LLT1 as a regulator of the immune response and a dual-target immunotherapy approach in colorectal cancer directed at NK cells and T lymphocytes

In recent years, cancer treatment has undergone a revolution thanks to immunotherapy – a method that mobilizes the immune system to fight cancer cells. Many of these therapies are based on blocking so-called immune checkpoints, which are natural mechanisms that suppress the activity of lymphocytes. In cancer, these checkpoints are often exploited by tumor cells to escape destruction by the immune system. While research has primarily focused on checkpoints such as PD-1 or CTLA-4, there are other, less well-known mechanisms that may open new avenues for more effective treatments.

One such mechanism is the interaction between the CD161 receptor – present on both natural killer (NK) cells and T lymphocytes – and its ligand LLT1. When LLT1 binds to CD161, it sends an inhibitory signal that weakens the defensive functions of these immune cells. Our previous studies have shown that activation of CD161 limits the ability of NK cells to kill cancer cells. Despite its important role in immune regulation, the LLT1–CD161 axis remains poorly understood. Our most recent findings indicate that colorectal cancer cells produce more LLT1 than healthy cells. Furthermore, elevated LLT1 levels are also detected in the blood of patients, suggesting that this protein may be released from cancer cells and exert a suppressive effect on the immune system not only at the tumor site, but also systemically throughout the body. High levels of LLT1 are also associated with poorer prognosis – not only in colorectal cancer but in other cancers as well, as shown by analyses of publicly available genomic databases. Additionally, we suggest that LLT1 expression may be regulated by microRNAs – small molecules that modulate gene activity. We have discovered that the microRNA expression profile in colorectal cancer cells differs from that in healthy cells, which may explain the overproduction of LLT1 in tumors.

Importantly, unlike other checkpoint receptors such as PD-1, LAG-3, or NKG2A, CD161 is found on both NK and T cells, making it a particularly attractive therapeutic target – its blockade could restore the functions of both key immune cell types simultaneously. Currently, monoclonal antibody therapies targeting CD161 are under development, but they are expensive to produce and require intravenous administration. In our project, we aim to focus on an alternative: small-molecule inhibitors (SMIs), which can be taken orally, are cheaper to manufacture, and have the potential to act intracellularly as well.

The goals of our project are: 1) to determine the levels of LLT1 in the blood of colorectal cancer patients and assess their impact on lymphocyte function; 2) to investigate the mechanisms regulating LLT1 production in cancer cells, with particular focus on the role of microRNAs; and 3) to identify and test small-molecule compounds that can block the formation of the LLT1–CD161 complex in cell and animal models of colorectal cancer.

Achieving these objectives will help us better understand the role of the LLT1–CD161 axis in suppressing immune responses in cancer and may lead to the development of new, effective therapies. Moreover, the solutions developed may also be applicable in the treatment of other conditions associated with immune exhaustion, such as chronic viral infections.