방사선치료 저항성 연구 동향분석

Comprehensive Understanding of Radioresistance in Anti-Cancer Therapy

2018. 10. 24
방사선기술의 의학적 이용
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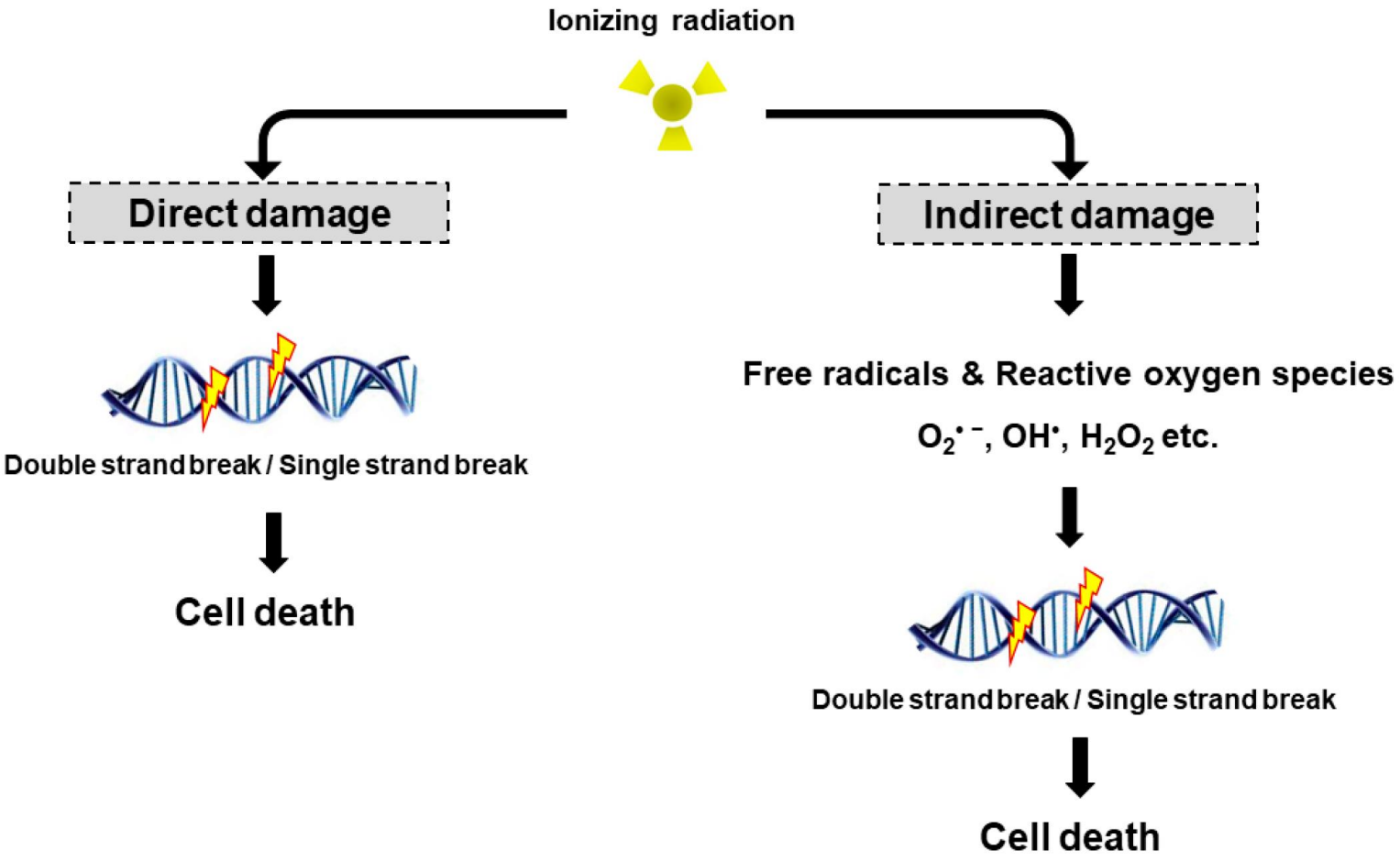
Contents

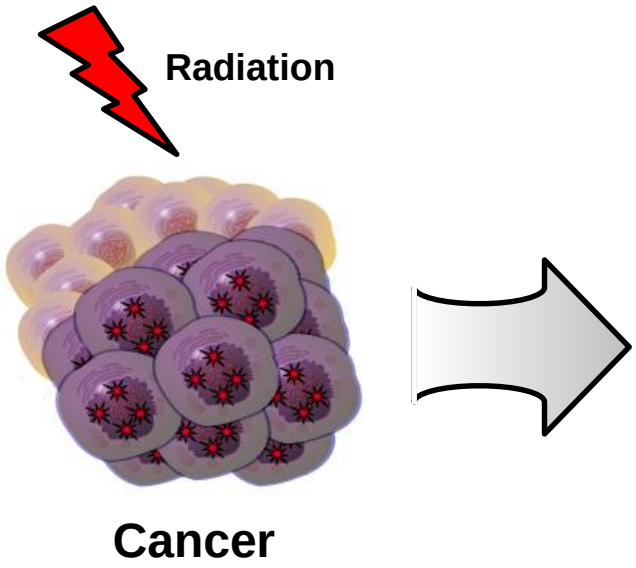
Direct and Indirect Damage by Ionizing Radiation



- Radiation can directly interact with cellular DNA and cause damage.
- The indirect damage caused by the free radicals is derived from the ionization or excitation of the water component of the cells.

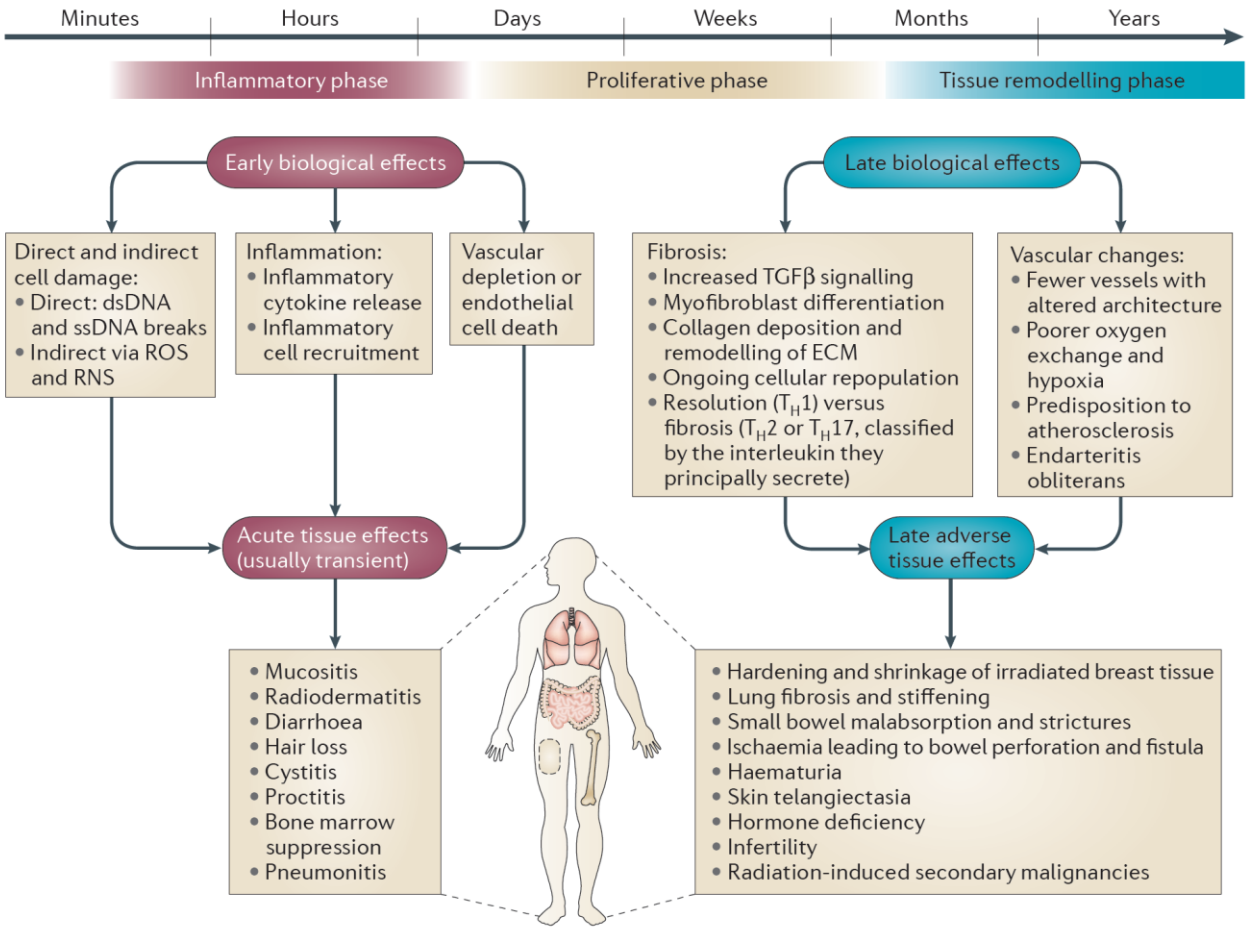
Int J Mol Sci. 2017;18(12)

Possible Side Effects of Radiotherapy



- **Short-term side effects**
  - ✓ ***Resistance to radiation***
  - ✓ Normal tissue injury
  - ✓ EMT, infiltration
- **Long-term side effects**
  - ✓ Metastasis(aggressiveness)
  - ✓ Recurrence
  - ✓ Metabolic disease
  - ✓ Emotional side effects

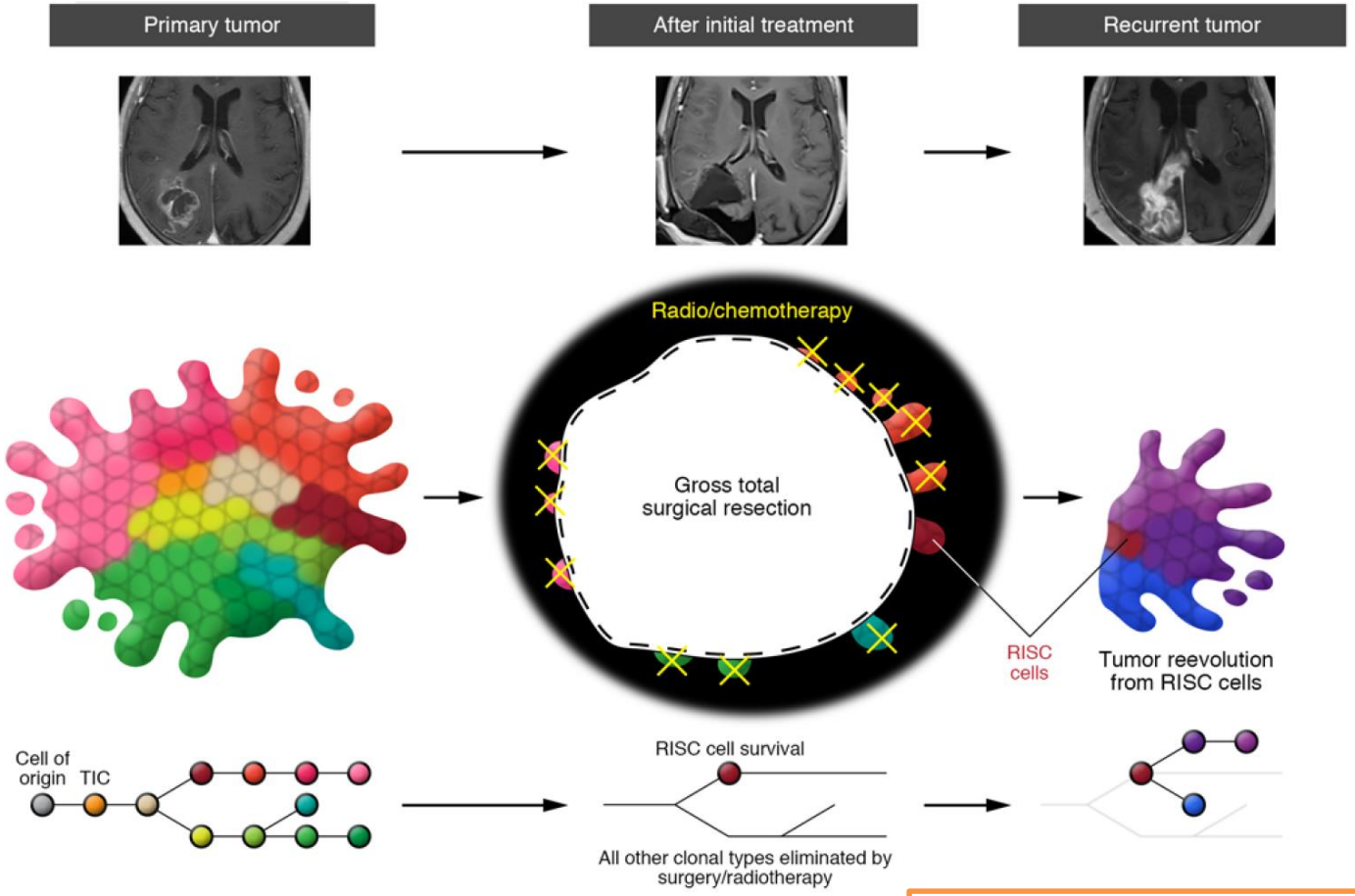
Biological Effects and Normal Tissue Toxicity After Radiotherapy



- Early biological events cause acute tissue effects, which are usually transient and normally resolve within 3 months of completing treatment.
- Higher radiation dose per fraction seems to increase the severity of late adverse effects.

