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Researchers find how a common genetic mutation makes cancer radiation resistant

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(PhysOrg.com) -- Many cancerous tumors possess a genetic mutation that disables a tumor suppressor called PTEN. Now researchers at Washington University School of Medicine in St. Louis have shown why inactivation of PTEN allows tumors to resist radiation therapy.

The PTEN gene produces a protein found in almost all tissues in the body. This protein acts as a tumor suppressor by preventing cells from growing and dividing too rapidly. Mutations in PTEN are frequently found in prostate cancer and endometrial cancer, melanoma and certain aggressive brain tumors.

Tumors with PTEN mutations are often resistant to radiation therapy, and Tej K. Pandita, Ph.D., a researcher with the Siteman Cancer Center at Washington University School of Medicine and Barnes-Jewish Hospital, and his colleagues have been trying to find out why. That information could enable researchers to develop drugs that overcome that resistance and increase the effectiveness of radiation treatments.

In an article to be published in the journal Cell Cycle, they demonstrate that PTEN-deficient cells have defective checkpoints. As cells grow and divide, they pass through several phases. Checkpoints operate during each phase and assess whether a cell is healthy enough to continue growing and dividing. If not - for example, if there is damage to genetic material resulting from radiation treatments — signals from checkpoints should tell the cell to wait until repairs are made or should induce the cell to die.

The finding that checkpoints are affected in PTEN-deficient cells is contrary to some previous research, which had suggested instead that cells with PTEN mutations had defective DNA repair mechanisms. But Pandita showed that DNA repair is independent of PTEN function in tumor cells grown in the laboratory. That indicated that defective DNA repair is not the cause of the unstable genomes frequently seen in PTEN-deficient tumor cells and not the explanation for radiation resistance in these tumors.

"The defective checkpoints contribute to radioresistance," says Pandita, associate professor of radiation oncology and of genetics. "When a cell gets damaged by radiation, normally checkpoints will make it stop growing to repair the damage. If the checkpoints are working but the cell has a defective DNA repair system, the cell will be radiosensitive. But if the checkpoints don't operate, the cell can bypass DNA repair and continue to grow and divide. Then the cells are radioresistant."

The results indicate that to increase radiation sensitivity in tumors with PTEN mutations it will be necessary to develop drugs that correct for the faulty checkpoint processes, Pandita says. Work continues in the laboratory to further unravel the details of the checkpoint system and its role in radiation therapy resistance.

Citation:
Gupta A, Yang Q, Pandita RK, Hunt CR, Xiang T, Misri S, Zeng S, Pagan J. Jeffrey J, Puc J, Kumar R, Feng Z, Powell SN, Bhat A, Yaguchi T, Wadhwa R, Kaul SC, Parsons R, Khanna KK, Pandita TK. Cell cycle checkpoint defects contribute to genomic instability in PTEN deficient cells independent of DNA repair. Cell Cycle. 2009 July 15;14(8):1-13.

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