**Title**
The preneoplastic genome: transcriptomic drivers of squamous cell carcinoma development

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**Abstract**

**The preneoplastic genome: transcriptomic drivers of squamous cell carcinoma development**

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Cutaneous squamous cell carcinoma (cuSCC) comprises 15-20% of all skin cancers, accounting for over 700,000 cases in the U.S. annually. Most cuSCC arise in association with a distinct precancerous lesion, the actinic keratosis (AK). In order to identify potential targets for molecularly targeted chemoprevention, we performed integrated cross-species genomic analysis of cuSCC development through the preneoplastic AK stage using matched human samples and a solar UV- driven Hairless mouse model. We performed RNA-seq and microRNA-seq on samples from both patients undergoing Mohs surgery and the mouse model. Using cross-species TRANSFAC and linear mixed effects model methodology, we identified the major transcriptional and microRNA drivers of this progression sequence showing that the key genomic changes in cuSCC development occur primarily in the normal skin to AK transition. As a proof of principle validation of our methods, we have shown that MEK is an effective chemoprevention and therapeutic target for cuSCC in cells and in-vivo. Our data validate the use of this UV-driven mouse cuSCC model for cross-species analysis and demonstrate that cuSCC bears deep molecular similarities to multiple carcinogen-driven SCCs from diverse sites, suggesting that cuSCC may serve as an effective, accessible model for multiple SCC types and that common treatment and prevention strategies may be feasible.