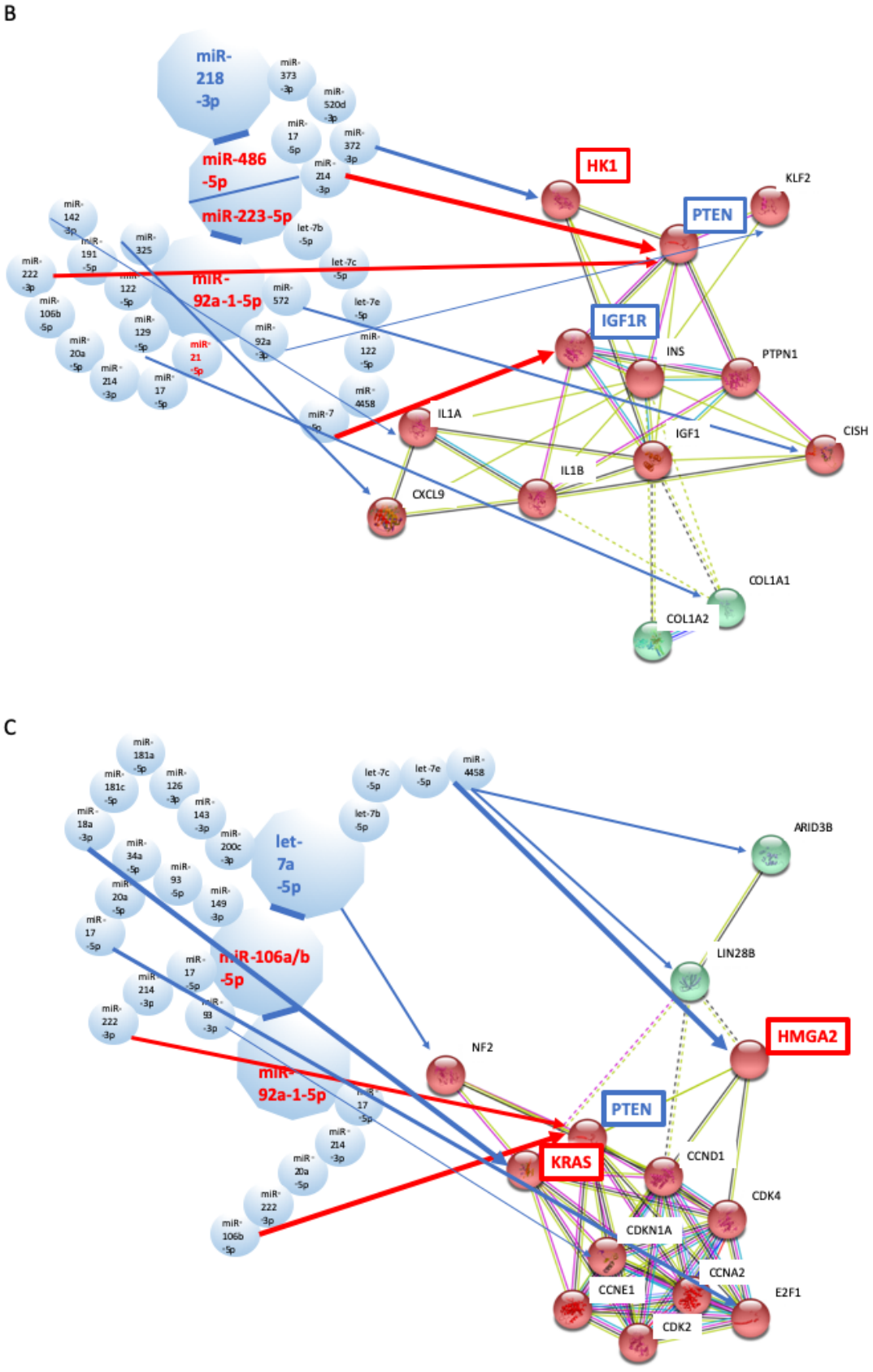
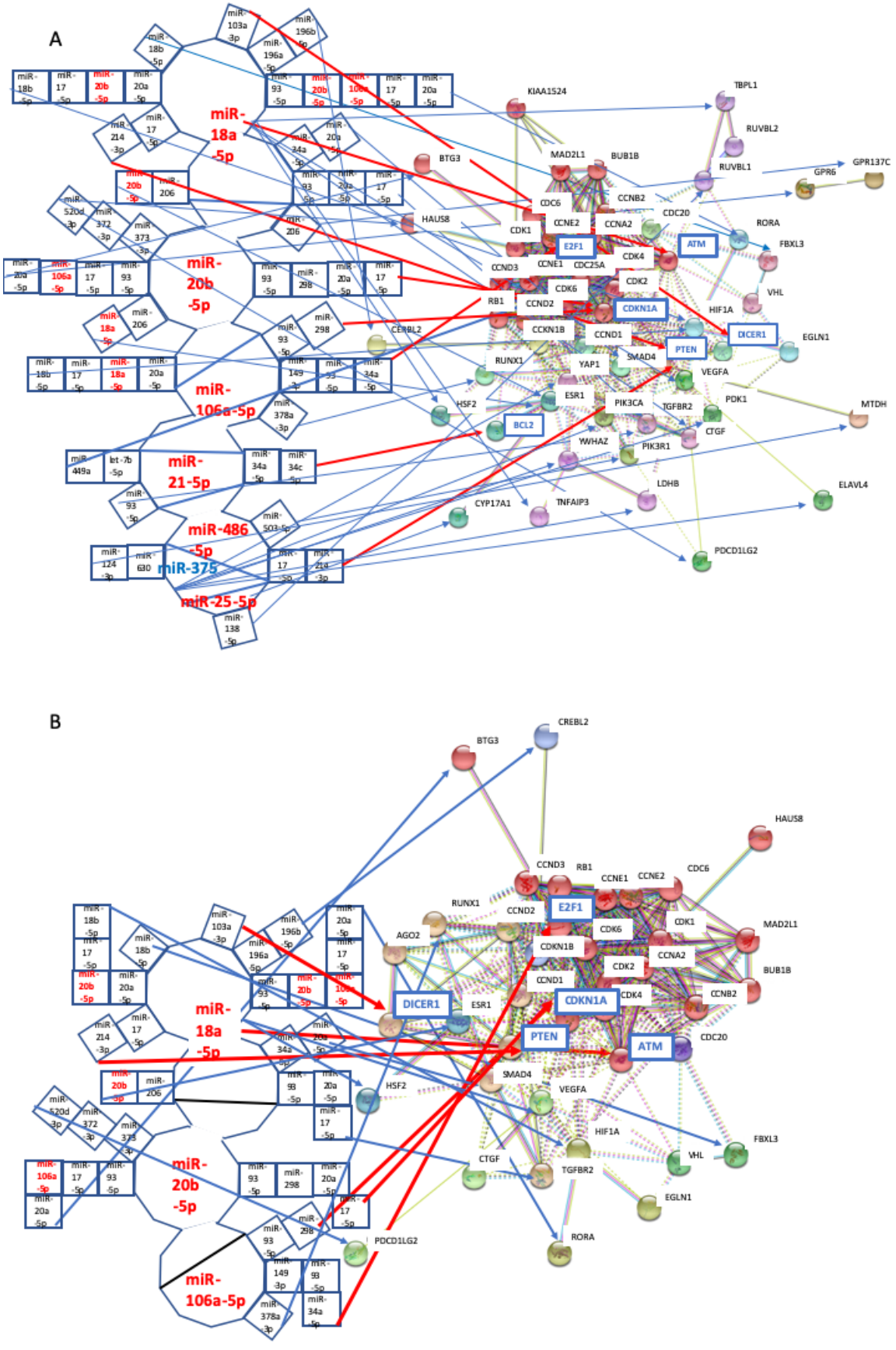


