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Chapter

Comprehensive Molecular Characterization of Squamous Cell Carcinomas

Corina Lorz, Carmen Segrelles, Ricardo Errazquin and Ramon Garcia-Escudero

Abstract

Over the last two decades, a number of high-throughput technologies (genome- and proteome-based) have been developed and applied on different cancer types such as squamous cell carcinomas (SCCs) arising from aerodigestive and genitourinary tracts. These analyses, when comprehensively utilized, have clearly contributed to a better understanding of the molecular hallmarks, oncogenic pathways and immunological features of SCCs. This chapter aims to describe the SCCs most important molecular aberrations as well as their molecular classification, highlighting the commonalities and differences among them, independent of their body site origin. The most frequently altered oncogene is PIK3CA, involved in the PI3K/AKT/mTOR pathway and frequently activated in many human cancers. However, alterations in the cell-cycle control TP53 gene occur in the vast majority of SCCs. New possible molecular therapies, common to all SCCs, are discussed in light of a comprehensive, panSCC analysis.

Keywords: squamous cell carcinoma, human papillomavirus, genomics, Fanconi anemia, TCGA, mutation, copy number alteration, cancer treatment, biomarker

1. Introduction

Squamous cell carcinomas (SCCs) represent highly common solid cancers that arise from stratified and pseudo-stratified epithelia of the skin, and aerodigestive and genitourinary tracts. Although SCCs from different body sites share histological characteristics, they are molecularly and clinically heterogeneous, and a major cause of cancer mortality [1]. Reported risk factors for SCCs, depending on the body site, include alcohol intake (head and neck, and esophagus), cigarette smoking (bladder, lung, head and neck, and esophagus), UV light exposure (skin) and infection with human papillomavirus (HPV) (skin, head and neck, and cervix uteri). HPV infects epithelial cells and transforms them through the oncogene action of viral genes. E6 and E7 genes from some HPVs infecting head and neck and cervix uteri inhibit the function of the important tumor suppressors p53 and pRb, respectively [2, 3]. The initiation of SCCs is due to genomic perturbations, genetic mutations, and/or altered expression of key molecules mainly involved in cell-cycle control, signaling and cell adhesion pathways, squamous differentiation and chromatin regulation [1, 4]. A number of reports show that SCCs from different

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anatomical locations have common features despite the fact that they are clinically treated as separate entities. These findings suggest an integrated view of the disease and possible new methods for prevention and treatment.

Here we review reports in which hundreds of SCCs have been comprehensively characterized at the molecular level using different high-throughput technologies. Such analyses highlighted commonalities and differences between SCCs, independent of body site origin, and allow their classification based on molecular aberrations. New possible molecular therapies, common to all SCCs, are discussed in light of the comprehensive, panSCC analysis.

2. Molecular features of SCCs

SCCs from different anatomical sites have been molecularly characterized using various genome-wide technologies (**Table 1**). Despite early reports describing most frequent mutations using next-generation sequencing (NGS) such as whole-exome sequencing (WES) in many cancer types [5], most of the comprehensive analyses have been done within the context of The Cancer Genome Atlas (TCGA) consortium. TCGA is an USA project which has generated comprehensive, multi-dimensional maps of the key genomic changes in the main types of cancer (http://cancergenome.nih.gov/). Microarray- and/or NGS-based technologies have been used in order to determine mutations in protein coding genes, expression levels of messenger RNA (mRNA) and micro RNA (miRNA) molecules, DNA-methylation and genome copy-number variation (CNA) (**Table 1**). Moreover, an important subset of cancers has been characterized at the protein level, using Reverse Phase Protein Array (RPPA) (**Table 1**). Recently, the TCGA launched a set of publications reporting pancancer analyses of more than 11,000 tumors from 33 types of cancers [4] (https://www.cell.com/pb-assets/consortium/pancanceratlas/pancani3/index.html), including SCCs from 5 individual body sites: lung (LUSC), head and neck (HNSC), esophageal (ESCA), cervical (CESC), and bladder (BLCA) cancers. Most of the molecular features described here are based on the TCGA panSCC analysis, in which around 1400 SCCs from those body sites were analyzed simultaneously [6]. Although skin SCC is the second most frequent cancer in Caucasians [7], no comprehensive, genome-wide analysis has been reported. Interestingly, most frequent mutations using NGS-based technologies in skin SCC showed many similarities with SCC from other body sites [8, 9].

