Striking a balance: the Goldilocks effect of CD8α expression on NK cells

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Commentary

NK cells are cytotoxic innate immune cells involved in antitumor immunity, and they provide a treatment option for patients with acute myeloid leukemia (AML). In this issue of the *JCI*, Cubitt et al. investigated the role of CD8α, a coreceptor present on approximately 40% of human NK cells. IL-15 stimulation of CD8α− NK cells induced CD8α expression via the RUNX3 transcription factor, driving formation of a unique induced CD8α (iCD8α+) population. iCD8α+ NK cells displayed higher proliferation, metabolic activity, and antitumor cytotoxic function compared with preexisting CD8α+ and CD8α− subsets. Therefore, CD8α expression can be used to define a potential dynamic spectrum of NK cell expansion and function. Because these cells exhibit enhanced tumor control, they may be used to improve in NK cell therapies for patients with AML.

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Regulation of NK cell activation
NK cells are specialized innate lymphoid cells that mediate cellular cytotoxicity without the need for antigen priming (1). Their functional responses are regulated by a balance between signals from activating and inhibitory receptors (2–5). The killer cell immunoglobulin-like receptor (KIR) family encodes both inhibitory and activating receptors (2–5). The effect of CD8α on NK cell function is context dependent. CD8α+ NK cells exhibit greater cytotoxic function against leukemia cells (8, 9). However, prior work by Fehniger and colleagues using cytokine-induced memory-like NK cells demonstrated that high levels of CD8α on donor memory-like NK cells correlated with treatment failure in patients with relapsed/refractory acute myeloid leukemia (AML) after adoptive transfer (10). In this issue of the JCI, Cubitt and colleagues then sought to study the potential role of CD8α in IL-15 signaling and proliferation (11). They found that CD8α+ NK cells had greater survival and proliferation in response to IL-15 in vitro. In line with these findings, CD8α+ NK cells expanded more compared with their CD8α− counterparts in xenogeneic adoptive transfer experiments with IL-15 dosing. The authors also asked whether IL-15 controls CD8α expression and found that IL-15 induced a subset of CD8α+CD56dim cells to upregulate CD8α, constituting an induced CD8α+CD56dim (iCD8α+) population (Figure 1). This phenomenon seemed more pronounced in CD56dim cells, though the authors mainly focused on CD56dim NK cells. Interestingly, only CD8α expression increased, not CD8αβ, suggesting that IL-15 specifically regulates CD8α. Further analysis of this population revealed that iCD8α+CD56dim cells exhibited more proliferation in response to IL-15 in vitro and in vivo compared with CD8α− cells.

Conflict of interest: FC is a consultant for Fate Therapeutics and receives research support.
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NK cells are cytotoxic innate immune cells involved in antitumor immunity, and they provide a treatment option for patients with acute myeloid leukemia (AML). In this issue of the JCI, Cubitt et al. investigated the role of CD8α, a coreceptor present on approximately 40% of human NK cells. IL-15 stimulation of CD8α+ NK cells induced CD8α expression via the RUNX3 transcription factor, driving formation of a unique induced CD8α (iCD8α+) population. iCD8α+ NK cells displayed higher proliferation, metabolic activity, and antitumor cytotoxic function compared with preexisting CD8α− and CD8α+ subsets. Therefore, CD8α expression can be used to define a potential dynamic spectrum of NK cell expansion and function. Because these cells exhibit enhanced tumor control, they may be used to improve in NK cell therapies for patients with AML.

