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YOU ARE INVITED TO ATTEND THE

DEFENSE OF THE DOCTORAL

DISSERTATION

"An Exploration into Natural Killer Cells in Hepatocellular Carcinoma: L-Selectin (CD62L) and NK Function"
Identification of CD62L^{high} as a Marker for Dysfunctional NK cells in Hepatocellular Carcinoma

by

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M.D./Ph.D. Program

B.S. 2016, University of Pittsburgh, Pittsburgh, PA

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Friday, June 10th, 2022
2:00 P.M.
Zoom

https://rutgers.zoom.us/j/8485324440?pwd=SXBZSWhhSCs4dThaRGw2clZsWFAyQT09
Meeting ID: 848 532 4440
Password: 12345

Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver cancer with a rapidly increasing mortality rate and marginally effective treatment. While immunotherapy drugs such as atezolizumab (PD-L1 inhibitor) and bevacizumab (VEGF inhibitor) have become promising treatment strategies for HCC, one challenge for liver cancer immunotherapy is restoring dysfunctional immune cells in the liver tumor microenvironment (TME). While several studies largely focus on infiltrating cytolytic T lymphocytes, the potentials of other types of cytotoxic lymphocytes [e.g., natural killer (NK) cells] are much less explored. Here, we apply a novel NK expansion system to propagate primary NK cells from different areas of HCC tissues in combination with RNA-seq technologies to dissect the molecular basis of NK dysfunction in the HCC TME. Our results show that primary NK cells can be expanded from the tumors and surrounding liver tissue from explanted HCC livers. These expanded NK cells were investigated by RNA-Sequencing (RNA-Seq) and other approaches. RNA-Seq data show there are differentially expressed genes in NK cells derived from different areas of HCC liver tissue based on etiology which correlates with NK cell dysfunction observed *in vitro* and *ex vivo*. Specifically, we observed that tumor etiology may affect the distribution of an NK subset that bears the L-selectin (CD62L) receptor during *ex vivo* expansion. We also confirm that Hepatitis C virus-infected HCC cells increase the expansion of $CD62L^{+}$ NK cells, induce CD62L ectodomain shedding resulting in a concomitant decrease in membrane expression of NK activation molecules (such as NKp46, CD69, CD107a, and the activated form of LFA-1), and increase NK apoptosis. We also identified previously implicated genes such as *Lag3* and *IL10* in tumor-derived NK cells from NASH-HCC patients. We propose that $CD62L^{high}$ can be used a marker for dysfunctional NK cells in HCC, which provides a better understanding of the complex intercellular signaling that occurs between HCC cells and NK cells in the TME. In the future, we aim to target CD62L-related pathway genes (e.g., *SELL*, *SELPLG*, *KLF2*) to improve the cytolytic capacity of tumor-infiltrating NK cells and support the clinical development of NK cell therapy for solid malignancies.