Body site	Sample size (SCC size)	Genome-wide molecule*	Reference
Head and neck	279 (279)	DNA-meth, CNA, DNA-seq, mRNA, miRNA, proteome	[10]
Lung	178 (178)	DNA-meth, CNA, DNA-seq, mRNA, miRNA	[11]
Esophagus	164 (90)	DNA-meth, CNA, DNA-seq, mRNA, miRNA, proteome	[12]
Cervix uteri	228 (144)	DNA-meth, CNA, DNA-seq, mRNA, miRNA, proteome	[13]
Bladder	131 (19)	DNA-meth, CNA, DNA-seq, mRNA, miRNA, proteome	[14]
Bladder	412 (42)	DNA-meth, CNA, DNA-seq, mRNA, miRNA, proteome	[15]
Pancancer12	3,527 (546)	DNA-meth, CNA, DNA-seq, mRNA, miRNA, proteome	[16]
Pancancer33	~10,000 (~1,400)	DNA-meth, CNA, DNA-seq, mRNA, miRNA, proteome	[4]
PanSCC	~1,400 (~1,400)	DNA-meth, CNA, DNA-seq, mRNA, miRNA, proteome	[6]

**DNA-meth: DNA methylation; CNA: DNA copy number alteration; DNA-seq: whole exome sequencing; mRNA: messenger RNA; miRNA: micro RNA; proteome: reverse phase protein assay (RPPA).*

Table 1.
List of publications with genome-wide analysis of SCC.

2.1 Mutations in cancer genes

The most frequent mutated gene found in SCCs is *TP53* (64% in panSCCs) [4, 6, 16], (**Figure 1**) a tumor suppressor gene whose main function is to prevent genome mutations [17]. Missense "hot spots" mutations are very common, which result in dominant-negative and/or gain-of-function properties [18]. Although *Tp53* was found to be highly altered in many other cancer types [19], frequencies depends on the type, stage, body site, and other factors. Mutations in *TP53* are infrequent in HPV(+) SCC cancers, possibly because p53 functions are compromised as the protein is degraded by the activity of the viral E6 oncogene. Individually, frequent *TP53* mutations are found in SCCs within BLCA [15], ESCA [12], HNSC [10] and LUSC [11], and to a lesser extent in CESC whereby the majority of tumors are HPV(+) [13]. Other mutated genes involved in cell-cycle control include CDK inhibitor *CDKN2A* and the *RB1* gene, although less frequently. The incidence of *CDKN2A*/*RB1* mutations is much reduced in HPV(+) HNSC and CESC, as the E7 viral oncogene can bind and inactivate pRb protein, coded by *RB1*, thus rendering direct genetic mutation dispensable [10, 13]. Another important group of mutated genes include regulators of squamous differentiation, such as *NOTCH1*, *AJUBA* or *ZNF750* (**Figure 1**) [4, 6, 16].

