Abstract

Skin cancer incidence is quickly escalating worldwide, and chemical exposure likely contributes to this consequence. Most "classic" chemical carcinogens bind to and activate the aryl hydrocarbon receptor (AhR), and this receptor facilitates carcinogen clearance by regulating the genes involved in the hydroxylation and hydrophilic conjugation of carcinogens. Previous evidence has demonstrated that the nuclear receptor peroxisome proliferator-activated receptor-β/δ (PPARβ/δ) attenuates skin tumorigenesis, and it was hypothesized that PPARβ/δ alters carcinogen metabolism by modulating AhR-dependent signaling. Surprisingly, the absence of PPARβ/δ modulates AhR-dependent basal and inducible expression of metabolism enzymes in primary mouse keratinocytes. Subsequent analyses have demonstrated that the AhR signaling pathway is functional in PPARβ/δ-null keratinocytes; however, AhR binding to target gene promoters is reduced in PPARβ/δ-null keratinocytes. The fact that basal and inducible expression is altered in the absence of PPARβ/δ suggests that epigenetic regulation may be occurring. Methylation of DNA at cytosine-phosphate-guanine (CpG) islands or histones commonly mediates chromatin structure, and computational analyses have identified putative CpG islands within AhR target gene promoters. This proposal aims to investigate DNA and histone methylation at AhR target gene promoters using bisulfite sequencing and chromatin immunoprecipitation to determine if epigenetic methylation patterns explain the observed PPARβ/δ-dependent modulation of AhR-dependent signaling.