

Industrial & Physical Pharmacy Seminar

IPPH 69600

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“Immunometabolic Modulation of Engineered NK Cells for Immunotherapy of Solid Tumors”



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First Seminar**

Natural killer (NK) cells have efficient intrinsic recognition capabilities toward abnormal cells. This fact makes them particularly attractive as safe effector cells for cancer immunotherapy. Nutrient availability is critical for effector responses of NK cells, including glucose and glutamine. Glutamine and glutaminase, in particular, are essential factors that contribute to the proliferation of cancer as well as the expansion and anti-tumor activity of NK cells. Given that glutamine, however, is a crucial fuel for tumor cells, targeting glutamine metabolism is an attractive anti-cancer strategy that is being actively studied. However, it is important to consider the likely impact of such strategies on the anti-tumor immune response. Studies have shown that treating immune cells with glutaminase inhibitors reduces their proliferation and anti-tumor activity. There is a need to extend this research area and discover new strategies to genetically engineer NK cells to make them resilient to function normally even in the absence of glutamine as an energy source. Here, we are exploring how targeting glutamine can affect NK cell function and immunotherapy. We report the effect of glutaminase inhibitors on NK cell proliferation and antitumor activity. We have found that viability and anti-tumor cytotoxicity of NK cells is reduced when they are treated with inhibitors of glutamine metabolism. Specifically, inhibiting glutamine uptake has a significant detrimental effect on NK cell cytotoxicity and proliferation against glioblastoma (GBM) cancer targets, highlighting the need for this nutrient to sustain NK cell processes in the tumor microenvironment. We also performed transcriptional gene expression analysis to define how targeting glutamine metabolism alters the immune constituency of the tumor microenvironment. Immunotherapeutic responses also depend on how NK cells are sourced. We previously reported that chemically defined and serum- and feeder-free differentiation generates NK cells that are highly pure and predominantly CD56+/CD16+/CD3- and which express NK activation markers NKG2D, NKp30, NKp44, NKp46, and DNAM-1. We are now modulating the activity of engineered CAR-iPSC-NK cells by targeting glutamine metabolism, to generate metabolically resilient and functionally robust CAR-iPSC-NK cells. These results have the potential to lead to improved NK cell quality and activity and represent a significant step toward off-the-shelf immunotherapies for solid tumors.