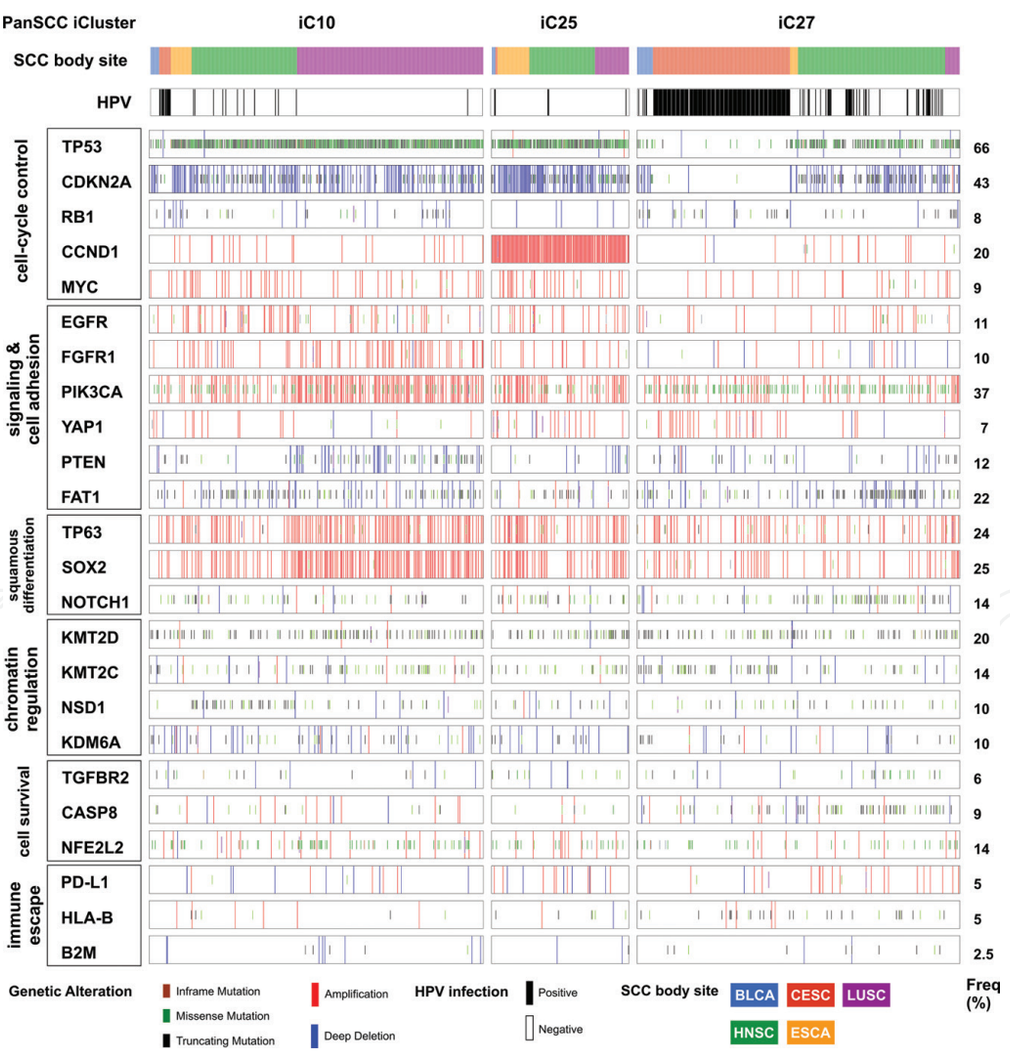

Figure 1.
Relevant mutations and CNA alterations in SCCs from BLCA, CESC, LUSC, HNSC and ESCA. Tumors are grouped into iC10, iC25 and iC27 clusters. Genes are grouped into functions. Frequency of alterations per gene is shown. HPV infected samples are indicated. Tumors having WES and CNA data, and belonging to iC10, iC25 and iC27 clusters are shown (n = 1098). Data are from the cBioportal for Cancer Genomics (http://www.cbioportal.org/) [20].

Other mutated genes include *KMT2D*, *NSD1*, *EP300*, or *KDM6A*, all of them involved in chromatin regulation through histone post-translational modifications. *PIK3CA*, *PTEN*, *FAT1*, *EPHA2* or *RASA1* genes, also mutated, are involved in important signaling and cell adhesion pathways of epithelial cells. There are also mutations in genes important in cell survival, like *TGFBR2* or *CASP8*. Mutations of *HLA-A* and *HLA-B* and deletions of *B2M*, implicated in immune escape, also exist (**Figure 1**) [4, 6, 16].