Figure 3. METS simulation of gastric cancer and *H. pylori* infection by the miRNA hub. The hub miRNAs were searched from all QCR METS simulation in Figure 2. The miRNA hub was determined by the cluster of protein/protein interaction, and then METS simulation was re-performed in *H. pylori* infection (A), gastric cancer in the stage I (B) and gastric cancer in the stage I-IV (C). miRNAs: upregulation, red; downregulation, blue. Proteins: augmentation, red; suppression, blue.


A
miR-18a-5p
miR-20b-5p
miR-106a-5p
miR-21-5p
miR-486-5p
miR-375
miR-25-5p
KIAA1524
TBPL1
RUVBL2
RUVBL1
GPR137C
GPR6
BTG3
MAD2L1
BUB1B
CDC6
CCNB2
CDC20
HAUS8
CDK1
CCNE2
CCNA2
E2F1
ATM
RORA
FBXL3
CCND3
CCNE1
CDC25A
CDK4
CDK2
CDK6
RB1
CCND2
CDKN1A
VHL
HIF1A
CCKN1B
CCND1
DICER1
EGLN1
CREBL2
RUNX1
YAP1
SMAD4
PTEN
VEGFA
ESR1
PIK3CA
PDK1
HSF2
TGFBR2
MTDH
BCL2
CTGF
YWHAZ
PIK3R1
LDHB
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CCNE1
CCNE2
CDC6
RUNX1
CCND2
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CDK1
MAD2L1
AGO2
CDK6
CDKN1B
CCNA2
BUB1B
CDK2
CCND1
DICER1
ESR1
CDK4
CDKN1A
CCNB2
PTEN
ATM
CDC20
SMAD4
VEGFA
HSF2
HIF1A
FBXL3
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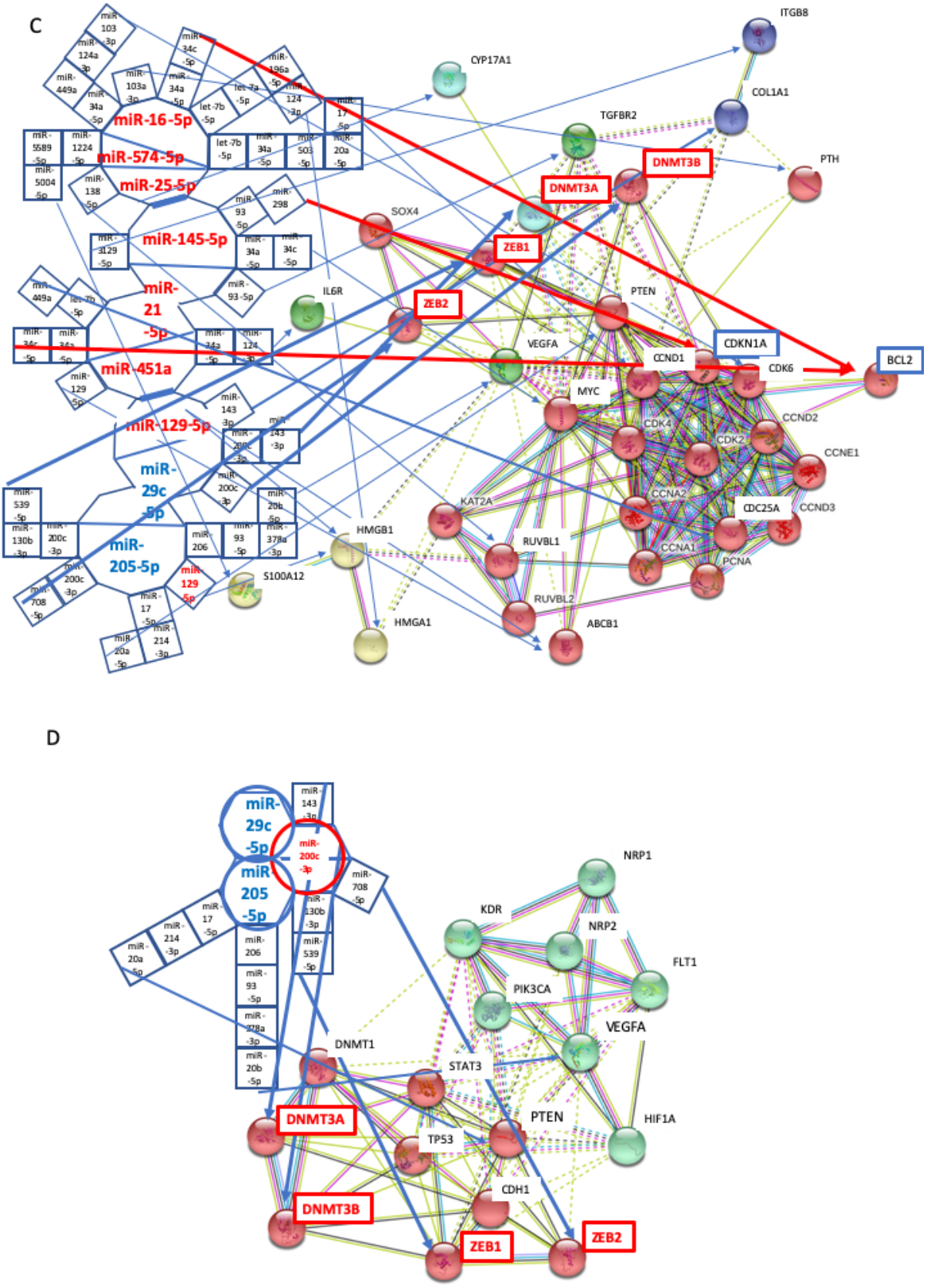

Figure 4. METS simulation of ESCC. The results of METS simulation were represented as (A) ESCC in the stage of 0-I of all QCRs, (B) ESCC in the stage of 0-I of the miRNA hub, (C) ESCC in the stage of I-IV of all QCRs and (D) ESCC in the stage of I-IV of the miRNA hub. miRNAs: upregulation, red; downregulation, blue. Proteins: augmentation, red; suppression, blue.

3-kinase (PI3K)/AKT to activate [46]. Therefore, Inhibition of IGF1R induces suppression of AKT under the signal transduction pathways. Thus, at least, *H. pylori* infection may rationally be explained by reduction for the possibility of oncogenesis.

