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Unraveling cancer lineage drivers in squamous cell carcinomas

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Abstract

Cancer hijacks embryonic development and adult wound repair mechanisms to fuel malignancy. Cancer frequently originates from de-regulated adult stem cells or progenitors, which are otherwise essential units for postnatal tissue remodeling and repair. Cancer genomics studies have revealed convergence of multiple cancers across organ sites, including squamous cell carcinomas (SCCs), a common group of cancers arising from the head and neck, esophagus, lung, cervix and skin. In this review, we summarize our current knowledge on the molecular drivers of SCCs, including these five major organ sites. We especially focus our discussion on lineage dependent driver genes and pathways, in the context of squamous development and stratification. We then use skin as a model to discuss the notion of field cancerization during SCC carcinogenesis, and cancer as a wound that never heals. Finally, we turn to the idea of context dependency widely observed in cancer driver genes, and outline literature support and possible explanations for their lineage specific functions. Through these discussions, we aim to provide an up-to-date summary of molecular mechanisms driving tumor plasticity in squamous cancers. Such basic knowledge will be helpful to inform the clinics for better stratifying cancer patients, revealing novel drug targets and providing effective treatment options.

Keywords

Squamous cell carcinomas; lineage driver; adult stem cells; skin; wounds

1. Introduction

The idea that cancer reactivates embryonic developmental pathways otherwise inaccessible to adult homeostatic tissues in order to sustain malignant behavior has drawn fascinations from cancer and development biologists for many decades. The similarity between cancer and adult wound repair has also gained increasing interests and are of recent intensive

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research focus (Arwert, Hoste, & Watt, 2012; Beachy, Karhadkar, & Berman, 2004; Dvorak, 1986; Ge & Fuchs, 2018; Martin et al., 2014; Nieto, 2013; Schafer & Werner, 2008). These hypotheses share a similar perspective and draw analogy between a malignant disease to embryonic development, injury repair and tissue regeneration, suggesting cancer hijacks embryogenesis or wound repair mechanisms to sustain malignancy.

Defined by the two golden standards, long-term self-renewal and multi-lineage differentiation (Till & McCulloch, 1961), adult stem cells are the essential units for postnatal tissue remodeling and repair. They come in different flavors: some are constantly cycling, such as those in the hematopoietic system, the gastrointestinal tract, and the skin; and others that are deeply quiescent unless confronted with injury, for example, the skeletal muscle and the brain. There are tissue types whose progenitor or differentiated cells can be adapted to tissue damage repair, such as the lung, the liver and the pancreas. Adult stem cells, or other resident cell types capable of adopting the fate to drive tissue repair and regeneration, are *bona fide* cells of origin in cancer.

Cancer plasticity mirrors that of adult stem cells bearing tissue repair responsibilities, regardless of whether they function in a constitutive or facultative fashion (Beck & Blanpain, 2013; Blanpain, 2013; Huntly & Gilliland, 2005; Meacham & Morrison, 2013; L. V. Nguyen, Vanner, Dirks, & Eaves, 2012; Pardal, Clarke, & Morrison, 2003; Reya, Morrison, Clarke, & Weissman, 2001; Stingl & Caldas, 2007; Visvader, 2011; Visvader & Lindeman, 2008). While embracing the enthusing marriage of cancer and stem cell biology, it is important not to over-interpret cancer stem cell as a new cell type, nor that they invent their own cellular machinery and molecular pathways. Rather, hallmarks of cancer (Hanahan & Weinberg, 2000, 2011) are manifestations of malignant cells hijacking the existing lineage programs of adult stem cells, and rewiring them from the steady state to a stress-induced network during tumorigenesis (Ge & Fuchs, 2018). Together with the coopted microenvironment (Dotto, 2014; Junttila & de Sauvage, 2013; Kalluri, 2003), they drive malignant initiation and progression.

