Researchers identify molecule that helps cancer stay alive, use antibody therapy against it

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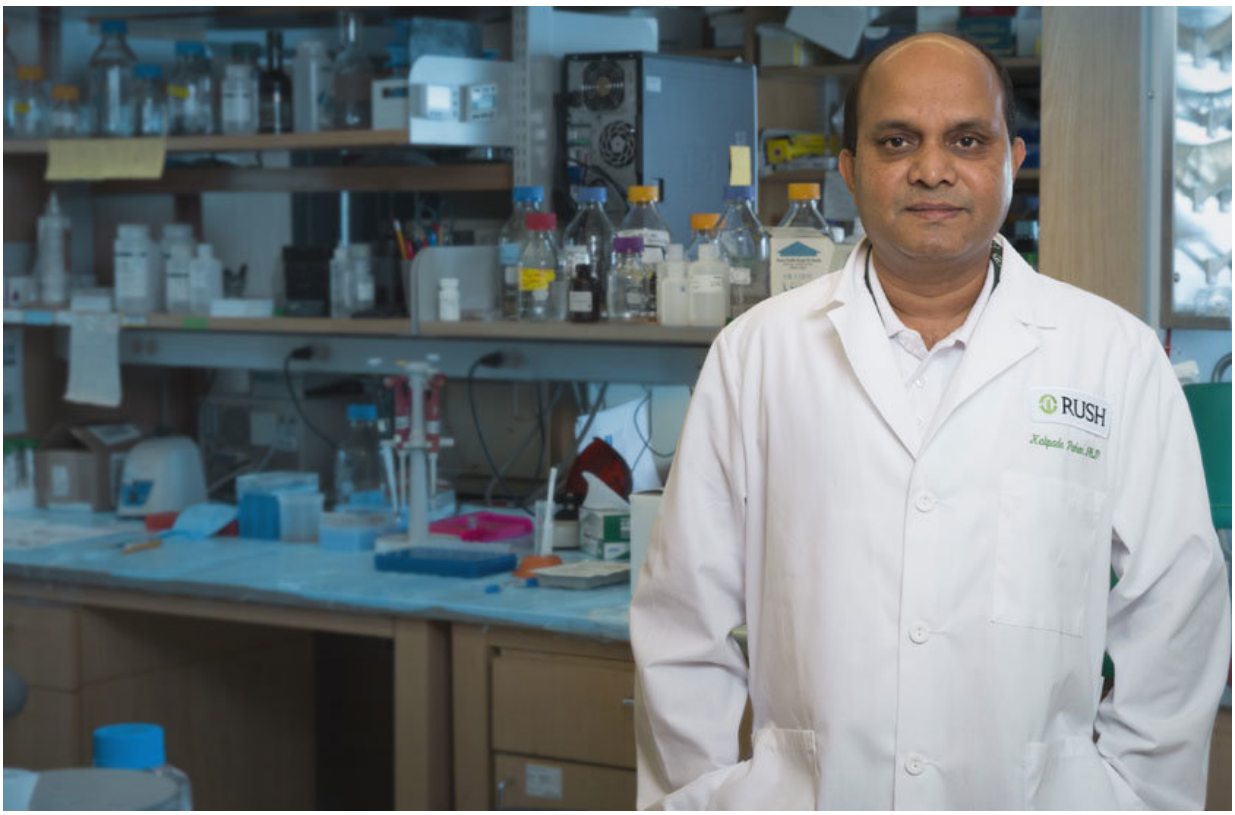

Kalipada Pahan, Ph.D. Credit: Rush University Medical Center

Certain cancer cells stave off their death with help from a particular molecule in a protein involved in the body's immune system response, a

research team at Rush University Medical Center has found. The researchers also have shown that neutralizing the molecule with a customized antibody therapy they developed can kill some types of cancer cells and shrink prostate tumors in mice.

The team's findings, published in the *Proceedings of the National Academy of Science* this week, offer hope for an effective new immunotherapy for some cancers within a few years. Kalipada Pahan, PhD, the Floyd A. Davis professor of neurology at Rush and lead investigator of the study, called the results "a promising avenue of treatment for this devastating group of diseases."

Zeroing in on how cancer avoids dying

One of the reasons cancer is difficult to stop is that cancer cells do not routinely die off like other cells in the human body, a normal process known as apoptosis. Using different types of mouse and human cancer cells, blood from human prostate cancer patients, and mice with prostate cancer tumors, the Rush team honed in on the mechanism cancer cells use to evade cell death.

The researchers suspected the involvement of a molecule known as p40, which is a type of monomer—single molecules that can bind with other molecules like it to form a larger molecule, called a polymer. The p40 monomer is a member of IL-12 group of proteins that facilitate communication between cells. IL-12 plays an important role in cell-driven immune responses.

The other three members of the IL-12 family, called IL-12, IL-23 and p40 homodimer, are pro-inflammatory and do not support the growth of cancer cells. "On the other hand, p40 monomer was considered as an inactive partner and therefore, we suspected an opposite role of this molecule in cancer cell survival," Pahan says.

Looking at different mouse and human cancer cell lines, the team found higher levels of p40 than of the other components of IL-12 in prostate, breast and liver cancer cells (levels of p40 and p40 2, a related element, were roughly the same in mouse lung cancer cells). They also found what the paper calls "significantly higher" p40 levels in the blood of prostate cancer patients, compared with healthy control subjects of about the same age.

"A clear association emerged between elevated levels of p40 and certain kinds of cancer," Pahan says.

Lowering p40 levels led to cancer cells dying and tumors shrinking

The researchers then deployed a targeted monoclonal antibody, or MAB—an individual type of antibody manufactured in a laboratory to find a particular protein—that would neutralize only p40. They used a MAB they originally raised in 2007 that worked in all three settings—mouse and human cell lines, human blood, and living mice with tumors.

The team saw that when p40 levels dropped, cancer cells died (though lung cancer cells were not affected), and prostate tumors treated with the MAB in the corroborating mouse model shrank significantly. Levels of interferon-gamma (IFN-gamma) protein, which is capable of killing tumor cells on its own, also rose sharply.

The study clearly implicated p40 as the cancer cells' helper in avoiding cell death. The fact that the customized MAB had no effect on mouse lung cancer cells points to the likely "specificity" of the findings, the paper notes.

Cancer cells appear to produce a surplus of p40, which diminish the amount and effect of IFN-gamma in the cell, the paper states. "Deploying a targeted MAB against p40 exposes cancer cells to the normal process of cell death, and in turn eventually leads to the shrinking of tumors," Pahan says.

Pahan is hopeful the p40 MAB used in his study will be ready for clinical trials within a few years. "Now we need to humanize this MAB and translate the finding to the clinic," Pahan said. "If these results are replicated in cancer patients, it would be an exciting development in cancer treatment."

More information: Madhuchhanda Kundu et al. Selective neutralization of IL-12 p40 monomer induces death in prostate cancer cells via IL-12–IFN-γ, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1705536114

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