Nat Rev Cancer. 2015;15(7):409-25

Tumor Recurrence After Radiotherapy

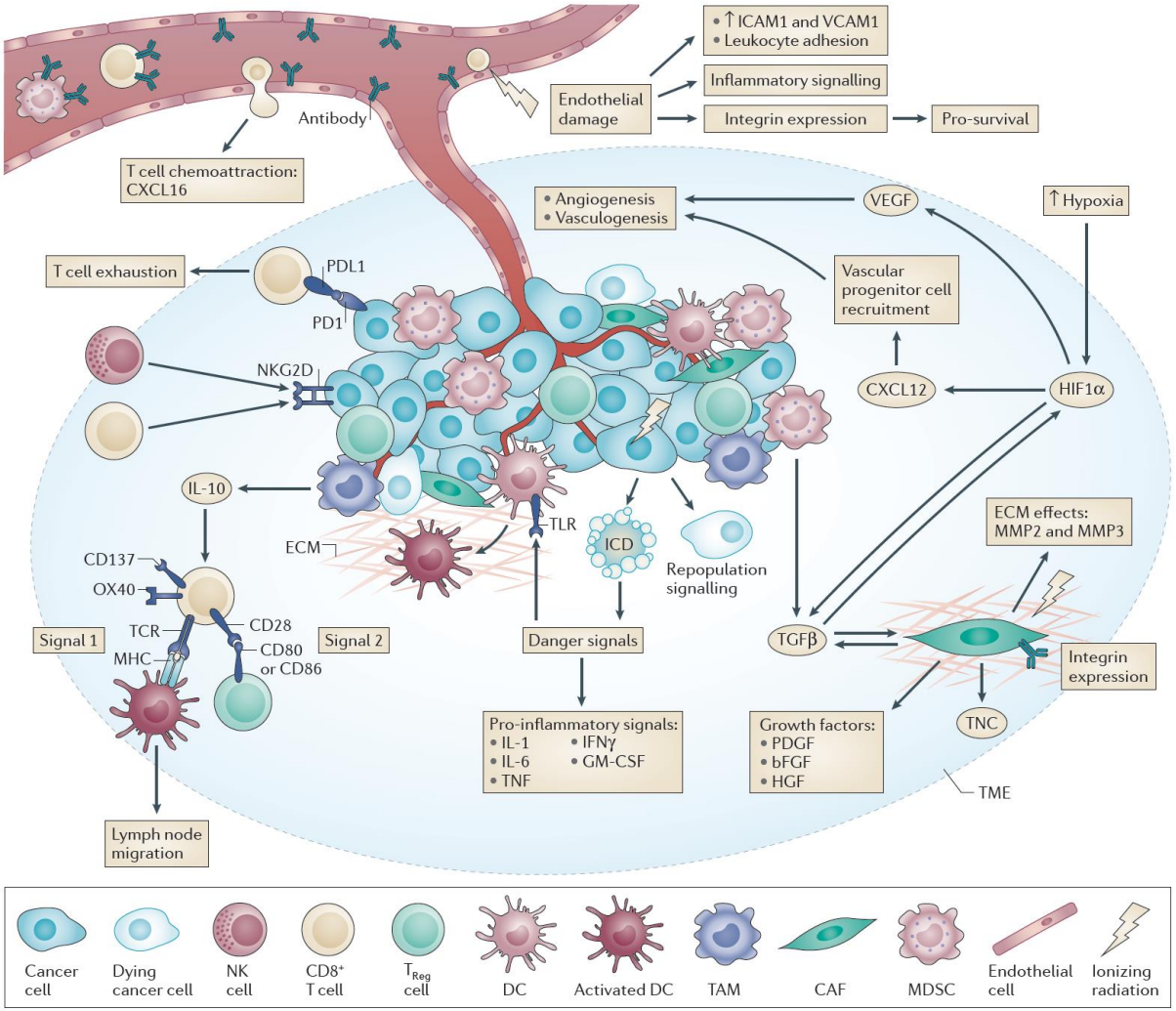


RISC : Radiation induced second cancers

The survival of recurrence-initiating stem-like cancer cells that have acquired adaptive resistance to therapy after initial treatments, and their evolution into a recurrent tumor.

J Clin Invest. 2017;127(2):415-426

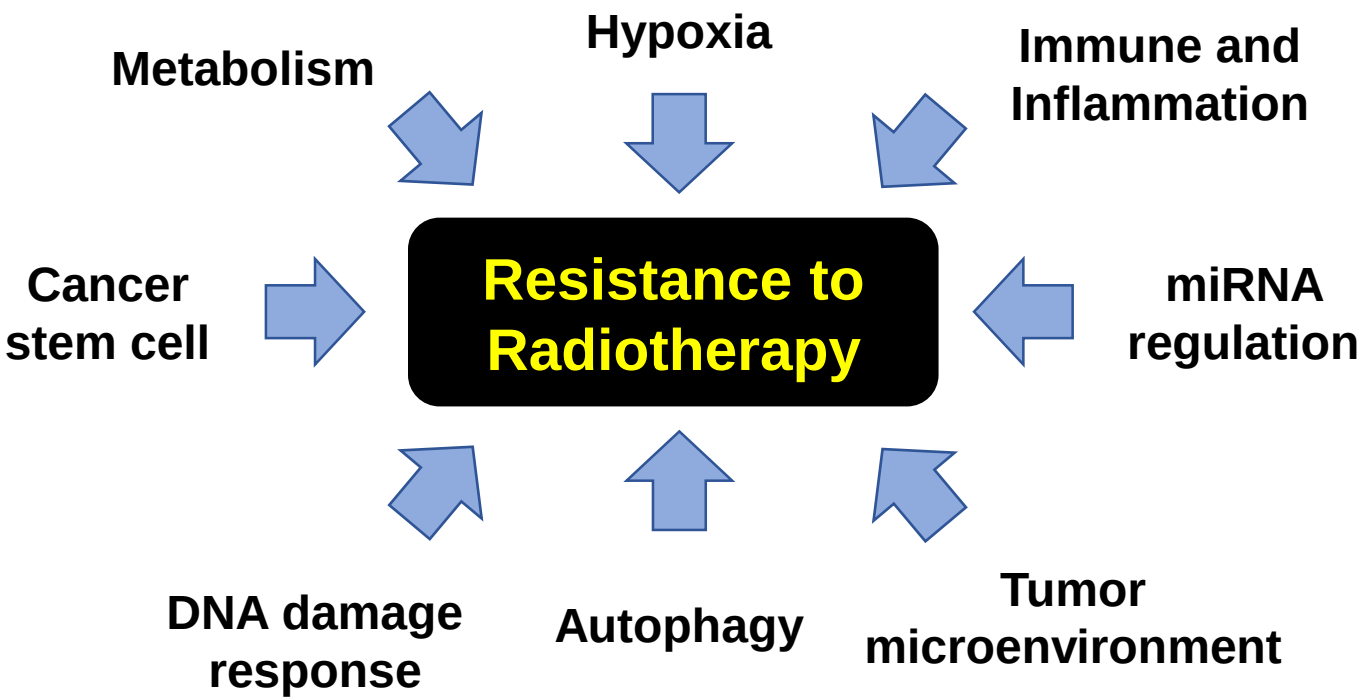
Radiation Effects on the Tumor Microenvironment



Damage from ionizing radiation leads to effects on numerous cell types within the tumor microenvironment

Nat Rev Cancer. 2015;15(7):409-25

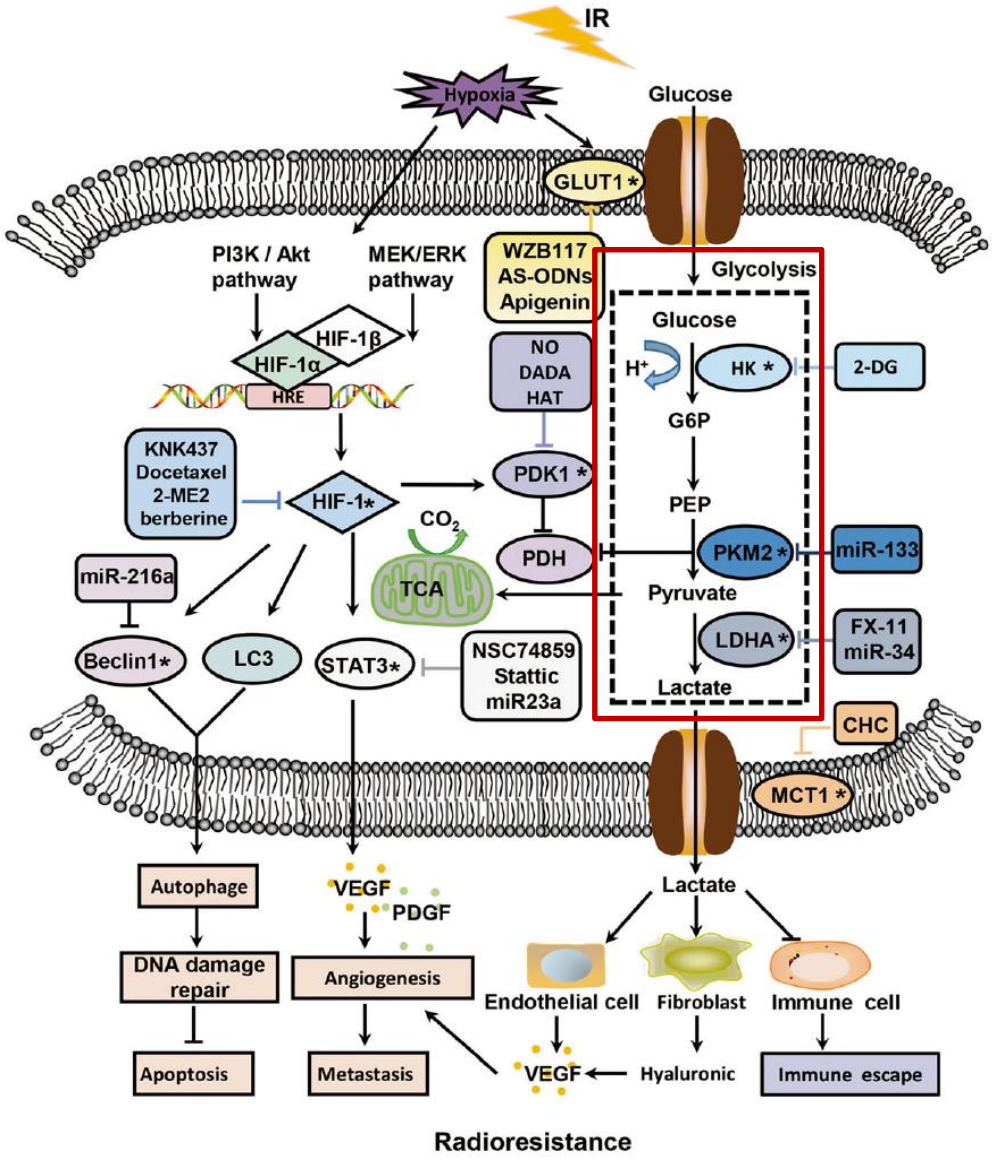
Key Regulators Inducing Radioresistance



Several pathways and their associated marker proteins are responsible for cancer radioresistance and their therapeutic implications in terms of cancer cell death of various types and characteristics are critical issues

Contents

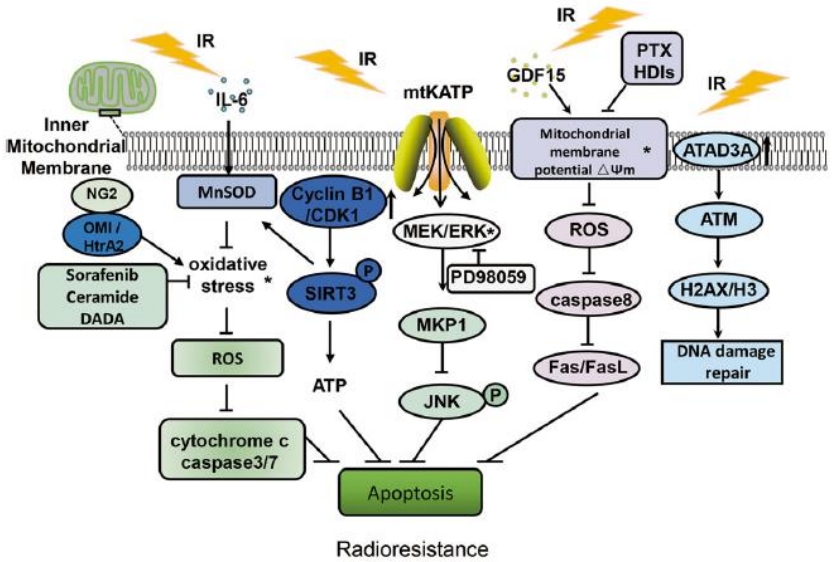
Key Regulators Inducing Radioresistance (1) : Metabolism



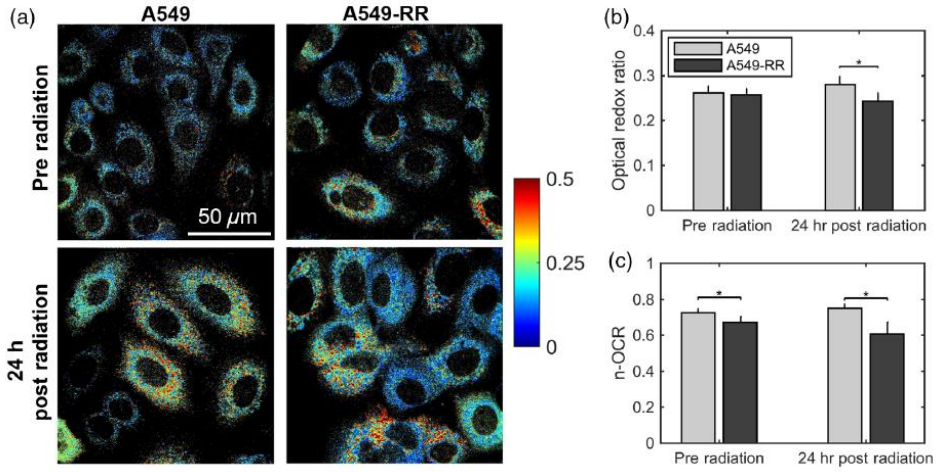
- The enzymes in the **glycolytic pathway** play an important role in the process of radioresistance and can serve as targets for improving the efficacy of radiotherapy.
- In addition, **HIF** is able to activate glycolytic enzymes and promote the occurrence of radioresistance by inducing cell autophagy and angiogenesis.

