Researchers uncover novel gene that regulates leukemia development and progression

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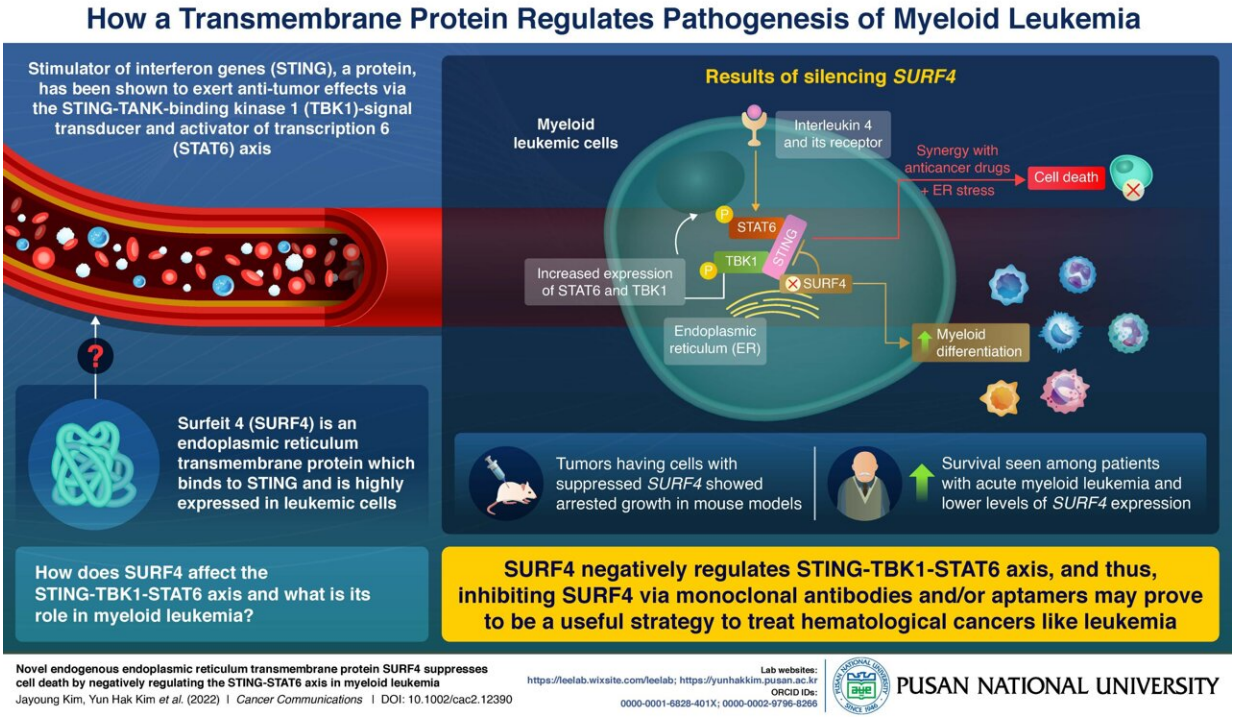

Researchers from Pusan National University find that suppressing the expression of SURF4 reduces pathologic processes that contribute to leukemia progression. Credit: Professor Dongjun Lee, Pusan National University

Leukemia, a type of blood cancer, affected around 2.3 million people around the world in 2015. Acute myeloid leukemia (AML)—a

particularly aggressive disease—generally starts in the bone marrow, when stem cells cannot differentiate into white blood cells, which reduces the number of healthy blood cells in the body, leading to a very weak immune system, among other problems.

Given the prevalence and implications of this disease, there has been a lot of research on the development and progression of leukemia. This has led to the discovery of a protein, stimulator of interferon genes (STING), which interacts with two other proteins—TANK-binding kinase 1 (TBK1) and signal transducer and activator of transcription 6 (STAT6)—to exert anti-cancer effects in blood cancers.

Researchers have also observed that a particular gene—surfeit 4 (SURF4)—is highly expressed in leukemic cells, and its protein, SURF4, binds to STING. However, we are still unclear about how SURF4 affects the STING-TBK1-STAT6 axis, and what role it plays in leukemia. So, a team of researchers from Pusan National University, Republic of Korea set out to understand this. They were led by Professors Dongjun Lee and Yun Hak Kim, who explain the rather humanitarian motive for their research.

"Children who suffer from AML relapses seldom survive. This makes studying the mechanisms of AML very important. Uncovering the effects of proteins like SURF4 may lead to new therapeutic strategies for AML, which hasn't happened in four decades," the team reports. The team ran a series of experiments, the findings of which are detailed in a letter to the editor, published on November 6, 2022 in *Cancer Communications*.

First, using multiple short hairpin RNA constructs to target SURF4, the team suppressed its expression in myeloid leukemic cells and compared these to control leukemic cells. The former showed increased cell differentiation, cell death, and accumulation of ROS. Tumors containing

these cells also displayed arrested growth when inoculated in mice.

The researchers additionally compared SURF4 expression levels among patients with AML and saw that patients with higher SURF4 expression levels had significantly shorter survival. It was also observed that SURF4 expression was much higher in patients suffering from AML compared to healthy people. These observations suggest that SURF4 regulates cell death and differentiation in AML. Interestingly, SURF4 silencing did not affect the cell cycle status.

"Our research shows the role played by SURF4 in myeloid leukemia. It negatively regulates the STING-TBK1-STAT6 axis and inhibits the death of cancer cells. We also found that depletion of SURF4 synergistically works with anti-cancer drugs to reduce myeloid leukemic cell burden," says Prof. Lee.

"Therefore," Prof. Kim concludes, "inhibiting SURF4 expression using monoclonal antibodies and/or aptamers may present a better alternative to current cancer therapies that wipe out the immune system and have multiple side effects. This is a promising option for the treatment of hematological cancers."

More information: Jayoung Kim et al, Novel endogenous endoplasmic reticulum transmembrane protein SURF4 suppresses cell death by negatively regulating the STING-STAT6 axis in myeloid leukemia, *Cancer Communications* (2022). DOI: 10.1002/cac2.12390

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