Identification of Critical Pathways Altered by Radiation Exposure and Drug Target Analysis

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Purpose/Objective(s):

1.) Identify candidate genes and pathways that are differentially expressed in human cells exposed to ionizing radiation.
2.) Identify drugs that significantly target these genes and pathways.

Methods and Materials

A rigorous, in-depth meta-analysis of public transcriptomics data from 5 hand-curated studies for human cells exposed to 2, 5, or 10 Gy of ionizing radiation from the Gene Expression Omnibus (GEO) online repository was performed. These data sets were categorized into two groups based on the type of cell line (normal or cancer), and each group was analyzed separately, comparing irradiated and non-irradiated samples. Gene expression and pathway analysis was performed on each data set. In addition, a drug target analysis was performed to identify drugs that significantly target the genes and pathways that were found to be differentially expressed.

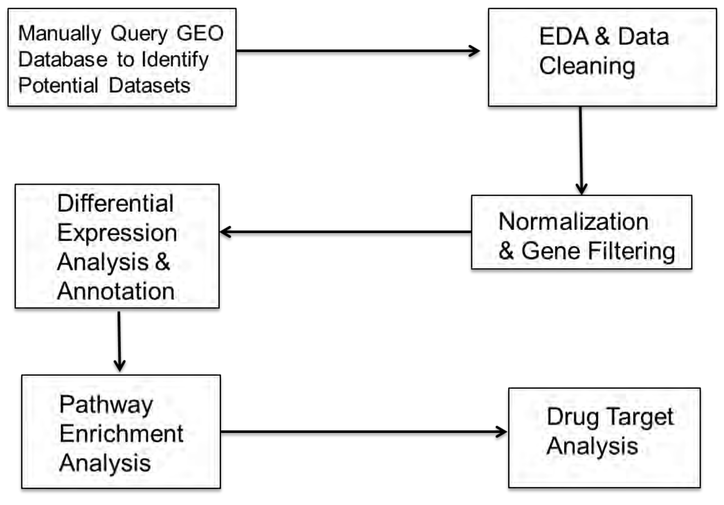

Fig. 1. Workflow diagram . The raw CEL files for each GEO dataset were obtained with EDA and data cleaning performed in R. Differential expression (DE) analysis followed by annotation was performed for each dataset. After the DE analysis a pathway enrichment analysis was performed for each dataset. After this individual pathway analysis, analysis across all datasets was done to identify significant pathways across all datasets. A drug target analysis was then performed on these pathways.

Results

The meta-analysis of these data sets found pathways that were significantly enriched for individual data sets. In addition, the following pathways were found to be significantly enriched across all cancer group data sets: Cell Cycle Mitotic, DNA Replication, Mitotic M-M/G1 phases, AKT phosphorylates targets in the cytosol, M Phase, and Mitotic Prometaphase. Finally, the following putative candidate drug targets for these pathways were identified: POLA1, POLA2, PLK1, CENPE, AURKB, CDKN1B, and RB1.

Drug Target	Pathways Targeted	Number of Significant Pathways Targeted
PLK1	DNA Replication	5/6
	Mitotic M-M/G1 phases	
	M-phase	
	Mitotic Prometaphase	
	Cell Cycle (Mitotic)	
CENPE	DNA Replication	5/6
	Mitotic M-M/G1 phases	
	M-phase	
	Mitotic Prometaphase	
	Cell Cycle (Mitotic)	
POLA1	DNA Replication	3/6
	Cell Cycle (Mitotic)	
	Mitotic M-M/G1 phases	
POLA2	DNA Replication	3/6
	Cell Cycle (Mitotic)	
	Mitotic M-M/G1 phases	
CDKN1B	DNA Replication	3/6
	Cell Cycle (Mitotic)	
	AKT Pathway	
AURKB	M Phase	2/6
	Mitotic Prometaphase	
RB1	Cell Cycle (Mitotic)	2/6
	DNA Replication	

Table 1. Identification of common drug targets shared in at least 2 of the 6 cancer pathway.

Drug Target	Drug	Effect
PLK1	BI-2536 intracellular	Inhibited
CENPE	GSK923295 intracellular	Inhibited
POLA1	Clofarabine intracellular	Inhibited
	Fludarabine cytoplasm	
POLA2	Dacarbazine intracellular	Inhibited
CDKN1B	ABT100 intracellular	Inhibited
AURKB	ENMD-2076 intracellular	Inhibited
	TAK-901 intracellular	
	AT9283 intracellular	
	Barasertib intracellular	
	Tozasertib intracellular	
	CYC116 intracellular	
	SNS314 intracellular	
RB1	Amsilarotene intracellular	Inhibited

Table 2. Drug targets and the associated drugs associated with the cancer pathway analysis. Interestingly, each of the drugs identified in our analysis inhibited their respective drug targets.

Conclusions

We have identified common cancer pathways associated with radiation response. We note that different pathway members were contributed by the individual data sets emphasizing the importance of meta-analysis. In addition, the identified drug targets and pathways could aid development of precision medicine approaches that could be utilized to predict patient outcome in radiation therapy. These results highlight the importance of secondary analysis of public data and lay the groundwork for future research in the development of pharmaceutical compounds and identification of associated pathways to predict patient response to radiation therapy.

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