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COMMENTARY FROM THE EDITORIAL BOARD

The genetic evolution of skin squamous cell carcinoma: tumor suppressor identity matters

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Cutaneous squamous cell carcinoma (cSCC) is the second most common human malignancy, often arising from the progression of benign lesions called actinic keratosis (AK). The progression from AK to cSCC is likely a multistep process involving sequential DNA mutations in oncogenes and tumor suppressor genes, leading to increased genomic instability and/or loss of cell cycle control. Some driver mutations involved in human cSCC have been identified, although the pathogenesis of cSCC at the molecular and genetic level remains largely unknown.

The tumor suppressor gene *Tp53* is very frequently mutated in cSCC, ranging from 44% in a cohort of about 800 patients with cSCC (http://cancer.sanger.ac.uk/cosmic) to 79% in advanced cSCC; http://www.cbioportal.org/index.do) (Fig. 1).[1] Similarly, *NOTCH1* and *NOTCH2* are often mutated in cSCC (Fig. 1).[2] In contrast to other tissues in which NOTCH signalling is crucial for stemness and favours tumor formation, in the epidermis NOTCH promotes epidermal differentiation, thereby inhibiting skin tumorigenesis (reviewed in[3]).

Other tumor suppressor genes such as *CDKN2A* and *KMT2D* are also mutated with a similar frequency (Fig. 1). KMT2D is a histone lysine methyltransferase frequently mutated in oesophageal squamous cell cancer, in breast fibroepithelial tumors and in lymphoma.[4–7] While KMT2D acts as bona fide tumor suppressor in lymphomas,[8,9] future studies are required to determine its role in skin tumorigenesis. Other well-characterized tumor suppressor genes, such as *Rb1* and *Pten*, are also mutated in cSCC, albeit at a lower frequency (Fig. 1).

Among the genes carrying activating mutations in cSCCs are members of the RAS family, HRAS and KRAS (Fig. 1). While the mutation frequency for each of these genes is low, their combined mutation frequency is more than 10%. In addition, other components of the RAS signalling pathway, such as the epidermal growth factor receptor (*EGFR*) and the effector *BRAF*, are also mutated in cSCCs at a low frequency (Fig. 1).

Cutaneous squamous cell carcinomas have been extensively studied in mouse models using a chemical carcinogenesis protocol, causing mutations in either HRAS in 67% of the tumors or, less frequently, in KRAS (19%).[10] Most genetic models that have been studied to date take advantage of inducible mutations in KRAS in combination with other oncogenes or tumor suppressor genes.[11–13]

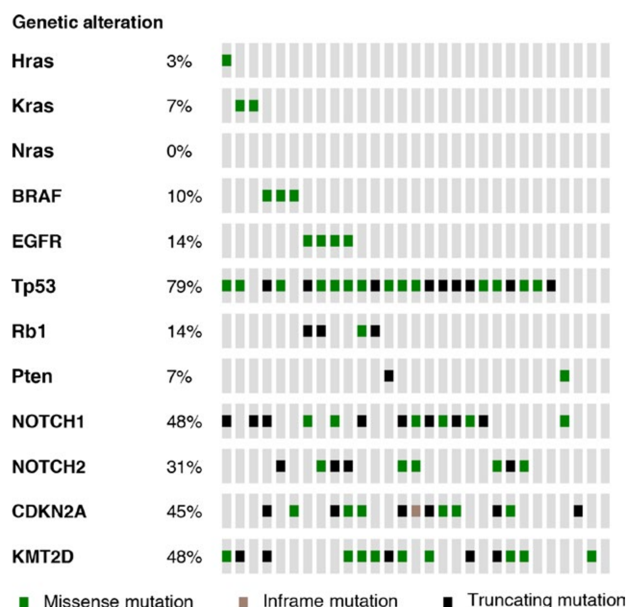

FIGURE 1 More frequently mutated genes in advanced Cutaneous squamous cell carcinoma (cSCC). Targeted sequencing of 504 cancer-associated genes on lymph node metastases in 29 patients with cSCC[23–25]

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One important, unanswered question in skin tumor biology is whether the severity of the tumor is related to the different underlying mutations, cell of origin or variable genomic instability.

To dissect this question, in a recently published issue of *Experimental Dermatology*, Flores et al. test the hypothesis that a specific population of cells within the epidermis has the capability to generate different types of tumors depending on the tumor suppressor gene that is deleted. To this purpose, they generated three mouse models in which an activating KRAS mutation was accompanied by concomitant deletion of genes encoding distinct tumor suppressor genes (*Trp53*, *Pten* or *Rb1*) in the hair follicle stem cell compartment (HFSC).[14] An extensive pathological examination was performed to analyse the resulting phenotypes in detail. The HFSC was chosen because its composition is relatively homogenous, being localized in the hair follicle bulge, and can be specifically targeted by Cre recombinase with a keratin 15 promoter. Previous studies have shown that both interfollicular epidermis and the HFSC and their immediate progeny are competent to generate cSCCs.[12,15]

In this context, KRAS-activating mutations coupled with *p53* deletion led to aggressive SCC, including high-grade spindle cell SCC as previously described.[11–13] In contrast, KRAS activation coupled with *Rb1* deletion led to benign papillomas, and hypertrophy of the infundibulum and sebaceous glands. Similarly, KRAS activation coupled with *Pten* deletion caused squamous hyperplasia eventually leading to papillomas or keratoacanthomas, and benign tumors of the skin characterized by rapid growth and spontaneous regression.[16] This study is in agreement with the observation that *Tp53* is mutated in a high percentage of human cSCCs, whereas *Pten* and *Rb1* are infrequently mutated. Therefore, the main finding of the present work is that a specific subset of epidermal stem cells can give rise to a variety of tumorigenic phenotypes depending on the tumor suppressor that is deleted, and that the identity of the tumor suppressor lost in the process of carcinogenesis determines the phenotype of the tumor.[14]

This study by Flores and colleagues should inspire future research to further address the roles of other oncogenes and tumor suppressors in cSCC formation, in particular those that are more frequently mutated in cSCCs, such as *NOTCH1*, *NOTCH2*, *CDKN2A* and *KMTD2*. An important emerging question in cSCC research is whether the order in which mutations of oncogenes and tumor suppressors occur is relevant for the severity of the disease. For instance, ultraviolet (UV)-induced mutations in *Tp53* may often be an early event since these mutations are found in normal-appearing skin (reviewed in[1]). In addition, the influence of overexpression of regulatory genes such as *TP63*[1,17] and *SOX2*[18–20] will have to be further studied in cSCC. Future experiments could make use of recently developed technologies that take advantage of intra-vital imaging[21] to study early stages of the precursor lesions and to follow the fate of tumorigenic cells in real time when different tumor suppressors are lost.

Another interesting point that will need to be addressed in the future is how the combination of mutations or deletions of several genes may influence each other. Genome editing techniques, such as the CRISPR/CAS9 technology that enables concomitant or sequential genomic mutations,[22] will allow rapid development of models bearing combinations of mutations or deletions of multiple genes simultaneously.

In conclusion, the present work sets the basis for more sophisticated studies aimed at modelling cSCC in mice to identify innovative therapeutic targets for treating this cancer.

CONFLICT OF INTERESTS

The authors have declared no conflicting interests.

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