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Team discovers new mechanism allowing tumor cells to escape immune surve

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The immune system plays a pivotal role in targeting cancer cells for destruction. However, tumor cells are smart and have developed ways to avoid immune detection. A collaborative team of researchers at Moffitt Cancer Center recently discovered a novel mechanism that lung cancer cells use to block detection by a type of immune cell called a natural killer cell (NK cell).

NK cells find and destroy virally infected cells and also play an important role in detecting and killing tumor cells. However, tumors produce high amounts of a protein called Transforming Growth Factor-Beta (TGF-β) that suppresses the activity of NK cells.

A team of researchers led by Julie Y. Djeu, Ph.D., associate center director of education and training at Moffitt, discovered that TGF-β produced by tumor cells causes NK cells to make high levels of a molecule called microRNA-183 (miR-183). MicroRNAs are important regulators of gene expression. They bind to genetic components called RNA and target them for destruction. Scientists discovered in the early 2000s that deregulation of microRNAs can lead to the development of cancer.

Djeu's laboratory reported that miR-183 binds to the RNA for a protein called DAP12, resulting in significantly lower levels of DAP12 in NK cells. DAP12 plays a critical role in activating the NK cells' cytotoxic pathways; therefore, lower levels of DAP12 in NK cells results in a reduced ability to target tumor cells.

The researchers confirmed their observations by studying tissue from lung cancer tumors. They discovered that in normal tissue NK cells had moderate to high levels of DAP12; however, the NK cells within or surrounding the tumor had significantly reduced levels of DAP12.

Djeu explained that, "The world of microRNAs is just being explored, especially within cancer cells, to identify what they control. How microRNAs might intercept immune cells in cancer is unknown and we were able to provide insight into a critical means by which cancer cells exploit miR-183 to dampen immune cell function."

Lung cancer causes the most cancer-related deaths in the United States, and researchers are searching for new cellular targets to increase survival rates. Inhibiting TGF-β is not ideal because it is critical to normal cellular processes. However, the Moffitt scientists suggest that it may be possible to target the TGF-β-miR183-DAP12 pathway in patients with lung cancer to activate the immune system and kill cancer cells.

More information: This study appeared online in *Proceedings of the National Academy of Sciences* on February 28.

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