2.2 panSCC molecular clustering

High-throughput technologies have allowed the identification of tumor subgroups within specific cancer types, like the 'intrinsic subtypes' of breast cancer [21], occasionally having important clinical differences and outcomes [22]. Tumor subgroups based on genome-wide molecular analyses have been reported also for HNSC [10], LUSC [11], BLCA [14, 15], CESC [13] and ESCA [12]. Such classifications are based on molecular features like mutations, CNA, DNA-methylation, or expression of mRNAs, miRNAs, proteins [10–15] and long non-coding RNAs [15, 23, 24].

The existence of hundreds of primary tumors from different cancer types within TCGA having multiplatform molecular data have allowed the integrated identification of their differences and commonalities, regardless of body site [4, 6, 16]. One of such analyses, performed over 1400 SCCs from five different locations (LUSC, HNSC, CESC, ESCA and BLCA), discovered the existence of different SCC tumor clusters based on CNA (six clusters), DNA methylation (five clusters), mRNA expression (six clusters), miRNA expression (five clusters), and RPPA-based protein expression (eight clusters) [6]. These clusters highlight significant molecular features in SCC versus non-SCC, and between SCCs. Moreover, the iClustering method [25], which performs clustering from multi-type genomic data, showed the presence of 3 main iClusters: iC10, iC25 and iC27 [6] (**Figure 1**). Most HPV(−) tumors grouped in iC10 and iC25, associated with smoking history, organ site and molecular aberrations (**Figure 2A**), while most HPV+ CESC and HNSC samples mapped within iC27 having non-smoking individuals (**Figure 2A**). All tree SCC-clusters displayed significant chromosome 5q and 3p copy gains, concomitant with overexpression in 3q genes SOX2, TP63, and TP73, implicated in squamous differentiation and stemness (**Figure 1**) [6]. iC25 cluster bear 11q gains, and iC10/iC25 included 9p losses. Most iC10/25 HPV(−) SCC tumors displayed genome-wide hypomethylation with high DNA CNA, and associated augmented mRNA and miRNA levels. Some HPV(−) SCCs and most iC27 HPV(+) HNSCs and CESCs, showed wider hypermethylation and reduced CNAs, correlated with reduced mRNA and miRNA expression [6].

Kaplan-Meier curves demonstrated significant differences in overall survival and progression-free interval between the iClusters, even after adjusting for distinct body sites or disease stages (**Figure 2B**). Patients within iC25 display poorer prognosis, possibly associated to higher CNA aberrations and genome instability (**Figures 1** and **2B**). Therefore, panSCC analysis showed the existence of a prevalent SCC group, having a combination of recurrent CNA and other alterations, and other subtypes whereby HPV infection and other alterations have a greater role.

2.3 Cancer genes in CN alterations

Oncogenic transformation from normal tissues occurs upon the accumulation of small mutations and also larger alterations, giving rise to deletion (DEL) or amplification (AMP) of regions and altering the normal diploid state of the genome. Negative regulators of cell-cycle control like CDKN2A and RB1 are frequently deleted in SCCs (**Figure 1**). Contrarily, CCND1, MYC, and CCNE1 genes appear frequently amplified, and therefore, their function in cell proliferation. Important

