Glutaminase – HIF1α axis in regulation of NK cell cytototoxicity

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NK cells are one of the key immune cell subsets responsible for malignant or virus-infected cells surveillance and removal. During transition from steady state to activated state, NK cells switch their metabolism towards glycolysis in order to support high energetic and proteosynthetic demands linked with cytotoxic and effector functions. After target cell encounter, NK cells degranulate and expose the marker of degranulation lysosomal associated membrane protein (LAMP1 – CD107a) on cell surface. It was shown that glutamine metabolism does play a role in NK cell effector functions. Surprisingly, the exact immunometabolic regulation of NK cell cytotoxicity is still unclear. Our aim was to test if glutaminase regulate NK cell effector function. NK cells were expanded for 14 days with irradiated K562 cell line and with the addition of IL-2 and IL-15. The expanded NK cells were treated at day 14 with the inhibitor of glutaminase (BPTES) followed by cytotoxic, metabolic and gene expression analysis. Using inhibitor of glutaminase, we have shown that disruption of amino acid metabolism impaired killing ability of expanded NK cell through upregulation of HIF1α. Our data confirms that ability of NK cells to kill target cell is dependent on glycolysis upregulation and fatty acid/amino acid oxidation and that disruption of metabolic pathways impair their killing ability. Results thus define novel evidence about effector functions and metabolic regulation of activated NK cells and help to understand cytotoxic machinery and its link to NK cell metabolism.

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