The roles of cell cycle and BRCA1 in the DNA damage response

Shihori Tanabe[1)], Sabina Quader[2)], Ryuichi Ono[3)], Horacio Cabral[4)], Kazuhiko Aoyagi[5)], Akihiko Hirose[1)], Hiroshi Yokozaki[6)], Hiroki Sasaki[7)]

1. Div. Risk Assess., CBSR, Natl. Inst. Health Sci., 2. iCONM, 3. Div. Cell. Mol. Tox., CBSR, Natl. Inst. Health Sci., 4. Dept. Bioengineer., Grad. Sch. Engineer., The Univ. of Tokyo, 5. Dept. Clin. Genomics, FIOC, Natl. Cancer Ctr. Res. Inst., 6. Dept. Path. Grad. Sch. Med., Kobe Univ., 7. Dept. Transl. Oncol., FIOC, Natl. Cancer Ctr. Res. Inst.

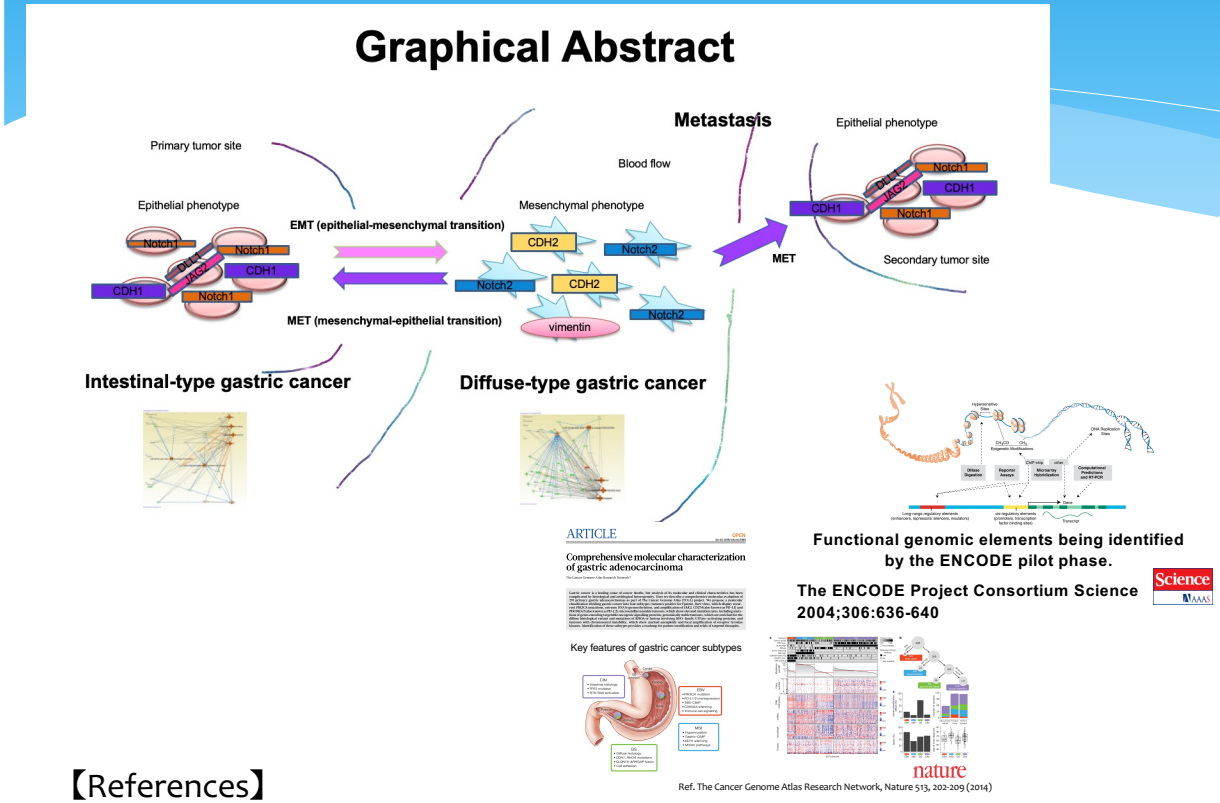
The 1st International Electronic Conference on Cancers: Exploiting Cancer Vulnerability by Targeting the DNA Damage Response