Although basic helix-loop-helix transcription factor 38 (TWIST1) expression high was implicated in positive proliferation of gastric cancer cell [47] and DNA methyltransferase 1 (DNMT1) expression was higher in gastric cancer than normal, para-cancerous and dysplasia tissues in the bioinformatic meta-analysis [48]. TWIST expression was suppressed by miR-151a-3p upregulation with miR-539-5p (Figure 2A and 3A) and DNMT1 is also blocked by miR-148a-3p upregulation with miR-185-5p, miR-152-3p, miR-126-3p and miR-140-5p (Figure 2A). miR-148a-5p was downregulated in gastric cancer and miR-148a-5p suppressed DNMT1 in gastric cancer cells [49], in contrast, DNMT1 was overexpressed in gastric cancer and hypermethylation of DNA by DNMT overexpression reduced expression of miR-148a-5p [50]. Subsequently, *H. pylori* infection was predicted as non-oncogenic because of downregulation of DNMT1 and TWIST1 as above described in AKT2/IGF1R pathway.

Further, ATPase H+ transporting accessory protein 2 (ATP6AP2) was downregulated by upregulation of miR-148a-3p with miR-152-3p (Figure 2A) and ATP6AP2/renin receptor expression was decreased in *H. pylori*-infected gastric biopsies of gastritis [51]. Functional loss of ATP6AP2 induced to be pathognomonic for tumour in granular cells [52]. Although granular cell tumour is rare neoplasm to exhibit non-aggressive behaviour, relation between proton pump and ATP6AP2 may have some responsible for development of gastritis because ATP6AP2 is a subunit of v-H+ ATPase and it is essential for v-H+ ATPase to canonically function as a proton pump through plasma membrane [53]; however, the decrease in the stomach by proton pump inhibitor reduces the infiltration of *H. pylori* [54]. Furthermore, after *H. pylori* eradication successfully, long-term proton pump inhibitor users increased the risk of gastric cancer [55]. The data suggested that v-H+ ATPase inhibition would be pathogenic but not oncogenic. On the contrary, another V_1A subunit of v-H+ ATPase was 76% positive in gastric cancer tissues and siRNA of V_1A inhibited proliferation of gastric cancer cells [56]. v-H+ ATPase subunits would be a target of several cancers involving in gastric and oesophageal cancers [57]; however, there is some possibility that subunit inhibitor or proton pump inhibitor is not directly a proton pump inhibitor *in vivo* [58]. The pharmaceutical effects of subunit inhibitor should be evaluated by the miRNA expression profile under the treatment of subunit inhibiting agents [25]. These evidences strongly support that pathogenicity of *H. pylori* infection may be pre-oncogenic in the quantum network of miRNA/mRNA genes via proton pump inhibition during long-term under the presence of oncogenic CagA and sRNA products of *H. pylori* [59,60].

Although the network analysis of gastric cancer has been performed with and without *H. pylori* using The Cancer Genome Atlas (TCGA) database, the results of the analysis were limited by the small sample size of TCGA. PI3K/AKT pathway inhibition was found as effects of oncoprotein CagA [61]. However, the same PI3K/AKT pathway was implicated in gastric cancer by the network analysis of miRNA/mRNA using TCGA data without *H. pylori* connection [62]. It would be due to approximate 90% of *H. pylori* infectious rate [26,63], but approximately only 1-3% of people infected were developed to gastric cancer [64]. In a most recent report by Bayesian meta-analysis provided an accurate interpretation of randomized evidence, the preventive effectiveness of eradication in *H. pylori* has been resulted as an insufficient evidence to support or refute that for therapy in gastric cancer [65]. In previous meta-analysis, eradication therapy of *H. pylori* prevented gastric cancer [66]; however, most of data was calculated by the risk ratio [67]. In the case of the risk difference (absolute risk) in meta-analysis, the effectiveness of *H. pylori* eradication therapy was not statistically significant [68]. Since it has been remained whether *H. pylori* is still a friend or a foe [69], the outcome remains dubious. Therefore, the MMP of miRNA including the common miRNA markers between *H. pylori* infection and gastric cancer was further investigated by quantum network analysis.

Gastric cancer

In 2018 new gastric cancer incidence around world was 1,033,701 on the fourth ranking and death cases were 782, 685 on the third ranking (gco.iarc.fr/today/data/factsheets/cancers/7-Stomach-fact-sheet.pdf). Compared with other cancers, the incidence and mortality rates have been recently reduced; however, gastric cancer has still been a mortal disease depending on the lifestyle. More than 70% of gastric cancer occur in the developing areas in East Africa, East Asia, and parts of Central and South America. It is due to poor hygiene and higher *H. pylori* prevalence rates. *H. pylori* is the class I carcinogen of gastric cancer classified by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO). Reduction of risk factors in gastric cancer, such as *H. pylori* eradication, improved hygiene, food preservation, fall in smoking, etc. has decreased cancer incidence; however, 5-year survival rates was 25% in period 2005-2007 by EUROCARE-5 (eurocare.it) [70]. The problem is the late diagnosis because of asymptomatic or else unspecified in early gastric cancer. Most gastric cancers are advanced at detection while endoscopy in dyspepsia was recommended at age over 45 years [71] and gastric cancer has a poor prognosis. Therefore, non-invasive diagnose marker is critical for reduction of 5-year survival.

Classical standard biomarkers, CEA, CA19-9 and their combination have applied for gastric cancer, however, they were quite low sensitivity and specificity [72]. Epigenetic alteration, hypermethylation of SOX 17 has been shown to diagnose in early gastric cancer [73] and hypermethylation was found in *H. pylori*-related gastric cancer [74]. DNA methylation was gradually decreased in *H. pylori*-infected gastritis independent of CagA status, therefore, hypomethylation has a problem about specificity between *H. pylori*-related gastritis and gastric cancer. Further, Sox17 hypermethylation would not succeed to diagnostic distinguish between gastritis and gastric cancer with or without *H. pylori* infection at all.

After data mining, in the stage I of GC, upregulation of miR-21-5p, miR-223-5p, miR-16-5p, miR-25-5p, miR-92a-1-5p, miR-451a and miR-486-5p, and downregulation of miR-218-1-3p were selected as biomarkers in plasma specimens [10, 11]. In the case of stage I-IV (I: 23.8%, II: 21.2%, III: 43.5%, IV: 11.1%, unknown: 0.4%), upregulation of miR-17-5p, miR-106a/b-5p, miR-21-5p, miR-19a-5p, and miR-92a-1-5p, and downregulation of let-7a-5p were selected as biomarkers in plasma specimens [12,13]. Since the aetiology differences of human disease were identified by the combination of miRNAs into MMP as described previously [9], if the same target in different miRNA combinations is selected between *H. pylori* infection and gastric cancer, the infection by *H. pylori* may be involved in gastric cancer. To elucidate gastric cancer induction by *H. pylori*, commonly etiologic factors among infection and carcinogenesis were investigated by computer prediction with quantum network analysis in early stage of gastric cancer. Although expression of IGF1R were downregulated by