J Exp Clin Cancer Res. 2018;37(1):87

Key Regulators Inducing Radioresistance (1) : Metabolism



Mitochondrial metabolism and radioresistance



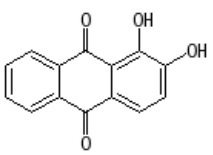
Radiation causes a decrease in the optical redox ratio, indicating increased glycolytic metabolism

Items	Targets	Radiosensitizer
Glycose metabolism	GLUT1	Apigenin,WZB117
	MCT1	CHC
	LDHA	FX-11, miR-34
	PKM2	miR-133, DADA
	HK2	2-DG
	HIF	Chetomin, KNK437, 2-ME2, Barberin, NVP-BEZ235, miR-216a NSC74859, Stattic, Docetaxel miR-21, miR-124, miR-144
Mitochondrial metabolism	Oxidative stress	Sorafenib, Ceremides, DADA
	MMP	PD98059, HDIs, Paclitaxel

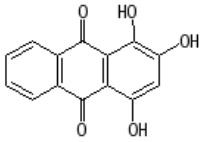
Metabolism-associated targets in radioresistance and the radiosensitization methods

J Exp Clin Cancer Res. 2018;37(1):87
J Biomed Opt. 2017;22(6):60502

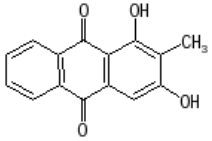
Key Regulators Inducing Radioresistance (1) : Metabolism



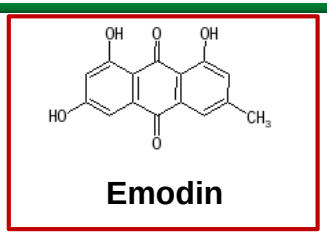
Alizarin



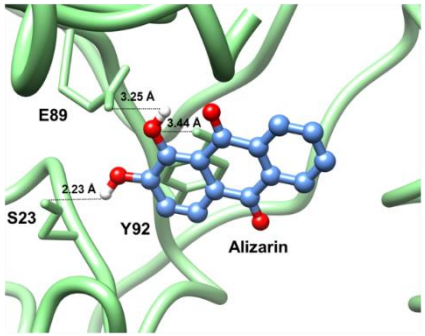
Purpurin

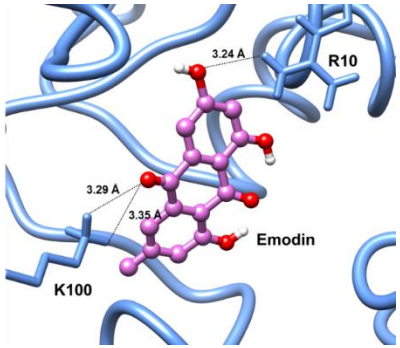


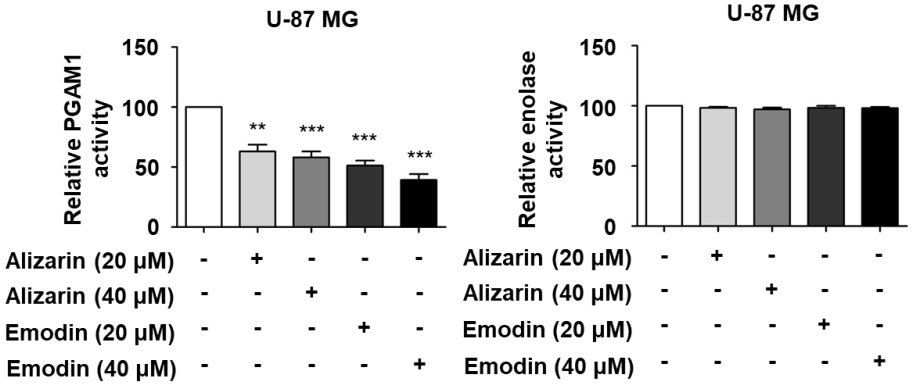
Rubiadin

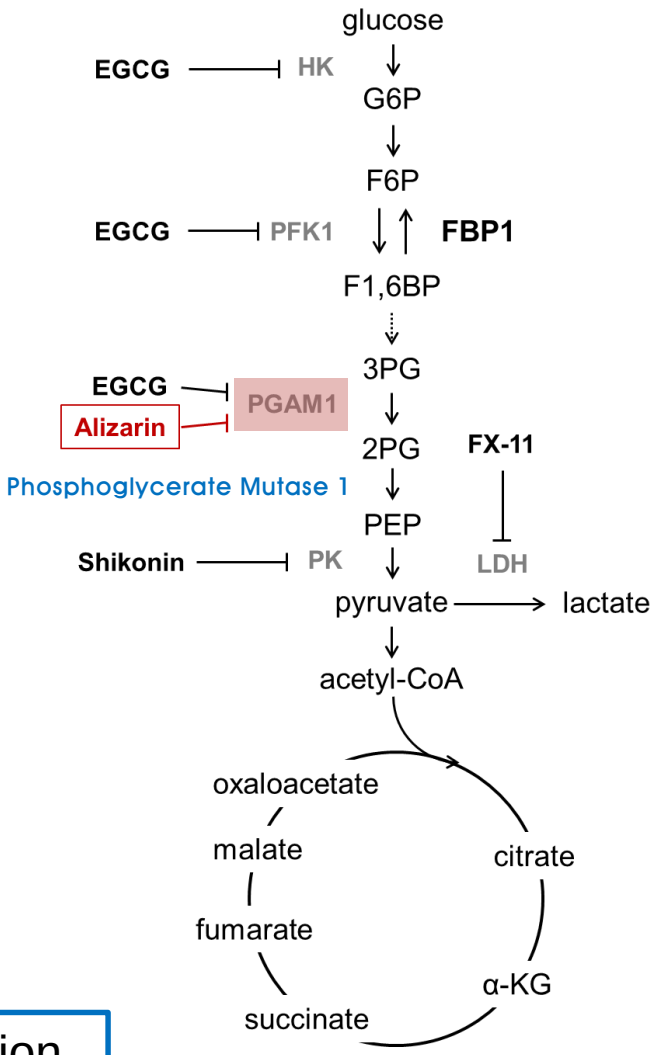


Emodin





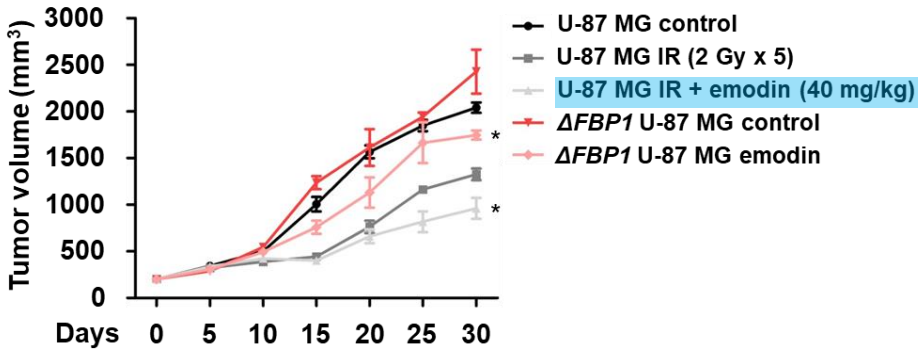


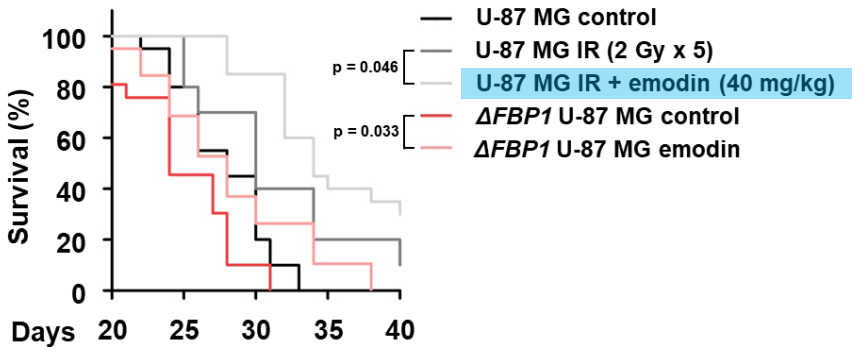


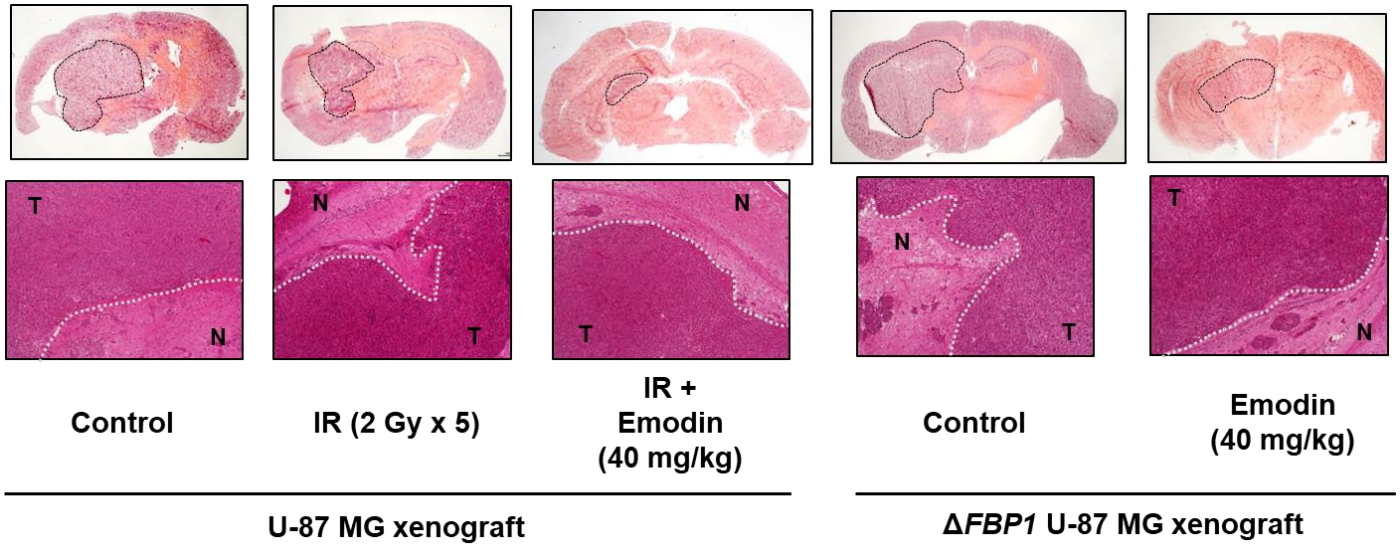
TOM-derived PGAM1 inhibitors rescue FBP1 repression and IR-induced aggressiveness of GBM

Oncogene (2018) [under review]

Key Regulators Inducing Radioresistance (1) : Metabolism



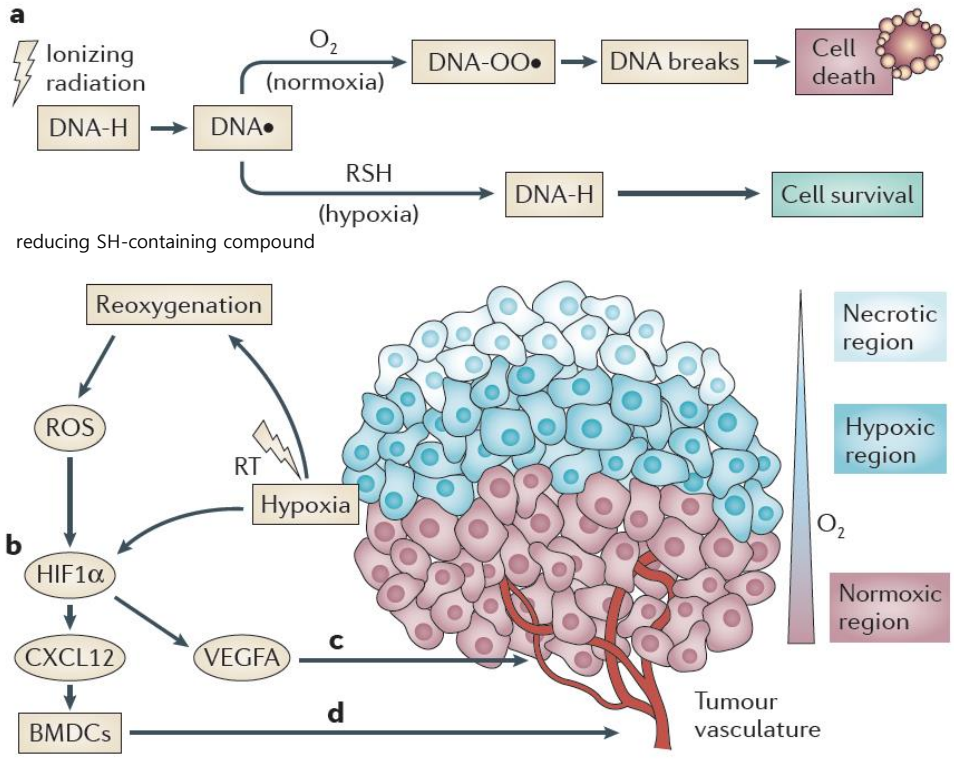




Emodin inhibited radiation-induced GBM aggressiveness in orthotopic xenograft mouse models

Oncogene (2018) [under review]

Key Regulators Inducing Radioresistance (2) : Hypoxia



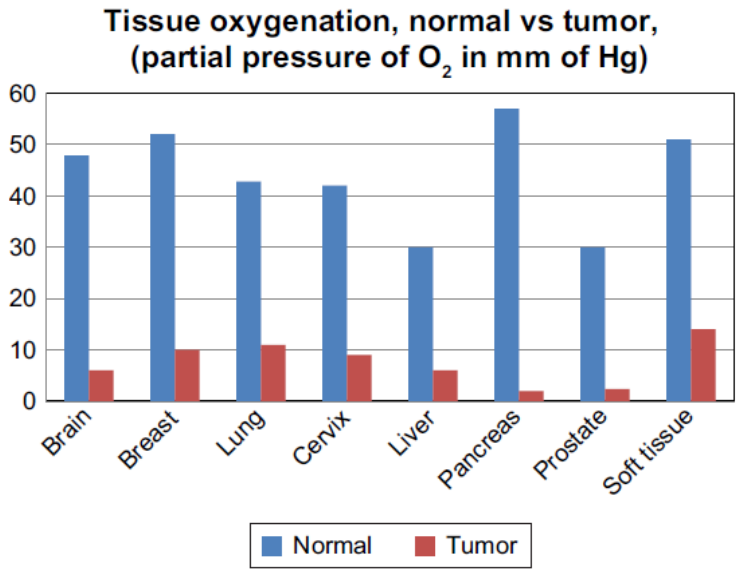


Table 1 Effect of oxygen tension on cancer therapy[a]

Critical O_2 tension (mmHg)	Function or parameter observed
30–35	Effectiveness of certain (passive) immunotherapies
15–35	Cell death with PDT
25–30	Cell death on exposure to χ- and γ-radiation
10–20	Binding of hypoxia markers
1–15	Proteome changes
0.2–1	Genome changes

- Profound hypoxia promotes changes in the proteome and genome.
- Genomic instability, in turn, promotes dedifferentiation and progression of the aggressive cancer genotype and phenotype.