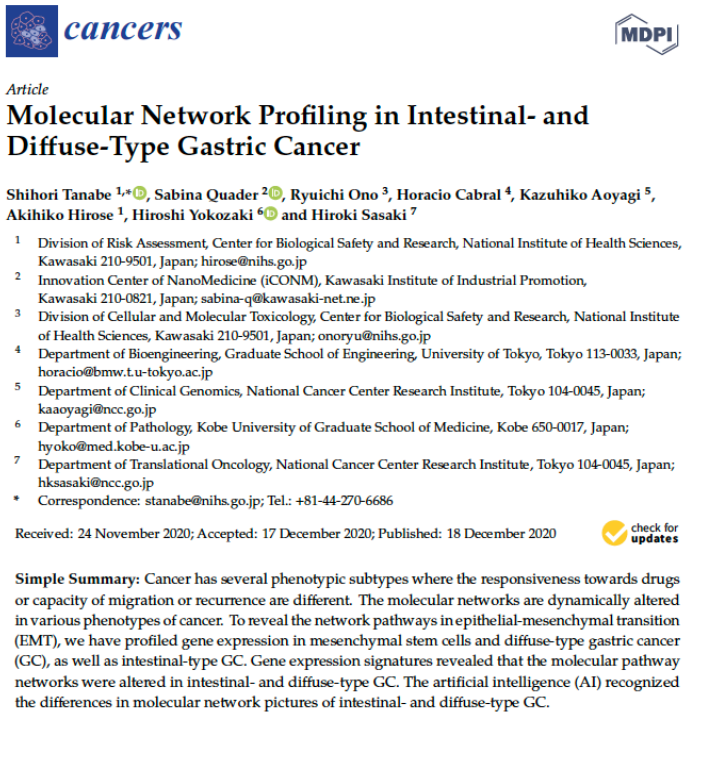
February 1-14, 2021, @Online

Abstract

* Molecular network activation states alter dynamically in biology and diseases. In cancer stem cells (CSCs), epithelial-mesenchymal transition (EMT) networks play an important role to acquisition of the drug resistance and cancer malignant feature. To reveal the network pathways in EMT and CSCs, gene expression in diffuse- and intestinal-type gastric cancer (GC) have been analyzed. The several canonical pathways have been found to be altered in diffuse- and intestinal-type GC. Canonical pathway on Cell Cycle: G1/S Checkpoint Regulation was activated in diffuse-type GC, and Cyclins and Cell Cycle Regulation was activated in intestinal-type GC. In Cell Cycle: G1/S Checkpoint Regulation, DNA damage induces p53, which was predicted to be activated in diffuse-type GC. Canonical pathway related to Role of BRCA1 in DNA Damage Response was activated in intestinal-type GC, where BRCA1 which is related to G1/S phase transition was up-regulated. Cell cycle regulation may be altered in EMT condition in diffuse-type GC.

Background and Objectives




cancers

MDPI

Article

Molecular Network Profiling in Intestinal- and Diffuse-Type Gastric Cancer

Shihori Tanabe [1,*], Sabina Quader [2], Ryuichi Ono [3], Horacio Cabral [4], Kazuhiko Aoyagi [5], Akihiko Hirose [1], Hiroshi Yokozaki [6] and Hiroki Sasaki [7]

1 Division of Risk Assessment, Center for Biological Safety and Research, National Institute of Health Sciences, Kawasaki 210-9501, Japan; hirose@nihs.go.jp
2 Innovation Center of NanoMedicine (iCONM), Kawasaki Institute of Industrial Promotion, Kawasaki 210-0821, Japan; sabina-q@kawasaki-net.ne.jp
3 Division of Cellular and Molecular Toxicology, Center for Biological Safety and Research, National Institute of Health Sciences, Kawasaki 210-9501, Japan; onoryu@nihs.go.jp
4 Department of Bioengineering, Graduate School of Engineering, University of Tokyo, Tokyo 113-0033, Japan; horacio@bmw.t.u-tokyo.ac.jp
5 Department of Clinical Genomics, National Cancer Center Research Institute, Tokyo 104-0045, Japan; kaaoyagi@ncc.go.jp
6 Department of Pathology, Kobe University of Graduate School of Medicine, Kobe 650-0017, Japan; hyoko@med.kobe-u.ac.jp
7 Department of Translational Oncology, National Cancer Center Research Institute, Tokyo 104-0045, Japan; hksasaki@ncc.go.jp
* Correspondence: stanabe@nihs.go.jp; Tel.: +81-44-270-6686

Received: 24 November 2020; Accepted: 17 December 2020; Published: 18 December 2020

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Simple Summary: Cancer has several phenotypic subtypes where the responsiveness towards drugs or capacity of migration or recurrence are different. The molecular networks are dynamically altered in various phenotypes of cancer. To reveal the network pathways in epithelial-mesenchymal transition (EMT), we have profiled gene expression in mesenchymal stem cells and diffuse-type gastric cancer (GC), as well as intestinal-type GC. Gene expression signatures revealed that the molecular pathway networks were altered in intestinal- and diffuse-type GC. The artificial intelligence (AI) recognized the differences in molecular network pictures of intestinal- and diffuse-type GC.

【References】

1. Tanabe, S.; Quader, S.; Ono, R.; Cabral, H.; Aoyagi, K.; Hirose, A.; Yokozaki, H.; Sasaki, H. Molecular Network Profiling in Intestinal- and Diffuse-Type Gastric Cancer. *Cancers* **2020**, *12*, 3833. https://doi.org/10.3390/cancers12123833

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4. Tanabe, S., Aoyagi, K., Yokozaki, H., and Sasaki, H. (2014). Gene expression signatures for identifying diffuse-type gastric cancer associated with epithelial-mesenchymal transition. *Int. J. of Oncol.* **44,** 1955-1970. https://doi.org/10.3892/ijo.2014.2387

Canonical pathways altered in diffuse- and intestinal-type GC

canonical pathway

Canonical Pathways	Tcga Cin	Tcga Gs
Cell Cycle: G1/S Checkpoint Regulation	-1.147	2.982
Sumoylation Pathway	1.069	2.673
FAT10 Cancer Signaling Pathway	-0.632	1.897
Relaxin Signaling	-3	1.5
Role of CHK Proteins in Cell Cycle Checkpoint Control	-0.5	1
HIPPO signaling	-1	1
IL-22 Signaling	-0.707	0.707
Cell Cycle: G2/M DNA Damage Checkpoint Regulation	-1.528	0.655
Ovarian Cancer Signaling	-3.162	0.632
HGF Signaling	-2.183	0.243
Glioblastoma Multiforme Signaling	-2.668	0.243
Cholesterol Biosynthesis III (via Desmosterol)	2.449	0
Cholesterol Biosynthesis II (via 24,25-dihydrolanosterol)	2.449	0
Cholesterol Biosynthesis I	2.449	0
Glioma Signaling	-1	-0.333
gamma-glutamyl Cycle	-0.447	-0.447
Pancreatic Adenocarcinoma Signaling	0	-0.5
Wnt/beta-catenin Signaling	-0.6	-0.6
Role of BRCA1 in DNA Damage Response	0.816	-1.225
ATM Signaling	1.043	-1.46
Mitotic Roles of Polo-Like Kinase	1	-1.5
3-phosphoinositide Biosynthesis	0.378	-1.512
Methionine Degradation I (to Homocysteine)	1.633	-1.633
Small Cell Lung Cancer Signaling	-1.155	-1.732
Cell Cycle Regulation by BTG Family Proteins	1.155	-1.732
NER Pathway	0.209	-1.877
Pyrimidine Ribonucleotides Interconversion	1.265	-1.897
Purine Nucleotides De Novo Biosynthesis II	0	-2
Pentose Phosphate Pathway	-1	-2
Pyrimidine Ribonucleotides De Novo Biosynthesis	0.905	-2.111
Aldosterone Signaling in Epithelial Cells	-0.905	-2.111
Aryl Hydrocarbon Receptor Signaling	-0.447	-2.236
Dolichyl-diphosphooligosaccharide Biosynthesis	0.378	-2.646
tRNA Charging	-1.5	-3
Cyclins and Cell Cycle Regulation	0.894	-3.13
Estrogen-mediated S-phase Entry	1.5	-3.5