It has been increasingly demonstrated in various cancer types, that tumor cells exhibit a lineage addiction phenotype and are heavily dependent on their specific lineage survival pathways based on their tissue of origin (Garraway & Lander, 2013; Garraway & Sellers, 2006). Such cancer vulnerability is rooted in lineage programs derived from embryonic development and postnatal injury repair. For example, melanoma is highly addicted to SOX10 and MITF transcription factors, both of which are master regulators of neural crest lineage development and differentiation, from which melanocytes and melanomas originate (Garraway et al., 2005). Basal cell carcinomas (BCCs) of the skin, exquisitely rely upon Sonic hedgehog signaling, mirroring hair follicle morphogenesis programs during embryogenesis (Youssef et al., 2012). Cutaneous squamous cell carcinomas (cSCCs) hijack adult wound repair mechanisms. In both cases, adult stem cells adopt expended fate to cope with stress, a phenomenon referred to as “lineage infidelity” (Ge et al., 2017). It is functionally required to sustain malignancy and to drive re-epithelialization during wound healing (Ge & Fuchs, 2018; Ge et al., 2017).

In this review article, we center our discussions around squamous cell carcinomas (SCCs), a common group of cancers, occurring in many organs. We survey up-to-date large-scale sequencing studies, and summarize genomic and molecular profiles of SCCs from the head and neck, esophagus, lung, cervix and skin. Cutaneous SCCs have been functionally characterized in genetically engineered mouse models (GEMMs), patient-derived tumor graft models, and *in vitro* cultures. Based on these studies, we review the idea behind cancer plasticity and lineage addiction, and how it relates to adult stem cell plasticity and wound repair. Finally, we discuss the translational significances and clinical implications based on our knowledge of cancer plasticity.

2. Squamous cell carcinomas of the stratified epithelia and squamous lineage convergence

SCCs are one of the most frequent human solid cancers that arise from the skin epithelia, the epithelial lining of respiratory, digestive, and genital tracts including the head and neck, esophagus, lung, cervix, and anogenital region, many exhibiting a poor prognosis (Dotto & Rustgi, 2016; Facompre, Nakagawa, Herlyn, & Basu, 2012). SCCs across different body sites exhibit strong resemblance in their histopathological features. The defining “squamous” characteristics include the presence of keratins, tonofilament bundles, hemidesmosomes and desmosomes. Notably, the relative frequencies of developing SCCs across these tissues differ. At the head and neck and anogenital regions and uterine cervix, the majority of cancers are SCCs. SCCs are also considerably frequent among esophageal and lung carcinomas, although their incidences are relatively lower than adenocarcinomas in these two organ sites. In general, SCCs are the second most common skin cancers next to BCCs; although this ratio is skewed in a subset of patient groups (discussed below).

Cancer genomic studies have revealed striking molecular convergence in mutational landscapes and molecular profiles across SCCs arising in various organs (Campbell et al., 2018; Dotto & Rustgi, 2016; Hoadley et al., 2018; Hoadley et al., 2014; Schwaederle, Elkin, Tomson, Carter, & Kurzrock, 2015). Below we compare the major SCC types and summarize our current understanding of their molecular alterations.

2.1. Head and neck squamous cell carcinomas

The majority of head and neck cancers are SCCs that develop in the upper aerodigestive mucosal epithelium, with an incidence of more than 650,000 cases per year worldwide, and have a 5-year survival rate of ~50% (Argjris, Karamouzis, Raben, & Ferris, 2008; Haddad & Shin, 2008). Strong risk factors include exposure to carcinogens including tobacco and alcohol (Argjris et al., 2008; Brennan et al., 1995; Haddad & Shin, 2008), alpha-type (mucosotropic) human papillomavirus (HPV) infection (D'Souza et al., 2007; Gillison et al., 2000; P. J. Snijders et al., 1992; Syrjanen, 2005), and genetic predisposition (Cloos et al., 1996; Hopkins et al., 2008; Kutler et al., 2003).