upregulation of the common miR-223-5p combination of let-7b-5p, let-7c-5p, let-7c-5p, miR-122-5p in Figure 2B (the total layer) and 3B (the miRNA hub), miR-4458 and miR-7-5p, and AKT connection in *H. pylori* infection was not involved in stage I gastric cancer (Figure 2A and 2B). The common miRNA/target connection on IGF1R protein was found in the miRNA hub of quantum network of stage I gastric cancer (Figure 3A and 3B); therefore, *H. pylori* could affect miRNA expression in the early gastric cancer. On the contrary, enforced expression of phosphatase and Tensin homolog (PTEN) resulted in decreasing of IGF1R expression upon gastric adenocarcinoma cells [75]; however, tumor suppressor PTEN was strongly blocked by both upregulation of miR-486-5p with miR-17-5p and miR-214-3p, and upregulation of miR-92a-1-5p plus miR-21-5p with miR-17-5p, miR-214-3p, miR-20a-5p, miR-106b-5p and miR-222-3p (Figure 2B and 3B). PTEN expression is low in gastric cancer [76] and the downregulation of PTEN is implicated in induction [77], maintenance of a malignant state [78], and progression and metastasis of gastric cancer [79]. These data were strongly supported by our *in silico* simulation that in the stage I-IV, PTEN was strongly repressed by upregulation of miR-106a/b-5p with miR-17-5p, miR-93-5p and miR-298, and upregulation of miR-92a-1-5p with miR-17-5p, miR-106b-5p, miR-214-3p, miR-20a-5p and miR-222-3p in Figure 2C (the total layer) and 3C (the miRNA hub).

In the stage I-IV, miR-21-5p was upregulated in the total layer of gastric cancer (Figure 2B and 2C). miR-21-5p and miR-222-5p were upregulated in the plasma of gastric cancer [80], and high expression of miR-21-5p and miR-222-3p in the fixed tissues was related to poor survival of gastric cancer [81]. Further, in the stage I-IV, miR-17/92 cluster was upregulated in the total layer of gastric cancer (Figure 2B and 2C). miR-17/92 cluster including miR-17-5p, miR-92a-1-5p, miR-20a-5p, miR-106a/b was increased in the plasma of gastric cancer and was associated with the progression of gastric cancer [82,83]. On the other hand, downregulation of let-7a-5p upregulated KRAS and HMGA2 with miR-200c-5p, miR-143-3p, miR-126-3p, miR-181a-5p, miR-181c-5p and miR-18a-3p, and with let-7b-5p, let-7c-5p, let-7e-5p and miR-4458, respectively (Figure 2C and 3C). Although KRAS mutation and amplification were found in 5% and 7% of gastric cancer in the data of TCGA [84], *H. pylori*-infected patients with KRAS mutation contained only 0.5-0.2% of gastric cancer, and there was no correlation between *H. pylori* infection and KRAS mutation in gastric cancer [85,86] and KRAS mutation was not associated with histological progression of gastric cancer with *H. pylori* [87]. Therefore, it has still not been cleared in the aetiology of KRAS activation upon gastric cancer; however, transactivation of KRAS via ZNF312b was increasing human gastric tumour progression in nude mouse [88]. Our quantum prediction shows a novel insight that KRAS upregulation by downregulation of let-7a-5p combination would maintain gastric cancer progression without mutation and amplification of KRAS gene. let-7a-5p was significantly downregulated in gastric cancer specimens and inhibited its proliferation [89]. The proliferation of gastric cancer cells has been inhibited by Chinese herbal medicine, Yangzheng Sanjie decoction through upregulation of let-7a-5p [90]. Furthermore, overexpression of HMGA2 was also associated with poor prognosis of gastric cancer in a meta-analysis [91,92]. Oncogenic KRAS expression induced HMGA2 [93], and RUNX/TP53 negative gastric epithelial cells induced spontaneous EMT under upregulation of HMGA2 by the EGFR/RAS pathway [94]. Thus, upregulation of KRAS and HMGA2 by downregulation of let-7a-5p might be implicated in gastric cancer progression among stage I to IV and the etiologic characters of gastric cancer are highly distinct from those of *H. pylori* infection except for IGF1R downregulation.

Hexokinase 1 (HK1) was upregulated by downregulation of miR-218-3p with miR-93-5p, miR-373-3p, miR-520d-3p and miR-372-3p (Figure 2B and 3B). HK1 was overexpressed in gastric cancer tissues, and overexpression of HK1 was associated with lymphatic metastasis and clinical staging in gastric cancer [95]. Warburg effect (aerobic glycolysis) including HK1 activation contributes to tumorigenesis [96]. IGF1R inhibition is the common tuning between *H. pylori* infection and early gastric cancer, and inhibition of IGF1R expression would induce high susceptibility to glucose transporting via insulin receptor (INSR) [97,98] because of 87-97% presence of INSR in gastric cancer [99]. Stress, such as mal-foods or urease of *H. pylori* mutated ΔCagA directly induced hypoxia-induced factor (HIF) [100] and hypoxia promotes gastric cancer malignancy via HIF activation [101]. Further, hypoxia suppressed let-7a in hypoxic human tumour cells [102] and downregulated let-7 family in rat cardiac fibroblast [103]. Warburg effect and hypoxia by stress of *H. pylori* infection were associated with cancer, and its chemotherapy and radiation resistances [104,105]. As shown in Figure 3, these evidences suggested that *H. pylori* infection would additionally contribute to progression of malignancy in gastric cancer cells via glucose metabolic pathway on a paradox in Zen Buddhism riddle, called 'Koan' with direct tumour initiation upon host condition by suppression of PTEN, and via KRAS conversion from downregulation to upregulation (Figure 3A and 3C). The discrepancy between statistic meta-data between significant of the risk ratio and no significant of the absolute risk may be due to the paradoxical effect of *H. pylori* infection for gastric cancer. This early process would be followed by PTEN/KRS/HMGA2 protein hub for further progression of metastatic gastric cancer. Therefore, in Figure 3, it is easily understood with the common miR-223-5p/IGF1R connection that even though people who infected with *H. pylori*, stress would rarely induce tumorigenic malignancy in the stomach, which was supported by low incidence of gastric cancer in high infectious rate of *H. pylori* [64].

Esophageal cancer

H. pylori infection has been observed by upper gastrointestinal endoscopic biopsy and esophagectomy, and there was a negative association between *H. pylori* infection and a reduced risk of ESCC [5]. Other reports have also showed significantly no correlation between *H. pylori* infection and ESCC risk by a meta-analysis [106-108]. Therefore, ESCC cases are a control of *H. pylori* infection-positive in the etiological relation of cancer.

Oesophageal cancer has two pathological subtypes, one is oesophageal squamous cell carcinoma (ESCC) and the other is adenocarcinoma (AC). Oesophageal cancer is the 7th leading cause of cancer-related death and ESCC is approximate 90% of oesophageal cancer cases in apart of Asia and Sub-Saharan Africa [109]. For diagnosis of oesophageal cancer invasive endoscopy and biopsy are the gold standard techniques even less symptomatic at early stage of oesophageal cancer. Non-invasive tumour markers, CEA, CA 19-9, CA125 and SCC were too low sensitivity to develop mass screening and were not correlated with stage of oesophageal cancer [110]. Therefore, the diagnosis of oesophageal cancer occurs late and 5 years survival rate is very low about 15-20% in US [111]; however, early stage diagnosis by endoscopy and surgical treatment increased 5 years survival rate as high as 85% [112]. Early and significant screening more is increasing survival rate and it is suggested that the prediction of cancer could prevent development of clinical symptom in disease from healthy individuals.

