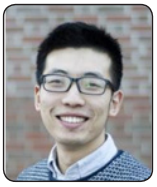
Journal of Microbiology and Immunology

Abstract



# IL-15 activates phosphodiesterase 4A and renders NK cells less susceptible to prostaglandin E2-mediated suppression

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## Abstract:

The persistence of NK-cells is limited by various immunosuppressive factors within solid tumor microenvironments including prostaglandin E2 (PGE2). We sought to investigate if activation by the type I cytokines IL-2 and IL-15 differ in their ability to render NK-cells resistant to PGE2-mediated suppression.

Cytokine-activated NK-cells were tested for their function and ability to infiltrate lung adenocarcinoma tumors in the presence of PGE2. Experimental finding was extended to the analysis of NK-cell infiltration in patients with lung adenocarcinoma and TCGA data analysis was performed to investigate differences in NK-cell gene expression in relation to Prostaglandin E Synthase (PTGES) expression. IL-15 enriched a subset of CD25+/CD54+ NK-cells compared with IL-2 (52.6% vs 10.4%), superior mTOR activity ($p<0.05$) and activity of the cAMP hydrolysing enzyme phosphodiesterase 4A (PDE4A). This distinct population of NK-cells shows improved ability to form cell clusters. When exposed to PGE2, The CD25+/CD54+ population maintained ability to kill K562 targets (6 time higher, $p<0.05$) compared with CD25-/CD54-, and to infiltrate lung adenocarcinoma 3D spheroids. In a cohort of patients (n=10) with lung adenocarcinoma, the frequency of NK-cells (CD56+/CD3-) expressing CD54 is significantly higher in the central tumor compared with the invasive margin and normal tissue ($p<0.01$). Furthermore, PTGES affects the prognostic value of NK-cells where a high-NK cell gene signature is associated with significantly improved overall survival in patients with high PTGES expression ($p<0.05$).


Our data uncover functional mechanisms used by IL-15 treated NK cells to persist in tumors and overcome the PGE2-mediate immune suppression, and strategies to selectively expand CD25+/CD54+ NK cells for adoptive cell therapy should be considered.

## Biography:

Chen Ziqing is currently associated with Karolinska Institute, Sweden

## Recent Publications:

1. Neo, Shi Yong, Ying Yang, Ran Ma, Xinsong Chen, Ziqing Chen, Nicholas P. Tobin, Emily Blake et al. "CD73 Immune Checkpoint Defines Regulatory NK-cells within the Tumor Microenvironment." The Journal of clinical investigation (2019



**Citation: Chen Ziqing; IL-15 activates phosphodiesterase 4A and renders NK cells less susceptible to prostaglandin E2-mediated suppression; Immunology Webinar 2020; August 30, 2020; Osaka, Japan**