Tcga Gs

- NULL
- -3.5
- -3.13
- -3
- -2.646
- -2.236
- -2.111
- -2
- -1.897
- -1.877
- -1.732
- -1.633
- -1.512
- -1.5
- -1.46
- -1.225
- -0.6
- -0.5
- -0.447
- -0.333
- 0
- 0.243
- 0.632
- 0.655
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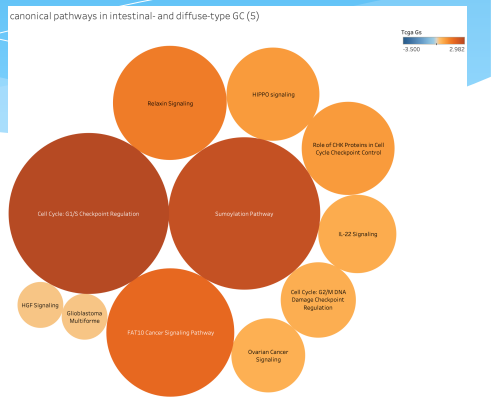
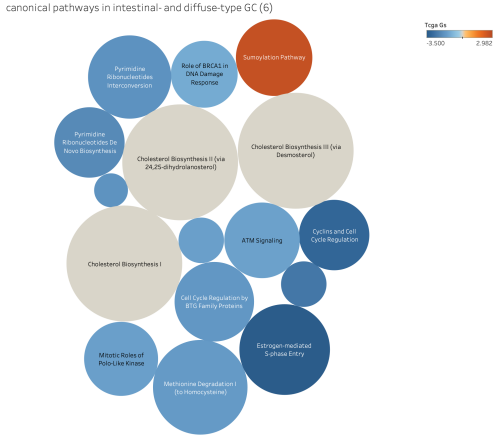
- 1
- 1.5
- 1.897
- 2.673
- 2.982

Tcga Gs

-3.500 2.982

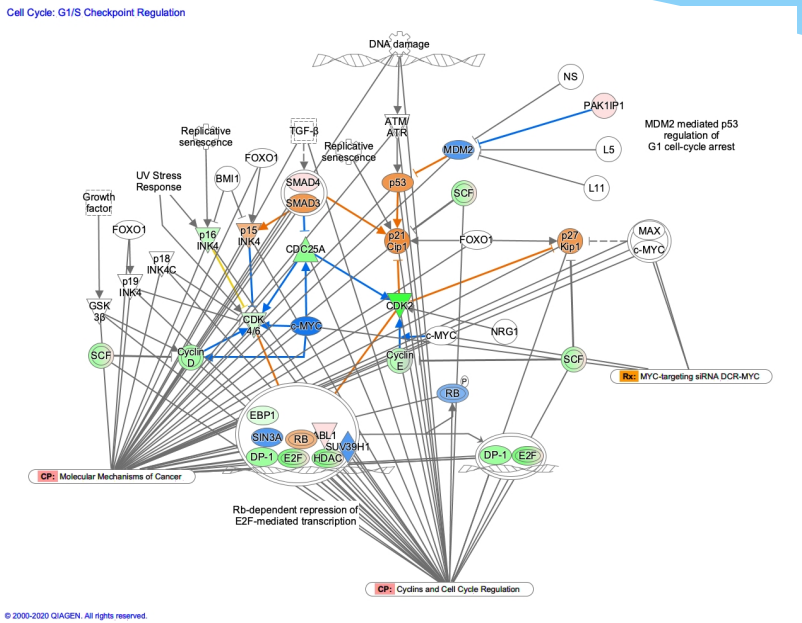


Size shows the activation score in diffuse-type GC.
Color indicates the activation score in diffuse-type GC.

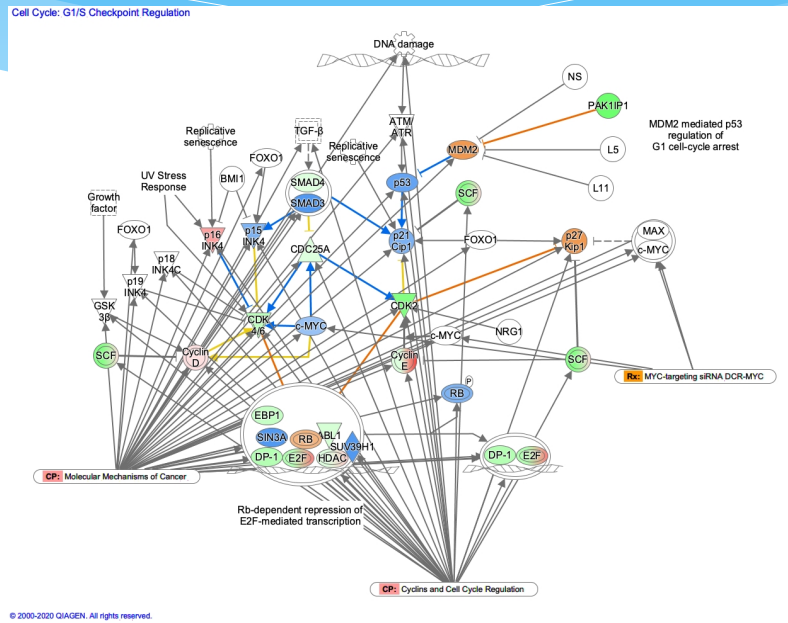


Size shows the activation score in intestinal-type GC.
Color indicates the activation score in diffuse-type GC.

