Tumor suppressor protein plays key role in suppressing infections

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Researchers have found that a previously uncharacterized tumor-suppressor protein plays an important role in the functioning of the immune system. The study, which will be published in the June 22 issue of the *Journal of Biological Chemistry*, unites studies of immunology and cancer biology.

The gene encoding the protein Arl11 (part of the Ras GTPase family of proteins) is frequently turned off or mutated in cancer cells; conversely, when a functioning Arl11 gene is inserted into lung carcinoma cells, the cells die. These types of evidence have led scientists to categorize Arl11 as a tumor-suppressor protein. But it was almost completely unknown what Arl11's fundamental role was in healthy cells and healthy organisms.

"We really wanted to know how this protein works," said Amit Tuli, the investigator at the CSIR-Institute of Microbial Technology in India who oversaw the study.

Tuli's team began its investigation with the observation that the gene encoding Arl11 was turned on, or expressed, in immune cells called macrophages. Macrophages are white blood cells that destroy pathogens and other foreign substances by consuming them.

Performing experiments in cultured cells from mice and humans, the team found that Arl11 was crucial for macrophages to be able to detect and destroy pathogens. Arl11 was turned on in macrophages when they

encountered bacteria (or components from bacterial cell membranes). Macrophages in which Arl11 expression was silenced did not engulf bacteria the way they were supposed to or release signaling molecules called cytokines that activate other immune cells. When macrophages were infected with Salmonella, those lacking Arl11 were unable to stop the bacteria from proliferating.

"This is the first study which provides the first clue to the cellular function of Arl11," Tuli said. "Our study reveals that Arl11 expression actually increases when macrophages encounter a pathogen... this increasing expression of Arl11 is very much required to control the functions of macrophages."

Arl11 appears to act by initiating a signaling cascade called the ERK/MAP kinase pathway, which is known to regulate the division of cells and is therefore implicated in cancer. Depending on whether the pathway is turned on briefly or for extended lengths of time, cells either proliferate or die. This connection probably underlies Arl11's connection to cancer, which Tuli's team is now exploring. The discovery also opens up new directions of research.

"Understanding how the immune system functions is crucial not only for immunotherapy against cancer, but it can also be important (for conditions involving) inflammation, which actually damages the normal tissues," Tuli said. "I think it's really relevant in the future to study Arl11 expression in such conditions, for example, autoimmune diseases or obesity."

More information: Subhash B Arya et al, Arl11 regulates lipopolysacchride-stimulated macrophage activation by promoting MAPK signaling, *Journal of Biological Chemistry* (2018). DOI: 10.1074/jbc.RA117.000727