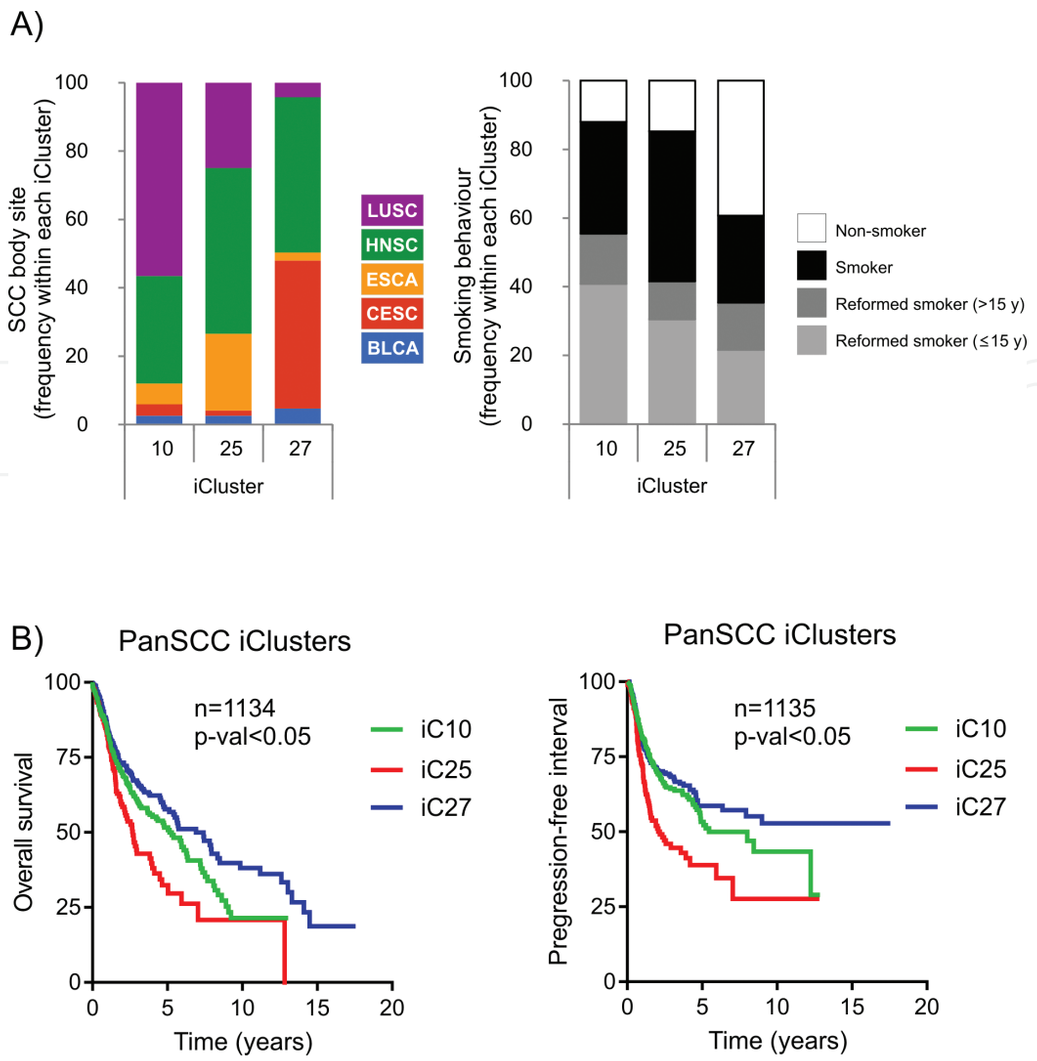

Figure 2.
Clinical features of main panSCC iClusters, including body site distribution and patient smoking history frequencies within each iC10, iC25 and iC27 (A), and survival curves with 2 endpoints: overall survival and progression-free interval (B). Clinical data obtained from Liu et al. [26]. P-values were calculated after multivariate Cox regression analysis, using iClusters and body sites or pathologic tumor stage.

positive mediators of signaling and cell adhesion pathways are frequently amplified (EGFR, ERBB2, FGFR1, PIK3CA, AKT1, AKT3, MAPK1, YAP1), and tumor suppressors like PTEN or FAT1 are deleted. Chromosome 3q genes TP63 and SOX2 are highly frequently co-amplified, and overexpression of their mRNAs is a common SCC feature as mentioned above (**Figure 1**) [6]. Squamous differentiation genes which are deleted also exist, like NOTCH1 and ZNF750. Frequent deletion of chromatin regulation genes occurs, like ARID1A, NSD1, KMT2C or KDM6A. There are also alterations in cell survival genes, like NFE2L2 (AMP), BCL2L1 (AMP), and BCL2L2 (DEL). Importantly, some main immune escape regulators are segregated in CNA regions, like PD-L1 (AMP) or B2M (DEL) (**Figure 1**).

