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Perspective

The Immunomodulatory and Anti-Inflammatory Effect of IRG1/Itaconate Axis in Chronic Prostatitis

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INTRODUCTION

The endogenous small molecules itaconate is a typical metabolite of metabolic reprogramming of macrophages. Itaconate is a derivative of the tricarboxylic acid cycle intermediate cis-aconitate, produced by the enzyme cis-aconitate-decarboxylase, which is encoded by IRG. Itaconate has recently emerged as an important bridge among metabolism, immune response, and inflammatory conditions. Studies have shown that itaconate exerts immunomodulatory and anti-inflammatory role via multiple mechanisms. Itaconate has an electrophilic α, β unsaturated carboxylic acid to form adducts with thiol sidechains. Itaconate and its derivatives can alkylate the cysteine residues of multiple proteins and affect their function, including KEAP, GAPDH, JAK, NLRP, STING, and SYK. Ubiquitination is another post-translational modification that regulates a large number of cellular processes. Recent studies showed that itaconate and its derivatives can alter protein expressions by ubiquitination modification9. Itaconate can interact with proteins involved in protein ubiquitination to stabilize CPTa. Itaconate can inhibit the ZNF598-dependent ubiquitination of Nrf2 to increase Nrf2 expression.

DESCRIPTION

IRG1/itaconate, as a protective metabolic pathway, has multiple protective biological characteristics such as antibacterial, anti-inflammatory, and antioxidant properties. Recent studies suggested that itaconate can attenuate various noninfectious inflammatory conditions that involve macrophages, such as periodontitis, pulmonary fibrosis, sepsis, spinal cord injury, abdominal aortic aneurysm, osteoarthritis. However, the effect of IRG1/itaconate in chronic prostatitis remain unknown.

A small molecule derived from the tricarboxylic acid cycle intermediate cis-aconitate, in modulating immune response and inflammation. Itaconate has been found to affect various proteins involved in cellular processes through alkylation and ubiquitination modifications. Moreover, recent studies have highlighted its protective effects in various inflammatory conditions mediated by macrophages, such as periodontitis, pulmonary fibrosis, sepsis, spinal cord injury, abdominal aortic aneurysm, and osteoarthritis. The specific role of IRG1/itaconate in chronic prostatitis, particularly Chronic Pelvic Pain Syndrome (CP/CPPS), remains unclear. CP/CPPS is characterized by inflammation and autoimmune imbalance, with leukocytes, especially T-lymphocytes and macrophages, playing a significant role. The expression of IRG1 was found to be elevated in the prostate of patients with moderate to severe inflammation, and treatment with 4-Octyl itaconate alleviated experimental autoimmune prostatitis by inhibiting NLRP3 inflammasome activation in a study.

Chronic prostatitis and Chronic Pelvic Pain Syndrome (CP/CPPS), classified as NIH category III Prostatitis, showed a detrimental effect on sperm and had detrimental effects on the quality of life16. However, the pathophysiology of CP/CPPS has not been elucidated. Recent studies showed that CP/CPPS is an inflammatory disease mediated by autoimmune imbalance. Diffuse distributions of leukocytes, predominantly dominated by T-lymphocytic and macrophages were found in prostate of CP/CPPS patients. Increased counts of leukocytes, mainly $CD4^+$ T lymphocytes and macrophages in semen was found in CP/CPPS patients20. These finding suggested the vital roles of $CD4^+$ T lymphocytes and macrophages in the development of EAP.

CONCLUSION

In recent study, we found high expressions of IRG1 in human prostate with moderate and severe inflammation, and treatment with 4-Octyl itaconate can alleviate experimental autoimmune prostatitis by inhibiting the NLRP3 inflammasome activation in vivo. However, there are still multiple aspects that need to be explored regarding the role of IRG1/itaconate in CP/CPPS patients. (1) The change in the expression of itaconate in expressed prostatic secretion and serum of CP/CPPS patients, and its diagnostic value for CP/CPPS patients remain unknown. (2) Is there a change in the expression of IRG1 and the production of itaconate in macrophages or T lymphocytes in CP/CPPS patients? (3) Further study is needed to investigate the

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effects and mechanisms of IRG1/itaconate on macrophage polarization and T cell differentiation in CP/CPPS patients.