Nat Rev Cancer. 2015;15(7):409-25
Int J Nanomedicine. 2018:13 6049–6058

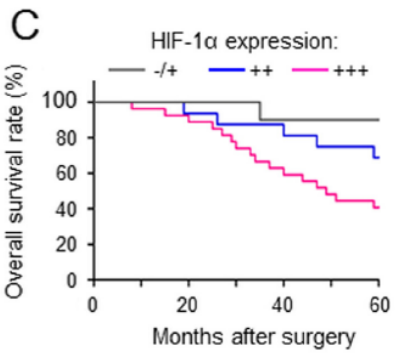
Key Regulators Inducing Radioresistance (2) : Hypoxia

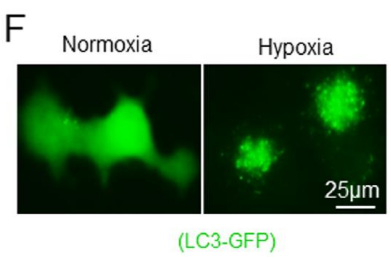
Table 2 Cancer drugs less effective in hypoxia

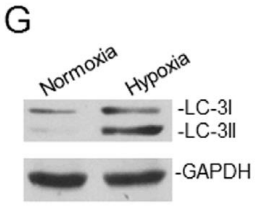
Drug	Type of drug	References
5-Fluorouracil	Antimetabolite	24
Actinomycin D	Antitumor antibiotic	20, 21, 24
Bleomycin	Antitumor antibiotic	20, 21, 24
Carboplatin	Alkylating agent	24
Cisplatin	Alkylating agent	25
Docetaxel	Plant alkaloid, mitosis inhibitor, taxane	21
Doxorubicin	Anthracycline antibiotic	24
Etoposide	Plant alkaloid, topoisomerase II inhibitor	24
Gemcitabine	Antimetabolite	24
Irinotecan	Plant alkaloid, topoisomerase I inhibitor	22
Melphalan	Alkylating mustard analog	22
Methotrexate	Antimetabolite	24
Oxaliplatin	Alkylating agent	25
Procarbazine	Alkylating agent	20, 21
Sorafenib	Multikinase inhibitor, antiangiogenic	22
Streptonigrin	Antitumor antibiotic	21
Temozolomide	Alkylating agent	21
Thiotepa	Alkylating agent	20
Vincristine	Plant alkaloid, vinca alkaloid	20, 21
VP-16	Plant alkaloid, topoisomerase II inhibitor	20

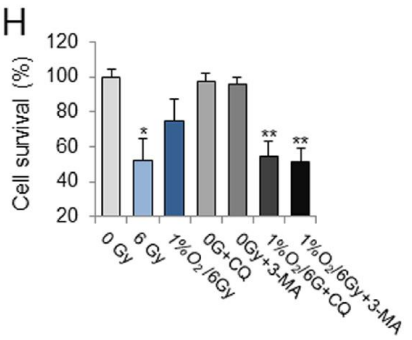
B

	HIF-1α expression level			
	-	+	++	+++
Osteosarcoma (n=89)	7 (7.9%)	16 (18.0%)	25 (28.1%)	41 (46.1%)
Osteochondroma (n=28)	23 (82.1%)	5 (17.9%)	0 (0.0%)	0 (0.0%)









Hypoxia-induced autophagy is an additional mechanism in human osteosarcoma radioresistance

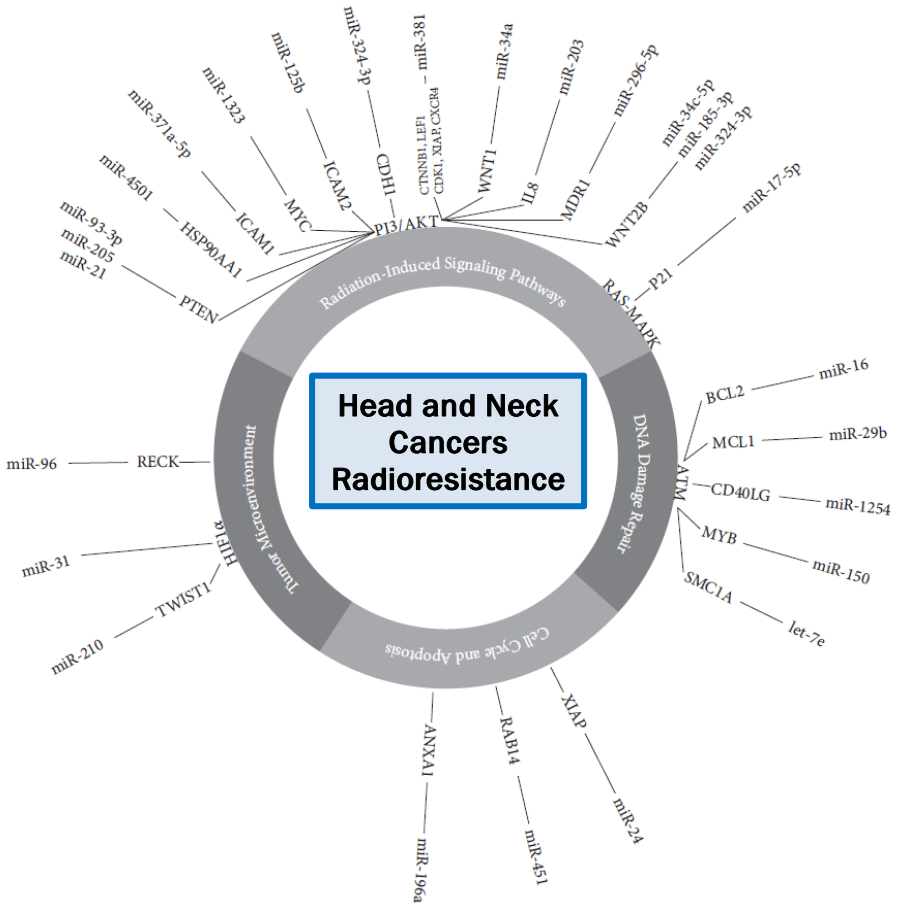
Int J Nanomedicine. 2018:13 6049–6058
J Bone Oncol. 2016;5(2):67-73

Key Regulators Inducing Radioresistance (3) : miRNA Regulation

Table 1: Expression of radioresistance associated miRNAs in head and neck cancers.

Expression in tumor	miRNA	Carcinoma type	Reference
Upregulated (Onco-miR)	miR-451	NPC	[5]
	miR-31	OAC	[6, 7]
	miR-150	HNSCC	[8]
	miR-1254	HNSCC	[8]
	miR-16	HNSCC	[8]
	miR-29b	HNSCC	[8]
	miR-196a	HNSCC	[9]
	miR-210	HNSCC	[10]
	miR-1323	NPC	[11]
	miR-34c-5p	NPC	[11]
	miR-371a-5p	NPC	[11]
	miR-205	NPC	[12]
	miR-23a	NPC	[13]
	miR-96	ESCC	[14]
	miR-296-5p	LSCC	[15]
	miR-21	NPC	[16, 17]
Downregulated (TS-miR)	miR-324-3p	NPC	[11]
	miR-141	ESCC	[18]
	miR-18b	ESCC	[18]
	miR-301a	ESCC	[18]
	miR-24	LSCC, NPC	[19, 20]
	miR-let 7e	HNSCC	[8]
	miR-4501	NPC	[11]
	miR-93-3p	NPC	[11]
	miR-324-3p	NPC	[21]
	miR-34a	NPC	[22]
	miR-185-3p	NPC	[23]
	miR-381	ESCC	[24]
	miR-125b	OSCC	[25]
	miR-17-5p	OSCC	[26]
	miR-203	LSCC, NPC	[27, 28]

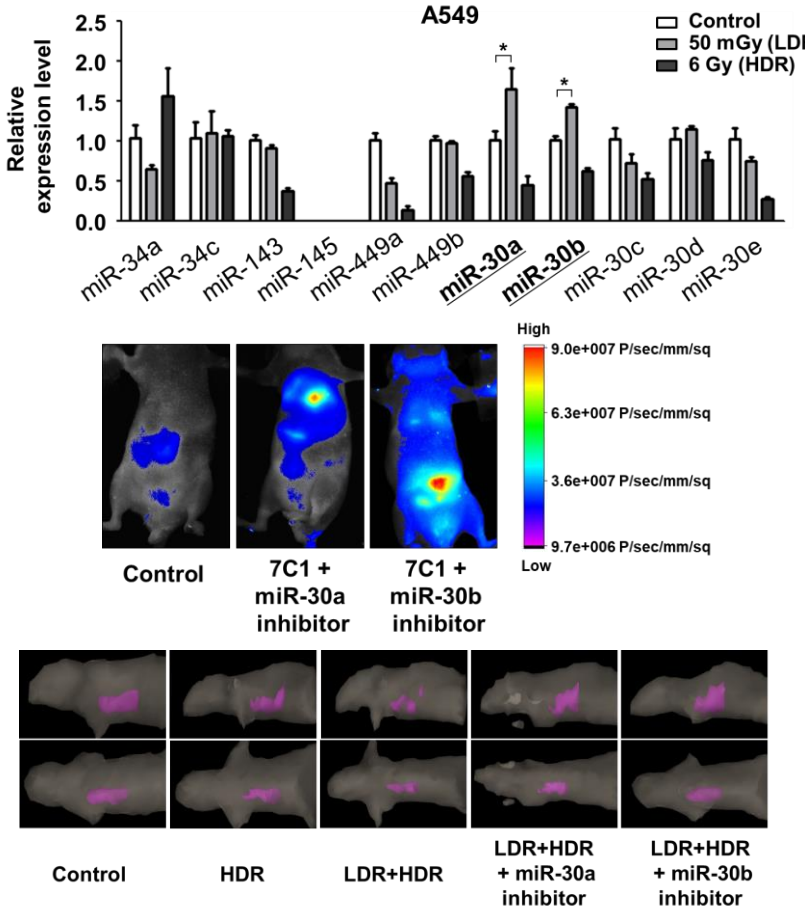
HNSCC: head and neck squamous cell carcinoma; NPC: nasopharyngeal carcinoma; OSCC: oral squamous cell carcinoma; OAC: oral adenocarcinoma; LSCC: laryngeal squamous cell carcinoma; ESCC: esophageal squamous cell carcinoma.

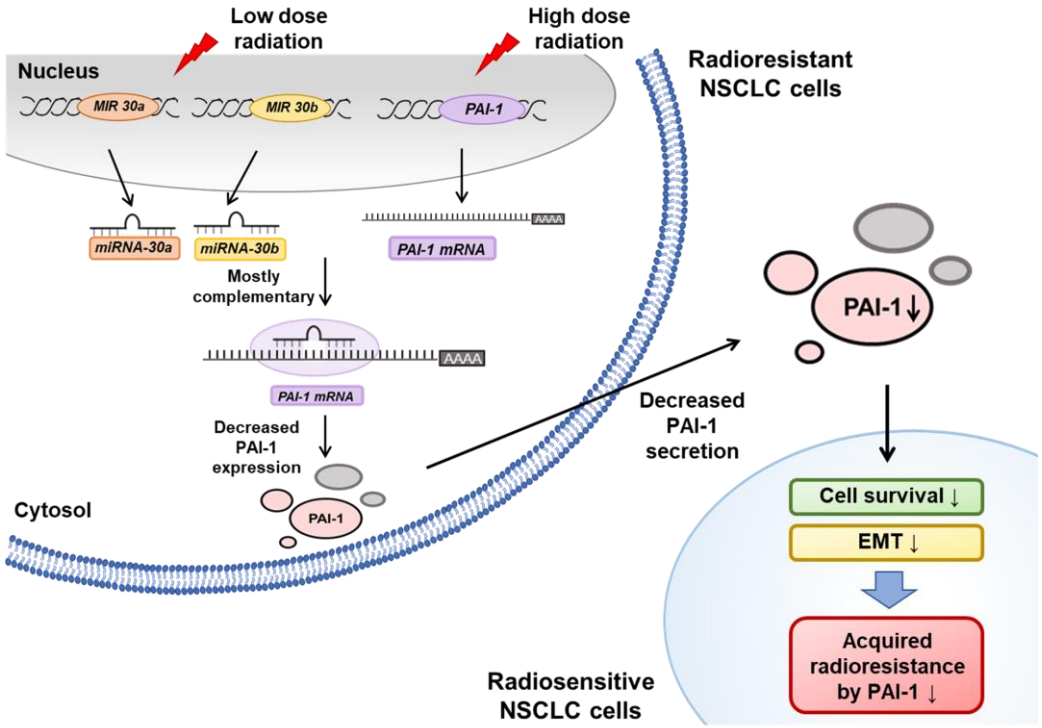


It has been found that regulation of DNA damage repair, apoptosis, proliferation, and angiogenesis is often controlled by **microRNAs** in head and neck cancer

Dis Markers. 2017;2017:8245345

Key Regulators Inducing Radioresistance (3) : miRNA Regulation

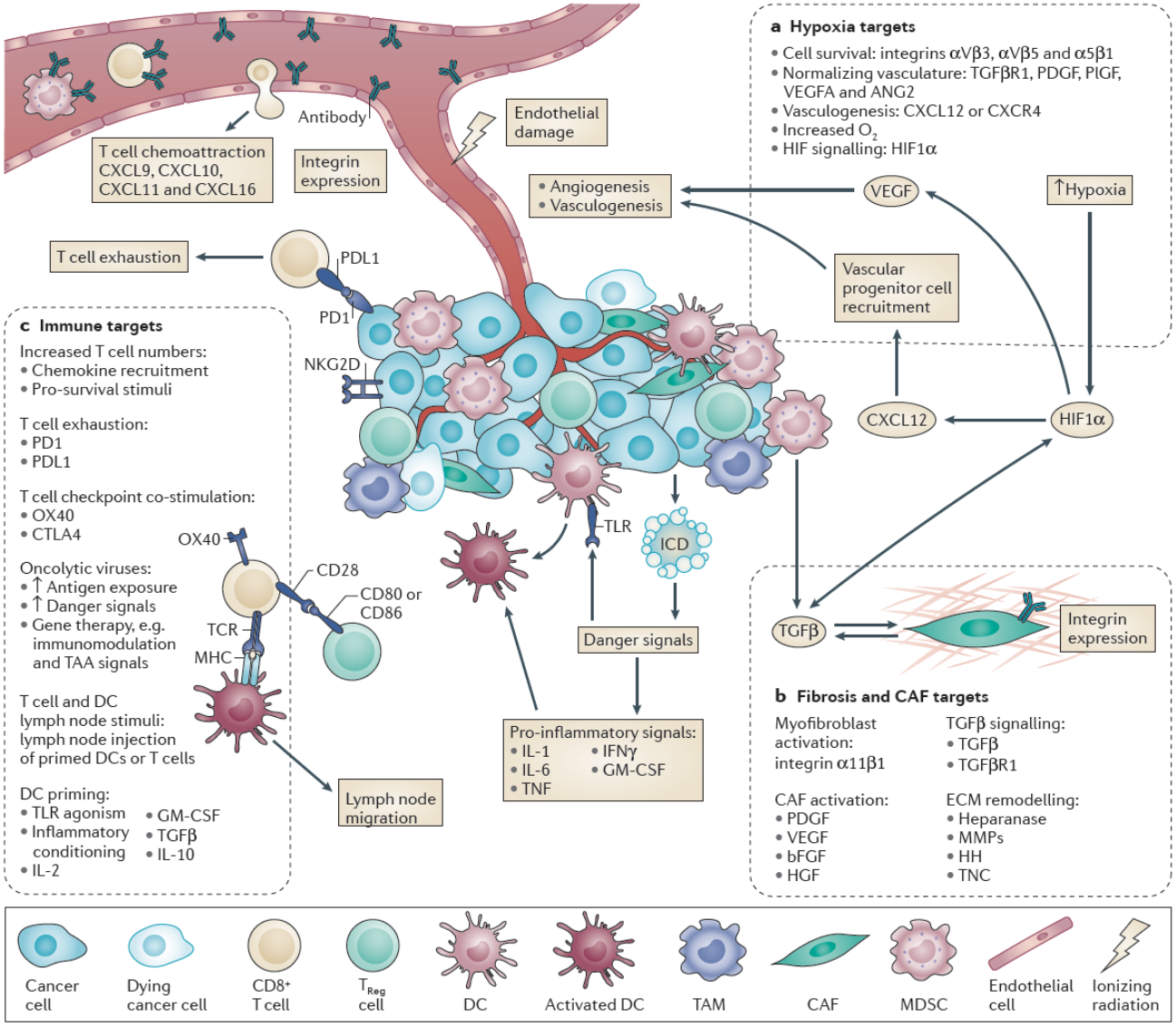




Our findings indicated that low-dose radiation (LDR) treatment or LDR-induced miRNAs can be a new strategy to improve lung cancer radiotherapy