In the stage 0-I of ESCC, upregulation of miR-18a-5p, miR-20b-5p, miR-106a-5p, miR-21-5p, miR-486-5p and miR-25-5p, and downregulation of miR-375 were observed as biomarkers in plasma specimens [14,15]. As shown in Figure 4A (the total layer) and 4B (the miRNA hub), ataxia telangiectasia mutated (ATM) was suppressed by upregulation of miR-18a-5p. ATM is serine/threonine kinase and is belong to the PI3/PI4 kinase family. DNA damage activates ATM and the activated ATM phosphorylates Chk1 and Chk2, then ATM stabilizes TP53 by phosphorylation. Both Chk1 and Chk2 are implicated in the G2/M cell cycle checkpoint, therefore, ATM is an influencer of repairing DNA damage before the mitosis [113,114]. Caffeine treatment inhibited ATM and it showed several of the phenotypic alteration in the cells [115]. Further, ATM mutation results centromeric instability and increasing of susceptibility to a variety of cancer [116,117]. Although Jaridonin inhibited proliferation of ESCC through G2/M arrest, Jaridonin activated ATM and arrested G2/M cell cycle, and ATM inhibition by caffeine reversed ATM activation in human ESCC [118]. These data suggested that ATM suppression by miR-18a-5p would be unstable DNA damage response and would progress carcinogenesis in oesophageal epithelial cells.

CDKN1A was inhibited by miR-20b-5p plus miR-93-5p, miR-298, miR-20a-5p and miR-17-5p, and miR-106a-5p plus miR-93-5p and miR-298 (Figure 4A and 4B). miR-20b-5p and miR-106a-5p are localized as polycistronic genes into the cluster miR-106a/363 in the chromosome X [119]. Although miR-20b, miR-363-3p and miR-363-5p in miR-106a/363 cluster showed an anti-proliferating effect on oral carcinoma [120], different combination of miR-106a-5p with miR-20b-5p in miR-106/363 cluster would be oncogenic because the target of CDKN1A as a cyclin kinase (Cdk) inhibitor is a tumour suppressor and low concentrations of p21 (Cip1/Waf1/CDKN1A) promote proliferation of tumour cells [121]. Further, E2F1 was decreased by miR-106a-5p with miR-149-3p, miR-93-5p and miR-34a-5p (Figure 2A and 2B). E2F1 is phosphorylated by ATM and Chk2 kinases in response to DNA damage, therefore, suppression of ATM expression would also E2F1 activation and low level of expression of E2F1 would maintain malignant state [122]. DICER suppression by miR-18a-5p plus miR-103a-3p was predicted (Figure 4A and 4B), as described previously, decreasing of DICER expression was oncogenic on the stage zero of colorectal cancer [24]. miR-18a-5p with miR-17-5p and miR-214-3p inhibited tumour inhibitor PTEN expression (Figure 4A and 4B). The prediction is supported by the Sun's report [123] that 51.4% of ESCC tumours were negative of PTEN expression and PTEN expression in ESCC was statistically lower than non-tumour oesophageal epitheliums. HIF1A was inhibited by upregulation of miR-18a/b-5p, miR-20a/b-5p and miR-17-5p and BCL2 is blocked by upregulation of miR-21-5p plus miR-34a/c-5p (Figure 4A), however, expression of hypoxia-related target HIF1A was inversely associated with that of oncogene BCL2, which is related to the response of photodynamic therapy against early ESCC [124]. Therefore, expressions of HIF1A and BCL2 may be dependent on miRNA-17/92 cluster as well as the oxygen in early oesophageal cancer.

In the process of transition on the stage from I to IV (I-II: 36.6%, III-IV: 63.4%), downregulation of miR-29c-5p and miR-205-5p, and upregulation of miR-16-5p, miR-574-5p, miR-25-5p, miR-21-5p, miR-451a and miR-129-5p were detected as biomarkers in patient sera [16-19]. Although inverse correlation among levels of DNMT3A and DNMT3B and the expression of miR-29 was found in hepatocytes [125], downregulation of miR-29c-5p would enhance the DNMT3A and DNMT3B expressions in Figure 4C (the total layer) and 4D (the miRNA hub). In cancer cells, generally, CpG rich regions including promoter of DNA are usually heavily methylated [126] and aberrant DNA methylation is implicated in ESCC progression [127]. Since DNA CpG methylation is contributed by DNMT3A and DNMT3B, a methylation signature of DNA was identified in ESCC patients with lymph node metastasis at statistically significant accuracy [128]. Therefore, hypermethylation of DNA would be involved in epithelial-mesenchymal transition (EMT). Further, ZEB1 high expression was related with the malignancy of various cancer and EMT [129]. The evidence supported our simulation that miR-29c-5p suppression augments expression of its targets ZEB1 and ZEB2, probably associated to upregulation of miR-200c-3p (Figure 4C and 4D) because of increasing of miR-200c-3p in ESCC cell line [130] and tumour of patients [131].

As CDKN1A expression was blocked by miR-17/93 family in stage 0-I of ESCC (Figure 4A and B), upregulation of miR-145-5p with miR-93-5p and miR-298 reduced expression of CDKN1A in stage I-IV (Figure 4C). Further, BCL2 was also inhibited by upregulation of miR-21-5p and miR-16-5p with miR-34a-5p and miR-34c-5p (Figure 4C). However, miR-34a-5p was downregulated in ESCC cells [132,133] and miR-34a/c-5p were inactivated by CpG methylation in patients with ESCC [134,135]. Therefore, it is suggested that cell cycle may not be so essential for progression of oncogenesis in ESCC late stages because of suppression of cycling inhibitor CDKN1A and inhibition of oncogene BCL2, and there is no common etiologic factor between *H. pylori* infection and ESCC.

Fresh vegetable and fruit diets to *H. pylori* infection in stomach

As mentioned above, some people in Asia persistently infected with *H. pylori* do not suffer from high incident rates of gastric cancer by availability of fresh fruits and vegetables [3,4]. Since miRNAs of fruits and vegetables have been stably incorporated into the human circulating system and estimated in human tissues [9,136], the xenotropic miRNAs (xenomiRNAs) could affect the protein expression of tumour cells through tuning by the interaction between xenomiRNA and target mRNA [9,137]. Watermelon, *Citrullus lanatus*, is one of common fruits in Asia, and its plant miRNAs have been investigated in human plasma [138]. Six xenomiRNAs in watermelon juice were detected in the dynamic physiological pattern in human plasma at the absorption rate of 0.004 to 1.31%. The top 5 of high absorbed xenomiRNAs, MIR157a, MIR156a, MIR172a, MIR168a and MIR162a were contained in apple fruit, and banana and tomato vegetables [139], which are also common food in Asia. The five plant miRNAs were homologically compared with human miRNAs, especially, on the sequences of the seed 8 nucleic acids in the 5' terminal region (Table 2). The seeds of MIR157a, MIR156a, MIR172a, MIR168a and MIR162a were 88, 75, 75, 63 and 75% homologous to those of miR-4520-3p, miR-4644, miR-103a-2-5p, miR-4289 and miR-3125, respectively. Plant miRNAs could have similarly been functioned to human homologous miRNAs [9,137], therefore, the seeds of five human miRNAs were used for further analysis.