Despite being predominantly squamous cancer, HNSCCs are notoriously known for their heterogeneity, including histological subclasses (Woolgar & Triantafyllou, 2009), genomic alterations (Agrawal et al., 2011; Akagi et al., 2014; Beder et al., 2003; Berenson, Yang, &

Mickel, 1989; Bhattacharya et al., 2011; Bockmuhl et al., 1997; Cancer Genome Atlas Network, 2015a; C. H. Chung, Ely, et al., 2006; C. H. Chung, Parker, et al., 2006; Fadlullah et al., 2016; Hayes et al., 2016; Hedberg et al., 2016; Hermesen et al., 2001; Jin et al., 2006; Kalu et al., 2017; Lechner et al., 2013; Li et al., 2014; Maitra et al., 2013; Martin et al., 2014; McBride et al., 2014; Morris et al., 2017; Pickering et al., 2013; A. M. Snijders et al., 2005; Stransky et al., 2011; Sun et al., 2014; Walter et al., 2013; Zhao et al., 2011), and transcriptional signatures (Cancer Genome Atlas Network, 2015a; Cao et al., 2013; C. H. Chung et al., 2004; He et al., 2016; Martin et al., 2014; Walter et al., 2013).

HPV infection status is a major contributing factor in segregating HNSCCs' genomic and transcriptional landscapes. HPV impacts host function via protein interactions (Eckhardt et al., 2018), or via integration into the host genome, which may additionally affect host gene expression (Parfenov et al., 2014). HPV+ HNSCCs exhibit distinct gene expression profiles (Slebos et al., 2006), copy number alterations (Klussmann et al., 2009; Smeets et al., 2006), and mutational preferences (Gaykalova et al., 2014; Gillison et al., 2019; Keck et al., 2015; Seiwert et al., 2015). Not surprisingly, HPV+ HNSCCs strongly cluster with other HPV+ tumors (mainly CxSCC, see below) based on pan-SCCs integrative comparisons, known as "iCluster 27" (Campbell et al., 2018; Hoadley et al., 2018) (Figure 1). In most SCCs HPV infections and TP53 mutations are mutually exclusive (Balz et al., 2003; Braakhuis et al., 2004; Hafkamp et al., 2003; Westra et al., 2008). Unlike HPV- HNSCCs, HPV+ ones preserve wild type alleles of TP53 and CDKN2A, and lack EGFR mutations (Cancer Genome Atlas Network, 2015a; C. H. Chung, Ely, et al., 2006). Instead, they are uniquely mutated in TRAF3 and E2F1 (Cancer Genome Atlas Network, 2015a). Of importance, HPV + HNSCCs typically exhibit better prognosis compared to the HPV- group (Ang et al., 2010; Ragin & Taioli, 2007), potentially associated with the preponderant wild type status of TP53 in the former group (Poeta et al., 2007; Zhou, Liu, & Myers, 2016).

Among HPV- HNSCCs, it is interesting to note two subgroups that are uniquely distinct from the rest of HPV- tumors, and rather share some common traits with HPV+ tumors. One subgroup has remarkably low copy number alterations just as HPV+ tumors (Cancer Genome Atlas Network, 2015a). Both HPV+ and this subgroup of HPV- HNSCCs belong to the "M" class tumors (Figure 1), known as cancers dominated by mutational alterations, as opposed to the "C" class tumors dominated by copy number changes (Ciriello et al., 2013). In particular, these HPV- HNSCCs include tumors with HRAS-activating-mutations and are mutually exclusive of TP53 mutations (Figure 1). Importantly, this subgroup of TP53 wild type HPV- HNSCCs also tend to exhibit better prognosis similar to HPV+ tumors (Smeets et al., 2009). Meanwhile, most HNSCCs with CASP8-inactivating-mutations also reside within this group, many with co-occurring HRAS mutations. These HRAS-CASP8 mutated tumors, however, differ from their HPV+ counterparts in their methylation patterns, and each belongs to a hypermethylated cluster "C4" and "C2", respectively, when comparing across Pan-SCCs, resulting in suppressed candidate drivers e.g., TET1, FANCF and PAPRG (Campbell et al., 2018). Transcriptionally, they both fall under the umbrella of so-called "basal" group (Cancer Genome Atlas Network, 2015a; C. H. Chung et al., 2004; Walter et al., 2013). Unlike HPV+ group, "basal" group diverges considerably at the genomic level, encompassing tumors with HRAS/CASP8 mutations, NOTCH1 mutations, and those with 11q amplification (Cancer Genome Atlas Network,

2015a). The latter is a signature shared across SCCs known as “iCluster 25” (Campbell et al., 2018; Hoadley et al., 2018) (Figure 1).

