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JNCASR FINDS KEY PROTEIN CONFERRING RADIATION SENSITIVITY IN CANCER CELLS

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Mystery unravelled: This is the first time any study has shown that genome organisation is directly responsible for autophagy regulation in cells, say Sweta Sikder (left), Tapas Kundu and Ravi Manjithaya.

Researchers at the Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bengaluru, have unravelled the molecular mechanism by which autophagy pathway (a pathway recycles unnecessary or dysfunctional cell components) that gets enhanced leading to human cells becoming resistant to radiation. The immediate medical implication of the finding will be in treatment of certain cancer patients. The JNCASR research team led by Tapas K. Kundu from the Molecular Biology and Genetics Unit discovered that absence or downregulation of a particular protein — positive co-activator 4 (PC4) — is responsible for enhanced autophagy.

When a cell experiences stress, its DNA gets damaged. Cells with damaged DNA can either die or can activate the autophagy pathway and recycle the damaged cell components and survive. Lack of PC4 protein leads to irregular nuclear shape and defects in chromosome distribution in daughter cells. However, these changes do not lead to cell death but enhanced autophagy. The increased level of autophagy allow cells to withstand the stress caused by gamma radiation.

“What we found was that cells despite several defects upon PC4 downregulation not only did not die, they actually displayed increased proliferation. This was not expected,” says Sweta Sikder from JNCASR and first author of a paper published in *FEBS Journal.* “When the cells lacking PC4 protein were exposed to gamma radiation for 24 hours, there was greater induction of autophagy. This observation suggests that gamma radiation further triggers the induction of autophagy in the cells, thus allowing cells to survive the effects of radiation.”

Studies have shown that in some cancers, resistance to gamma radiation is achieved through enhanced autophagy. So, the team set to investigate if autophagy was indeed enhanced in the cells where the PC4 protein is absent or downregulated. “We did observe enhanced autophagy in the cells that had depleted levels of PC4 protein. We now know how the cells survived gamma radiation,” says Ravi Manjithaya from JNCASR and one of the authors of the paper.

To validate increased autophagy in cells that had depleted PC4, the researchers used inhibitors of autophagy pathway. “The inhibitors reduced autophagy and the cells that lacked PC4 protein started to die when exposed to gamma radiation,” says Prof. Kundu, who is currently the Director of CSIR-Central Drug Research Institute, Lucknow. The team also silenced the gene responsible for autophagy induction to revalidate the findings. Even in this case, the proliferation rate reduced drastically.

The final validation was by restoring (or rescuing) the protein expression in the PC4 knockdown cells. When the PC4 protein was restored to normal levels, autophagy reduced. The team thus confirmed that in cells with depleted PC4 protein the autophagy is enhanced making the cells not only to survive but to also proliferate at an increased rate and also become resistant to gamma radiation.

“This is the first time any study has shown that genome organisation is directly responsible for autophagy regulation in cells,” says Prof. Kundu.

“We found that in cancers cells that are relatively less malignant, the PC4 level is normal and autophagy is low. But in such cells, if the PC4 is depleted then the cells become highly aggressive,” explains Prof. Kundu. “And if you inhibit the autophagy in such cells, the proliferation comes down.”

Explaining the possible medical implication of their study, Prof. Kundu says that in some cancers the autophagy gets enhanced. And this is seen only in the cancer cells and not in normal cells of the cancer patients suggesting that future cancer therapies may involve supplementation with autophagy inhibitors.

“In the present study, we generated a stable PC4 knockdown cell line for screening autophagy inhibitors. We are in the process of licensing the cell line,” Prof. Kundu says.

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