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Anti-inflammatory Properties of Andrographolide Analogue AL-1 and its Regulatory Effects on STAT3, p38-MAPK, and NF-ϰB Pathways

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SUMMARY. Inflammation is closely linked to the pathogenesis of various human diseases. AL-1, a conjugate derived from andrographolide, has been previously shown to exhibit anti-inflammatory activities, but its underlying molecular mechanisms remain unelucidated. The present study revealed that in RAW264.7 macrophages stimulated by lipopolysaccharide (LPS), the marked upregulation of inflammatory mediators, including IL-1β, IL-6, IL-8, MCP-1, TNF-α, VCAM-1, and VEGF, was significantly reduced by AL-1 treatment. Additionally, the anti-inflammatory activity of AL-1 was mediated through the inhibition of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) induction, as well as the attenuation of their downstream metabolites, nitric oxide (NO) and prostaglandin E2 (PGE2). Mechanistic investigations further revealed that AL-1 attenuated the DNA-binding activity of nuclear factor-ϰB (NF-ϰB)/p65 and inhibited the phosphorylation of signal transducer and activator of transcription-3 (STAT3) as well as p38-mitogen-activated protein kinase (p38-MAPK). Collectively, these observations indicate that AL-1 exerts its anti-inflammatory properties through the downregulation of p38-MAPK, STAT3, and NF-ϰB signaling cascades, thereby highlighting its potential as a promising therapeutic candidate for the prophylaxis and treatment of inflammatory disorders.

RESUMEN. La inflamación está estrechamente relacionada con la patogénesis de diversas enfermedades humanas. Se ha demostrado previamente que AL-1, un conjugado derivado del andrografólido, exhibe actividades antiinflamatorias, pero sus mecanismos moleculares subyacentes siguen sin dilucidarse. El presente estudio reveló que, en macrófagos RAW264.7 estimulados con lipopolisacárido (LPS), la marcada sobreexpresión de mediadores inflamatorios, como IL-1β, IL-6, IL-8, MCP-1, TNF-α, VCAM-1 y VEGF, se redujo significativamente con el tratamiento con AL-1. Además, la actividad antiinflamatoria de AL-1 se vio mediada por la inhibición de la inducción de la óxido nítrico sintasa inducible (iNOS) y la ciclooxigenasa-2 (COX-2), así como por la atenuación de sus metabolitos posteriores, el óxido nítrico (NO) y la prostaglandina E2 (PGE2). Las investigaciones mecanicistas revelaron además que AL-1 atenuó la actividad de unión al ADN del factor nuclear-ϰB (NF-ϰB)/p65 e inhibió la fosforilación del transductor de señales y activador de la transcripción-3 (STAT3), así como de la proteína quinasa activada por mitógeno p38 (p38-MAPK). En conjunto, estas observaciones indican que AL-1 ejerce sus propiedades antiinflamatorias mediante la regulación negativa de las cascadas de señalización de p38-MAPK, STAT3 y NF-ϰB, lo que destaca su potencial como un candidato terapéutico prometedor para la profilaxis y el tratamiento de trastornos inflamatorios.

KEYWORDS: AL-1; anti-inflammation; NF-ϰB; p38 MAPK; STAT3

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