Regulation of Keratinocyte differentiation by sphingosine 1-phosphate

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Abstract

Sphingosine 1-phosphate (S1P) lyase is an intracellular enzyme that catalyzes the irreversible degradation of S1P and has been suggested as a therapeutic target for the treatment of psoriasis vulgaris. Here, we demonstrated that S1P lyase inhibition reduced cell proliferation and induced differentiation of keratinocytes. To identify the physiological functions, we inhibited S1P lyase by S1P lyase-specific inhibitor (SLI) or SGPL1-specifc small interference RNA (siSGPL1). Treatment with SLI caused G1 arrest by upregulation of p21, p27 and induced keratin 1, an early differentiation marker, in human epidermal keratinocytes, neonatal (HEKn). Similar to the pharmacological effects, genetic suppression by siSGPL1 arrested cell cycle at G1 phase and differentiation was activated. In addition, suppression by siSGPL1 upregulated keratin 1 as well as late differentiation markers including involucrin and loricrin. When hyperproliferation of HEKn cells was induced by interleukin-17 (IL-17) and interleukin-22 (IL-22), pharmacological inhibition of S1P lyase by SLI decreased proliferation and activated differentiation of HEKn cells simultaneously. In addition, SLI ameliorated imiquimod-induced psoriatic symptoms including erythema, scaling, and epidermal thickness in vivo. Collectively, these findings suggest that S1P lyase is a modulating factor for proliferation and differentiation, and could be a therapeutic target for psoriasis in human keratinocytes.

Keywords

sphingosine 1-phosphate, keratinocytes, differentiation, sphingosine 1-phosphate lyase, cell cycle, psoriasis.