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The impact of vitamin A metabolites on natural killer cell functions

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Vitamin A, a fat-soluble micronutrient, plays an indispensable role in embryogenesis and development, and was also reported to regulate immune responses. In mammals, Vitamin A-enriched tissues, such as liver, gut or fat, comprise various immune cells. NK cells, circulating innate lymphocytes, are frequently recruited to tissues during inflammatory responses. NK cells contribute to tissue homeostasis by eliminating abnormal cells and modulating immune responses. However, the influence of vitamin A in regulating NK cell-mediated immune responses remains unclear.

Here, we investigated the effect of the vitamin A metabolite, all-*trans* retinoic acid (*at*RA) on murine NK cells. We showed that *at*RA induced transcriptional and phenotypic reprogramming of NK cells, depicted as altered expression of transcription factors, receptors, adhesion molecules and metabolizing-enzymes. In addition, *at*RA altered effector functions of NK cells, which led to a reduced production of inflammatory cytokines, such as interferon gamma (IFN-γ), in response to various stimuli. Our data revealed that *at*RA reduced ability of NK cells to induce maturation of dendritic cells (DCs) or to remove immature DCs, resulting in an increased number of immature antigen-presenting cells. NK cells treated with *at*RA supported FoxP3 expression and proliferation of regulatory T cells, promoting immune-regulatory microenvironment.

Furthermore, *at*RA altered mitochondrial fitness and metabolisms of NK cells by enhancing mitochondrial respiration. Peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear receptor, was upregulated by NK cells upon exposure to *at*RA. The conditional deletion of PPARγ in NK cells caused impaired glycolysis and mitochondrial respiration, and the malfunction of metabolism of PPARγ-deficient NK cells could be rescued by *at*RA.

In summary, we identify a novel role of vitamin A in shaping molecular and functional characteristics of NK cells. We demonstrate regulatory functions of vitamin A-exposed NK cells and their ability to regulate other immune cells, which might contribute to tolerogenic immune responses.