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12-Hydroxyeicosatetraenoic acid levels are increased in actinic keratoses and squamous cell carcinoma.

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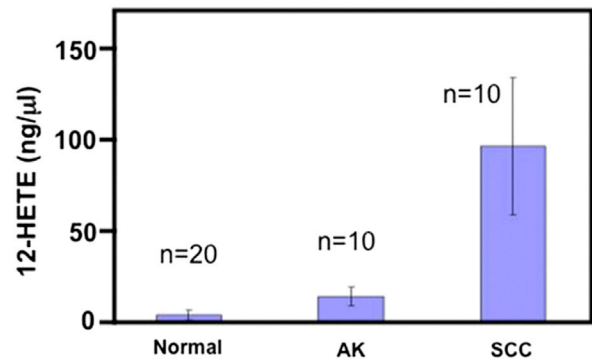
## LETTER

## RESEARCH LETTER

### 12-Hydroxyeicosatetraenoic acid levels are increased in actinic keratoses and squamous cell carcinoma

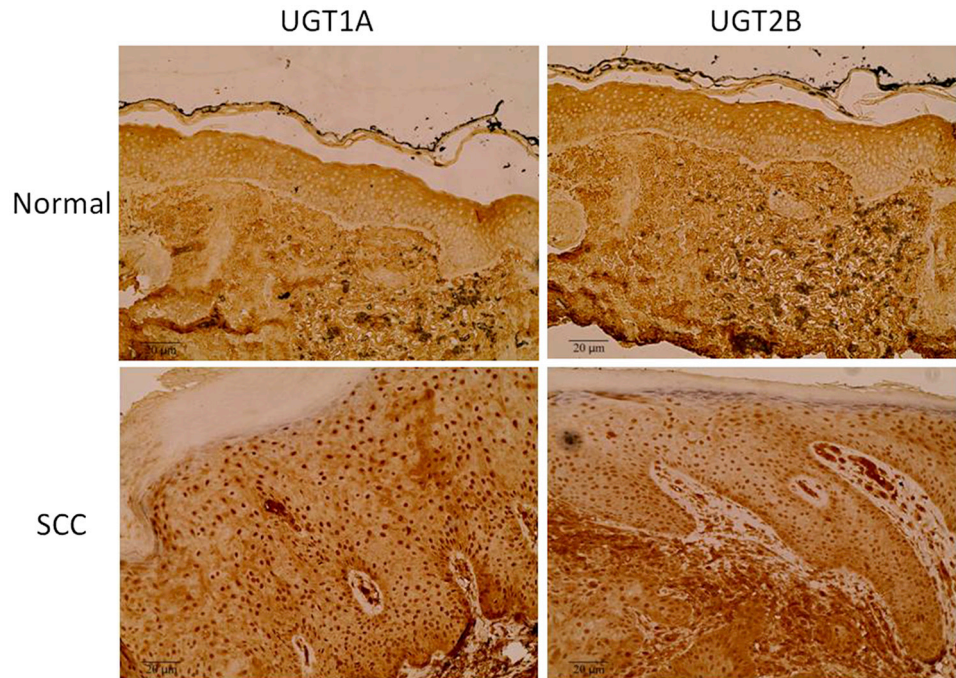
*To the Editor:* Actinic keratoses (AKs) and squamous cell carcinomas (SCCs) are common skin lesions that are often caused by ultraviolet (UV)–induced photo-carcinogenesis. It is well known that UV induces increased expression of cyclooxygenase 2 (COX-2) and production of prostaglandin E<sub>2</sub> in human skin. Although the arachidonic acid metabolism pathway has been studied extensively, the role of its downstream products in carcinogenesis has not been evaluated in human skin. The lipoxygenase (LOX) pathway is known to play a critical role in skin tumor progression in mouse models<sup>1</sup>; however, its relevance to nonmelanoma skin cancer is less well established. 12-Hydroxyeicosatetraenoic acid (12-HETE) is a potent proinflammatory chemotactic mediator found in higher concentrations in sun-exposed skin that is known to drive carcinogenesis in a manner similar to prostaglandin E<sub>2</sub>.<sup>1,2</sup> The UDP-glucuronosyltransferases (UGTs) have been shown to be downregulated in primary melanocyte and keratinocyte cell lines after UV exposure.<sup>3</sup> It is hypothesized that UGT activity is reduced during skin cancer progression, resulting in increased 12-HETE signaling. Our objective was to measure levels of 12-HETE in human AK and SCC biopsies.

12-HETE expression was measured quantitatively by using mass spectrometry in nonlesional skin, AKs, and SCCs. A 3-fold increase was noted in AKs and a 20-fold increase in SCCs (Fig 1) compared with nonlesional skin. Both of these increases were statistically significant ( $P < .01$ ). Immunohistochemistry was used to detect enzyme expression of UGT in nonlesional skin and SCC skin. When paraffin-embedded tissue of nonlesional skin and SCC skin were stained for UGT (Fig 2), both UGT1A and UGT2B were expressed throughout the epidermis. The expression of these 2 proteins in nonlesional skin appeared to be exclusively cytoplasmic because no staining was detected in the nuclei. The opposite staining pattern was observed in SCC tissue. Both UGT1A and UGT2B expression appeared to be almost exclusively nuclear. This striking difference in expression patterns suggests that UGTs are dysregulated in SCCs. The staining of AKs for UGT was highly variable and showed no consistent pattern.



**Fig 1.** 12-HETE levels in nonlesional skin, AKs, and SCC. 12-HETE levels were measured in nonlesional skin, AKs, and SCCs, and 12-HETE was found to be elevated in AK and SCC skin. 12-HETE, 12-Hydroxyeicosatetraenoic acid; AK, actinic keratosis; SCC, squamous cell carcinoma.

Several UGT1A polymorphic variants have been found to be associated with an increased risk for SCC of the head and neck.<sup>4</sup> Thus, it is possible the mislocalized UGTs observed in this study are polymorphic variants. Our findings support the hypothesis that nonmelanoma skin cancer progression involves deregulation of the LOX pathway, specifically 12-HETE. Most importantly, this data provides evidence that an effective chemopreventive agent might need to target both pathways of arachidonic acid metabolism, particularly prostaglandin E<sub>2</sub> and 12-HETE. The finding of elevated 12-HETE levels coupled with altered UGT localization in AK and SCC skin suggests that deregulated LOX signaling plays a role in tumor progression and that the LOX signaling pathway could serve as a potential therapeutic target. In a clinical trial, the chemopreventive role of the COX-2 inhibitor celecoxib was evaluated; the results of this study suggested that COX-2 inhibition could slow nonmelanoma skin cancer progression.<sup>5</sup> We hypothesize that celecoxib does not prevent new precancerous lesions because it does not inhibit 12-LOX (an enzyme in the LOX signaling pathway).<sup>5</sup> Furthermore, it has been reported that inhibition of COX-2 results in increased 12-LOX activity, suggesting complementary roles of these enzymes in cancer progression.<sup>1</sup> Therefore, an agent (or agents) that can block both 12-LOX and COX-2 might be better at preventing UV-induced skin damage, formation of precancerous lesions, and, ultimately, nonmelanoma skin



**Fig 2.** Immunohistochemical staining of UDP-glucuronosyltransferases UGT1A and UGT2B in nonlesional skin and SCC skin. SCC, Squamous cell carcinoma.

cancer. Future studies will explore this potentially important chemoprevention strategy.

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