Ginsenoside 20(R)-Rg3 enhances natural killer cell activity by increasing NK activating receptor expression through MAPK/ERK signaling pathway

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Traditional herbal medicine, ginseng is one of the most widely used herbal remedies for various diseases around the world. Ginsenoside Rg3 (G-Rg3), the main components of ginseng, has been known to have many pharmacological activities, such as anti-inflammatory, anti-tumor, anti-oxidant, anti-obesity and immunomodulatory activities. However, the effect of G-Rg3 on natural killer (NK) cells in human is not fully understood. In this study, we investigated the effect of G-Rg3 on NK cell function as well as NK cell differentiation and elucidated its mechanism. We found that G-Rg3 increased the cytotoxicity of NK cells concomitantly with increasing the expressions of NK activating receptors such as NKp44, NKp46 and NKp30. In addition, G-Rg3 increased mRNA expression of NK cytotytic molecules such as granzyme B and perforin, and expression of CD107a which is used as a marker of NK cell degranulation was also increased in NK cells treated with G-Rg3 compared to untreated control. We evaluated which MAPK signaling pathway is involved in the G-Rg3 mediated cytolytic activity, Rg3 treatment increased the phosphorylation levels of extracellular signal-regulated kinase (ERK) and inhibition of ERK abolished increased NK cell cytotoxicity by G-Rg3 treatment suggesting involvement of ERK pathway. On the other hand, G-Rg3 did not affect the differentiation rate of human cord blood (CB)-derived NK cells, but increased the functional maturation of differentiated NK cells and promoted their cytotoxicity. G-Rg3 has two optically active isomers, 20(R)-Rg3 and 20(S)-Rg3, and 20(R)-Rg3 was effective on NK cell activation through ERK signaling pathway, while 20(S)-Rg3 had no effect on NK cell activity.