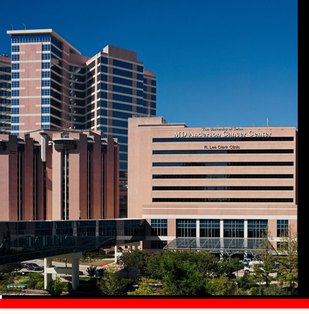

A Review of the Genomic Landscape of early cutaneous Squamous Cell Carcinoma

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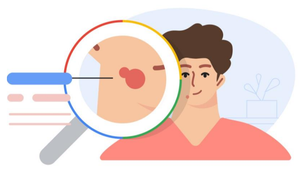
Introduction

- 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 **nonlethal 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 progressions** 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.



References

Methods

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

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

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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 the ability for preliminary search strategies to include known, relevant citations. A Covidence library was created to manage and de-duplicate the citations.

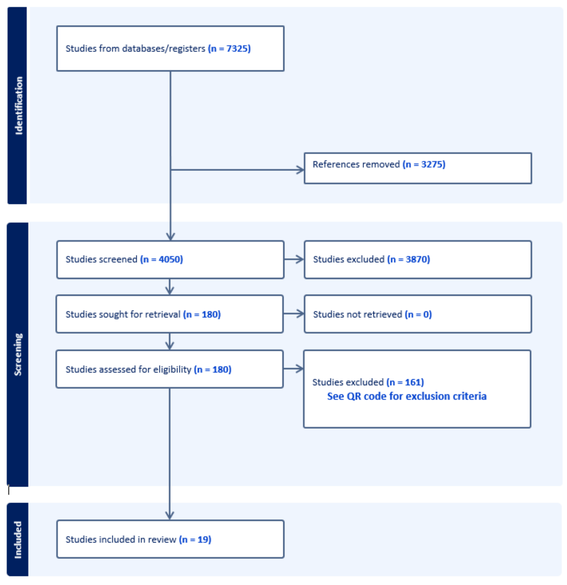

Table 1: PRISMA Diagram

Results

Gene	Lesions Studied	Deregulation in Precursors	Deregulation in cSCC	Reference
TP53	SES (n=11) PIP (n=15) KA (n=10) AK (n=41) cSCCIS (n=26) cSCC (n=30)	Clonal and subclonal mutations found in all precursors	Expansion of clonal and subclonal populations	5,7,8,12
	SES (n=375) AK (n=18) cSCCIS (n=40) cSCC (n=27)	Large portion of mutations found in precursors		7,14,18,22
NOTCH1	SES (n=1838) KA (n=6) AK (n=26) cSCCIS (n=12) cSCC (n=32)	Large portion of mutations found in precursors	Similar proportion of mutations to precursors	7,9,11,12,13, 16,18
	IS AKs (n=23) IC AKs (n=14) cSCC (n=15)		Showed upregulation in AK to cSCC transition, contrasting most studies	21
NOTCH2	SES (n=242) AK (n=10) cSCC (n=9)	Large portion of mutations found in precursors		7,18
NOTCH3	SES (n=3) AK (n=7) cSCCIS (n=3) cSCC(n = 10)	Gains in copy number alterations in precursors	No lesions found with similar gains	12
	SES (n=234)	Large portion of mutations found in precursors		18
FAT1	SES (n=1712) AK (n=10) cSCC (n=9)	Large portion of mutations found in precursors	Similar proportion of mutations to precursors	7,9,18
CDKN2A	SES (n=3) AK (n=7) cSCCIS (n=3) cSCC(n = 10)		Loss in copy number alterations	12
	AK (n=9) cSCCIS (n=9) cSCC (n=13)	Greater number of mutations found in cSCC compared to AK and cSCCIS		13
	AK (n=8) cSCCIS (n=30) cSCC (n=18)	Greater portion of mutations in AK than cSCCIS		14
	SES (n=234)		Greater number of mutations found in cSCC compared to NS	18
PIK3CA	SES (n=1470)	Activating mutations under positive selection, inactivating mutations under negative selection		9
RB1	AK (n=17) cSCCIS (n=39) cSCC (n=31)	Driver mutations in cSCCIS, not AK	Limited new driver mutations	13,14
TGFB	IS AKs (n=23) IC AKs (n=14) cSCC (n=15)	Progressively downregulated in NS to AK transition	Significantly more mutated and downregulated	21

Table 2: **Common Driver Genes** in early cSCC formation. (SES=sun exposed skin, PIP=P53 immunopositive patch, KA=keratoacanthoma, AK=actinic keratosis, cSCC=cutaneous squamous cell carcinoma, cSCCIS=cSCC in situ, IC=immunocompetent, IS=immunosuppressed)

Gene	Lesions Studied	Deregulation in Precursors	Deregulation in cSCC	Reference
FOSL1, BNC1	SES (n=23) AK (n=59) cSCC (n=46)		Increased expression compared in cSCC to SES and AK	10
NEK10	SES (n=23) AK (n=59) cSCC (n=46)	Decreased expression in AK compared to SES	Decreased expression in cSCC compared to cSCC	10
ID4	NSES (n=60) SES (n=60) NS (n=202) cSCC (n=202)	Promoter methylation increased in SES compared to NSES	Increased promoter methylation in cSCC compared to NS	15
MIR21, MIR31	NS (n=21) AK (n=21) cSCC (n=21)	Progressively upregulated in AK compared to NS	Progressively upregulated in cSCC compared to AK	7
MIR497	NS (n=9) SES (n=15) AK-KIN1/2 (n=6) AK-KIN3 (n=6) cSCC (n=19)	Progressively downregulated along NS to AK-KIN3 transition	Progressively downregulated along AK to cSCC transition	19
uc011fnr.2	NS (n=3) AK (n=2)	Downregulated in AK compared to NS		17
MEF2A	NS (n=12) AK (n=33) cSCCIS (n=11) cSCC (n=35)	Identified as a key transcriptional regulator in basal undifferentiated keratinocytes*		20
CACNA1	IS AKs (n=23) IC AKs (n=14) cSCC (n=15)	Harbors greater mutations in AK compared to NS		21
KCNK5	IS AKs (n=23) IC AKs (n=14) cSCC (n=15)	Downregulated and harbors greater mutations in AK compared to NS		21
HMCN1	IS AKs (n=23) IC AKs (n=14) cSCC (n=15)	Mutated in large portion of AKs		21
SLFN	SES (n=10) cSCCIS (n=10)	Positive selection for mutant clones		22
NEURL1	SES (n=10) cSCCIS (n=10))	Increased expression in cSCCIS compared to SES		22
HEPHL1, FBN2, TCN1, SULF1/2	NSES (n=6) SES (n=6) AK (n=6) cSCC (n=6)		Significantly more expressed in cSCC compared to AKs or NES	23

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=immunocompentent, IS=immunosuppressed). *refers to a non-deregulation description

Results

- Most studies concluded that ***TP53***, ***NOTCH***, and ***FAT1*** mutations were 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.