Abstract

NK cells, a subset of innate lymphoid cells, play a crucial role in recognizing and eliminating virally infected or cancerous cells, making them a promising cell-based immunotherapy for AML patients. However, NK cell-based immunotherapies face unforeseen efficacy problems. Intracellular Ca^{2+} signalling was shown to play a crucial part in NK cell cytotoxicity. Maintaining the intricate balance of intracellular Ca^{2+} signalling is vital for NK cell-mediated target cell killing. In the complex microenvironment of the patient's body, NK cells encounter various stimuli, which can potentially disrupt the balance of intracellular Ca^{2+} signalling. Stimulation of PRRs was shown to affect intracellular Ca^{2+}, further influencing overall NK cell cytotoxicity. This study investigated the impact of TLR stimulation on Ca2+ signalling and NK cell functions. The effect of TLR stimulation was assessed using Ca^{2+} influx measurement, functional cytotoxicity, and degranulation assay, as well as gene expression analysis. Exposure to TLR ligands resulted in elevation of intracellular Ca^{2+} levels, accompanied by a reduction of cytotoxic activity at low effector-to-target ratios. An increasing trend in degranulation was observed. Furthermore, gene expression analysis unveiled upregulation of NFAT and Orai1 in NK cells stimulated with TLR ligands. These findings suggest that chemotherapy-induced overexpression of DAMP molecules, may disrupt the Ca^{2+} homeostasis of adoptively transferred NK cells, impairing their cytotoxic activity, and contributing to the suboptimal outcomes of NK cell immunotherapy for AML patients.

Key words: AML, NK cell, Ca^{2+}, TLR, cytotoxicity, chemotherapy, immunotherapy