Commentary

The kinome pathways in radioresistance breast cancer stem cells

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Radiotherapy (RT) has been considered as a key part in treatment of breast cancer patients, and is an obligatory for those undergo conservative surgery which could decrease the local recurrence rate. However, for those patients who still relapse, the exact mechanism behind radioresistance is still largely unrevealed. In this current article, Guo *et al.* and his colleges have been developed an approach for profiling the global kinome to give better understanding of the expression pattern of the human kinases in cells and tissues (1).

RT is the using of ionizing radiations for treatment many types of cancers. There are different sources of ionizing radiations, radioactive isotopes which used as local site or systematically. On the other hand, there is another type which used external beam RT that used high energy of X-ray, in this type the radiation doses are subdivided into different small dosage for several weeks and this is to allow the normal tissues to recover after sub-lethal radiation damage between treatments. Despite of the significantly reduction of the recurrence after a wide local excision (WLE) for localized ductal carcinoma in situ (DCIS) and to early invasive cancers and RT to axilla in node-positive invasive cancers, there are patients who have relapse with unknown reasons (2-5).

One of the newly reason for the radioresistance is the presence of tumor rescuing units also known as cancer stem like cells in enriched form which play an important role in resistance to multiple therapy including radiation, to support this concept many researches have been conducted on the cancer cells and they found that cancer stem cells are repopulated after radiation treatment and get more resistance to radiations than non-stem cells and this is the failure of the therapy (1,6,7). On the other hand, the exact molecular mechanism underlying the radioresistance is still unclear.

From this point, researchers have been found that the radioresistance is made by prosurvival genes induced by signaling pathways including protein kinases and transcription factors (8,9).

Identifying the most important kinases in radioresistance cancer cells will help us to narrow our focusing on specific target and development the appropriate therapies.

To unveil the most significant kinome pathways which are associated with radioresistance breast cancers, Guo *et al.* in this paper (1) used MCF7/C6 a radioresistance clone and MCF7/WT to quantify the entire kinome in both type of cells and he constructed a MRM library with selected peptides and more than 300 unique kinases and applying LC-MRM coupled with isotope-coded desthiobiotin-conjugated ATP-affinity probes to quantify the entire kinome in this cell line as they had done. In brief, he used probes with three components: enrichment moiety, linker and binding moiety for labeling cell lysates and followed by schedule LC-MRM which produces high specificity, sensitivity, reproducibility than other approaches. As a result, he was able to identify and quantify in current paper 120 kinases and he found one third of these kinases had up and down regulated in these two types of cell lines which suggest the direct role of ionizing radiation in altering signaling pathways as well as the resistance for therapy.

However, the other type of kinases which had not quantified, we need further experimental analysis with advanced approaches to overcome this issue which has been

suggested by Guo *et al.* in this paper.

Of the signal pathways that he quantified using LC-MRM coupled with isotope-coded desthiobiotin-conjugated ATP-affinity probes, MAPK, Toll-like receptor (TLR), and ErbB has been quantified. However, Guo *et al.* has found there are common pathways which are up and down regulated in the two cell lines which suggested by the author that have other cellular pathways. Marampon *et al.* (9) showed that activation of signaling kinase pathways (MERK/ERK) result in radioresistance and inhibit these kinases pathways will enhance radiosensitive. Other groups had provided an evidence that HER2 (Her2+/CD44+/CD24–/^{low}) mediate prosurvival signals and overexpressing BCSCs is the mediator for aggressive phenotype and radioresistance (10,11) in addition there are many studies suggest the correlation between ERBB inhibition and radiosensitive (12-14), which is inconsistence with Guo *et al.* data, he revealed that ERBB signal is downregulated or inhibited in MCF7/C6 which is radioresistance cell line compare to MCF7/Wt.

Guo *et al.* found CHK1, CDK1, CDK2 and DNA PKcs kinases are overexpressed and activated in radioresistance cell and he confirmed their expressions by western blot to provide a proof about the agreement with MRM based targeted approach. Also Ropolo *et al.* (15) has concluded that glioma stem cells CD133+ display an activation of CHK1 and CHK2 and basal activation of checkpoint proteins that might contribute to their radioresistance.

Elongation of cell cycle checkpoint proteins was also found in PC-3RR, DU145RR and LNCaPRR CaP cell lines (16,17).

In addition to that, many researchers have been used cell cycle check point inhibitor in different cell lines and all of them have found to increase radiosensitive (18,19) which make an important cell cycle in cancer stem cell in radioresistance.

In fact, Guo *et al.* provide a recent and advance approach in understanding the kinome signaling alteration in radioresistance cell with the ability to apply for further cell lines which are radiosensitive or radioresistance and to provide the affordable road for targeting these changed kinases which has been found the role in regulating cell cycle progression. For that better understanding the kinome pathways in radiosensitive and radioresistance cells will lead to more opportunities for intervention and prevention of resistance.

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Footnote

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