Protein targets of miR-4520-3p, miR-4644, miR-103a-2-5p, miR-4289 and miR-3125 were investigated by miRNA target searching tools. The 3' untranslated regions (UTRs) of RHOA, SIX1 and DNMT1 had target sites of miR-4644 and miR-185-5p, and the 3'UTR of POTEE has the target site of miR-103a-2-5p (Data not shown). Since miR-4644 and miR-103a-2-5p would be functioned to MIR156a and MIR172a, respectively, the secondary structure of MIR156a and MIR172a to the target regions were computed by mfold and CentroidFold (Figure 5).

Table 2. Plant seed homology in human miRNAs

Plant miRNAs	ID sequences	SNS	Human miRNAs		ID sequences		SNS	Homology*
MIR 157a	>ath-miR157a-5p MIMAT0000172	6	miR-4520-3p		>hsa-miR-4520-3p MIMAT0019057		6	88
	UUGACAGAAG AUAGAGAGCAC				UUGGACAGAAA ACACGCAGGAA			
MIR 156a	>ath-miR156a-5p MIMAT0000166	7	miR-4644	miR-185-5p	>hsa-miR-4644 MIMAT0019704	>hsa-miR-185-5p MIMAT0000455	9	75
	UGACAGAAGA GAGUGAGCAC				UGGAGAGAGAAA AGAGACAGAAG	UGGAGAGAAAG GCAGUUCCUGA		
MIR 172a	>ath-miR172a MIMAT0000203	5	miR-103a-2-5p		>hsa-miR-103a-2-5p MIMAT0009196		5	75
	AGAAUCUUGA UGAUGCUGCAU				AGCUUCUUUACA GUGCUGCCUUG			
MIR 168a	>ath-miR168a-5p MIMAT0000198	9	miR-4289		>hsa-miR-4289 MIMAT0016920		6	63
	UCGCUUGGUG CAGGUCGGGAA				GCAUUGUGCA GGGCUAUCA			
MIR 162a	>ath-miR162a-5p MIMAT0031876	8	miR-3125		>hsa-miR-3125 MIMAT0014988		9	75
	UGGAGGCAGCG GUUCAUCGAUC				UAGAGGAAGC UGUGGAGAGA			

*8 seed,

Plant miRNAs	Targets	⊿G
MIR156a	RHOA	-4.8
	SIX1	-14.1
	DNMT1	-5.4
MIR172a	POTEE	-4.5

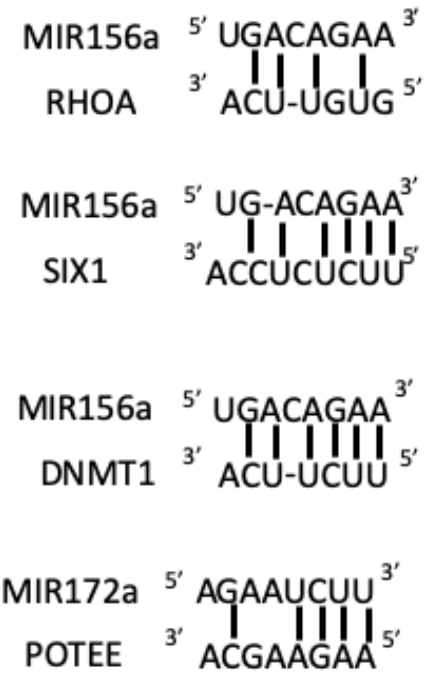

Figure 5. Investigation of protein mRNA 3' UTR against plant miRNAs. The target site specificity of plant miRNAs, MIR-156a and MIR-172a were searched in silico. The processes of the searching human protein targets against plant miRNAs were described in results and discussion. The free energy values (ΔG) were calculated between the sequences of the miRNA seed and 3'UTR (the upper table). The seed region of two plant miRNAs and protein 3'UTR target were paired (The lower picture).

To determine the target site specificity of xenomiRNAs, the free energy values (ΔG) were calculated. The ΔG of MIR156a were -4.8, -14.1 and -5.4 to RHOA (3'UTR position of 92-98), SIX1 (3'UTR position of 196-203) and DNMT1 (3'UTR position of 306-312), respectively. The ΔG of MIR172a was -4.5 to POTEE (3'UTR position of 32-39). These data suggested that there would be possible target sites of plant xenomiRNA in human protein mRNA 3'UTR [9].

The quantum data of Watermelon was cohered to *H. pylori* infection quantum data. As shown in figure 6, protein phosphatase 2 subunits (PPP2Rs) protein/protein interaction in *H. pylori* infection was disappeared by watermelon feed. Although PPP2Rs were not directly tuned by the miRNA panel (Figure 2A), PPP2Rs were a tumour suppressor [140]. In vegetable (watermelon) quantum network, protein/protein interaction of PPP2Rs was rearranged to that of proteasome α and β subunits (PSMA and PSMB) (Figure 6). PSMA and PSMB are subunits of the 20S proteasome core structure and members of peptidase family [141]. PSMA7 was upregulated in gastric cancer, however, PSMA 1-4 were downregulated [142]. Further, proteasome inhibitor, bortezomib was not effective for the advanced adenocarcinoma of the stomach in phase II clinical trial [143]. Proteasome subunit function may have not so important role to control gastric tumorigenesis.

On the contrary, RHOA has been associated with the progression of gastric cancer and been a druggable therapeutic target [144]. RHOA was downregulated by MIR156a incorporation with host miR-483, miR-125a-3p, miR-31-5p and miR-155-5p (Figure 6), and suppression of RHOA would reduce expression of IGF1R and INSR [145,146]. Therefore, galactose metabolic pathways including Warburg effect (aerobic glycolysis) would be inhibited, and simultaneously cell proliferation signals would be blocked through IGF1R. Further, host miR-31-5p upregulation reduced ROHA expression and blocked tumorigenicity [147,148]. It is suggested that fresh vegetable's effects of anticancer in the stomach would be enhanced by fresh vegetable MIR156a diet cooperated with host miRNAs, such as miR-31-5p. In the case of *H. pylori* infection with fresh vegetable, plant MIR156a incorporation and upregulation of miR-143-3p by *H. pylori* infection inhibited RHOA, HRAS and KRAS (Figure 6). Since HRAS and RHOA were implicated in transformation [149], and KRAS as well [150],