Mol Ther. (2018) [In press]

Key Regulators Inducing Radioresistance (4) : Tumor Microenvironment

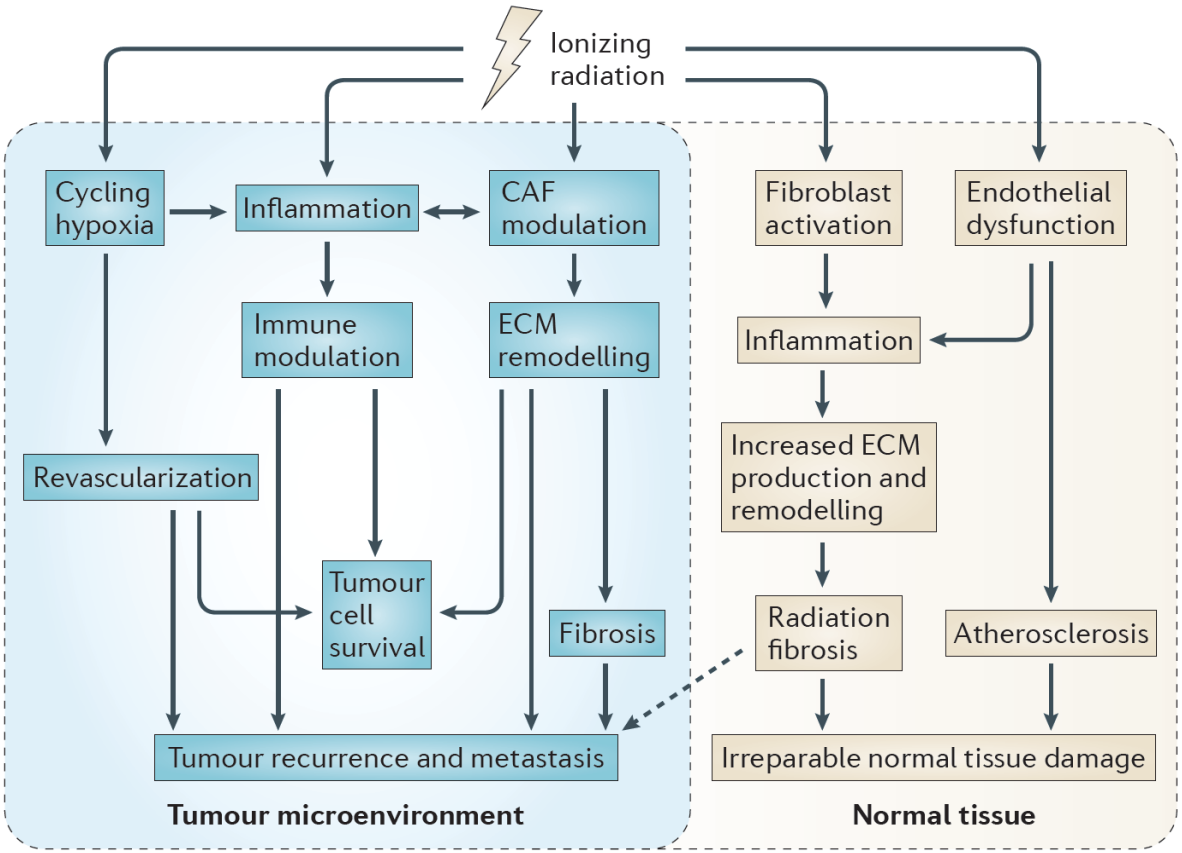


- After radiotherapy, there are numerous <u>potential targets within the tumor microenvironment</u> (TME) the modulation of which may lead to radiosensitization

  - ***Hypoxia targets***
  - ***Fibrosis and CAF targets***
  - ***Immune targets***

Nat Rev Cancer. 2015;15(7):409-25

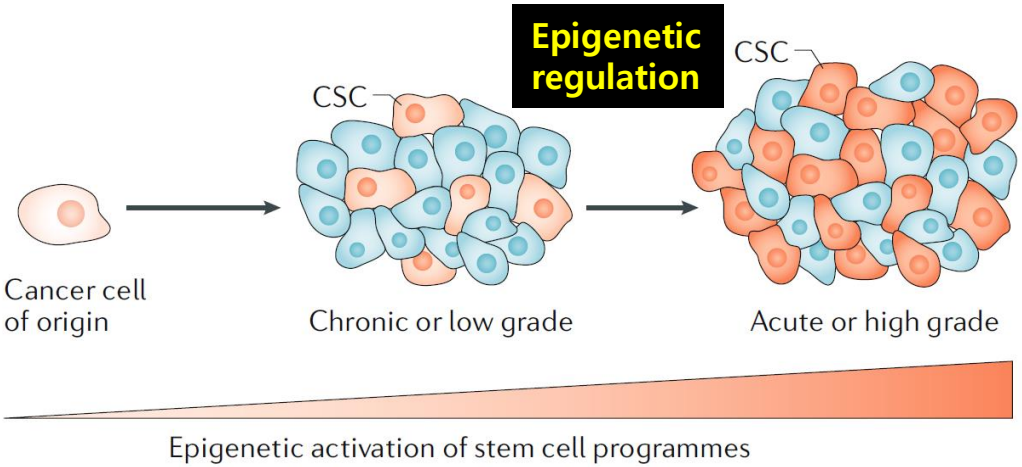
Key Regulators Inducing Radioresistance (4) : Tumor Microenvironment

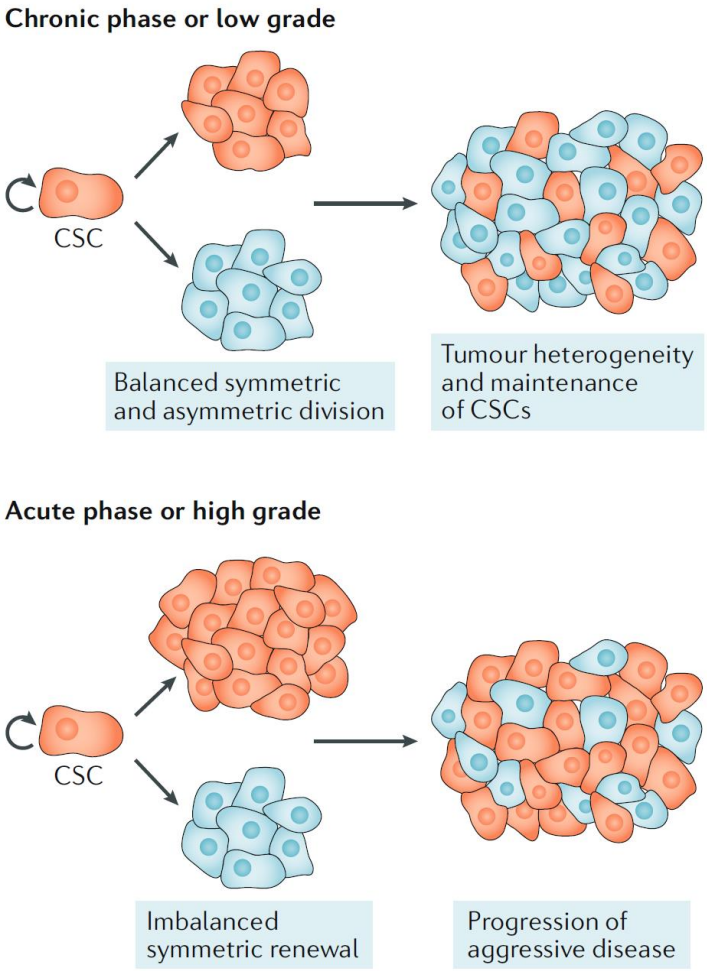


Radiotherapy-mediated changes in the tumor microenvironment are interconnected

Nat Rev Cancer. 2015;15(7):409-25

Key Regulators Inducing Radioresistance (5) : Cancer Stem Cells





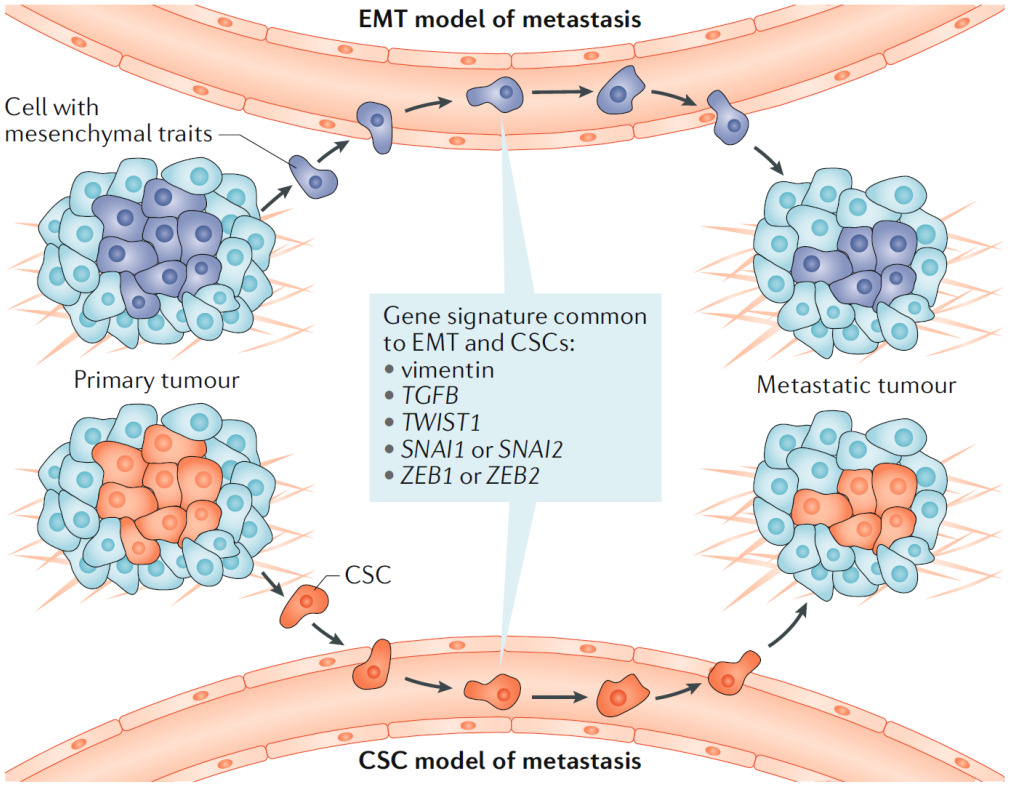
- In cancers, epigenetic reactivation of **stem cell programms** can promote propagation and progression to an aggressive state.
- The **disruption of asymmetric division** is one way in which cancer may progress to an aggressive state.

Nat Rev Cancer. 2018 Sep 18.
doi: 10.1038/s41568-018-0056-x.

Key Regulators Inducing Radioresistance (5) : Cancer Stem Cells

Table 1 | **Asymmetric division genes in cancer**

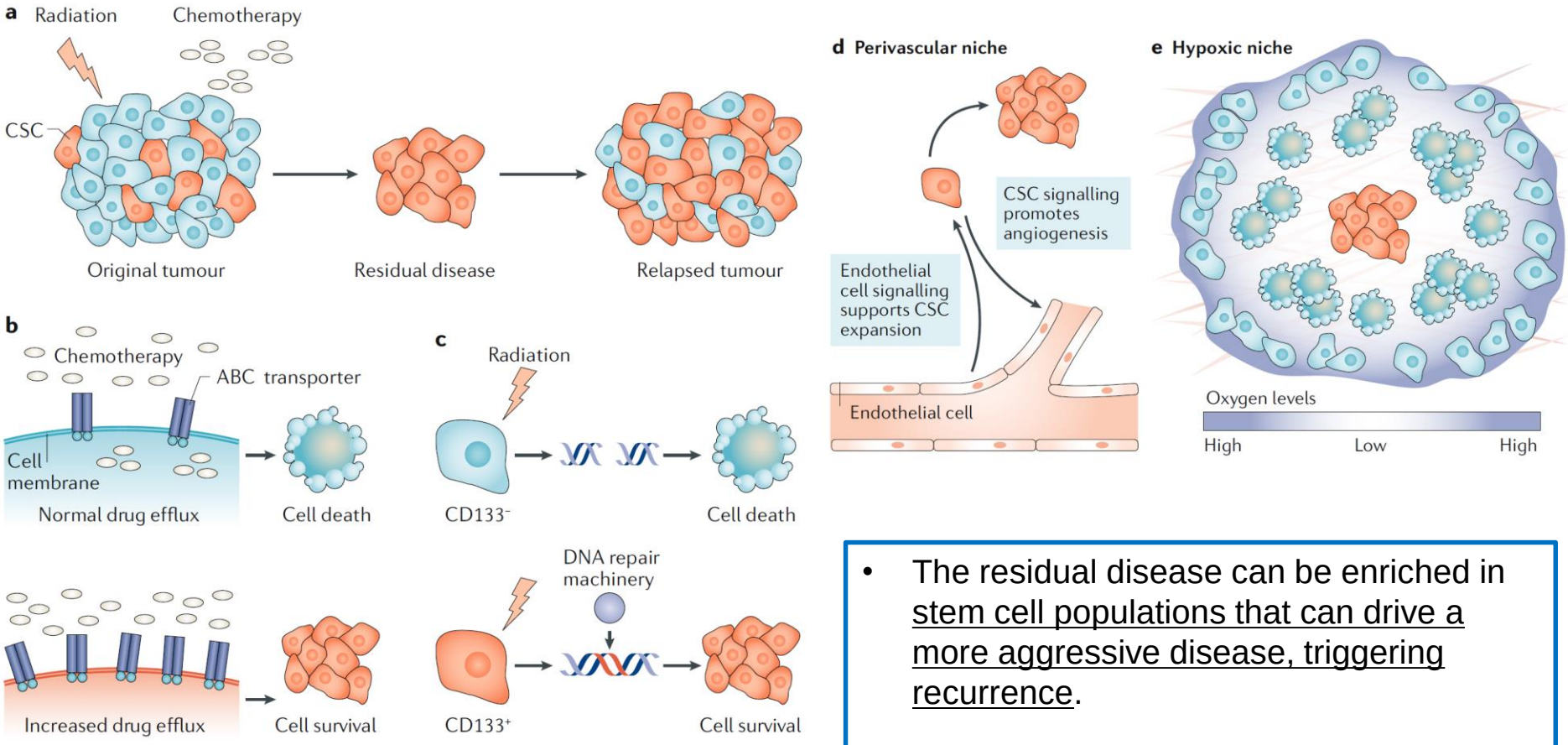
Protein	Function in asymmetric division	Cancer type	Effect on asymmetric division
LLGL1	Cell polarity	Leukaemia	Promotes asymmetric division
NUMB	Cell fate	Leukaemia, colon cancer and breast cancer	Promotes differentiation
MSI	Cell fate	Leukaemia	Promotes stemness
LIS1	Dynein binding and spindle orientation	Leukaemia	Promotes symmetric renewal
TRIM3	Cell fate	Brain cancer	Promotes asymmetric division
p53	Cell fate	Brain cancer, colon cancer and breast cancer	Promotes asymmetric division
miR-34a	Cell fate	Colon cancer and brain cancer	Promotes differentiation (targets NOTCH)
miR-146a	Cell fate	Colon cancer	Promotes symmetric renewal (targets NUMB)
lnc34a	Cell fate	Colon cancer	Promotes symmetric renewal (targets miR-34a)



The parallels between **EMT cells** and **CSCs** raise the possibility that they represent overlapping concepts.

