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"Type I interferon enhances TCR-dependent IFNγ production by γδ intraepithelial lymphocytes"

by
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Molecular Biology, Genetics, and Cancer Program

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Friday, March 22nd, 2024
11:00 AM
Cancer Center, G1196

Join Zoom Presentation:
https://rutgers.zoom.us/j/97782588542?pwd=VDZJRHBJeFAwa0V6VmJQRXE5Uk1JQT09

Meeting ID: 977 8258 8542
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ABSTRACT

The intestinal epithelium serves as a barrier that separates the host from commensal and pathogenic microbes within the intestinal lumen. Intraepithelial lymphocytes (IEL) expressing the γδ T cell receptor (TCR) survey the intestinal epithelium to limit the invasion of microbial pathogens. While TCRγδ signaling is not required for this surveillance behavior, the involvement of TCR signaling in γδ IEL-mediated host defense is largely unstudied. Type I interferon (IFN) is a family of pro-inflammatory cytokines that coordinates the antiviral immune response; yet how IFNα activates and contributes to γδ IEL antimicrobial effector function remains unclear. Our study examines how activation of TCR and IFNα signaling pathways regulate γδ IEL antimicrobial response, either independently or in a co-stimulatory manner. Using an *ex vivo* culture model, we find that type I IFN alone is unable to drive IFNγ production, yet low level TCR activation is sufficient to allow IFNα-mediated IFNγ production. Further investigation into the underlying molecular mechanisms of co-stimulation revealed that TCRγδ-mediated activation of NFAT and JNK is required for type I IFN to promote IFNγ expression in a STAT4-dependent manner. Transcriptomic profiling of freshly-isolated γδ IELs revealed that antimicrobial gene programs, including interferon-stimulated genes (ISG), were upregulated in response to type I IFN, which occurred independent of basal TCR signaling. In support of published studies demonstrating that γδ IELs exhibit reduced responsiveness to TCR agonist *in vivo*, we found that these sentinel lymphocytes produce limited IFNγ following *in vivo* administration of TCR agonist alone or in combination with IFNα. This may be due to reported defects in the TCRγδ signalosome, as activation of TCR downstream signaling pathways in the presence of type I IFN was able to induce γδ IEL IFNγ production in a STAT4-dependent manner. Taken together, these findings indicate that γδ IELs contribute to antimicrobial host immunity in response to type I IFN through rapid TCR-independent ISG expression, and under permissive conditions, may also promote TCR-dependent IFNγ production.