A drug that can stop tumors from growing

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Cancer doctors may soon have a new tool for treating melanoma and other types of cancer, thanks to work being done by researchers at the University of Colorado Cancer Center.

In a paper published in the journal *PNAS* last month, CU Cancer Center members Mayumi Fujita, MD, Ph.D., Angelo D'Alessandro, Ph.D., Morkos Henen, Ph.D., MS, Beat Vogeli, Ph.D., Eric Pietras, Ph.D., James DeGregori, Ph.D., Carlo Marchetti, Ph.D., and Charles Dinarello, MD, along with Isak Tengesdal, MS, a graduate student in the Division of Infectious Diseases at the University of Colorado School of Medicine, detail their work on NLRP3, an intracellular complex that has been found to participate in melanoma-mediated inflammation, leading to tumor growth and progression. By inhibiting NLRP3, the researchers found, they can reduce inflammation and the resultant tumor expansion.

Specifically, NLRP3 promotes inflammation by inducing the maturation and release of interleukin-1-beta, a cytokine that causes inflammation as part of the normal immune response to infection. In cancer, however, inflammation can cause tumors to grow and spread.

"NLRP3 is a member of a larger family that is involved in sensing danger signals," Marchetti says. "It is a receptor that surveils the intercellular compartment of a cell, looking for danger molecules or pathogens. When NLRP3 recognizes these signals, it leads to the activation of caspase-1, a protein involved in the processing and maturation of interleukin-1-beta into its biological active form, causing an intense inflammatory response. We found that in melanoma, this process is dysregulated, resulting in tumor growth."

The oral NLRP3 inhibitor used in their study (Dapansutrile) has already shown to be effective in clinical trials to treat gout and heart disease, and it is currently being tested in COVID-19 as well. The CU cancer researchers are now trying to find out if this NLRP3 inhibitor can be successfully used in melanoma patients who are resistant to checkpoint inhibitors.

"Checkpoint inhibitors increase the efficacy of the immune system to kill tumors, but sometimes tumors become resistant to this treatment," Marchetti says. "A big part of cancer research now is to find therapies that can be combined with checkpoint inhibitors to improve their efficacy."

With the hypothesis that an NLRP3 inhibitor is one of those therapies, CU Cancer Center researchers are studying the drug's effects on melanoma, as well as breast cancer and pancreatic cancer. In addition to improving the immune response, the NLRP3 inhibitor can also help reduce the side effects of checkpoint inhibitors. Marchetti says this research can make a big difference for melanoma patients who don't respond to checkpoint inhibitors alone.

"This was a very collaborative project that involved a lot of members of the university, and we are very excited about it," he says. This project is important because it further shows that NLRP3-mediated inflammation plays a critical role in the progression of melanoma, and it opens new strategies to improve patient care."

More information: Isak W. Tengesdal et al, Targeting tumor-derived NLRP3 reduces melanoma progression by limiting MDSCs expansion, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2000915118

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