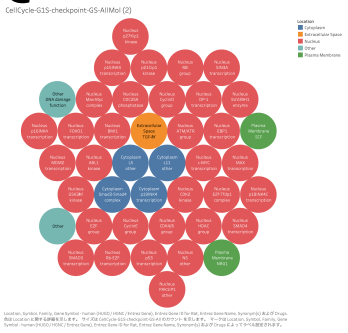
Cell Cycle: G1/S checkpoint Regulation pathway was activated in diffuse-type GC



Diffuse-type GC

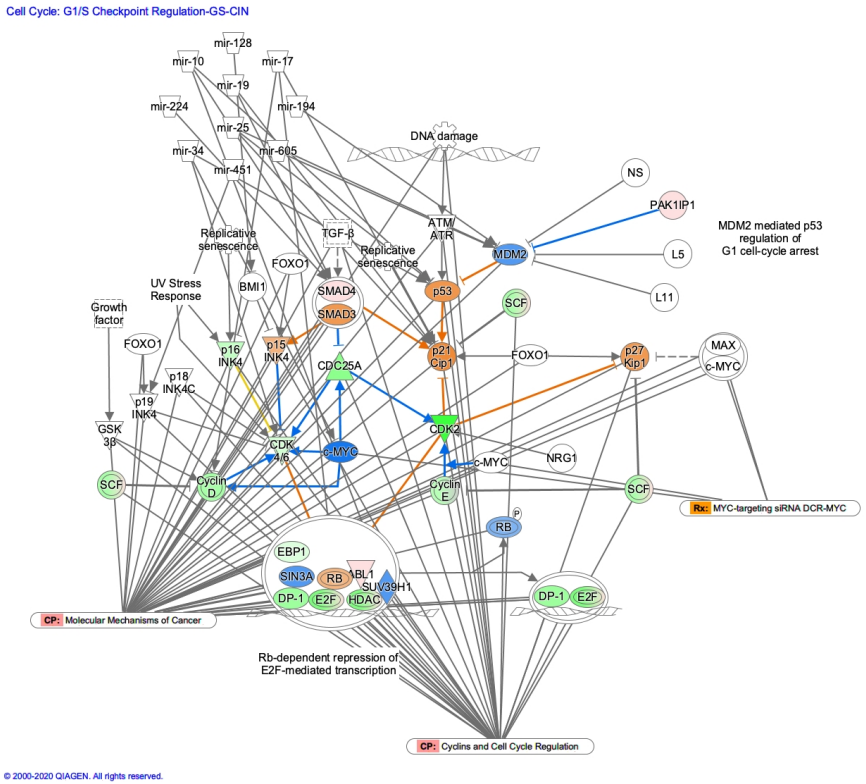


Intestinal-type GC



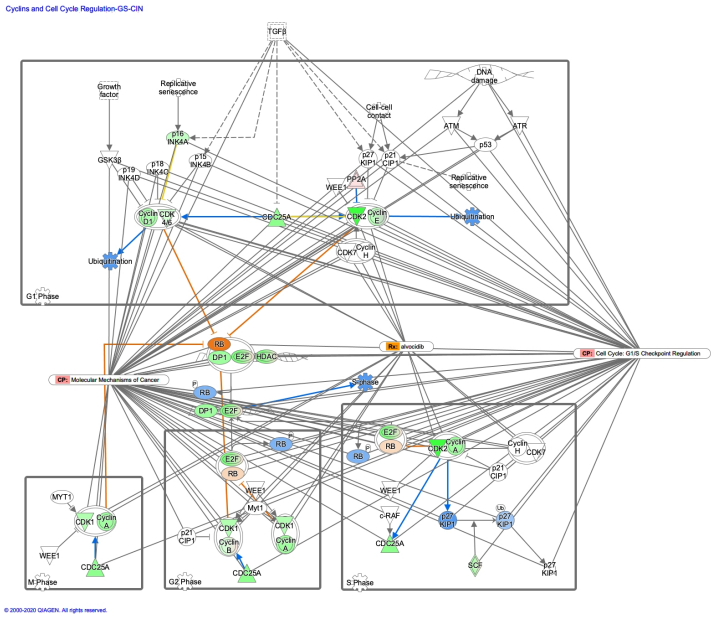
Direct relationships of miRNAs and targeted molecules in Cell Cycle: G1/S checkpoint Regulation pathway in diffuse-type GC

