J Blood Disord Transfus 2018,Volume:9
DOI: 10.4172/2155-9864-C3-038



# Calcimycin-induced IL-12 production enhances autophagy and restrict intracellular mycobacterial growth

**Shradha Mawatwal and Rohan Dhiman**
National Institute of Technology, India

Previously, we reported that calcimycin, calcium ionophore, exerts its anti-mycobacterial effect through (Purinergic Receptor P2X 7) P2RX7 dependent autophagy induction by regulating intracellular calcium-dependent ATP release. In the present study, we aim to check the role of immune regulators in regulation of calcimycin-induced autophagy against intracellular mycobacteria in THP-1 macrophages. We found significant mRNA expression of Interleukin-12 (IL-12) at 12 h in calcimycin treated macrophages than other pro-inflammatory cytokines like Tumour Necrosis Factor-αTNF-α and IL-1β through time kinetic experiment. Calcimycin treated macrophages also showed increased production of IL-12 with concomitant expression of IL-12 receptor (IL-12RB1 and IL-12RB2) at mRNA level. P2RX7 inhibitor 1-[N,O-bis(5-Isoquinolinesulfonyl)-N-methyl-L-tyrosyl]-4-phenylpiperazine (KN-62) and siRNA based P2RX7 inhibition abrogated release of IL-12 upon calcimycin treatment by affecting Jun N-terminal kinase (JNK) activation, IκBα phosphorylation, p65 translocation and inhibiting NF-κB activation. Further, inhibition of NF-κB activation by NF-κB activation inhibitor IV, inhibiting JNK activation by NSC33994 or prohibiting IL-12-IL-12R interaction by using anti-IL-12 neutralization antibody led to down-regulation of autophagy related markers like Beclin-1, autophagy-related gene (ATG) 7, ATG 3 and impairment of microtubule-associated protein 1A/1B-light chain 3-I (LC3-I) to LC3-II conversion. Blocking of autophagy led to significant growth of intracellular mycobacteria in calcimycin treated macrophages. Collectively, our study showed that calcimycin through P2RX7 binding modulates intracellular JNK-NF-κB signaling pathway which in turn regulates IL-12 mediated autophagic pathway in an autocrine fashion. This modulation result in IL-12 releases that inhibit intracellular survival of mycobacteria in THP-1 macrophages.

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