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DEFENSE OF THE DOCTORAL
DISSERTATION

“Division of labor between intestinal tissue-resident memory T
cell subsets during infection”

by
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Monday, July 11th, 2022
11:30 A.M.

Join in person: Cancer Center, G1196 – Space limited

Join Zoom presentation

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Meeting ID: 972 3274 6227

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ABSTRACT

Tissue-resident memory T cells (Trms) are an important subset of lymphocytes that are lodged within non-lymphoid tissues and carry out diverse functions to control local pathogen replication and prevent dissemination to other sites. CD103 has been used to broadly define subsets of Trm cells within the intestine and other tissues, with CD103⁺ and CD103⁻ Trms having unique transcriptional profiles. In a previous study, we identified local proinflammatory cytokines IL-12 and Type 1 IFN as important regulators of CD103⁻ Trm differentiation and persistence. Therefore, we examined the role of STAT4, in the programming of CD103⁻ Trm cells during infection. We demonstrate expansion, trafficking, and localization to areas of inflammation by both wild-type and STAT4 deficient T cells during infection. However, STAT4 deficiency altered early Trm differentiation with a reduction in the CD103⁻ Trm subset. The reduction in CD103⁻ Trm numbers was not due to impaired proliferation or survival of STAT4-deficient cells within the tissue. We demonstrate that STAT4 prevents CD103⁺ Trm differentiation and the expression of TGF- β regulated genes. Single cell RNA-sequencing revealed altered distribution of Trm populations in the absence of STAT4, and discrete functional capabilities of Trm subsets. Furthermore, we have defined a previously unknown role for intestinal CD103⁻ Trm cells as the primary responders to secondary infection. CD103⁻ Trm cells were preferentially reactivated and proliferated in situ, with limited contribution from circulating cells. Surprisingly, CD103⁺ Trm cells responded poorly to secondary infection, underwent limited expansion within the tissue, and did not exit the tissue and contribute to systemic recall responses. There was also limited plasticity of CD103⁺ Trms upon reactivation. The transcriptional profile of CD103⁻ Trm cells demonstrated maintenance of a circulating T cell gene signature along with genes indicative of increased migratory and T cell activation potential. We demonstrate that CD103⁻ Trm cells displayed increased sensitivity to TCR stimulation, both in vitro and in vivo, when compared to their CD103⁺ counterparts. Our studies reveal CD103⁻ Trm cells maintain both tissue residency and superior recall function and suggest even small populations of CD103⁻ Trm cells have the potential to contribute significantly to localized protective immunity in response to reinfection. Collectively, we demonstrate an unprecedented division of labor between intestinal CD8⁺ Trm populations and the requirement of STAT4 in regulating the differentiation and maintenance of CD103⁻ Trms.