Direct Relationship Type
RNA-RNA interactions: microRNA targeting

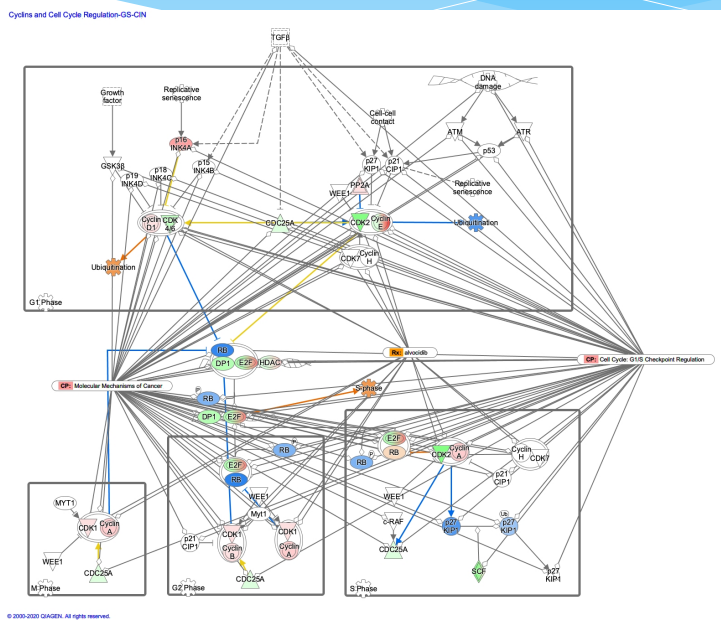


From Molecule(s)	To Molecule(s)
mir-10	SMAD4
mir-10	SUV39H1
mir-10	p53
mir-128	BMI1
mir-17	CyclinD
mir-17	RB
mir-17	p21Cip1
mir-19	SMAD4
mir-19	p21Cip1
mir-194	MDM2
mir-224	SMAD4
mir-25	MDM2
mir-25	p21Cip1
mir-25	p53
mir-34	CDK4/6
mir-34	c-MYC
mir-34	p53
mir-451	p19INK4
mir-605	MDM2

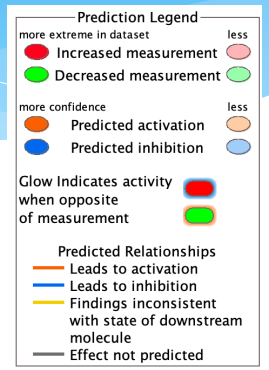
Cyclins and Cell Cycle Regulation pathway was activated in intestinal-type GC

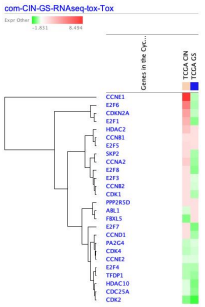


Diffuse-type GC



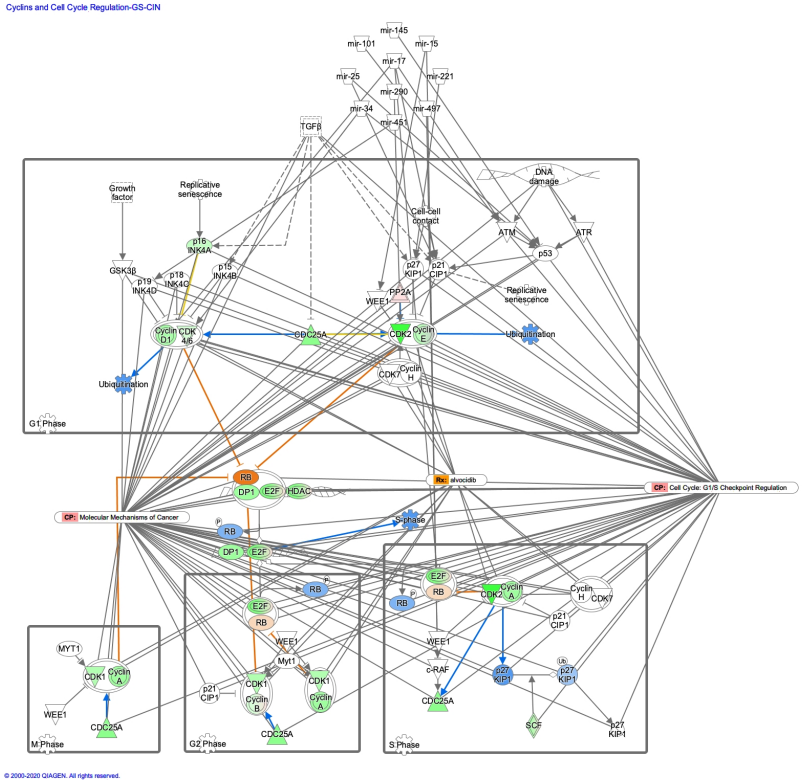
Intestinal-type GC





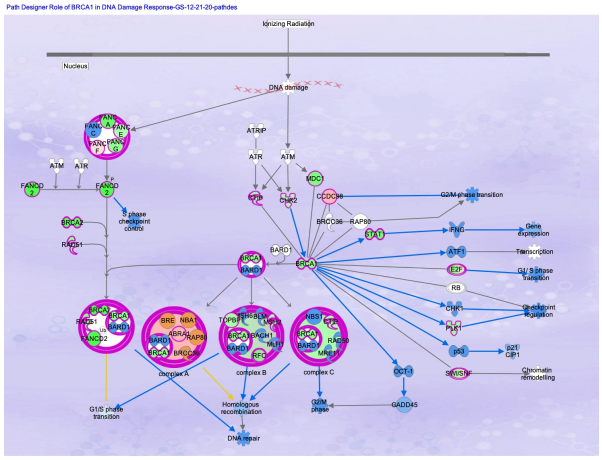
Direct relationships of miRNAs and targeted molecules in Cyclins and Cell Cycle Regulation pathway in diffuse-type GC

Direct Relationship Type
RNA-RNA interactions: microRNA targeting

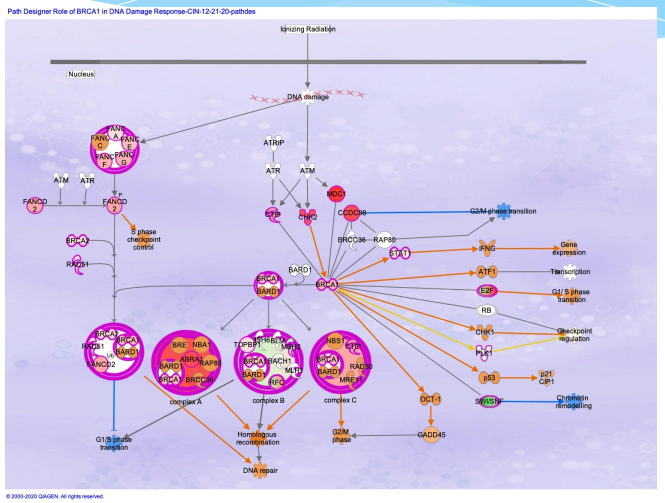


From Molecule(s)	To Molecule(s)
mir-101	ATM
mir-145	p53
mir-15	WEE1
mir-15	c-RAF
mir-17	ATM
mir-17	CyclinD1
mir-17	RB
mir-17	p21CIP1
mir-221	p27KIP1
mir-25	p21CIP1
mir-25	p53
mir-290	CDK2
mir-34	CDK4/6
mir-34	p53
mir-451	p19INK4D
mir-497	c-RAF