Another subgroup of HPV– HNSCCs intriguingly share transcriptional signature with HPV + tumors, so called the “atypical” group (Cancer Genome Atlas Network, 2015a; C. H. Chung et al., 2004; Walter et al., 2013) (Figure 1). The molecular basis for such transcriptional convergence is unclear, as their mutational landscape differs quite significantly. The atypical subgroup of HPV– HNSCCs, unlike HPV+ counterparts, have a plethora of common HNSCC mutations including the universal loss of TP53 and CDKN2A. In contrast to HPV+ tumors which occur predominantly in the oropharynx, this subgroup is enriched for laryngeal tumors and is associated with heavy smoking history (Cancer Genome Atlas Network, 2015a). In this regard, it shares similarity with another “classical” group which is also the main smoking group, commonly occurring in the larynx (Figure 1). These two groups contain the most NFE2L2/KEAP1 mutations resulting in aberrant NRF2 signaling, harbor the majority of NSD1 mutations, and maintain NOTCH wild type status. NFE2L2/KEAP1 mutated and NSD1 mutated tumors however exhibit minimal overlap with each other, and each belong to a methylation cluster “C1” and “C5”, respectively. In particular, methylation C5 cluster exhibits a strong association with NSD1 mutations, and presents a unique hypomethylation pattern with activation of putative drivers, e.g., LCK, suggesting (Campbell et al., 2018; Cancer Genome Atlas Network, 2015a), suggesting a potential functional interaction between NSD1 and hypomethylation landscape within this group of HNSCCs. In addition, “classical” HPV– group tends to be enriched with HNSCCs harboring 3q26-3q28 amplification, the genomic region containing SOX2/PIK3CA/TP63 genes, even though it occurs universally in all groups. In contrast, activating mutations in PIK3CA is prevalent in the “atypical” HPV– group (Cancer Genome Atlas Network, 2015a).

The remaining HPV– tumors have been referred to as the “mesenchymal” group, which exhibit intermediate levels of either 3q amplifications or NOTCH mutations, compared to classical and atypical groups, respectively. One caveat here could be that the stromal interference may mask tumor parenchymal alterations, thus, skewing molecular classifications. While the objective is to focus on samples with high tumor purity, and/or bioinformatically deconvolute such complexity, given the intertwined nature of tumor and its microenvironment in solid malignancies, the alternative approaches using single cell sequencing to dissect HNSCC heterogeneity (Puram et al., 2017), or FACS-sorting to enrich for epithelial cells using well-established cell-surface markers while excluding other lineages prior to sequencing are thereby warranted.

2.2 Esophageal squamous cell carcinomas

Esophageal carcinomas consist of two major types. Esophageal squamous cell carcinoma (ESCC) is prevalent worldwide, with an incidence of more than 450,000 cases per year, and is particularly common in certain regions of Asia. On the other hand, esophageal adenocarcinoma (ESAC) has a higher incidence in Western countries. Esophageal cancer patients have a 5-year overall survival rate of ~15%. Smoking and alcohol are common risk factors, which can synergistically couple with genetic variations to enhance esophageal

cancer risk (Cui et al., 2009; Rustgi & El-Serag, 2014). Unlike those in HNSCCs where HPV has well-established roles, involvement of HPV has been reported (Ludmir, Stephens, Palta, Willett, & Czito, 2015) but not confirmed for ESCC (Cancer Genome Atlas Network, 2017). Rather, Epstein-Barr virus (EBV) infection, has been strongly associated with ESCC (Shah & Young, 2009), similar to a small group of HNSCC, the non-keratinized nasopharyngeal carcinoma (Shah & Young, 2009).

