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YOU ARE INVITED TO ATTEND THE DEFENSE OF THE DOCTORAL DISSERTATION

"Understanding the mTOR axis to enhance the therapeutic efficacy of CD147-CAR-NK cells in treating hepatocellular carcinoma"

by
Minh Ma

Molecular Biology, Genetics, and Cancer Program

B.S., 2018, Biochemistry and Business Administration and Management, University of Missouri - Columbia

Thesis Advisor: Dongfang Liu, Ph.D.
Associate Professor
Department of Pathology, Immunology, and Laboratory Medicine

Friday, February 14th, 2025
11:00 AM
Cancer Center, G1196

Join Zoom Presentation:

https://rutgers.zoom.us/my/mtm265?pwd=cpuDZh9Dt8t91pNaAj2ibRsar5MFVq.1

Meeting ID: 752 174 6977

Password: 460397

ABSTRACT

Hepatocellular carcinoma (HCC), one of the deadliest solid tumors, is characterized by the overexpression of glycosylated CD147 (also known as Basigin or EMMPRIN), which is linked to poor prognosis. Our findings reveal that CD147 plays a pivotal role in shaping the HCC tumor microenvironment (TME) by driving the production of various immunosuppressive mediators, including prostaglandin E2 (PGE2). We show that elevated PGE2 levels impair the effector functions of chimeric antigen receptor natural killer (CAR-NK) cells expressing the CD147 single-chain variable fragment (scFv), referred to as CD147-CAR-NK cells, by inhibiting the mammalian target of rapamycin (mTOR) pathway. We demonstrate that combining an mTOR agonist with CAR therapy significantly enhances the therapeutic efficacy of CD147-CAR-modified immune cells (including both CD147-CAR-T and CD147-CAR-NK cells), effectively slowing HCC progression across multiple HCC models utilizing human CD147 transgenic (hCD147tg) mice and humanized mice. Notably, this combination therapy outperforms CD147-CAR-NK cells engineered to secrete IL-15 autonomously. Furthermore, the administration of mTOR agonists alone does not accelerate HCC growth. Mechanistic insights reveal that mTOR agonists predominantly activate mTOR complex 2 (mTORC2) in immune cells, leading to elevated intracellular perforin levels, enhanced lytic granule polarization at the immunological synapse (an interface between immune and tumor cells), and improved signaling pathways for cellular adhesion in CD147-CAR-NK cells. These findings suggest that the therapeutic potential of combining mTOR agonists with CAR-modified immune cells can improve outcomes in treating solid tumors. Furthermore, our results provide a foundation for the future optimization of mTOR agonists to enhance the efficacy of CAR-based immunotherapies.