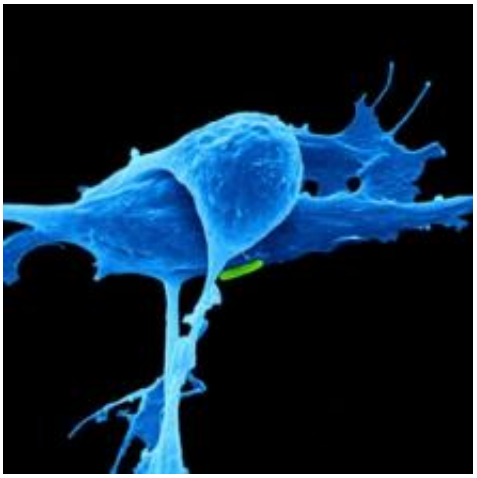
Cells identified that enhance tumor growth and suppress anti-cancer immune attack

December 18 2014, by Carrie Strehlau



A study led by St. Jude Children's Research Hospital scientists has identified the population of white blood cells that tumors use to enhance growth and suppress the disease-fighting immune system. The results, which appear in the December 18 edition of the scientific journal *Immunity*, mark a turning point in cancer immunology and provide the foundation for developing more effective immunotherapies.

For years, researchers have known that a diverse group of white blood cells called myeloid-derived suppressor cells (MDSC) are more abundant in cancer patients than in healthy individuals. The cells enhance cancer growth and suppress the specialized T cells that target and destroy tumor

cells. MDSCs have a common origin in the bone marrow, but leave to travel throughout the body and become immune cells with different functions. Blocking T cells is one of the main MDSC functions.

Until now, however, efforts to distinguish among the cell types and identify the population responsible for anti-tumor immune suppression have fallen short. The puzzle has hampered efforts to harness the immune system to fight disease.

Working in the laboratory and in mouse models of cancer, researchers on this study showed immune suppression associated with MDSCs is primarily the work of a type of white blood cells called monocytes. Monocytes give rise to macrophages that help clean up dead or damaged tissue, fight cancer and regulate the immune response.

"We have identified the monocytic cells as the important cell to target, not only in cancer but possibly for treatment of autoimmune disorders like rheumatoid arthritis or inflammatory bowel diseases where dampening the immune response could provide relief," said corresponding author Peter Murray, Ph.D., a member of the St. Jude departments of Infectious Diseases and Immunology. "We also identified growth factors and other molecules essential to the survival and function of these monocytic cells. Targeting these molecules could lead to more precise approaches for controlling the immune response at the tumor site.

"This study marks a significant step in efforts to understand, develop and optimize immunotherapies for treatment of cancer," he said.

Murray's interest in MDSCs dates to 2008 and coincided with research from other St. Jude investigators. Their studies provided insight into regulation of two forms of programmed cell-death pathways known as apoptosis and necroptosis. Cells use the pathways to get rid of damaged,

dangerous or unneeded cells.

From the laboratory of co-author Joseph Opferman, Ph.D., an associate member of the St. Jude Department of Cell and Molecular Biology, came evidence that switching off the MCL1 gene in bone marrow led to the death of granulocytes, but not monocytes, via apoptosis. Then work from Douglas Green, Ph.D., chair of the St. Jude Department of Immunology, highlighted the protein FLIP as a key regulator of both apoptosis and necroptosis. Selectively eliminating FLIP in mice resulted in an over-abundance of granulocytes and a reduction in monocytes and related cells.

In this study, researchers selectively eliminated MCL1 or FLIP to track how the loss of granulocytes or monocytes affected T cells in the laboratory and in mouse models of neuroblastoma and other cancers. The results showed that monocytic cells are primarily responsible for T cell suppression around tumors. Scientists are still determining the role of the granulocytes in tumors.

"We've known for decades that cancer has harnessed the immune system to keep pumping out large numbers of mature and immature myeloid cells from the bone marrow," Murray said. "Collaborating with the Opferman and Green laboratories gave us the tools we need to discriminate between the cell populations and identify monocytic cells as the important cells to target with immunotherapies."

The work also provided new details of how FLIP, MCL1 and the MCL1-like protein A1 work together to ensure survival of the monocytic population of MDSCs. For example, FLIP blocks programmed cell death via apoptosis and necrosis, but researchers showed that survival of monocytic cells required inhibition of just the apoptotic pathway. Investigators also identified the growth factor that regulates production of A1, which in the absence of MCL1 can block the

death of monocytes by blocking one of the cell death pathways.

Provided by St. Jude Children's Research Hospital