Genomic and molecular profiling of ESCCs have revealed commonly mutated pathways in cell cycle control, epigenetic regulation, and development (Cheng et al., 2016; Gao et al., 2014; Lin et al., 2014; Mathe et al., 2009; Qin et al., 2016; Sawada et al., 2016; Song et al., 2014; L. Zhang et al., 2015), many of which are also observed in SCCs from other organ sites. Together with ESACs (Bandla et al., 2012; Cancer Genome Atlas Network, 2017; L. Zhang et al., 2015), these studies highlighted common themes behind esophageal cancers and are very well conserved in other organs sites.

First of all, a clear divergence between ESCC and ESAC has been identified: ESACs are much closer to the adenocarcinomas of the stomach and present highly different molecular portraits than ESCCs (Cancer Genome Atlas Network, 2014a; Dulak et al., 2012; K. Wang et al., 2014). ESCCs are strongly enriched for amplifications of CCND1, 3q26-3q28, FGFR1, and mutations of NOTCH1, ZNF750, KDM6A (UTX), whereas EACs are specifically enriched for amplifications of ERBB2, VEGFA, GATA4, GATA6, and mutations in SMAD4 and ARID1A (Cancer Genome Atlas Network, 2017). CDKN2A is inactivated in both, yet it is mainly through deletion in ESCCs and epigenetic silencing in EACs (Cancer Genome Atlas Network, 2017). Divergence within esophageal carcinomas into ESCC and EAC is analogous to those observed in the lung (discussed below), and provides strong rationale for segregation of patient populations in clinical trials and treatments.

Next, ESCCs show a characteristic convergence with the rest of SCCs from other organ sites in terms of molecular subtypes (Figure 1). Based on integrated molecular characterizations (Shen, Olshen, & Ladanyi, 2009), ESCCs are further segregated into two major groups, ESCC1 and ESCC2 (Cancer Genome Atlas Network, 2017). ESCC1 is prevalent in Asian patients, exhibits highly aberrant NRF2 signaling due to NFE2L2/KEAP1/CUL3 mutations, accompanied with characteristic 3q amplification. These genomic alterations are strongly reminiscent to the HPV– “atypical” and “classical” HNSCC groups aforementioned (Cancer Genome Atlas Network, 2015a) (Figure 1).

A second ESCC subgroup, ESCC2 appears more common in East European and South American populations, exhibiting frequent NOTCH1 and ZNF750 mutations, features shared with the HNSCCs “basal” subgroup (Cancer Genome Atlas Network, 2015a) (Figure 1). APOBEC mutational signature is stronger in ESCCs compared to EACs, and appears to be further enriched in this particular ESCC2 group, especially patients from Ukraine and Russia. ESCC2 also has higher leukocyte infiltration (Cancer Genome Atlas Network, 2017), an interesting observation that may be further investigated in similar subgroups from other SCCs.

A third ESCC subgroup, ESCC3 has only very few cases and are found in North America populations, characterized by mutations in *ATG7*, *KMT2D* (*MLL2*), *PTEN*, *PIK3CA* (activating), with lower *TP53* mutation rates compared to other ESCCs. All four ESCC3 cases under study uniquely harbor *SMARCA4* mutations not shared with any other SCCs (Cancer Genome Atlas Network, 2017). In this regard, *SMARCA4* is frequently mutated in EAC (Cancer Genome Atlas Network, 2017) and LAC (Cancer Genome Atlas Network, 2014c), suggesting a potential close relationship between ESCC3 subgroup and adenocarcinomas.

2.3 Lung squamous cell carcinomas

Lung carcinomas, occurring at an incidence of 1.8 million cases per year world-wide, are divided into two major types, non-small cell lung cancer (NSCLC), which includes both lung adenocarcinoma (LAC) and lung squamous cell carcinoma (LSCC) and small cell lung cancer (SCLC), referring to small cell neuroendocrine carcinoma (SCNC). The 5-year survival rate for late stage lung cancer patients is only ~5%. Cigarette smoking is prevalent in North American patients, and strongly contributes to all histological types (Kenfeld, Wei, Stampfer, Rosner, & Colditz, 2008).