3. SCC and Fanconi DNA repair pathway

Fanconi anemia (FA) is a rare autosomal recessive genetic disorder in which patients can develop a life-threatening bone marrow failure in the early years after birth [27], which frequently requires allogeneic hematopoietic stem cell transplant [28]. In addition to this blood disorder, FA patients can develop leukemias and solid tumors, mainly SCC in the head and neck, skin, and anogenital regions [29].

Incidence of HNSC in FA is >500 times higher than in the general population, and average age of appearance is significantly earlier. Mutations occur in genes involved in the 'FA pathway' which is activated as a result of DNA replication or DNA damage, especially the damage triggered from DNA crosslinking agents. Some of these FA genes include *BRCA1* and *BRCA2* genes, well known breast cancer-susceptibility genes. Hitherto, there is no explanation for the high incidence of FA-HNSC, but it has been suggested that FA pathway defects might accelerate oncogenic transformation through the accumulation of mutations in a DNA repair-defective context [30]. In this sense, a number of reports showed tumor suppressor functions by FA genes, both in the FA as well as in non-FA human cancer [31].

Campbell et al. reported an unexpectedly high frequency (around 12%) of molecular aberrations involving top 10 FA pathway genes in panSCC from TCGA [6]. An analysis using all 22 FA pathway genes reported so far, demonstrated that almost 30% of SCCs within iC10, iC25 and iC27 clusters from BLCA, CESC, ESCA, HNSC and LUSC (314 out of 1098) display either point mutations or deletions in any FA gene (**Figure 3**). Whether all of these FA gene alterations are associated with defects in DNA-repair is unknown, but clinical implications would be important