CD8α and IL-15 signaling
NK cells are dependent on IL-15 for survival and proliferation. IL-15 also primes NK cells and enhances their cytotoxic function against cancer cells (12). Having evaluated the effect of CD8α on cytotoxicity, Cubitt and colleagues then sought to study the potential role of CD8α in IL-15 signaling and proliferation (11). They found that CD8α+ NK cells had greater survival and proliferation in response to IL-15 in vitro. In line with these findings, CD8α+ NK cells expanded more compared with their CD8α− counterparts in xenogeneic adoptive transfer experiments with IL-15 dosing. The authors also asked whether IL-15 controls CD8α expression and found that IL-15 induced a subset of CD8α+CD56dim cells to upregulate CD8α, constituting an induced CD8α+CD56dim (iCD8α+) population (Figure 1). This phenomenon seemed more pronounced in CD56dim cells, though the authors mainly focused on CD56dim NK cells. Interestingly, only CD8α expression increased, not CD8αβ, suggesting that IL-15 specifically regulates CD8α. Further analysis of this population revealed that iCD8α+CD56dim cells exhibited more proliferation in response to IL-15 in vitro and in vivo compared with CD8α− cells.

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βCD132 and IL-2/15R+ (termed persistent) and original CD8αα (also known as CD122), and common γ (also known as CD25), IL-2/15Rαβγ gated components of the IL-15 receptor: IL-15 signal and become sustained CD8αα NK cells. (C) In the third scenario, CD8αα NK cells with high expression of IL-15Rβ upregulate RUNX3 upon IL-15 stimulation and become induced CD8αα NK cells. These cells exhibit several beneficial properties, including enhanced tumor control.

Figure 1. Activation by IL-15 generates induced CD8αα NK cells. Cubitt et al. (11) present three scenarios for human NK cells responding to IL-15. (A) In the first scenario, CD8αα NK cells receive an IL-15 signal and become sustained CD8αα NK cells. (B) In the second scenario, CD8αα NK cells with low expression of IL-15Rβ are activated by IL-15 and fail to upregulate CD8αα, becoming persistent CD8αα NK cells. (C) In the third scenario, CD8αα NK cells with high expression of IL-15Rβ upregulate RUNX3 upon IL-15 stimulation and become induced CD8αα NK cells. These cells exhibit several beneficial properties, including enhanced tumor control.

(C) In the second scenario, CD8αα NK cells with low expression of IL-15Rβ are activated by IL-15 and fail to upregulate CD8αα, becoming persistent CD8αα NK cells. 

Therapeutic implications and future directions

The findings presented in Cubitt et al. provide insights into the dynamic reprogramming of NK cells and raise possibilities for advancing NK cell therapies (11). IL-15 priming increases NK cell cytolytic function (12). However, prolonged IL-15 stimulation results in NK cell exhaustion, characterized by decreased tumor control and diminished mitochondrial metabolic function (13). In this context, it will be useful to determine the trajectory of CD8α expression in relation to NK cell exhaus-
tion. Do NK cells begin as CD8α−, acquire CD8α upon IL-15 exposure to become the iCD8α+ as described by Cubitt et al., and then ultimately become exhausted, known in this context as “sustained” CD8α+? The enhanced metabolic activity of iCD8α+ NK cells compared with sustained CD8α+ NK cells suggests this possibility, though detailed studies are required. Furthermore, while Cubitt et al. (11) mainly focused on CD56dim NK cells, the magnitude of CD8α induction was greatest in CD8α+CD56bright cells. It will be helpful to further characterize iCD8α+CD56bright populations and their effect on tumor control, as IL-15–primed CD56bright NK cells can exhibit robust antitumor cytolytic activity (14).

The results of the study by Cubitt et al. (11) have important therapeutic implications. Perhaps CD8α+CD56dim or iCD8α+CD56dim are favorable for adoptive NK cell therapy in cancer, though additional tumor models need to be tested to prove preclinical efficacy. iCD8α+ NK cells displayed a potential memory-like phenotype, as they were able to kill tumor cells when rechallenged. How do iCD8α+ NK cells directly compare with CD8α− cytokine-induced memory-like NK cells (15, 16)? Finally, from a mechanistic perspective, further investigation into the role of CD8α is needed to clearly define its activating or inhibitory function on NK cell cytotoxicity. Furthermore, the role of CD8α in antibody-dependent cell-mediated cytotoxicity has not been explored in detail. Yet, for now, the main value of CD8α in NK cells may be the fact that they can define a highly responsive antitumor population that may be exploited to improve NK cell therapies for patients.

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