Role of BRCA1 in DNA Damage Response pathway was activated in intestinal-type GC

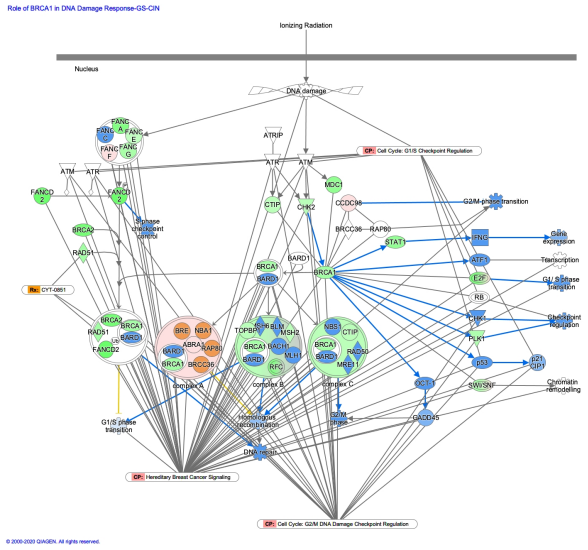


Diffuse-type GC

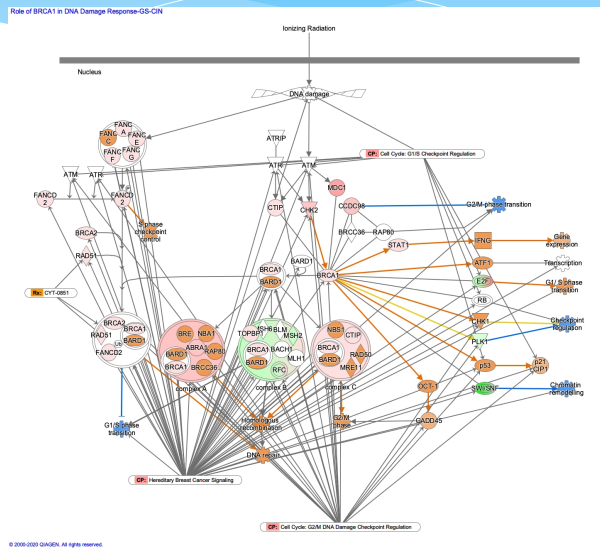


Intestinal-type GC

Role of BRCA1 in DNA Damage Response pathway was activated in intestinal-type GC



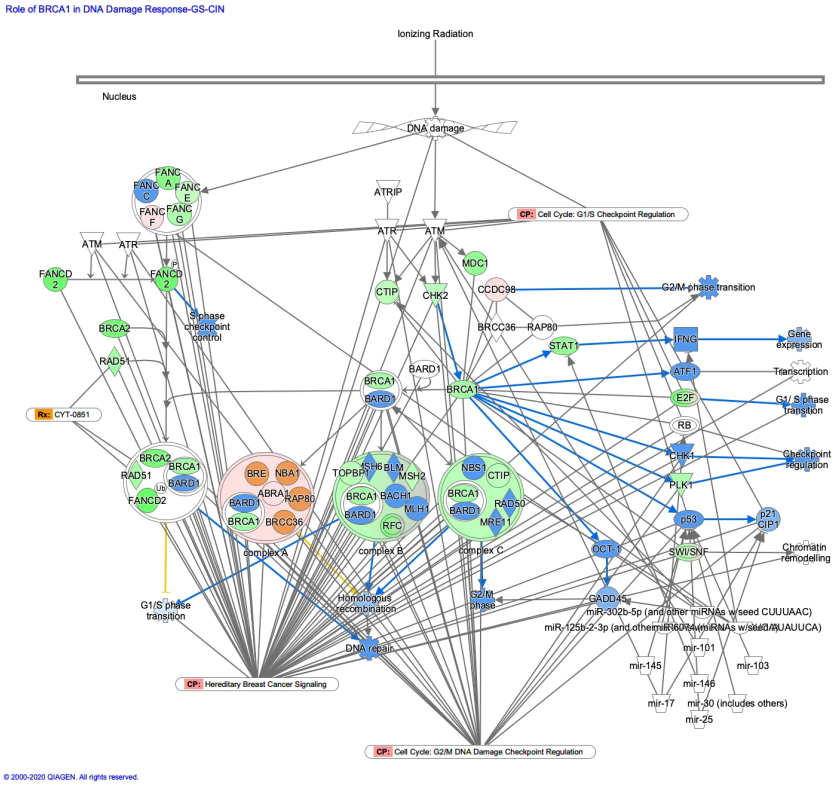
Diffuse-type GC



Intestinal-type GC

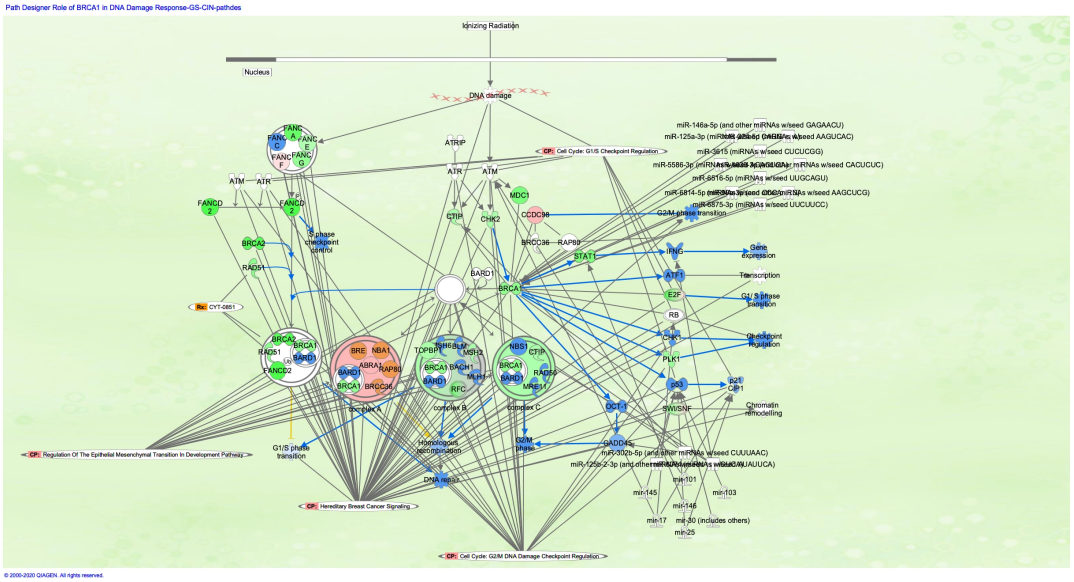
Direct relationships of miRNAs and targeted molecules in Role of BRCA1 in DNA Damage Response pathway in diffuse-type GC

Direct Relationship Type
RNA-RNA interactions: microRNA targeting



From Molecule(s)	To Molecule(s)
miR-125b-2-3p (and other miRNAs w/seed CAAGUCA)	p53
miR-302b-5p (and other miRNAs w/seed CUUUAAC)	BARD1
miR-302b-5p (and other miRNAs w/seed CUUUAAC)	CTIP
miR-302b-5p (and other miRNAs w/seed CUUUAAC)	GADD45
miR-6074 (miRNAs w/seed AUAUUCA)	FANCF
miR-6074 (miRNAs w/seed AUAUUCA)	IFNG