As lung cancers divergent into LAC, LSCC and SCNC, they also exhibit cross-organ convergence. For example, SCNCs are rare neuroendocrine cancers occurring in several organs, and lung SCNCs highly resemble SCNCs in the prostate at the molecular level, revealing a common neuroendocrine lineage program (Balanis et al., 2019; Park et al., 2018) and remarkable cancer plasticity (Niederst et al., 2015; Sequist et al., 2011) and prostate SCNC (Beltran et al., 2016; Ku et al., 2017; Mu et al., 2017; Zou et al., 2017). An important theme that has emerged through evaluation of SCNCs is that cell cycle regulators such as *RB* and *TP53*, are the likely master regulators of lineage reprogramming, and serve as barrier to cancer plasticity (Ku et al., 2017; Mu et al., 2017; Tan et al., 2014; Tschaharganeh et al., 2014; Weissmueller et al., 2014; J. Zhu et al., 2015; Zou et al., 2017).

Likewise, LSCCs converge with other SCCs at the level of copy number alterations (Bass et al., 2009; Beroukhim et al., 2010; Dutt et al., 2011; Hammerman et al., 2012; Ramos et al., 2009; Tonon et al., 2005) and somatic mutations (Hammerman et al., 2012; Hammerman et al., 2011; Kan et al., 2010; Kim et al., 2014; C. Li et al., 2015; Weiss et al., 2010). Based on integrated molecular analysis (Shen et al., 2009), LSCC can be subdivided into four distinct groups, exhibiting different genomic alternations, gene expression signatures, and prognosis (Hammerman et al., 2012; Wilkerson et al., 2010) (Figure 1). The “classical” group strongly resembles those of “classical” HNSCCs and ESCC1 tumors (Figure 1), exhibiting high level of *NRF2* signaling deregulation due to *NFE2L2/KEAP1/CUL3* mutations. Consistently, classical group also exhibits highest amount of hypermethylation, chromatin instability, and elevated levels of 3q26-3q28 amplification. Largely absent in this group are *NOTCH* mutations, along with newly discovered *ASCL4* and *FOXP1* mutations (Hammerman et al., 2012). This is reminiscent of cases observed in HNSCC and ESCCs, where *NOTCH* mutations are enriched in the “basal” group, but not in the “classical” group (Figure 1). Interestingly, LSCC “basal” group exhibits *NF1* mutations that are uncommon in other SCCs. The remaining two subgroups of LSCCs, “primitive”, and “secretory”, do not seem to

have clear transcriptional counterparts in the other SCC types. When focusing on methylation patterns, it is clear that a large proportion of LSCCs constitute a major group of methylation cluster “C3” featured with distinct hypomethylation patterns (Campbell et al., 2018)(Figure 1).

Similar to esophagus, LSCCs are clearly distinct from LAC (Campbell et al., 2016). Although many copy number alterations are shared between them, the 3q SOX2/TP63/PIK3CA amplicon is specific to LSCC (Tonon et al., 2005), similar to the “classical” HPV–HNSCCs. In contrast, NKX2-1 amplification, KRAS activation and STK11 inactivation are frequent in LAC (Weir et al., 2007) but are rare in LSCCs. EGFR alterations have been found in both, although their frequencies and types of mutations differ (Cancer Genome Atlas Network, 2014c; Rekhtman et al., 2012). Therapeutically targetable oncogenic fusion events specific for LACs, e.g., ALK, are absent in LSCCs (Cancer Genome Atlas Network, 2014c). In this regard, efforts have been made to seek targetable oncogenic events enriched in LSCCs, e.g., DDR2 and FGFR mutations (Dutt et al., 2011; Hammerman et al., 2011; Hedberg et al., 2016; Liao et al., 2013; Weiss et al., 2010).