Nat Rev Cancer. 2018 Sep 18.
doi: 10.1038/s41568-018-0056-x.

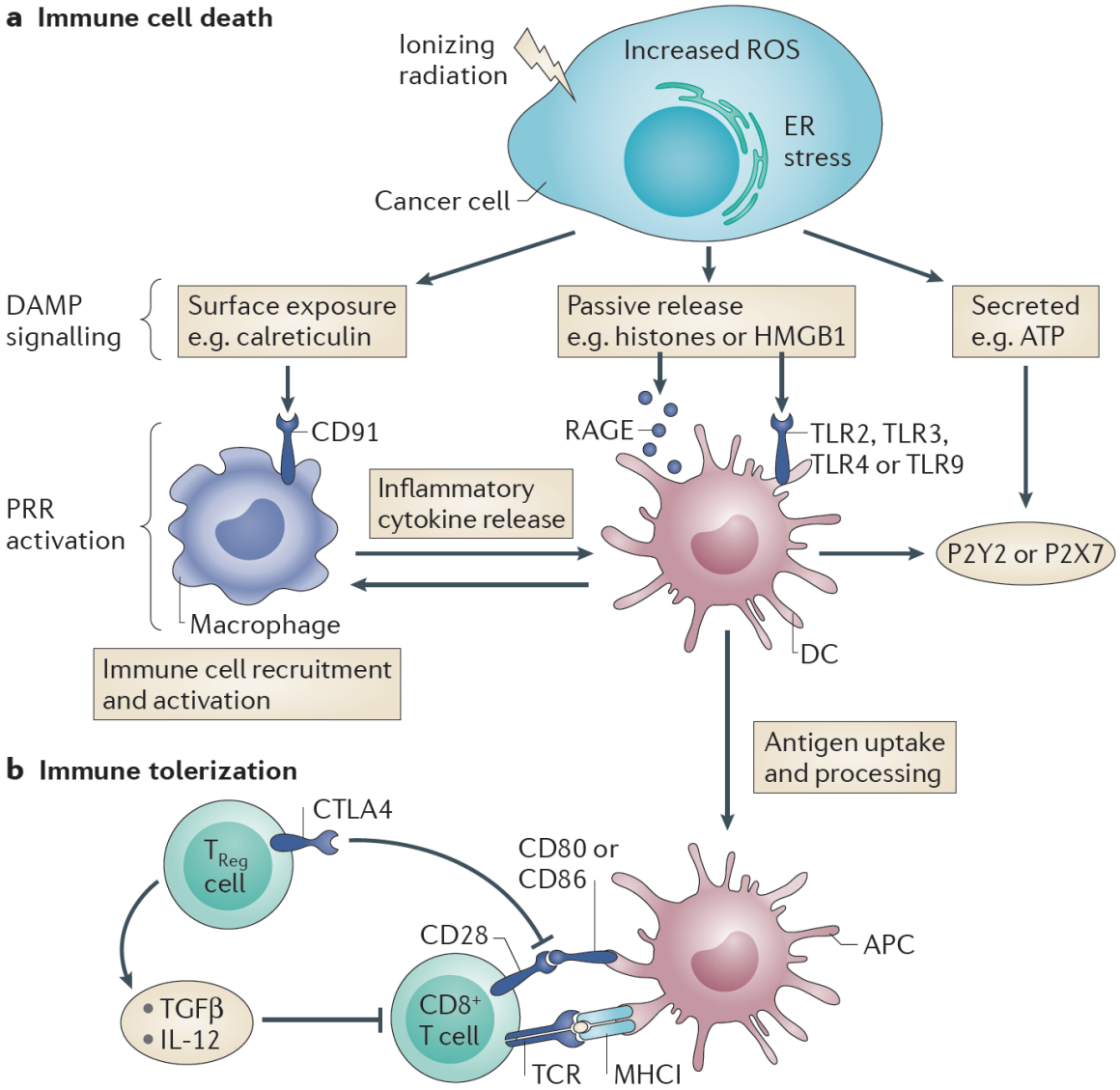
Key Regulators Inducing Radioresistance (5) : Cancer Stem Cells



- The residual disease can be enriched in stem cell populations that can drive a more aggressive disease, triggering recurrence.
- CSCs utilize the tumor microenvironment for increased survival.

Nat Rev Cancer. 2018 Sep 18.
doi: 10.1038/s41568-018-0056-x.

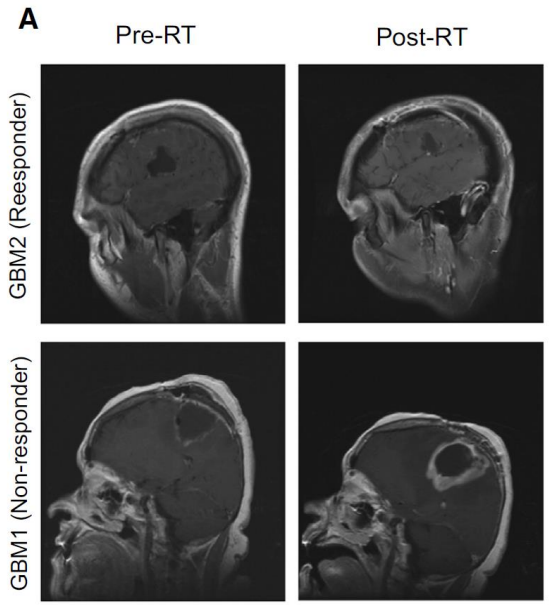
Key Regulators Inducing Radioresistance (6) : Immune and Inflammation

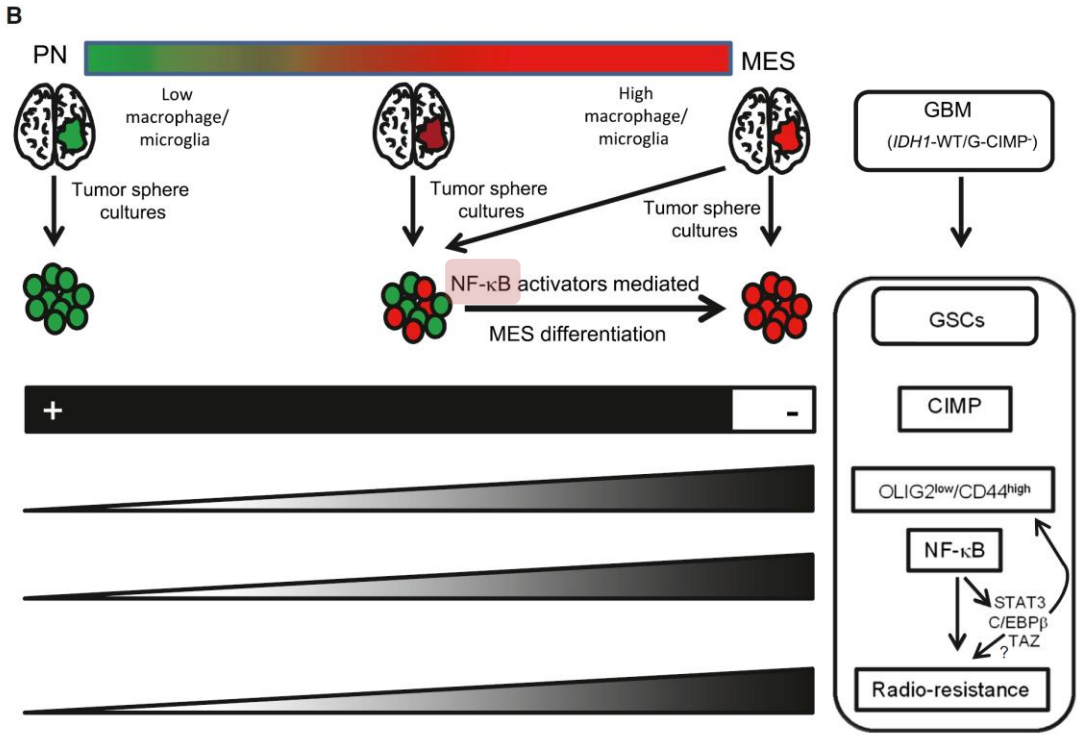


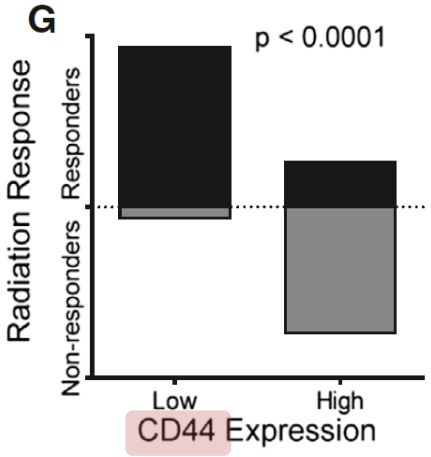
- Regulatory T cells express **CTLA4**, which has a higher affinity for CD80 and CD86 than CD28 and thus effectively inactivates the co-stimulatory signal, leading to ineffective T cell activation.
- Overcoming this process with appropriate immunomodulation allows for the effective exposure of cancer cells to the immune system

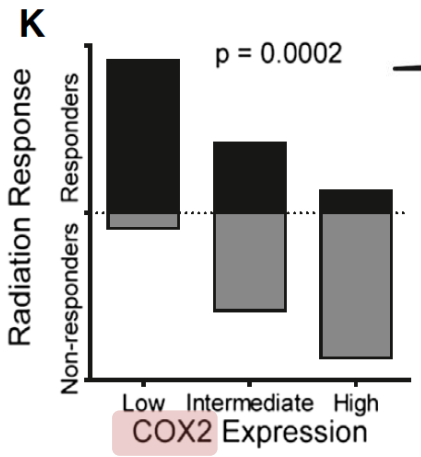
Nat Rev Cancer. 2015;15(7):409-25

Key Regulators Inducing Radioresistance (6) : Immune and Inflammation









- Radioresistance can be induced in PN/CIMP$^-$ GSCs by activation of NF-κB and downstream master TFs (STAT3, C/EBPb, and TAZ)
- MES GSCs are CIMP$^-$, predominantly express CD44, are radioresistant, and exhibit constitutive activation of NF-κB and downstream master TFs.

Cancer Cell. 2013;24(3):331-46

Key Regulators Inducing Radioresistance (7) : DNA Damage Response

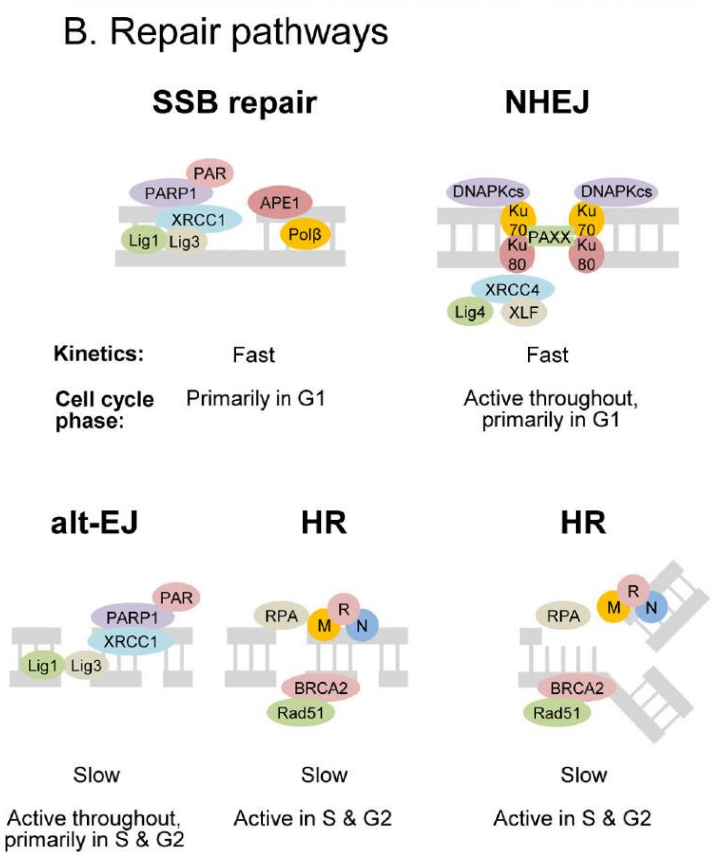


Table 1

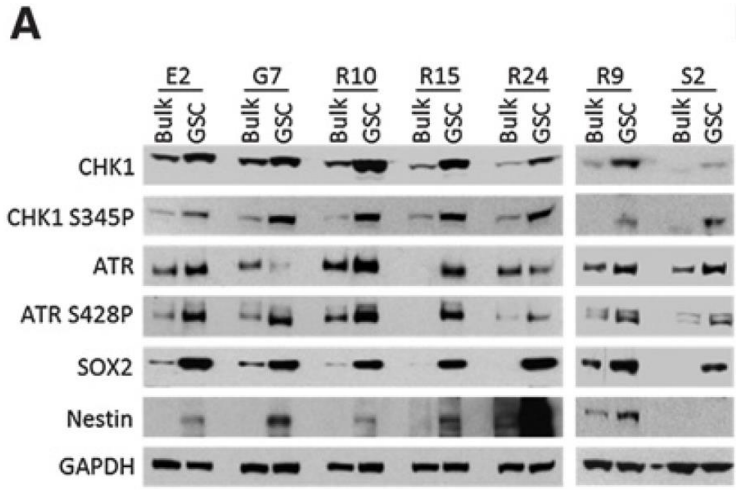
Agents targeting the DNA damage response in clinical and pre-clinical development*