miR-6074 (miRNAs w/seed AUAUUCA)	NBS1
mir-101	ATM
mir-103	p53
mir-145	p53
mir-146	STAT1
mir-17	ATM
mir-17	RB
mir-17	p21CIP1
mir-25	p21CIP1
mir-25	p53
mir-30 (includes others)	p53

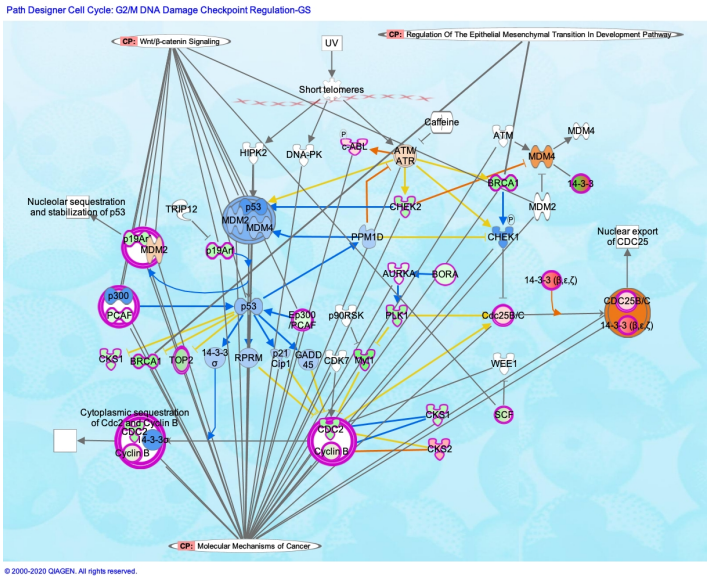
Direct relationships of miRNAs and BRCA1 in Role of BRCA1 in DNA Damage Response pathway in diffuse-type GC



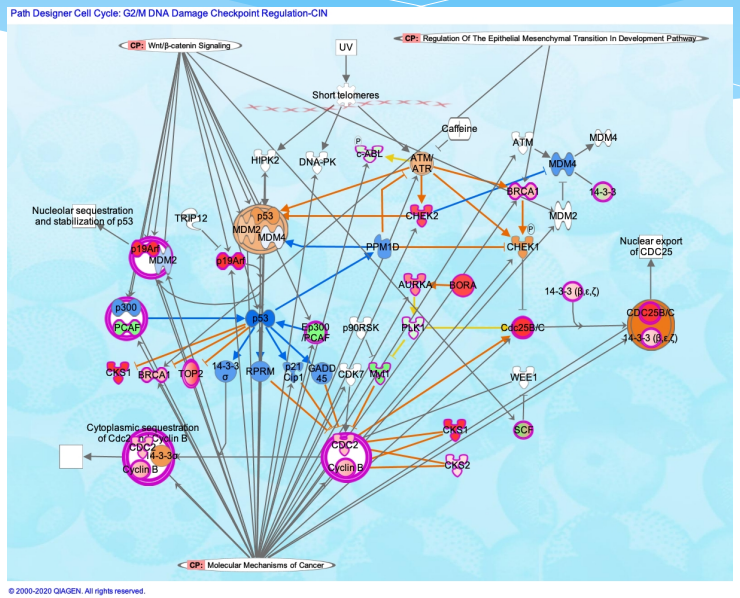
Ten miRNAs which have direct relationships between BRCA1 (Direct Relationship Type RNA-RNA interactions: microRNA targeting)

miR-125a-3p (miRNAs w/seed CAGGUGA)
miR-146a-5p (and other miRNAs w/seed GAGAACU)
miR-224-5p (miRNAs w/seed AAGUCAC)
miR-3615 (miRNAs w/seed CUCUCGG)
miR-4639-3p (and other miRNAs w/seed CACUCUC)
miR-5586-3p (miRNAs w/seed AGAGUGA)
miR-6516-5p (miRNAs w/seed UUGCAGU)
miR-6814-5p (miRNAs w/seed CCCAAGG)
miR-6875-3p (miRNAs w/seed UUCUUCC)
miR-99a-3p (and other miRNAs w/seed AAGCUCG)

