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# SIRT1 Promotes Differentiation of Normal Human Keratinocytes

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## Abstract

**Sir2 regulates lifespan in model organisms, which has stimulated interest in understanding human Sir2 homolog functions. The human Sir2 gene family comprises seven members (SIRT1–SIRT7). SIRT1, the human ortholog of the yeast Sir2 by closest sequence similarity, is a nicotinamide adenine dinucleotide ($NAD^+$)-dependent deacetylase with enzymatic properties indistinguishable from the yeast enzyme. We studied the involvement of SIRT1 in normal human keratinocyte physiology by a transcriptional microarray analysis of primary keratinocytes either overexpressing or underexpressing SIRT1. Using a systems biology analytical approach, we predicted that SIRT1 induces keratinocyte differentiation through a pathway integral to or overlapping with that of calcium-induced differentiation. We experimentally assayed this prediction and found that the SIRT1 inhibitor nicotinamide inhibited expression of keratinocyte differentiation markers, whereas a SIRT1 activator, resveratrol, enhanced expression of keratinocyte differentiation markers. Similar results were obtained in keratinocytes manipulated to overexpress or underexpress SIRT1, and modulating SIRT1 significantly affected keratinocyte proliferation rates. We conclude that SIRT1 functions in normal human keratinocytes to inhibit proliferation and to promote differentiation.**

**Abbreviations:**

$Ca^{2+}$, calcium; CEBPA, CCAAT/enhancer-binding protein alpha; NAA, nicotinamide; NHEK, normal human primary keratinocytes; PD, population doubling; PPARG, peroxisome proliferator-activated receptor gamma; RNAi, RNA interference; SIRT1, Silent mating type information regulation 2 homolog 1

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