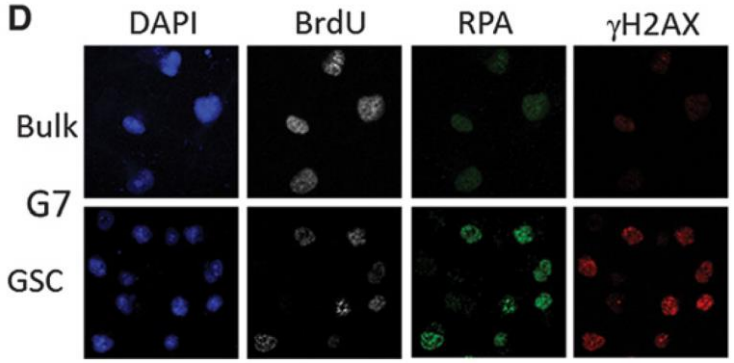
Target	Agent	Single agent development stage	Combination agent development stage	Reference or clinical trial identifier number(s)
ATM	KU55933, KU59403	Pre-clinical	Pre-clinical (RT, chemo)	58
	AZ32	-	Pre-clinical (RT)	22
ATR	AZD6738	Phase 1	Phase 1 (RT, chemo[1])	NCT02223923, NCT02264678
	VE-821/VE-822, VX-970	Pre-clinical	Phase 1 (chemo[2])	NCT02157792
			Pre-clinical (RT)	23
CHK1	LY2606368 (Chk1/2)	Phase 2	Phase 1 (chemo[3])	NCT02124148
	LY2603618	Phase 2	Phase 2 (chemo[4])	NCT01139775, NCT00839332
	MK8776	Phase 1	Phase 2 (chemo[5])	NCT01870596, NCT00779584
DNA-PK	CC-115 (DNA-PK & mTOR)	Phase 1	-	NCT01343625
	ZSTK474 (PI3 kinase)	Phase 2	-	NCT01682473
LIG4	SCR7	Pre-clinical	Pre-clinical (RT, chemo)	24
PARP	Olaparib	Approved	Phase 1 (RT, chemoRT[6])	NCT01460888, NCT01562210
			Phase 3 (chemo[7])	NCT01924533
	Veliparib	Phase 3	Phase 1 (RT)	NCT01264432, NCT01589419
			Phase 2 (chemoRT[8])	NCT01514201, NCT01386385
			Phase 3 (chemo[9])	NCT02163694, NCT02152982
	Niraparib	Phase 3	Phase 1 (chemo[10])	NCT01847274, NCT02044120
RAD51	RI-1	Pre-clinical	Pre-clinical (chemo)	37
	B02	Pre-clinical	Pre-clinical (chemo)	38
RPA	Compound 8	Pre-clinical	-	45
	HAMNO	Pre-clinical	Pre-clinical (chemo)	46
	SMI MCI13E	Pre-clinical	Pre-clinical (chemo)	47
WEE1	AZD1775	Phase 1	Phase 1/2 (RT, chemoRT[11])	NCT01922076, NCT02037230
			Phase 2 (chemo[12])	NCT02272790, NCT01076400

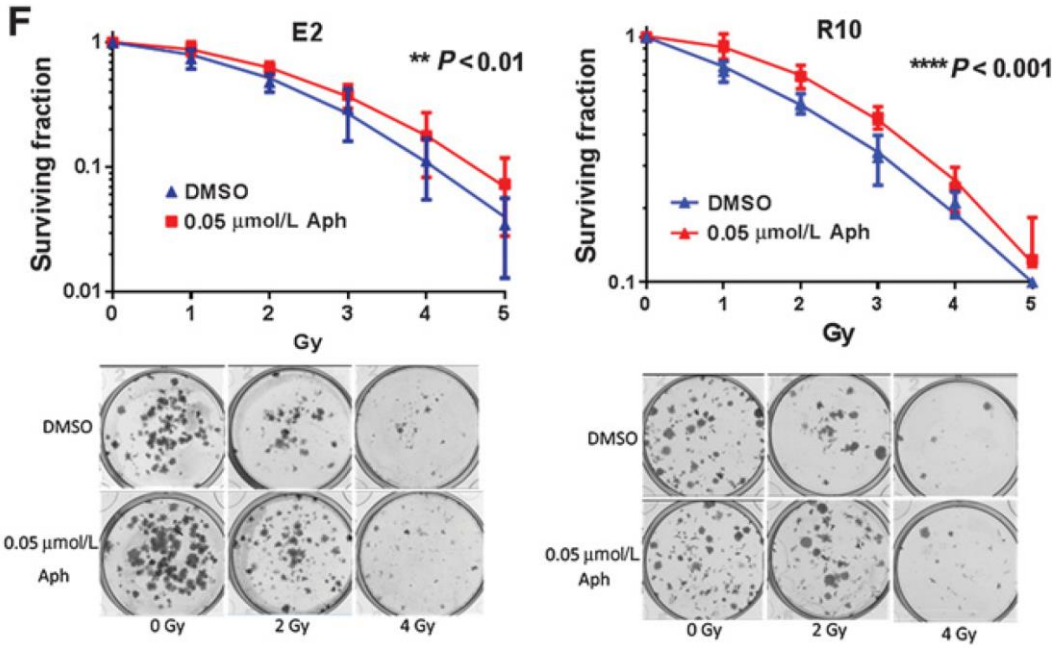
Single-strand breaks repair, double-strand breaks repair, non-homologous end-joining pathways and alternative-end-joining repair

Clin Cancer Res. 2015; 21(13): 2898–2904

Key Regulators Inducing Radioresistance (7) : DNA Damage Response





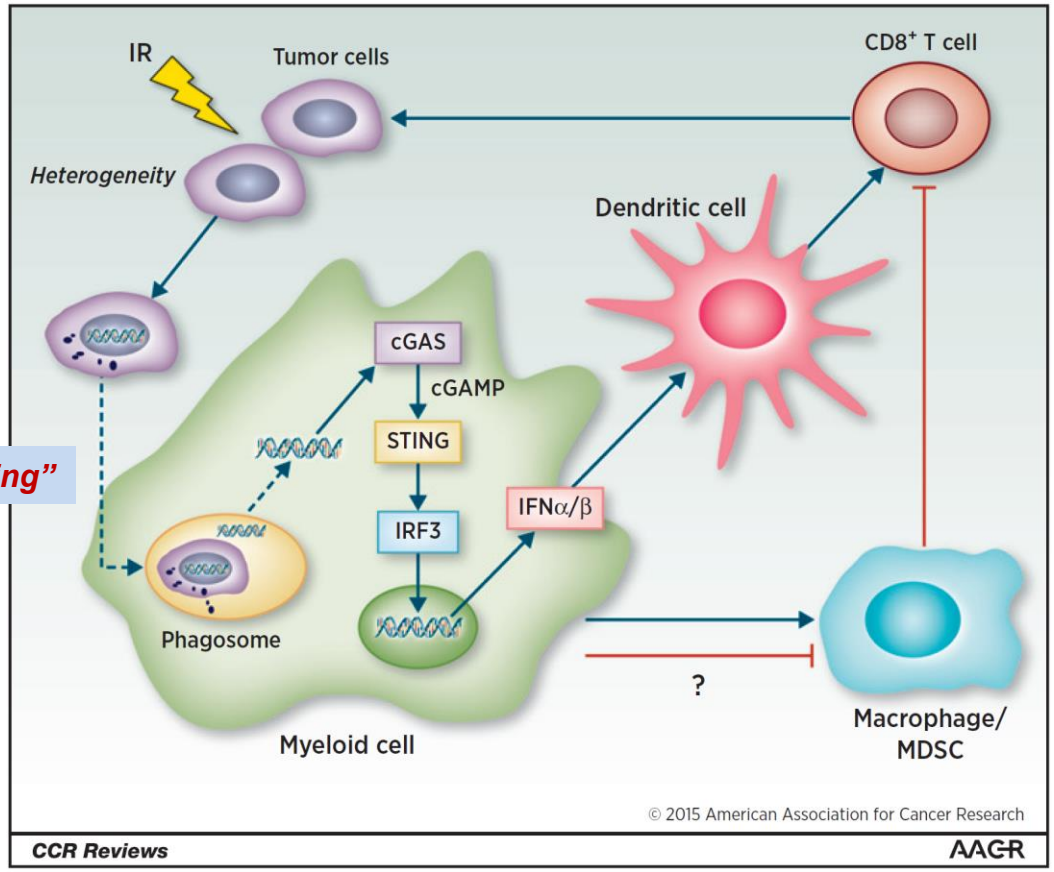


Radioresistant GSC demonstrate upregulation of DNA **replication stress (RS)** response markers, and exogenous RS generates radiation resistance in non-GSC.

Cancer Res. 2018;78(17):5060-5071

Key Regulators Inducing Radioresistance (7) : DNA Damage Response

"Cytosolic DNA sensing"



- Radiation results in the upregulation of "find-me" and "eat-me" signals from tumor cells
- However, the influx of macrophage and **MDSCs(myeloid derived suppressor cells)** after radiation attenuates $CD8^+$ T-cell responses to help tumor escape

Clin Cancer Res. 2016;22(1):20-5

Key Regulators Inducing Radioresistance (8) : Autophagy

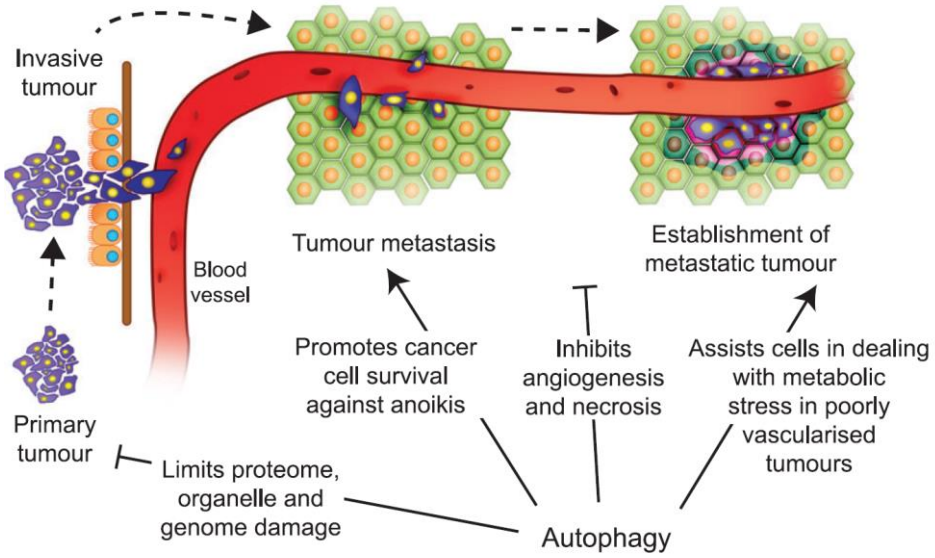


Table 2. Effect of various cancer treatments on autophagy

Name of treatment	Mechanism	Effect on autophagy	Autophagy function (pro-death or pro-survival for cancer cells)	References
Ionising radiation	Induces DNA damage	Induction	Pro-survival	(Chaachouay et al., 2011).
Tamoxifen	Binds and inhibits oestrogen receptors	Induction	Pro-survival	(Schoenlein et al., 2009)
Camptothecan	Downregulation of topoisomerase I and inhibition of DNA synthesis	Induction	Pro-survival	(Abedin et al., 2007)
5-Fluorouracil	Active metabolites that can inhibit thymidylate synthase and become mis-incorporated into DNA and RNA	Induction	Pro-survival	(Li et al., 2010)
Proteasome inhibitors	Inhibition of proteasome	Induction	Pro-survival	(Zhu et al., 2010)
Anti-HER2 antibodies	Inhibition of HER2 receptor signalling	Induction	Pro-survival	(Vazquez-Martin et al., 2009)
Rapamyin and rapamycin analogues	Inhibitor of mTOR	Induction	Pro-death	(Iwamaru et al., 2007; Konings et al., 2009)
Imatinib	Tyrosine kinase inhibitor	Induction	Pro-death	(Yogalingam and Pendergast, 2008; Basciani et al., 2007)
Bafilomycin	Inhibition of autophagy through blocking fusion of autophagosome and lysosome	Inhibition	Pro-survival	(Kanzawa et al., 2003)
Chloroquine	Inhibition of autophagy through blocking fusion of autophagosome and lysosome	Inhibition	Pro-survival	(Amaravadi et al., 2011)
3-methyladenine (3-MA)	PI3K inhibitor	Inhibition	Pro-survival	(Levy and Thorburn, 2011)

- **Autophagy** can both inhibit and promote cancer formation through different mechanisms, depending on the stage of tumor
- Autophagy is frequently upregulated in cancer cells following treatment with conventional drugs or exposure to ionizing radiation

J Cell Sci. 2012;125(Pt 10):2349-58

Key Regulators Inducing Radioresistance (8) : Autophagy

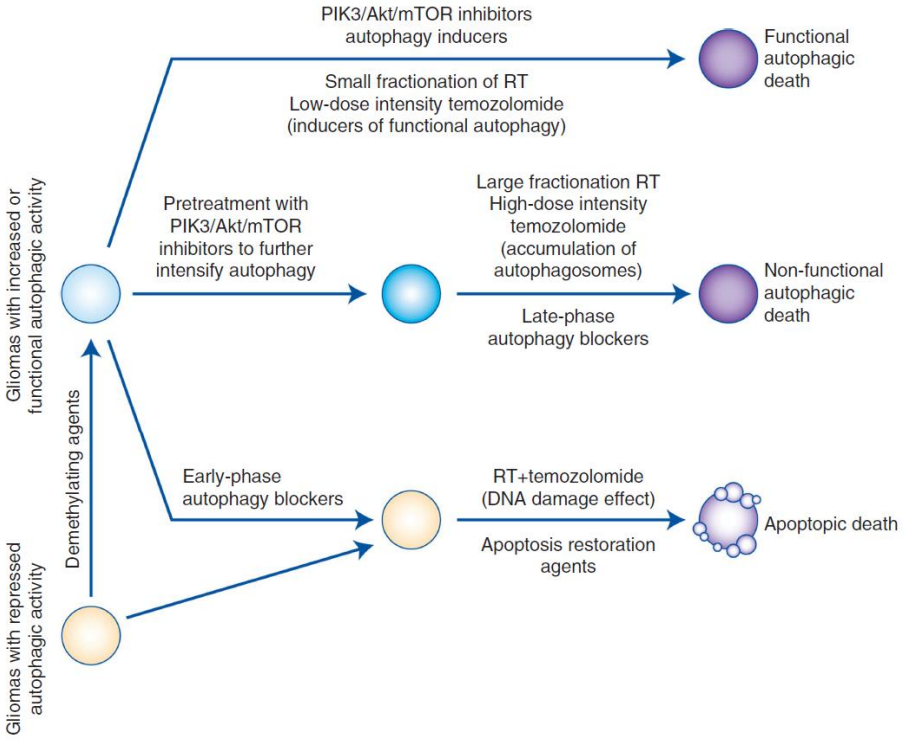


Table 1 Effects of autophagy modifications on improving radiosensitivity or radiotherapy efficacy

