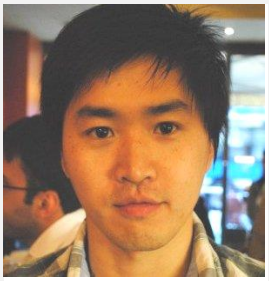
ImmunoTools *special* Award 2014



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Mechanistic and Functional Analysis of Interleukin-15 on Natural Killer Cells

Background

Natural killer (NK) cells are one of the major cell types in the innate immune system and contribute significantly in clearing invading pathogens and virally infected cells. Furthermore, NK cells have also demonstrated the ability to control and limit tumor initiation and development in a variety of mouse models and human studies. Recently, there is a growing interest in exploring the potential of using highly activated NK cells to treat patients with solid or haematological malignancies.

Different cytokines, including interleukin (IL)-2, 7, 12, 15, 18 and 21 have been shown to have stimulatory capacity of T or NK cells. IL-2 is one of the most frequently used cytokines for expanding T or NK cells for adoptive cell transfer. However, emerging data have emphasized the indispensible role of IL-15 during NK cell development and activation. Specifically, IL-15 knock-out mouse showed decreased numbers and dysfunctional NK cells. Emerging data also suggested using a combination of cytokines could result to cytolytic and proliferative benefits for human NK cells.

In the proposed study, we are focusing on understanding and analyzing the mechanistic and functional consequences, when NK cells are activated and expanded with IL-15, in comparison to IL-2 or other type I cytokines.

Our Hypothesis

We form the central hypothesis that IL-15 could facilitate activation and expansion of human NK cells. This is based on previously published data and our own observations. Firstly, IL-15 is of essential importance for NK cell development. Secondly, combination of IL-2 and IL-15 improved the yield and killing functions of expanded NK cells. Lastly, antigen presenting cells (APCs) utilize a unique *in trans* mechanism to activate NK cells by surface-binding IL-15.

Specific Aims

Specific Aim I: Evaluate the functions and signalling transduction of human NK cells when activated with IL-15.

A) Human NK cells will be isolated and activated with IL-15, and their killing functions and surface molecule expressions will be evaluated.
B) IL-15 activated NK cells will be tested for phosphorylations of various intracellular pathways.

Specific Aim II: Test the performance of IL-15-activated NK cells when exposed to immunosuppressive factors (PGE2, TGFb or IL-10), or co-cultured with tumor cells.

Specific Aim III: Analyze how IL-15 could modulate the interactions between NK cells and other immune cell types in comparison to other cytokines, ie dendritic cells, macrophages, Tregs or myeloid-derived suppressor cells (MDSCs).
A) Dendritic cells, macrophages or MDSCs will be generated from the established protocols and co-cultured with IL-15 or IL-2 activated NK cells.
B) If the NK cells were suppressed in A), specific pathways or factors will be analyzed to interpret the interplay between these cells.

Specific Aim IV: Incorporate IL-15 to our current NK cell expansion protocol and evaluate the functions and durability of the resulted NK cells.
A) We will replace IL-2 with IL-15 in our current NK cell expansion protocol and evaluate the yield, activation status and functions of expanded NK cells.
B) Further, other cytokines, such as IL7 or IL21 will also be tested, alone or in combination with each other, to select the most potent protocol for NK cell expansion.
C) Expanded NK cells from the best protocol will be tested in immunodeficient mouse model, to evaluate the ability to limit tumor growth *in vivo*.

Reagents provided by ImmunoTools could help our research in two ways:

ImmunoTools *special* AWARD for **Yumeng Mao** includes 25 reagents

FITC - conjugated anti-human CD14, CD15, CD16, CD25, CD27, CD56, HLA-DR, HLA-ABC,

PE - conjugated anti-human CD15, CD25, CD62L,

PerCP - conjugated anti-human CD45,

APC -conjugated anti-human CD14, CD16, CD56, CD69,

recombinant human cytokines: rh GM-CSF, IL-4, IL-6, IL-7, IL-10, IL-12, IL-15, IL-21, IL-22.

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