Cell Cycle: G2/M DNA Damage Checkpoint Regulation pathway in diffuse- and intestinal-type GC



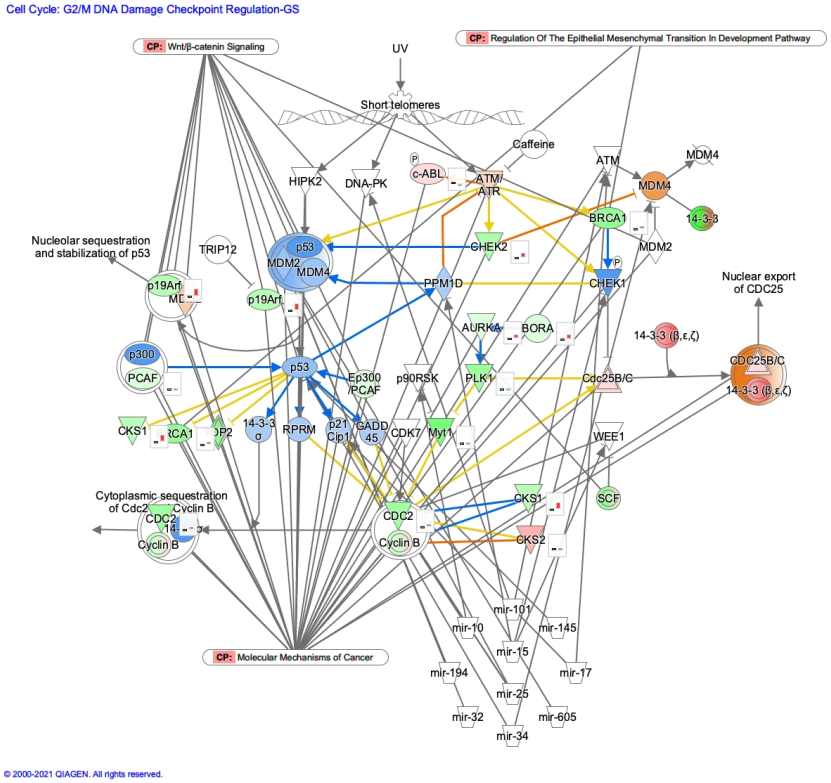
Diffuse-type GC



Intestinal-type GC

Direct relationships of miRNAs and targeted molecules in Cell Cycle: G2/M DNA Damage Checkpoint Regulation pathway in diffuse-type GC

Direct Relationship Type
RNA-RNA interactions: microRNA targeting



From Molecule(s)	To Molecule(s)
mir-10	p53
mir-10	p90RSK
mir-101	ATM
mir-101	DNA-PK
mir-145	p53
mir-15	CHEK1
mir-15	PPM1D
mir-15	WEE1
mir-17	ATM
mir-17	p21Cip1
mir-194	MDM2
mir-25	MDM2
mir-25	p21Cip1
mir-25	p53
mir-32	MDM2
mir-34	MDM4
mir-34	p53
mir-605	MDM2

Summary

- The several canonical pathways have been found to be altered in diffuse- and intestinal-type GC.
- Canonical pathway on Cell Cycle: G1/S Checkpoint Regulation was activated in diffuse-type GC, and Cyclins and Cell Cycle Regulation was activated in intestinal-type GC.
- In Cell Cycle: G1/S Checkpoint Regulation, DNA damage induces p53, which was predicted to be activated in diffuse-type GC.
- Canonical pathway related to Role of BRCA1 in DNA Damage Response was activated in intestinal-type GC, where BRCA1 which is related to G1/S phase transition was up-regulated.
- Cell cycle regulation may be altered in EMT condition in diffuse-type GC.

Acknowledgements

Maurice Whelan
Gladys Ouedraogo
Dan Villeneuve
Jason O'Brien
Ye Lin Jun
Nathalie Delrue
Christina Quaglio
Rex FitzGerald
Magdalini Sachana
Hristo Aladjov
Clemens Wittwehr
Mirjam Luijten
Tanja Burgdorf
Julija Filipovska
Bette Meek
Lidia Ceriani

Ed Perkins
Sabina Halappanavar
Masaaki Tsukano
Takashi Yamada
Iva Sovadicova
Josephine Kugler
Mike Wade
Lola Bajard
Anna Rourke
Ludek Blaha
Takao Ashikaga

Carlie LaLone
Brigitte Landesmann
Andrea Terron
Cinzia La Rocca
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Dries Knapen
Mark Viant
Carole Yauk
Tim Gant
Vinita Chauhan
Yasuhiro Yoshida
Shigeru Hisada
Ruthann Rudel
Jessica Helm

Shinpei Ijichi
Kohei Kessoku
Kengo Hayashi
Fabien Grasset
Naoko Ozaki
Masanori Uehara
Satoshi Uchida
Hiroaki Kinoh
Kazunori Kataoka

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- Members of EAGMST, WPHA, OECD
- Members of Division of Risk Assessment and All Divisions, National Institute of Health Sciences, Japan
- This research is supported by Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)) from Japan Agency for Medical Research and Development (AMED), and Ministry of Health, Labour and Welfare (MHLW), Japan.