A Review of the Genomic Landscape of Early Cutaneous Squamous Cell Carcinoma

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Introduction

• Cutaneous squamous cell carcinoma (cSCC) is the second most common cancer in the United States.1

• However, it is less researched than melanoma due a common misconception about its non-lethal nature (cSCC has death tolls on par with melanoma),2 and cSCC bears large mutational loads that are historically difficult to sequence and interpret due to UV radiation induced changes.3

• Current literature addressing cutaneous squamous cell carcinoma focuses on malignant and metastatic progression as opposed to early genetic progression and predisposition, the latter offering new intervention opportunities as many therapeutic interventions for advanced disease are not effective or poorly tolerated.4

• Exploring the genetic progresses from normal to precancer to malignancy provides foundational knowledge to drive research in diagnostic and therapeutic interventions to enhance the quality of care in cutaneous squamous cell carcinoma.

Methods

What genes are involved in the early genetic progression of cSCC, including driver mutations in chronically UV-exposed skin and actinic keratoses?

What research has identified novel driver mutations in early cSCC that can be further researched to develop better diagnostic, prognostic, and therapeutic interventions?

Developed a Systematic Literature Review addressing this knowledge gap

Included : Publications from January 2000 - June 2023, not limited by geography, full text availability in English, and inclusion of natural language terms for the concepts of cutaneous squamous cell carcinoma and genetic mutations.

MEDLINE, EMBASE, Cochrane Library, and PubMed sensitivity was tested by pruning searches with the terms in the title, abstract, and key words. We also included studies from the references of each other paper.

The search terms are not effective or poorly tolerated.

Table 1: PRISMA Diagram

Table 2: Common Driver Genes in early cSCC formation. (SES=sun exposed skin, PIP=Psoriatic immunopositive patch, KA=keratoacanthoma, AK=actinic keratosis, cSCC=cutaneous squamous cell carcinoma, cSCCIS=cSCC in situ, IC=immunocompetent, IS=immunosuppressed)

Table 3: Novel Driver Genes in early cSCC formation. (SES=sun exposed skin, NSES=non sun exposed skin, NS=normal skin, AK=actinic keratosis, KIN=keratinocyte intraepithelial neoplasia, cSCC=cutaneous squamous cell carcinoma, cSCCIS=cSCC in situ, IC=immunocompetent, IS=immunosuppressed. "refers to a non-deregulation description

Results

Most studies concluded that TP53, NOTCH, and FAT1 mutations are vastly common in normal skin, precursors, and cSCC suggesting lesser oncogenic deregulation.

CDKN2A had the most conflicting data across studies suggesting further investigation is needed.

Many studies concluded that clonal and subclonal populations exist harboring common driver mutations in precursors and will not evolve into cSCC until it has gathered considerably greater mutational burden, compared to precursors.

Many studies addressing polyclonality in cSCC conclude that epigenetic and non-genomic regulation play large roles in cSCC oncogenesis.

Discussion

• The genetic evolution from healthy skin to cSCC is a multifaceted process involving intricate molecular alterations, especially considering years of background UV exposure.

• Our findings highlight the importance of whole and larger genome sequencing in identifying novel driver mutations associated with AK and cSCC progression. The identified genes and dysregulated pathways provide potential targets for therapeutic interventions to prevent or treat cSCC.

• Furthermore, this study underscores the growing significance of personalized medicine, as the genetic heterogeneity observed in cSCC may benefit from tailored, individualized intervention.

• Continued research into the genetic and epigenetic evolution of early cSCC will enhance our understanding of skin cancer pathogenesis and aid in developing more effective diagnostic and therapeutic strategies.