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Partial Proteasome Inhibitors Induce Hair Follicle Growth by Stabilizing β-catenin

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Abstract

The activation of tissue stem cells from their quiescent state represents the initial step in the complex process of organ regeneration and tissue repair. While the identity and location of tissue stem cells are becoming known, how key regulators control the balance of activation and quiescence remains mysterious. The vertebrate hair is an ideal model system where hair cycling between growth and resting phases is precisely regulated by morphogen signaling pathways, but how these events are coordinated to promote orderly signaling in a spatial and temporal manner remains unclear. Here, we show that hair cycle timing depends on regulated stability of signaling substrates by the ubiquitin-proteasome system. Topical application of partial proteasomal inhibitors (PaPIs) inhibits epidermal and dermal proteasome activity throughout the hair cycle. PaPIs prevent the destruction of the key anagen signal β-catenin, resulting in more rapid hair growth and dramati cally shortened telogen. We show that PaPIs induce excess β-catenin, act similarly to the GSK3β antagonist LiCl, and antagonize Dickopf-related protein-mediated inhibition of anagen. PaPIs thus represent a novel class of hair growth agents that act through transiently modifying the balance of stem cell activation and quiescence pathways.

Keywords

Hair growth; Stem cells; Wnt signaling; Proteasome; Tissue regeneration

Introduction

Despite extensive interest in the identification of stem cells and their location within vertebrate tissues, a key remaining issue is the nature of signals that regulate the activation

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