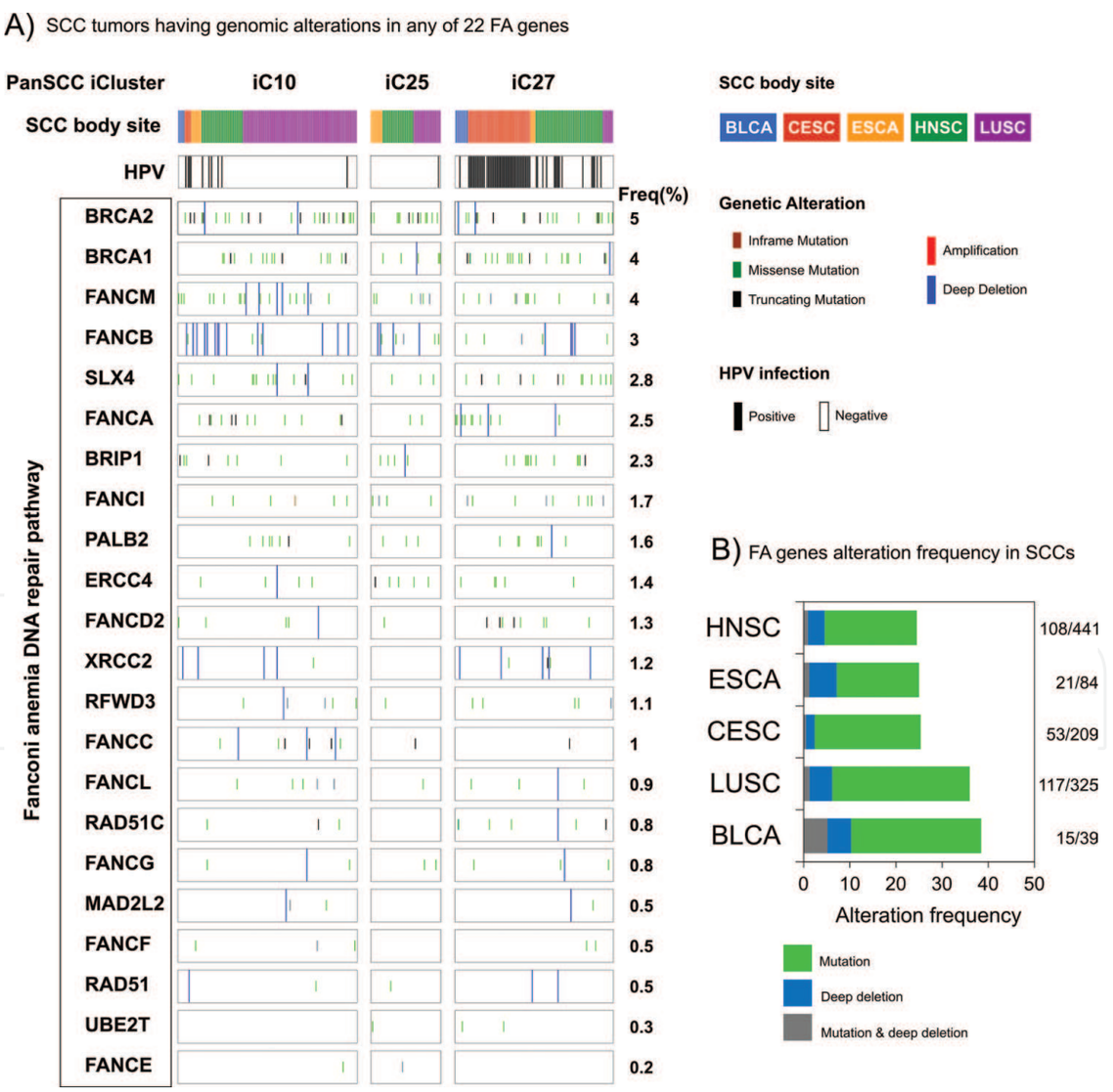

Figure 3.
Mutations and deep deletion in all 22 FA pathway genes in SCCs from BLCA, CESC, LUSC, HNSC and ESCA. (A) Tumors are grouped into iC10, iC25 and iC27 clusters. Frequency of alterations per gene is shown. HPV infected samples are indicated. (B) Alteration frequency in any FA gene is shown per body site. Tumors having WES and CNA data, belonging to iC10, iC25 and iC27 clusters, and having mutation/deep deletion are shown (n = 314). Data are from the cBioportal for Cancer Genomics (http://www.cbioportal.org/) [20].

as the FA pathway is a major predictor of cisplatin response in HNSC [32]. These findings suggest that acquired as well as germline alterations in this pathway may contribute to the development of a subset of SCC.

4. Molecular therapies against SCC

Patients suffering squamous cell carcinoma display poor overall survival, and the disease is difficult to treat. Independent of body site, the standard of care is based on surgery, radiotherapy and chemotherapy. Still, few molecular therapies are being used so far, and only in the latest stages of the disease, such as immunotherapies, cetuximab (antibody to EGFR) in HNSC or bevacizumab (antibody to VEGF) in cervical cancer. There is a clear need to develop new targeted therapies accompanied with accurate response biomarkers, so we can give more effective and less aggressive treatments to SCC patients. The profound knowledge about the molecular biology of SCCs that we have acquired over the last recent years, together with comparative efforts of tumors from different body sites, should help to design new clinical trials challenging current treatment modalities.

4.1 Immunotherapies in SCCs

As understanding of the underlying cancer biology and the complex interactions within the tumor microenvironment improves, there is gathering interest in and evidence for the role of immunomodulating agents in the management of cancer. Immune checkpoint inhibitors, which aim to hinder the inhibitory interaction between programmed cell death protein 1 (PD-1) and its ligand PD-L1, have demonstrated durable improvements in patient outcomes in many cancer types. Thus, pembrolizumab (anti-PD1) has been approved to treat HNSC, CESC, LUSC, and BLCA [33–35]. Clinical trials for pembrolizumab in ESCA are giving good responses [36]. Nivolumab has also reach FDA approval for HNSC, BLCA and LUSC [33–35]. Other existing immunotherapies include avelumab, atezolizumab and durvalumab for BLCA [34]. Although the use of immunomodulating agents in SCC treatment is giving good results, none of them are being used in first line so far and many patients do not respond. Therefore, future analyses and trials should focus on developing accurate response predictors to accelerate their use as first line in therapy.