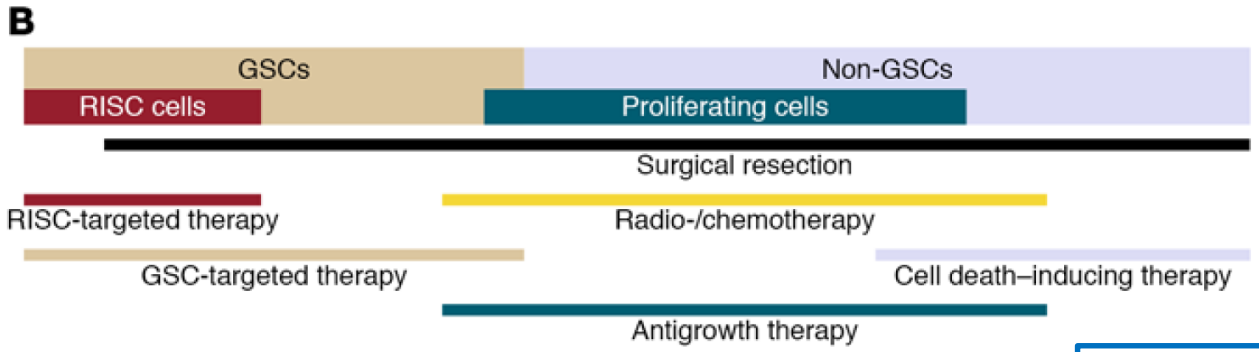
Cancer type	Cell line	Autophagy agent (Induction (+)/ Inhibition (–))	Autophagy pathway affected	Animal study (Yes (+)/ No (–))
Glioblastoma	T98G + U373MG	Rapamycin (+)	PI3K-Akt-mTOR (mTOR inhibitor)	-
	SU2	NVP-BEZ235 (+)	PI3K-Akt-mTOR (PI3K/mTOR inhibitor)	-
	U373MG	Chloroquine (–)	UPR (PERK)	+
Oral cancer	OC3 + SAS	Rapamycin (+)	PI3K-Akt-mTOR (mTOR inhibitor)	-
Lung cancer	H460	RAD001 (+)	PI3K-Akt-mTOR (mTOR inhibitor)	+
	H460	Rapamycin (+)	PI3K-Akt-mTOR (mTOR inhibitor)	+
	CDDP-Resistant H460	NVP-BEZ235 (+)	PI3K-Akt-mTOR (PI3K/mTOR inhibitor)	-
Breast cancer	MDA-MB-23 + MCF-7	RAD001 (+)	PI3K-Akt-mTOR (mTOR inhibitor)	-
	MCF-7	Rapamycin (+)	PI3K-Akt-mTOR (mTOR inhibitor)	-
Oesophageal cancer	EC109	Tunicamycin (+)	PI3K-Akt-mTOR (ER stressor)	+
Pancreatic cancer	MIA PaCa-2 + PANC-1	MG132 (+)	MAPK (JNK) (Proteasome inhibitor/ ER stressor)	+
Colorectal cancer	HCT-116	BCG/CWS (+)	MAPK (JNK/ERK)	+
	HCT-116 + HT-29	Chloroquine (–)	UPR (PERK)	+
Prostate cancer	Biopsy specimens	MG132 (+)	MAPK (JNK) (Proteasome inhibitor/ ER stressor)	-
	DU145 + PC3	RAD001 (+)	PI3K-Akt-mTOR (mTOR inhibitor)	-

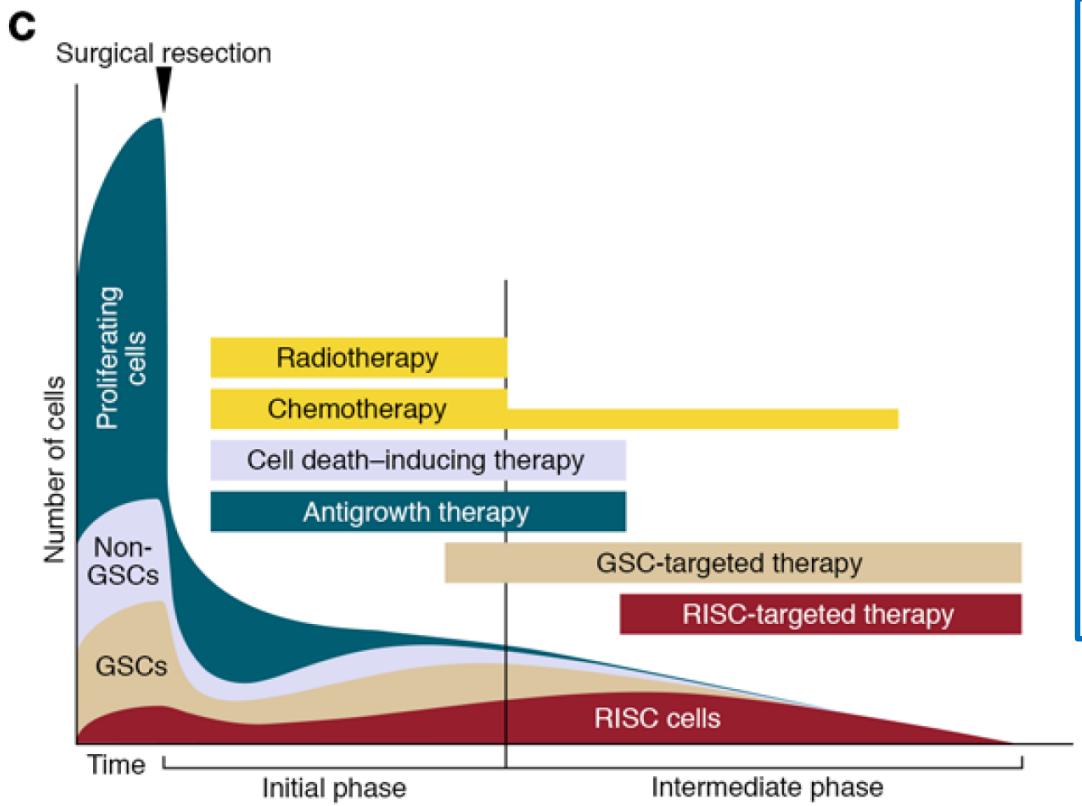
- The interfering autophagy makes a difference in the treatment of gliomas and glioblastoma
- Autophagy improves radiotherapy efficacy through various autophagy signalling pathways in different cancer types

Br J Cancer. 2016;114(5):485-96
Radiat Oncol. 2017;12(1):57

Contents

Ways to Overcome Radioresistance

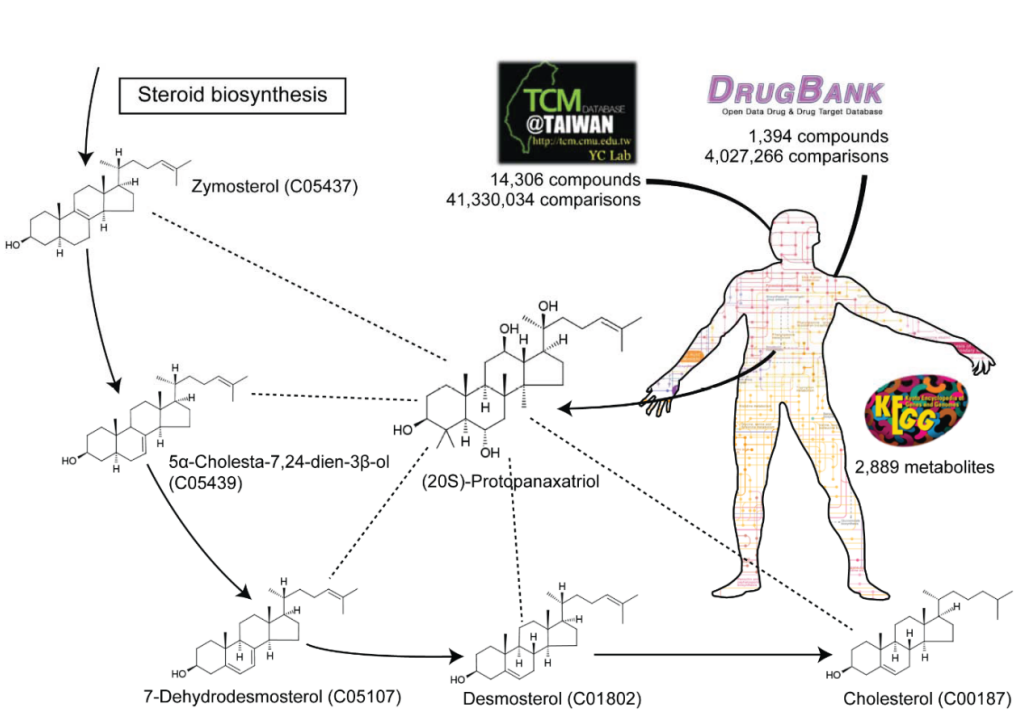


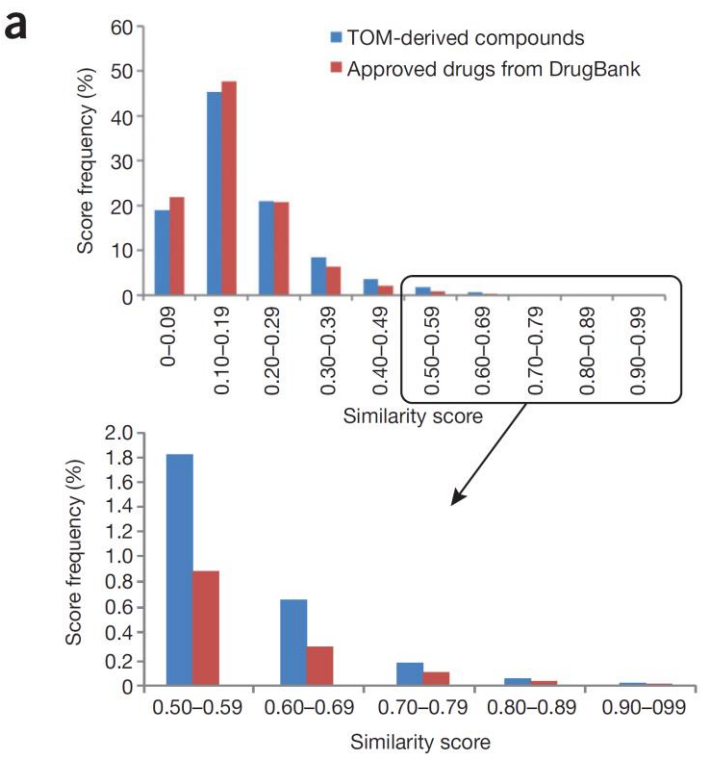


- <u>Autophagy can both inhibit and promote cancer formation</u> through different mechanisms, depending on the stage of tumor
- Optimal timing for each therapeutic option during the initial (primary treatment) and intermediate stabilization /remission period before recurrence) phases of therapy should be proposed

J Clin Invest. 2017;127(2):415-426

Ways to Overcome Radioresistance

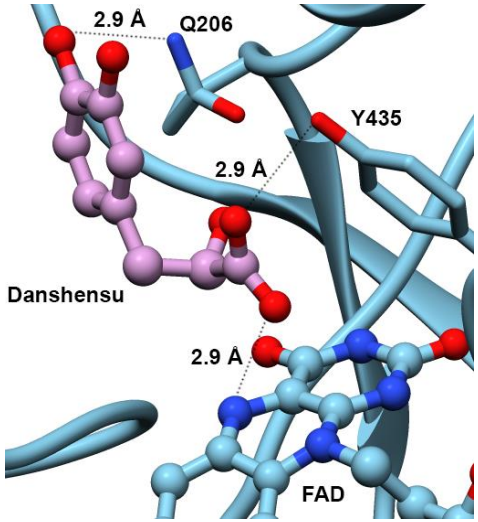


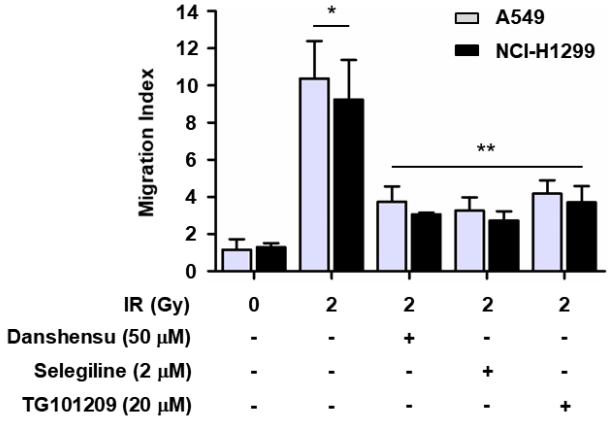


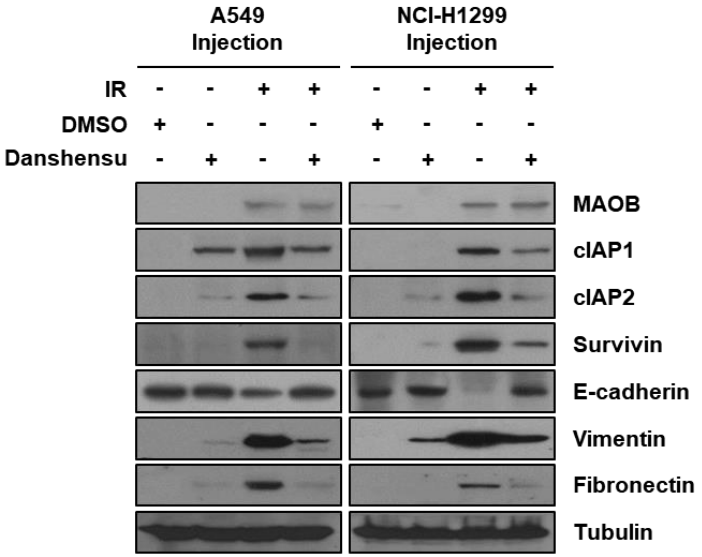
The compounds in natural products are structurally more similar to human metabolites than approved drugs from DrugBank (i.e., less side effects)

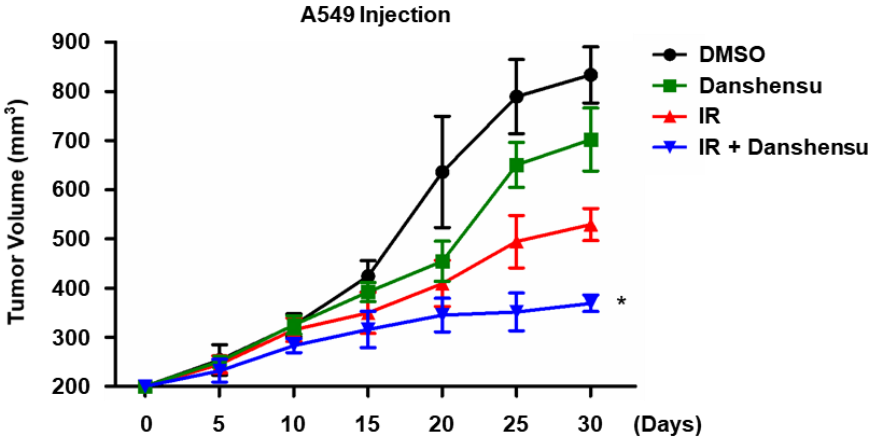
Nat Biotechnol. 2015;33(3):264-8

Ways to Overcome Radioresistance









Danshensu reduces MAOB activity and attenuates NF-κB signaling to elicit the radiosensitization of NSCLC

Sci Rep. 2016;6:21986

감사합니다 !