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# THE PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR $\gamma$ ANTAGONIST, GW9662, ALTERS UVB-INDUCED INFLAMMATORY RESPONSES, APOPTOSIS, AND DELAYED HYPERPROLIFERATION

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## Abstract:

It has recently been shown that the gamma subtype of the peroxisome proliferator-activated receptor (PPAR $\gamma$ ) is a target of ultraviolet B (290-320 nm; UVB) irradiation, and that PPAR $\gamma$  activation is necessary for full UVB-induced cyclooxygenase-2 (COX-2) induction. However, the biological significance of PPAR $\gamma$  activation in cutaneous photobiology is unknown. Acute UVB irradiation results in a characteristic series of events in the epidermis which includes: an initial edema response and subsequent inflammation, COX-2 induction, apoptosis, and a delayed hyperproliferative response. Therefore, the regulatory role of PPAR $\gamma$  activation was examined in this acute photoresponse using a topical application of the potent, irreversible PPAR $\gamma$  antagonist, GW9962. GW9662 was applied to the epidermis of SKH1 hairless albino mice at increasing doses (0.01-1.0mM) prior to UVB irradiation. The photobiological responses were examined through RT-PCR, skin thickness measurements, and immunohistochemistry, at 24 and 72 hours after UVB-irradiation. At the highest

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dose, GW9622 significantly inhibited UVB-induced inflammation, as measured by COX-2 induction at both 24 and 72 hrs. Inflammation assessed by skin thickness measurements indicated that lower doses mildly increased inflammation at 72 hrs, but suppressed inflammation at the highest dose. In contrast, GW9662 treatment dose dependently augmented UVB-induced apoptosis at 24 hours, while affecting the delayed hyperproliferative response at 72 hours in an inverse dose-response manner. The results from this study suggest that PPAR $\gamma$  is a key regulator of these photobiological responses. Because these responses are well known to be involved in tumor development and progression, this study also suggests a potential role for PPAR $\gamma$  in UVB-induced skin cancers.

## Description:

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