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APOBEC mutation drives early-onset squamous cell carcinomas in recessive dystrophic epidermolysis bullosa.

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Abstract

Recessive dystrophic epidermolysis bullosa (RDEB) is a rare inherited skin and mucous membrane fragility disorder complicated by early-onset, highly malignant cutaneous squamous cell carcinomas (SCCs). The molecular etiology of RDEB SCC, which arises at sites of sustained tissue damage, is unknown. We performed detailed molecular analysis using whole-exome, whole-genome, and RNA sequencing of 27 RDEB SCC tumors, including multiple tumors from the same patient and multiple regions from five individual tumors. We report that driver mutations were shared with spontaneous, ultraviolet (UV) light-induced cutaneous SCC (UV SCC) and head and neck SCC (HNSCC) and did not explain the early presentation or aggressive nature of RDEB SCC. Instead, endoge nous mutation processes associated with apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like (APOBEC) deaminases dominated RDEB SCC. APOBEC mutation signatures were enhanced throughout RDEB SCC tumor evolution, relative to spontaneous UV SCC and HNSCC mutation profiles. Sixty-seven percent of RDEB SCC driver mutations was found to emerge as a result of APOBEC and other endogenous mutational processes previously associated with age, potentially explaining a >1000-fold increased incidence and the early onset of these SCCs. Human papillomavirus-negative basal and mesenchymal subtypes of HNSCC harbored enhanced APOBEC mutational signatures and transcriptomes similar to those of RDEB SCC, suggesting that APOBEC deaminases drive other subtypes of SCC. Collectively, these data establish specific mutagenic mechanisms associated with chronic tissue damage. Our findings reveal a cause for cancers arising at sites of persistent inflammation and identify potential therapeutic avenues to treat RDEB SCC.