2.4 Cervical squamous cell carcinomas

Cervical carcinoma is the most common gynecological tumor, with an incidence of 570,000 cases per year worldwide. While patients presenting with early localized disease can be successfully treated with surgery or radiation, only 56% and 17% of patients remain alive at 5-years after diagnosis, when presenting with regional and distal metastasis, respectively. Ninety-five percent of cervical cancers are caused by persistent infections with carcinogenic alpha-type HPVs (Munoz et al., 2003; Schiffman et al., 2011; Uyar & Rader, 2014; Walboomers et al., 1999; zur Hausen, 2002). Effective vaccines against high-risk HPVs have been developed although the vaccination rate remains unsatisfactory.

Uterine cervical carcinomas are mainly squamous carcinomas (CxSCCs), followed by adenocarcinomas, with occasional cases of adenosquamous carcinomas. Again, genomic landscapes clearly segregate cervix cancers into several groups (Cancer Genome Atlas Research et al., 2017; T. K. Chung et al., 2015; Muller et al., 2015; Ojesina et al., 2014). Cervical adenocarcinomas belong to the “adeno” subgroup based on integrative molecular analysis, and diverge from CxSCCs with frequent amplifications of 17q12 (ERBB2), BCAR4 long non-coding RNA, 13q22 (KLF5), significant activation of hormonal signaling and ER α , FOXA1, FOXA2, FGFR1 pathways, and expression of KRT18 (non-stratified simple epithelial keratin). Overall, the cervical adenocarcinomas closely resemble endometrial carcinomas, whereas CxSCCs converge with HNSCCs, particularly the HPV+ HNSCCs (Cancer Genome Atlas Research et al., 2017). APOBEC mutagenesis signature is pronounced in cervical cancers across all groups, but is infrequent in the minority HPV–group, which is more closely related to endometrial carcinomas.

Under the similar integrative molecular analysis, CxSCCs can be further divided into 2 subgroups “keratin-high” and “keratin-low”. The former exhibits stronger squamous characteristics with higher level of TP63, squamous keratins e.g. KRT5, KRT6A, squamous miRNAs miR-205, miR-499. Keratin-high group is also enriched with PIK3CA, MAPK1, NFE2L2 and TGFBR2 mutations. In contrast, keratin-low group presents with relatively

higher frequencies of YAP activation (11q22 focal amplification) and epithelial-mesenchymal transition (EMT) features, including high levels of miR200a/b, intact TGFBR2 and suppressed ECAD. Like HPV+ HNSCCs, TP53 and CDKN2A are intact in CxSCCs. Distinct from other SCCs, in CxSCCs TP63 is co-amplified with TERC/MECOM but not SOX2/PIK3CA. NOTCH mutations are notably absent in CxSCCs. They also exhibit higher level of 11q22 focal amplifications compared to HPV– SCCs (Campbell et al., 2018; Cancer Genome Atlas Research et al., 2017). All of these CxSCC-specific characteristics highlight the unique biology behind HPV+ cancers.

2.5 Squamous-like carcinomas of other organs

While SCCs are common in the aforementioned organs, SCCs can also arise rarely in other organs such as the urinary bladder (Botelho, Machado, Brindley, & Correia da Costa, 2011; Odegaard & Hsieh, 2014), breast (Grabowski, Saltzstein, Sadler, & Blair, 2009), prostate (Malik et al., 2011), and thyroid (Tunio, Al Asiri, Fagih, & Akasha, 2012), as a result of chronic inflammation or metaplasia. Moreover, several organs can develop aggressive “squamous-like” carcinomas. A group of bladder cancers has been reported to express ‘basal and squamous’ markers including keratins, forming a tight cluster (Cancer Genome Atlas Network, 2014b; Ho, Kurtova, & Chan, 2012; Sjodahl et al., 2012) (Figure 1). Particularly, bladder SCCs are known to be associated with *Schistosoma haematobium* infections, due to either direct carcinogenic effect of their metabolites or more likely secondary to chronic inflammation (Botelho et al., 2011; Odegaard & Hsieh, 2014). In addition, some pancreatic ductal adenocarcinomas (PDACs) also exhibit clear squamous features (Figure 1) and are characterized by worse survival (Bailey et al., 2016; Collisson et al., 2011; Moffitt et al., 2015). Of significance, TP63, a classical basal squamous master regulator, is functionally involved in PDAC invasiveness (Bailey et al., 2016; Weissmueller et al., 2014), suggesting that some of the genes contributing to the squamous phenotype, beyond being biomarkers, could also be *bona fide* cancer drivers and are, thus putative therapeutic targets.

