Novel agent reactivates an immune call by LIF blockade

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SEOANE'S LAB AT VHIO FINDS A NEW TREATMENT

REACTIVATING THE ALARM SYSTEM AGAINST CANCER

Novel agent reactivates an immune call by LIF blockade. Credit: Joan Seoane/VHIO

Results from a study spearhead by researchers at the Vall d´Hebron Institute of Oncology (VHIO), show that the blockade of the multi-functional cytokine LIF induces tumor-infiltrating T cells to target and eliminate cancer. Reported today in *Nature Communications*, this research was led by corresponding and co-first author Joan Seoane, co-program director of preclinical and translational research at VHIO and ICREA research professor, and has now culminated in a Phase I clinical trial currently assessing the safety and efficacy of LIF inhibitors in patients across three sites: the Vall d'Hebron University Hospital (HUVH), Memorial Sloan Kettering Cancer Center (MSKCC—New York, USA), and the Princess Margaret Cancer Center (Toronto, Canada).

Developed by VHIO, novel agent MSC-1 inhibits LIF and has now been shown to have a dual mechanism of action. First, in tumors expressing high levels of LIF, this protein promotes the proliferation of cancer stem cells. LIF blockade eliminates these tumor-initiating stem cells, putting the brakes on metastatic cell spread and cancer recurrence. Additionally, elevated LIF expression disables the anti-tumor alarm system and stops the immune system from thwarting cancer's plans. Blocking LIF reactivates the alarm to call an anti-tumoral immune response.

Pioneer of previous LIF studies, Joan Seoane and his team were the first to establish a link between this multi-functional protein and cancer. They showed that LIF blockade eliminates cancer stem cells and prevents disease progression and recurrence. In the present paper, they reveal its

function in the immune system's anti-cancer response.

When foreign bodies or alterations in healthy cells are detected, a biological alarm alerts the immune system to act against them. "We have discovered that LIF silences this alarm, which enables cancer to dodge the immune system's innate response. It´s just like a bank robber deactivating an alarm to escape detection by the police," explains Joan Seoane.

More specifically, the researchers have shown that LIF inhibits the CXCL9 gene, which acts as a signal to lure immune system T cells. LIF blockade induces these immune system soldiers to invade, attack and destroy tumors. "We have observed that LIF inhibition in tumors expressing high levels of this protein reactivates the signal to T cells to target and destroy cancer," says Seoane.

This study also shows that combining LIF inhibition with anti-PD1 therapy powerful blows against cancer. According to Monica Pascual-García and Ester Bonfill, co-first authors and postdoctoral fellows of VHIO's Gene Expression and Cancer Group, once the T cells infiltrate the tumors, they are activated by anti-PD1 immunotherapy. In animal models, the pairing of both agents not only halted tumor growth but also, in some cases, made tumors disappear. In these cases, the immune memory is activated and the system remembers the tumor and prevents recurrence even when more tumor cells emerge.

After several years' research and validating LIF's promise as a therapeutic target in preclinical and experimental models, Joan founded Mosaic Biomedicals, a VHIO-born spin-off that launched to identify, develop, potentiate and translate novel therapies into benefits for patients at the bedside as quickly as possible. Mosaic has since brought the first-in-class MSC-1 LIF inhibitor closer to the clinic. This promising agent is currently being assessed in clinical trials for further

development.

Manipulating Mother Nature's love for LIF

LIF protects cancer in the same way a mother protects her embryo. Throughout evolution, LIF has emerged as a solver of a serious issue among mammals—the fact that one living being exists inside another. The embryo has antigens from the father, yet it is not rejected by the mother's immune system. LIF protects the embryo and induces the proliferation of embryonic stem cells, resulting in its safe development.

This present study exposes the parallels between embryogenesis and cancer. Joan's team has now shown that LIF assumes a crucial role in embryogenesis by protecting the embryo from the mother's immune system.

Cancer seizes on the molecular mechanism induced by LIF and uses it for its own gain. LIF is aberrantly expressed in some tumors when it shouldn't be, and shields tumors from the patient's own immune system in the same way that it protects the embryo. Similarly, instead of embryonic stem cells, when found in cancer, LIF promotes the proliferation of tumor stem cells.

This new therapeutic window is not open to all tumor types. It only shows promise for the treatment of tumors expressing high levels of LIF. The preselection of patients identified with high LIF levels detected in their tumors is critical in more precisely matching this novel therapy to those patients who would be most likely to benefit.

"Tumor types with typically high LIF levels include glioblastoma, pancreatic, ovarian, lung and prostate cancers. Importantly, we have also observed that these cancers are also more aggressive and indicative of a poor prognosis," says Seoane.

More information: Mónica Pascual-García et al. LIF regulates CXCL9 in tumor-associated macrophages and prevents CD8+ T cell tumor-infiltration impairing anti-PD1 therapy, *Nature Communications* (2019). DOI: 10.1038/s41467-019-10369-9