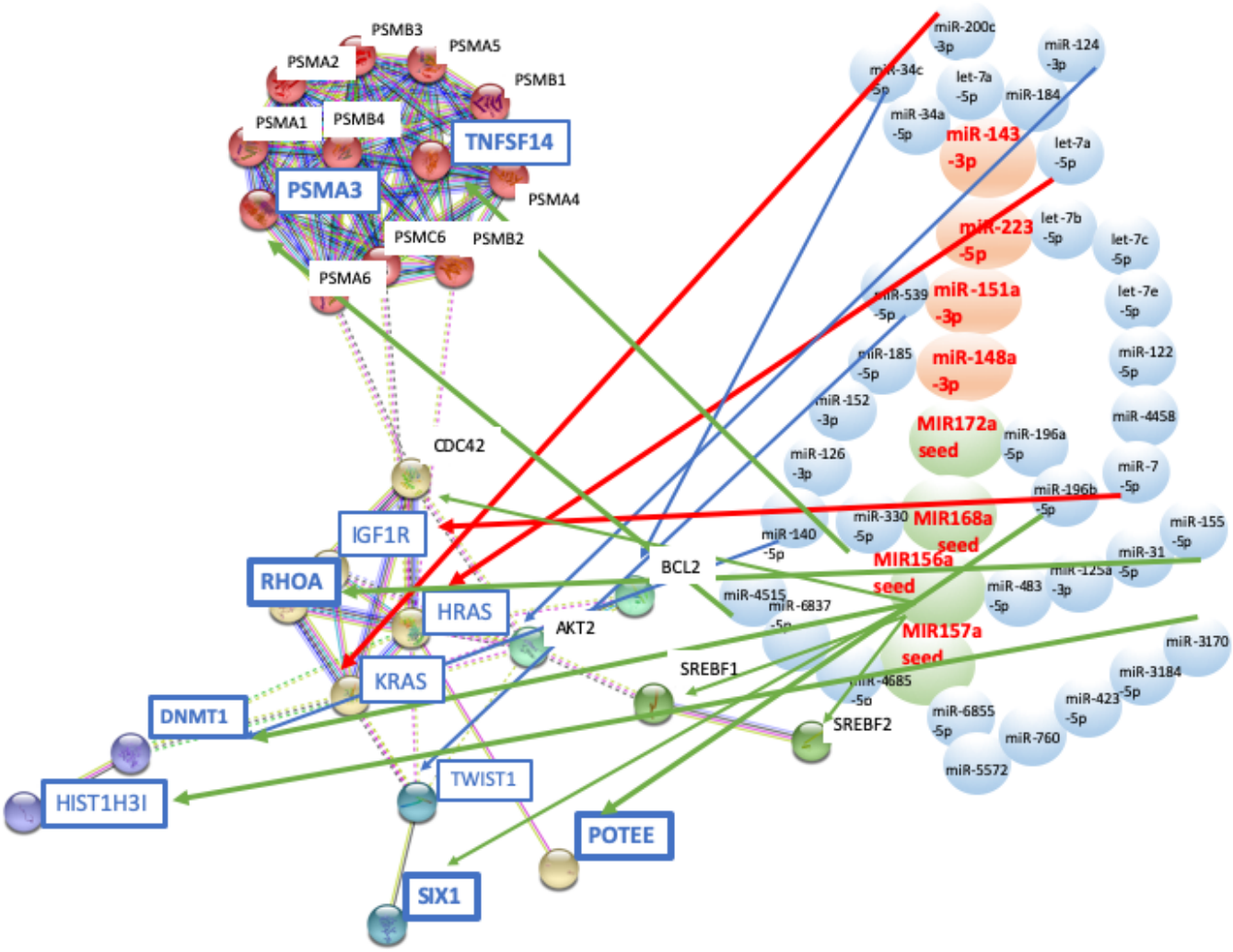

Figure 6. Coherence of the quantum code of vegetable miRNA and the miRNA hub in *H. pylori* infection. Four vegetable miRNAs' seed (green circles) and four miRNAs in *H. pylori* infection (orange circles) were applied for the METS analysis and the network was depicted. miRNAs: upregulation, red; downregulation, blue. Proteins: augmentation, red; suppression, blue.

fresh vegetable diet would augment suppression of carcinogenesis on the stomach under *H. pylori* infection. As described above, DNMT1 expression was high in gastric cancer [48], and Sine Oculis homeobox homologue (SIX) was also increased in gastric cancer. SIX was implicated in proliferation and invasion [151]. Consequently, three tumor-related proteins, ROHA, DNMT1 and SIX were downregulated by plant MIR156a feed (Figure 6).

Ankyrin domain family member E (POTEE) has been expressed in several cancers, such as the colon, prostate, lung, breast, ovary, lung and pancreas cancers [152,153]. POTEE was downregulated by plant MIR172a with host miR-196a-5p and miR-196b-5p (Figure 6). POTEF, which is an analogue of POTEE in the same group of POTE family, its antisense gene transcript repressed Toll-like receptor (TLR) and apoptosis as the antisense long non-coding RNA gene (*POTEF-AS1*) [154] and POTEE expression was upregulated in macrophages exposed to conditioned medium of cancer cells grown under hypoxia [155]. These evidences showed that POTEE function would be at least implicated in inflammation through stresses such as hypoxia and bacterial infection. Therefore, reduction of POTEE expression may inhibit carcinogenesis via suppression of the stress. Thus, the data suggests that plant xenomiRNAs, such as vegetable (watermelon) MIR156a with host miRNAs may cure *H. pylori*-infected people from paradoxical pre-cancerous state.

Dietary β-carotene is provitamin A and when ate and absorbed, it is formed as retinol, one of the major forms of vitamin A. Watermelon contains phytochemicals, such as β-carotene and lycopene as the effector to miRNA expression [156,157]. Lycopene induced let-7f in prostate cancer cells and inhibited their proliferation *in vitro* [158]; however, administration of high doses of lycopene dietary supplement clinically resulted to be associated with a higher incidence of prostate cancer in phase I-II study [159]. All-trans retinoic acid (ATRA) is an isomer of retinoic acid and ATRA has been functioned as anticancer agents against different cancers including gastric cancer and been modulated expression of miRNAs in different types of cancer [160,161]. Although ATRA upregulated miR-302b expression in glioblastoma and ATRA inhibited cell proliferation of glioblastoma [162], alteration of miRNA profile by ATRA in gastric cancer has not yet been reported anywhere. Therefore, treatment with phytochemicals of watermelon was not leveraged in a cooperative relationship with host miRNAs integrated into the quantum network simulation.

