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Inhibition of β-catenin Signaling by Nongenomic Action of Orphan Nuclear Receptor Nur77

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Abstract

Dysregulation of β-catenin turnover due to mutations of its regulatory proteins including APC and p53 is implicated in the pathogenesis of cancer. Thus, intensive effort is being made to search for alternative approaches to reduce abnormally activated β-catenin in cancer cells. Nur77, an orphan member of the nuclear receptor superfamily, plays a role in the growth and apoptosis of cancer cells. Here, we reported that Nur77 could inhibit transcriptional activity of β-catenin by inducing β-catenin degradation via proteasomal degradation pathway that is GSK3β and Siah-1 independent. Nur77 induction of β-catenin degradation required both the N-terminal region of Nur77, which was involved in Nur77 ubiquitination, and the C-terminal region, which was responsible for β-catenin binding. Nur77/ΔDBD, a Nur77 mutant lacking its DNA-binding domain, resided in the cytoplasm, interacted with β-catenin, and induced β-catenin degradation, demonstrating that Nur77-mediated β-catenin degradation was independent of its DNA-binding and transactivation and might occur in the cytoplasm. In addition, we reported our identification of two digitalis-like compounds (DLCs), H-9 and ATE-i2-b4, which potently induced Nur77 expression and β-catenin degradation in SW620 colon cancer cells expressing mutant APC protein in vitro and in animals. DLC-induced Nur77 protein was mainly found in the cytoplasm, and inhibition of Nur77 nuclear export by the CRM1-dependent nuclear export inhibitor leptomycin B or Jun N-terminal kinase inhibitor prevented the effect of DLC on inducing β-catenin degradation. Together, our results demonstrate that β-catenin can be degraded by cytoplasmic Nur77 through their interaction and identify H-9 and ATE-i2-b4 as potent activators of the Nur77-mediated pathway for β-catenin degradation.

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Conflict of interest The authors declare no conflict of interest.

Keywords

Nur77; β-catenin; Nongenomic; Cardenolide; Cancer