4.2 Possible new therapies targeting SCCs biomarkers

Deep molecular analyses of SCCs, as explained above, suggest that certain targeted therapies, at different stages of clinical trial or approval, might be adequate for SCC treatment. These include targeting the following biomarkers:

i. PIK3CA, which encodes p110α, a catalytic subunit of phosphoinositide 3-kinase (PI3K). Activated PI3K can activate PDK1 and AKT, triggering downstream effects on transcription, protein synthesis, metabolism, proliferation and apoptosis. The gene is amplified or mutated in about 37% of SCCs (**Figure 1**), and constitutes the most frequently mutated oncogene in cancers like HNSC, CESC, ESCA and LUSC. A number of clinical trials with p110α inhibitors as possible antitumor therapies are currently running. We have recently identified that HPV(−), HNSC tumors that overexpress PIK3CA display poor outcome and activation of the YAP1-nuclear function, a transcriptional co-factor within the Hippo growth pathway [37]. Therapies targeting nuclear YAP1 might also be effective in a subgroup of SCC patients [38].

ii. CCND1, which encodes cyclin D1, is a cell-cycle protein that regulates transition from G1-to-S phase through the formation of complexes with cyclin dependent kinases (CDKs), such as CDK4 and CDK6. CCND1 is amplified in 20% of panSCCs, and in 93% within the iCluster iC25 (**Figure 1**). CCND1 amplification is associated with poor prognosis, cisplatin resistance and EGFR-inhibitor resistance in HNSC [39]. Although targeting of cyclin D1 is not currently feasible, there are inhibitors of its binding partners CDK4/CDK6, which might be useful in the CCND1 amplification setting [40].

iii. CDKN2A, which encodes $p16^{INK4A}$, is a CDK4/CDK6 inhibitor that regulates cell-cycle. CDKN2A is mutated or deleted in 43% of panSCCs, mostly in the iC25 cluster (50%) (**Figure 1**). Similar to CCND1 amplified tumors, CDKN2A mutated/deleted tumors might respond to CDK4/CDK6 inhibitors [40].

iv. EGFR, which encodes the epidermal growth factor receptor protein, is mutated or amplified in 11% of panSCCs, mainly in HPV(−) tumors. Although EGFR is an attractive target for therapy by either small-molecule inhibitors [41] or blocking antibodies [42], current EGFR-related therapies in SCC are limited to cetuximab antibody in HNSC. Good responses are observed to inhibitors in lung tumors with activating EGFR mutations, but they occur in adenocarcinomas not in lung SCCs. Further research should be done with EGFR-therapies in panSCCs, understanding mechanisms of action as well as probing response efficacy in preclinical models.

5. Conclusions

Squamous cell carcinomas arising from five different body sites (bladder, cervix uteri, lung, head and neck, and esophagus) share many molecular aberrations, so that the majority of them can be classified in 3 main molecular clusters (iC10, iC25 and iC27). Principal differences between clusters include HPV infection, genome-wide DNA-methylation and CNA, and mutations/CNA in subsets of cancer genes. Amplification in CCND1 is prevalent in iC25 samples, and TP53 and CDKN2A deleterious modifications in HPV(−) tumors. iC25 tumors are HPV(−), display frequent genome alterations and smoking patients, as well as poorer clinical outcome. Importantly, there exist common features between panSCC clusters, such as oncogene PIK3CA mutations/amplifications, amplification in TP63 and SOX2, or mutations in chromatin modifier regulators (like KMT2C and KMT2D). The comprehensive, panSCC molecular analyses suggest that current and future clinical trials targeting aberrations in signaling/cell adhesion pathways (PIK3CA and EGFR inhibitors) and cell-cycle control (CDK4/CDK6 inhibitors) might have a great impact on SCC treatment and independently of their body site. Future research efforts should focus on developing accurate biomarkers of immunotherapies. Finally, basic and clinical investigators should work together to discover SCC vulnerabilities and derive new treatments, as well as understanding basic mechanisms of oncogenesis, tumor progression and therapy resistance.

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Conflict of interest

No 'conflict of interest' to declare.

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