Editorial

Molecular mechanisms underlying radioresistance: data compiled from isogenic cell experiments

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Radiotherapy is an essential component of cancer therapy. Theoretically, a sufficiently high dose of radiation should achieve complete tumor control. However, in three-dimensional conformal radiotherapy (3D-CRT), which is a commonly used modality, the dose delivered to the tumor is often compromised to prevent adverse effects on normal tissues surrounding the tumor. Newer modalities such as intensity-modulated radiotherapy, stereotactic body radiotherapy, and particle radiotherapy can achieve higher dose conformality than 3D-CRT, leading to a higher dose delivery to the tumor. However, these high-precision radiotherapy modalities are less prevalent than 3D-CRT. Therefore, to maximize the efficacy of medical resources for radiotherapy as a whole, stratification of tumors based on photon sensitivity is crucial. This would lead to the preferential use of high-precision modalities for the treatment of relatively radioresistant tumors. To this end, the molecular mechanisms underlying cancer cell radioresistance need to be elucidated.

In a study published in January, 2020, in *Annals of Translational Medicine* (1), Zhou *et al.* performed fractionated X-ray irradiation of a breast cancer cell line, MDA-MB-231, and established a radioresistant subline as well as mouse xenografts. Comparison of gene expression profiles between the parental line and the radioresistant subline identified *CDKN1A* and *SOD2* as upregulated genes in the radioresistant cells. The authors also demonstrated that high CDKN1A/SOD2 expression could predict a poor prognosis for breast cancer patients. These data provide insight into the response of breast cancer to radiotherapy. In addition, the models developed are a useful tool for further investigation into this issue.

Zhou *et al.* (1) demonstrated that the establishment and analysis of isogenic radioresistant sublines is a powerful strategy to explore the mechanisms underlying cancer cell radioresistance, which has been the subject of research for decades (*Table 1*). Previous studies suggested resistance to apoptosis (2,8-10,14,21,23) and high DNA repair capacity (7,9,13,19,23) as candidate mechanisms. In addition, studies show an association between radioresistance and high cellular migration (8,23,24) and antioxidant (1,9,17) capacities. Regarding the signaling pathways involved, the MAPK (18,22,24), PI3K (18,20,22,24), and JAK-STAT (12,22) axes consistently show increased activity in radioresistant cells. Activation of molecules associated with multi-drug resistance (9,25) and epithelial-mesenchymal transition (11), alterations of cell cycle profiles (1,23) and immune systems (16), and other mechanisms (3-6,15) have also been reported as possible mechanisms associated with radioresistance. These findings provide an important biological basis for understanding the mechanisms underlying radioresistance. However, there is considerable variation among studies in the establishment of radioresistant cell lines in terms of histology of the cell line and irradiation protocols (i.e., total dose, single dose, and irradiation interval) (*Table 1*). Cross-validation of the results

Table 1 Summary of previous studies that established isogenic radioresistant human cancer cell lines

Cancer type	Cell line	TD (Gy)	SD (Gy)	IR protocol	Main findings	Ref.
Neuroblastoma	IMR32	30–60	2	Every 5–7 days	Apoptosis↓	(2)
H&N SCC	OECM1, KB, SAS	60	2	NA	Gp96↑	(3)
H&N SCC	Hep-2	76.44	6.37	Every 2 wks	Telomerase activity↑	(4)
H&N SCC	SCC15, SCC25	60	2	NA	NM23-H1↑	(5)
Eso Ad	TE-2, TE-9, TE-13, KYSE170	60	2	IR upon regrowth	Expression change in various genes	(6)
Eso Ad	OE33	50	2	IR upon regrowth	Post-IR γH2AX foci↓	(7)
Eso SCC	TE-1, Eca-109	30	2	NA	Apoptosis↓, migration↑	(8)
SCLC	HR69	37.5	0.75	5 days, every 1–3 wks	MRP1↑, MRP2↑, GSTπ↑, Topoisomerase IIα↑, bcl-2↓	(9)
NSCLC	H460	80	2	Over 20 wks	TP53I3↓	(10)
NSCLC	A549	60	2	Over 24 wks	EMT-associated proteins↑	(11)
NSCLC	A549, H358, H157	80	2	Biweekly	JAK2↑, STAT3↑, Bcl2↑, Bcl-XL↑	(12)
NSCLC Breast cancer	A549, SK-BR-3	12–16	3–4	Every 10–12 days	DNA-PKcs↑	(13)
Breast cancer	MDA-MB-231	50	2–10	Over 6 wks	CDKN1A↑, SOD2↑	(1)
Breast cancer	MDA-MB-231	40–64	2–4	Weekly or biweekly	Apoptosis↓	(14)
Breast cancer	MDA-MB-231, MCF-7, T47D	40	2	Over 40 wks	26S proteasome↓	(15)
Breast cancer	MCF-7	64	1–4	Various	IFN-stimulating genes↑	(16)
Breast cancer	MCF-7	60	2	Over 6 wks	PrxII↑	(17)
Breast cancer	MCF-7, ZR-751	57	2–7.5	Weekly	EGFR↑, AKT↑, ERK↑	(18)
HCC	HepG2	1,600	0.5	Every 12 h	Post-IR γH2AX foci↓	(19)
HCC, UCC	HepG2, HeLa	31	0.5	Every 12 h, 6 days/wk	Cyclin D1↑, AKT↑	(20)
Pancreatic cancer	PANC-1, AsPC-1	65–120	5	Weekly	Bcl-XL↑	(21)
Prostate cancer	LNCaP, PC3, Du145	10	2	Daily	EGFR↑, MAPK↑, PI3K↑, JAK-STAT↑	(22)
Prostate cancer	22rv1	60	2	NA	Apoptosis↓, S-phase cells↑, DNA repair↑, migration↑	(23)
Skin SCC	A431	85	0.75–3	Over 28 wks	Migration↑, AKT↑, ERK↑	(24)
T-cell leukemia	CEM	75	1.5	5 days, every 3 wks	MRP↑	(25)

H&N, head and neck; SCC, squamous cell carcinoma, Eso, esophageal; Ad, adenocarcinoma; SCLC, small cell lung carcinoma; NSCLC, non-small cell lung carcinoma; HCC, hepatocellular carcinoma; UCC, uterine cervical cancer; TD, total dose; SD, single dose; IR, irradiation; NA, not accessible; wk, week; Ref, reference. ↑, upregulation or increase; ↓, downregulation or decrease.

is necessary in the future to build robust evidence that can be translated to the clinic.

In summary, studies on isogenic radioresistant cell lines provide clues to understand the mechanisms underlying cancer cell radioresistance, which will facilitate personalization of radiotherapy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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