Doctoral Dissertation Defense Announcement

Paytsar Topchyan

“CD4 T cell help and effector CD8 T cell differentiation in chronic viral infection and cancer”

Candidate for Doctor of Philosophy in Microbiology and Immunology
Graduate School of Biomedical Sciences
Medical College of Wisconsin

Committee in Charge:
Weiguo Cui, MD, PhD (Advisor and Chair)
Michael Dwinell, PhD
Nita Salzman MD, PhD
Subramaniam Malarkanan, PhD
Sridhar Rao, MD, PhD

Wednesday, March 16th, 2022 at 9:00 AM (CST)

Live Public Viewing: https://mcw-edu.zoom.us/j/97153348015?pwd=QkN2aylzMXJMctdoU3BnTXUvBEO2UT09
Zoom Meeting ID: 971 5334
8015 Passcode: 62811317
Graduate Studies:

Techniques in Molecular & Cell Biology
Cellular & Molecular Immunology
Ethics & Integrity in Science
Mucosal Immunology
Tumor Immunology
Immunological Tolerance
Research Ethics Discussion Series
Seminar
Reading and Research
Doctoral Dissertation
Abstract

During both chronic viral infection and cancer, CD8$^+$ T cells enter a dysfunctional state which prevents them from effectively targeting and killing virally infected cells and tumor cells, respectively. These antigen-experienced CD8$^+$ T cells consist of a heterogeneous population of memory-like progenitor, effector, and terminally exhausted cells that exhibit differing functional and self-renewal capacities. CD4$^+$ T cells play a critical role in the sustained effector CD8 T cell response against chronic viral infection and cancer. Recently studies have shown that interleukin (IL)-21-producing CD4$^+$ T cells help to generate effector CD8$^+$ T cells, which results in enhanced viral and tumor control. However, the molecular mechanisms by which CD4$^+$ helper T cells regulate the differentiation of effector CD8$^+$ T cells are not well understood. Additionally, it is not clear how and what type of CD4 T cell localization with progenitor CD8 T cells is responsible for effector differentiation.

First, using a translational melanoma model, we found that Basic Leucine Zipper ATF-Like Transcription Factor (BATF), a transcription factor downstream of IL-21 signaling, is critical to maintain CD8$^+$ T cell effector function within the tumor. We demonstrated that CD8$^+$ T cell-specific deletion of BATF resulted in impaired tumor control. Meanwhile, overexpressing BATF in CD8$^+$ T cells enhanced effector function and resulted in improved tumor control, bypassing the need for CD4$^+$ helper T cells. Transcriptomic analyses revealed that BATF-overexpressing CD8$^+$ T cells had increased expression of costimulatory receptors, effector molecules, and transcriptional regulators, which may contribute to their enhanced activation and effector function. This portion of our study revealed a previously unappreciated CD4$^+$ T cell-derived IL-21–BATF axis, which could be harnessed to develop novel immunotherapeutics.

We then utilized spatial transcriptomics (ST) and single-cell RNA sequencing (scRNA-seq) to study cellular heterogeneity and explore cellular localization and potential interaction between subsets within a chronic infection model. Our findings suggest that TFH cells are the IL-21 producing CD4 T cells that may localize with progenitor CD8 T cells within the splenic architecture. In addition, a lack of CD4 T cell help during chronic viral infection may result in disruption of the splenic architecture, which prevents the colocalization of TFH cells, thereby impairing progenitor to effector CD8 T cell differentiation. Taken together, our studies spatially and transcriptionally elucidate how IL-21 producing CD4$^+$ T cells help differentiate progenitor CD8 T cells towards effectors, providing prognostic and therapeutic insights against chronic infection and cancer.
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PERSONAL SUMMARY
Microbiology and Immunology PhD Candidate from the Medical Scientist Training Program at the Medical College of Wisconsin, completing dissertation research in Weiguo Cui’s laboratory, studying T cells in chronic viral infection and cancer. Research interests include T cell exhaustion, cancer immunology/immunotherapy and the tumor microenvironment. Medical interests include oncology and immunology, with the goal of becoming a physician scientist.

EDUCATION
Medical College of Wisconsin, 2016-Present  
Medical Scientist Training Program (MD/PhD), anticipated completion, May 2024

University of California, Los Angeles, School of Dentistry, 2015 - 2016  
Oral Biology, M.S.

University of California, Los Angeles, 2010 - 2014  
Major: Biology, B.S.  
Minor: Armenian Studies

RESEARCH EXPERIENCE
PhD Candidate, Graduate Researcher, Dr. Weiguo Cui’s Laboratory  
Blood Research Institute, Milwaukee, WI  
July 2018 to Present

Medical Student Researcher, Dr. Subramaniam Malarkannan’s Laboratory  
Blood Research Institute, Milwaukee, WI  
September 2016 to May 2017

Researcher, Dr. Anahid Jewett’s Lab  
UCLA School of Dentistry, Los Angeles, CA  
May 2012 to July 2016

FUNDING
Reprogramming tumor-reactive CD8 T cells by targeting the IL-21-BATF pathway to treat melanoma  
F30CA246920, NCI Fellowship Award  
January 2020-Present

LEADERSHIP EXPERIENCE
  • Co-Founder & Co-Director (2016-present) of Rise and Raise Premedical Mentorship Program
  • Co-President (2017-18) for American Medical Student’s Association (AMSA) at MCW

PUBLICATIONS


Chen Y, Shen J, Kasmani MY, **Topchyan P**, Cui W. Single-Cell Transcriptomics Reveals Core Regulatory Programs That Determine the Heterogeneity of Circulating and Tissue-Resident Memory CD8(+) T Cells. *Cells* 2021; 10(8).


Bui VT, Tseng HC, Kozlowska A, Maung PO, Kaur K, **Topchyan P**, et al. Augmented IFN-gamma and TNF-alpha Induced by Probiotic Bacteria in NK Cells Mediate Differentiation of Stem-Like Tumors Leading to Inhibition of Tumor Growth and Reduction in Inflammatory Cytokine Release; Regulation by IL-10. *Front Immunol* 2015; 6:576.

**POSTERS & TALKS**


MASTER’S THESIS


REFERENCES

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