Methylation profiling identifies two subclasses of squamous cell carcinoma related to distinct cells of origin

Rodríguez-Paredes M[1], (...), Winnefeld M[2],Lyko F[1] | [1]Division of Epigenetics, DKFZ-ZMBH Alliance, German Cancer Research Center, Heidelberg, Germany | [2]Research & Development, Beiersdorf AG, Hamburg, Germany

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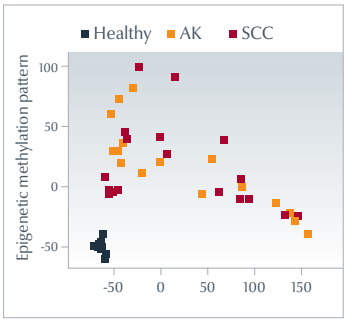
KEY FINDINGS

[1] Actinic keratosis (AK) shows similar aberrant epigenetic methylation pattern as squamous cell carzinoma (SCC)

[2] AK methylomes display typical cancer-related features such as CpG island hypermethylation indicating a significant malignant potential of AK



[1] Similar pattern of AK and SCC vs. healthy

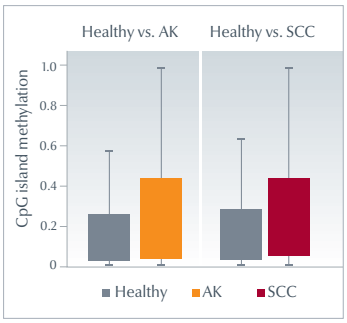
METHODS

To obtain healthy epidermis samples, suction blisters were induced on the forearms of healthy male volunteers. AK and SCC from three diagnostic stages of AK and SCC and the epidermal parts was separated from the dermal parts. Genomic DNA was isolated from epidermal samples (12 normal, 16 AK and 18 SCC epidermis samples) and DNA methylation profiles were obtained using Infinium 850k methylation arrays.

RESULTS

[1] Principal component analysis (PCA) clearly separated the normal epidermis from AK and SCC samples, but also indicated highly overlapping patterns between AK and SCC. No significantly differentially methylated probes were detected between AK and SCC.

[2] A comparison of the methylation status revealed robust hypermethylation of CpG islands in both AK and SCC samples. CpG islands are epigenomic substructures in the DNA and their hypermethylation is a specific feature of cancer methylomes.



[2] Cancer feature: CpG island hypermethylation

CONCLUSION

[1] Pronounced methylation differences between healthy and diseased (AK, SCC) epidermis samples were found suggesting substantial epigenetic similarities between the precancerous AK lesions and the SCC tumor samples.

[2] The premalignant AK samples already display key features of cancer methylomes and these features are conserved in SCC. These results indicate a significant malignant potential of AK.

SUMMARY STATEMENT PROF. DR. FRANK LYKO

Squamous cell carcinoma (SCC) is the second most common skin cancer type and progresses from a UV-induced precancerous lesion termed actinic keratosis (AK). Whether AK represents a benign precancerous lesion or malignant tissue is a matter of ongoing debate. Altered DNA methylation patterns are considered a classical hallmark of cancer, but their precise significance and functional relevance for tumorigenesis are still not completely understood.

We have performed a comprehensive analysis of DNA methylation patterns in epidermis samples from healthy skin, AK and SCC. Importantly, we found that the premalignant AK samples displayed classical features of cancer methylomes and were highly similar to SCC methylomes. Further analysis identified stem cell-related keratin and enhancer methylation patterns in one half of the AK and SCC samples, while the other half showed keratin and enhancer methylation patterns that were more closely related to the control epidermis.

These findings suggest the existence of two distinct subclasses of AK and SCC that originate from distinct keratinocyte differentiation stages and provide novel perspectives for the prevention, diagnosis and treatment of UV-induced skin lesions.

Since 2006, Dr. Frank Lyko has been Professor of Epigenetics at the Faculty of Medicine of the University of Heidelberg, heading the Division of Epigenetics at the German Cancer Research Center