Statistical analysis of the relation between cancers and fresh vegetable diet

To investigate whether *H. pylori* infection or fresh vegetable diet (watermelon) is pathogenetically associated with gastric cancer, statistical significance of the METS simulation has been examined. The valuation of statistical significance for carcinogenic pathology in the METS simulation was performed by the AUC in ROC using Excel and machine learning. As shown in Figure 7 and Table 3, tumorigenicity for gastric cancer in *H. pylori* infection (AUC: 0.57 in Excel, 0.4 in machine learning), and with fed fresh vegetables (AUC: 0.504 in Excel, 0.529 in machine learning) were statistically no significant compared with gastric cancer in the stage I (AUC: 0.78 p<0.001 in Excel, 0.9 p<0.05 in machine learning) and I-IV (AUC: 0.814 p<0.001 in Excel, 0.986 p<0.001 in machine learning). The AUC of ESCC 0-I and I-IV as the control were 0.676 (p<0.001) and 0.768 (p<0.001), respectively. By deep machine learning, the AUC of gastric and oesophageal cancers in the stage I-IV were 0.986 (p<0.001) and 0.924 (p<0.01), respectively. Accuracy and precision were 0.971 and o.965 in stage I-IV gastric cancer. In stage I-IV ESCC, the accuracy and precision were 0.818 and 0.947, respectively (Table 3), respectively. The statistical analysis from miRNA diagnostic marker data suggested in the quantum network that *H.pylori* infection (Figure 7, orange lines) and *H. pylori* infection with fresh vegetables and fruits (Figure 7, gray lines) would not be related to carcinogenesis upon the human stomach.

Conclusion

Liquid biopsy is an important tool for clinical diagnosis to predict early signs of human diseases. The miRNA panel in the circulating

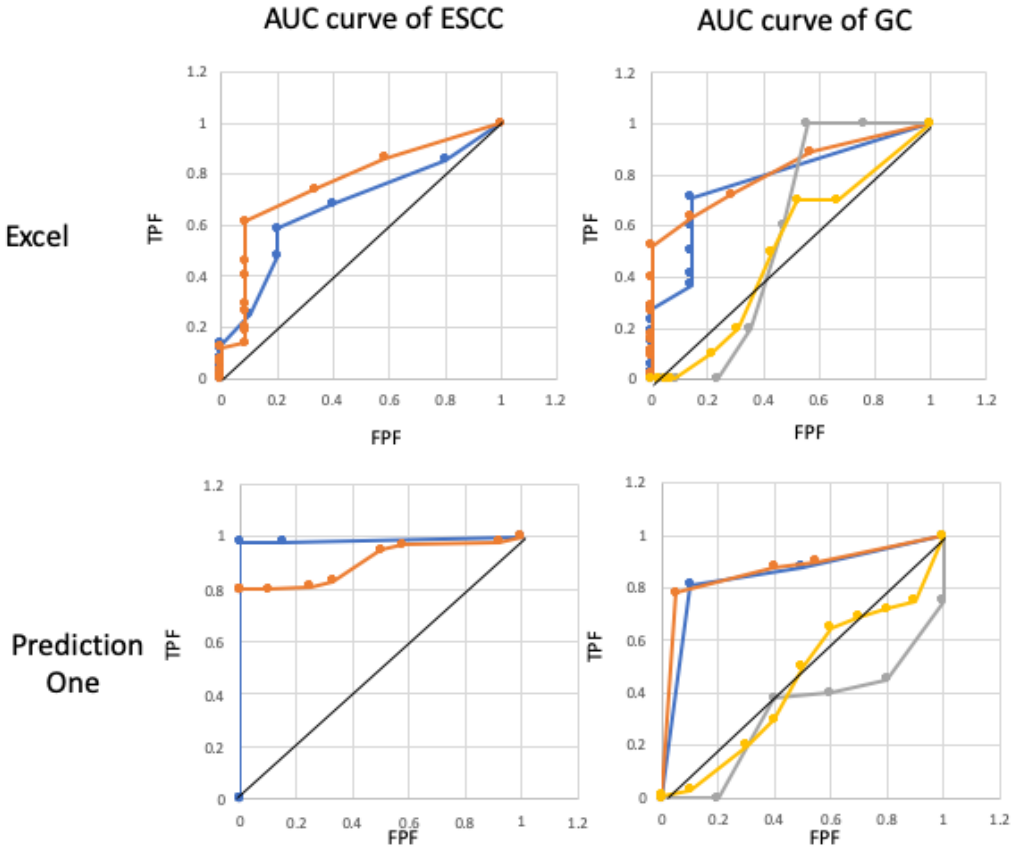

Figure 7. The AUC in ROC of ESCC, GC, *H. pylori* infection and vegetable diet. Statistical significance of the METS simulation has been analysed in ESCC (the left graphs) and GC (the right graphs) with the AUC by Excel (the upper graphs) and deep learning of Prediction One (the lower graphs). In ESCC, ROCs in blue and in brown showed as tumorigenicity of ESCC stage 0-I and stage I-IV, respectively. In GC, ROCs in blue and brown were presented in GC stage I and stage I-IV, respectively. H. pylori infection upon GC carcinogenesis: orange, H. pylori + vegetable (watermelon) upon GC carcinogenesis: gray.

Table 3. Statistical analysis of miRNAs association with cancers

		Excel*		Prediction One**			
Cancer & infection & Food	Cancer stage	AUC	p value	AUC	Accuracy	Precision	p value
ESCC	0-I	0.676	p<0.001	0.999	0.992	1	p<0.001
	I-IV	0.768	p<0.001	0.924	0.818	0.947	p<0.01
GC	I	0.78	p<0.001	0.9	0.812	0.869	p<0.05
	I-IV	0.814	p<0.001	0.986	0.971	0.965	p<0.001
Pylori		0.57	p<0.05	0.4	0.692	0.844	p<0.05
Pylori+Vegetable		0.504	p<0.05	0.529	0.827	0.824	p<0.01
*Two variable data for Excel, **Multivariable data for Prediction One							

system would be the first choice of a biomarker. An idea of the panel of miRNAs is unique one because multi-targeting character of miRNAs is deeply distinct from approximate one-to-one correspondence of mRNA/protein interaction. The network analysis of miRNA/mRNA requires to architect a high dimensional space for understanding of the etiological significance in the miRNA biomarker panel, therefore, algorithm of METS analysis based on quantum calculation has been newly developed from a computation processing with high dimensions of miRNA/miRNA and miRNA/mRNA interactions.

It has been shown by the quantum network analysis that the biological and pharmaceutical characters of the miRNA panel could be etiologically elucidated in human cancers [24,25]. It means that the miRNA panels would be available for a biomarker of human diseases' diagnosis and prediction. Although *H. pylori* infection may be on the minus one stage of gastric cancer, in argument, at the minus one stage of cancer, it would be difficult for such tiny lesion part of cancer to be specified. But by the METS analysis, it was shown that *H. pylori* infection may additionally contribute to progression of malignancy in gastric cancer cells via glucose metabolic pathway on a paradox in Zen Buddhism riddle. Further, plant xenomiRNAs in fresh vegetables and fruits could cure *H. pylori*-infected people from the paradoxical pre-cancerous state at least *in silico*, which would suggest that the minus one stage of cancer can be reversible to healthy state. In turn, the environmental stress, such as mal-diets, long-term less fresh vegetable and fruit, would dysregulate miRNA expression, additionally it may contribute most for increasing risk of gastric cancer. Therefore, after the life-style habits were changed or miRNA therapeutic agents were supplied to the minus one stage people, it may be enough to examine miRNA reversion to healthy profile because *H. pylori* infection would be reversibly oncogenic by eradication.

The quantum miRNA language would be useful for stage minus one diagnosis with miRNAs not only to develop miRNA and sponge medicines but also to make medical care guideline and to health guidance support system. Further investigations need for clinical usage.

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