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Researchers reveal how a protein common in cancers jumps anti-tumor mechanisms

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A Stony Brook University-led international team of infectious disease researchers have discovered how a cellular protein, called STAT3, which is overactive in a majority of human cancers, interferes with an antitumor mechanism in cells and therefore promotes the growth of cancer. The findings, to be published this week in the *Proceedings of the National Academy of Sciences* (*PNAS*) add to the understanding of cancer development and provide a basis for potentially new targeted methods to prevent and treat cancer.

In the paper, titled "STAT3 interrupts ATR-Chk1 signaling to allow oncovirus-mediated cell proliferation", lead author Sumita Bhaduri-McIntosh, MD, PhD, and colleagues made their discovery by using the Epstein-Barr virus (EBV) as a tool to probe fundamental cancer development-related questions. EBV, which causes infectious mononucleosis, is carried by approximately 95 percent of the world's population, is implicated in several types of lymphoma and other cancers, and was the first virus identified to cause cancer in humans.

"Our findings add to the short list of known mechanisms by which a key cellular anti-tumor barrier is breached by STAT3 prior to cancer development," said Dr. Bhaduri-McIntosh, an Assistant Professor in the Departments of Pediatrics and Molecular Genetics and Microbiology at Stony Brook University School of Medicine and pediatric infectious diseases specialist at Stony Brook Children's Hospital. "Because STAT3 interferes with this innate anti-tumor mechanism in cells, the opposite occurs when blood cells are infected in the lab with the cancer-causing

virus EBV, and the cells continue to divide – a necessary step in cancer development."

More specifically, Dr. Bhaduri-McIntosh explained that STAT3 damages a cancer-suppressing cellular activity called the DNA damage response (DDR). Normally this response pauses cell division allowing for repair of damaged DNA. This new study shows that EBV not only causes DNA damage when it infects and replicates in cells, but it also very quickly turns up a cellular protein, STAT3, which starts a chain reaction leading to a loss of this pause in cell division thereby promoting cell proliferation. This in combination with other pro-proliferative effects of the virus can lead to cancer.

Previous research has identified both STAT3 and another protein Chk1 as potential targets for cancer therapeutics. The authors write that their research results add fresh insight to anticancer drug development because they "provide a mechanistic link between the two, further lending support to these approaches."

Dr. Bhaduri-McIntosh emphasized that because STAT3 is involved in most cancers, their findings could potentially impact the prevention or treatment of several types of cancer – something that her lab is investigating. In addition to uncovering more about EBV-mediated cancers, the research is simultaneously helping the team to better understand EBV infections.

Paper coauthors include researchers from Stony Brook University, the National Institutes of Health, and research institutes in Germany and Australia.

More information: STAT3 interrupts ATR-Chk1 signaling to allow oncovirus-mediated cell proliferation, www.pnas.org/cgi/doi/10.1073/pnas.1400683111

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