The geranyl acetophenone tHGA attenuates human bronchial smooth muscle proliferation via inhibition of AKT phosphorylation

ABSTRACT

Increased airway smooth muscle (ASM) mass is a prominent hallmark of airway remodeling in asthma. Inhaled corticosteroids and long-acting beta2-agonists remain the mainstay of asthma therapy, however are not curative and ineffective in attenuating airway remodeling. The geranyl acetophenone 2,4,6-trihydroxy-3-geranyl acetophenone (tHGA), an in-house synthetic non-steroidal compound, attenuates airway hyperresponsiveness and remodeling in murine models of asthma. The effect of tHGA upon human ASM proliferation, migration and survival in response to growth factors was assessed and its molecular target was determined. Following serum starvation and induction with growth factors, proliferation and migration of human bronchial smooth muscle cells (hBSMCs) treated with tHGA were significantly inhibited without any significant effects upon cell survival. tHGA caused arrest of hBSMC proliferation at the G1 phase of the cell cycle with downregulation of cell cycle proteins, cyclin D1 and diminished degradation of cyclin-dependent kinase inhibitor (CKI), p27Kip1. The inhibitory effect of tHGA was demonstrated to be related to its direct inhibition of AKT phosphorylation, as well as inhibition of JNK and STAT3 signal transduction. Our findings highlight the anti-remodeling potential of this drug lead in chronic airway disease.