Attenuation of inflammatory arthritis through downregulating Dusp2 by salubrinal

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Salubrinal is a synthetic agent that inhibits the de-phosphorylation of eukaryotic translation initiation factor 2 alpha (eIF2α) and attenuates cellular stress to the endoplasmic reticulum. It has been also reported that it exerts beneficial effects on neuronal and skeletal diseases in various animal models. Recently, we have reported that salubrinal suppresses inflammatory responses in a mouse model of anti-collagen antibody-induced arthritis by inhibiting dual-specificity phosphatase 2 (Dusp2). Dusp2 is highly expressed in activated immune cells, and it dephosphorylates threonine and tyrosine residues on mitogen-activated protein kinases (MAPKs). A deletion of Dusp2 is shown to reduce inflammatory responses in the mouse model of rheumatoid arthritis. In this highlight, we describe salubrinal’s action as a Dusp2 inhibitor and review salubrinal’s beneficial effects on inflammatory responses.

Keywords: Salubrinal; inflammatory responses; Dusp2; CAIA

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Beneficial effects of salubrinal in animal models

Salubrinal is a synthetic chemical agent which is known to specifically prevent the de-phosphorylation of eIF2α by inhibiting protein phosphatase 1 (PP1) [1]. It is also known as a suppressor of cellular stress to the endoplasmic reticulum, and salubrinal’s therapeutic effects have been reported using animal models for various diseases. For instance, salubrinal is shown to attenuate β-amyloid-induced neuronal death as well as kainic acid-induced hippocampal cell death [2, 3]. Furthermore, it suppresses migratory behaviors of breast cancer cells through eIF2α-mediated downregulation of Rac1 GTPase [4].

In skeletal tissues such as bones and joints, salubrinal is reported to promote osteoblastogenesis through upregulating activating transcription factor 4 (ATF4) [5], and it suppresses osteoclastogenesis through downregulating AP1 (e.g., c-Fos and JunB), and nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1) [6]. In chondrocyte cells activated by IL1β and TNFα, salubrinal is also reported to downregulate expression and activity of MMP13 through suppression of p38 and NFκB signaling [7].

Salubrinal’s suppression of inflammatory cytokines

We first examined whether salubrinal is able to suppress the action of inflammatory cytokines in activated immune cells. Primary macrophages and RAW264.7 cells were activated by lipopolysaccharide (LPS), while Jurkat T lymphocytes and HMC-1.1 mast cells were activated by phorbol myristate acetate (PMA) and ionomycin. Salubrinal
Principal component analysis (PCA) of the gene we employed RAW264.7 cells as well as Jurkat cells. As two representative immune cells, salubrinal-driven suppression of inflammatory cytokines in predicted a set of genes that potentially lead to downregulation of Dusp2. Using a mouse model of inflammatory arthritis, we have also shown that salubrinal attenuates pathogenesis of inflammatory arthritis in the fore and hind paws. Collectively, the present study indicates that as an inhibitor of Dusp2, salubrinal may provide a novel therapeutic possibility for inflammatory arthritis such as rheumatoid arthritis.

**Conflict of interest**

All authors declare that they have no conflicts of interest.

**References**