Another group of cancers that show similarities to SCCs is the basal-like subtype of breast cancer (Figure 1) (including the aggressive triple-negative subgroup) and they are also known to share a molecular profile with LSCC (C. H. Chung, Bernard, & Perou, 2002). This resemblance can also be extrapolated to other gynecological tumors including ovarian cancers (Hoadley et al., 2014). Of note, TP63 signaling is activated in these basal-like breast and ovarian cancers, yet appears to be still stronger in SCC subgroup (Hoadley et al., 2014).

Together, there are multiple implications behind such molecular convergence of squamous cancers (Figure 1). From the view of development biology and cancer cell of origin, it reflects common lineage specification and differentiation programs among these epithelial cells across different organs. From a cancer therapeutic perspective, drugs that are efficient in a particular disease subgroup may be effectively used to treat cancers of different organs exhibiting similar molecular signatures. Therefore, future studies geared toward identifying new and specific driver genes or pathways that lead to squamous lineage acquisition and dependency are likely to aid the discovery of cancer specific vulnerabilities and novel drug targets.

3. Lessons from skin SCC genomics and “cancer are wounds that never heal”

The sheer abundance of non-melanoma skin cancers including BCC and SCC, occurring at an incidence of 2 to 3 million cases per year world-wide, exerts a substantial burden on our healthcare and society (Alam & Ratner, 2001; Johnson, Rowe, Nelson, & Swanson, 1992; Madan, Lear, & Szeimies, 2010; Nagarajan et al., 2019). While ultraviolet light (UV) exposure is the principal risk factor for skin cancer, interesting association of certain types of HPV with cutaneous SCCs (cSCCs) have been observed (Nagarajan et al., 2019). Although cSCCs are easily treated in the general population, a subset of patients develops highly aggressive disease with extremely poor prognosis (Lawrence & Cotel, 1994). Surgical, radiation and chemotherapies remain as standard treatments with low efficacy for metastatic disease, until the recent advent of immunotherapy, which has resulted in exceptionally high response rates (Gross et al., 2019; Migden et al., 2018).

To date, numerous studies have been conducted to interrogate mutational landscapes of cSCCs (Brown et al., 2004; Cho et al., 2018; Durinck et al., 2011; Y. Y. Li et al., 2015; Oberholzer et al., 2012; Pickering et al., 2014; Purdie et al., 2009; South et al., 2014; N. J. Wang et al., 2011). Indeed, many mutations and altered pathways are shared with SCCs from other organ sites, including alternations in HRAS and PI3K signaling, squamous differentiation genes, cell cycle regulators, and epigenetic regulators. Interestingly, NOTCH mutation rate appears to be much higher in cSCCs compared to other SCCs, and HRAS/CASP8 mutations are also prevalent in cSCC, similar to the basal groups of other SCCs (Figure 1). On the other hand, it remains unclear whether a group of 3q amplification, NRF2 de-regulation, or NSD1 mutation has an equivalent counterpart in cSCC, given UV damage rather than smoking is top risk factors for skin cancer. Besides discovering recurrent mutations, several important insights into the fundamental properties of adult normal epithelia can be learned from genomic studies of cSCCs.

Mutations in cancer drivers such as TP53 (Brash et al., 1991; Pierceall, Mukhopadhyay, Goldberg, & Ananthaswamy, 1991), NOTCH (Durinck et al., 2011; Pickering et al., 2014; South et al., 2014) and HRAS (Daya-Grosjean, Robert, Drougard, Suarez, & Sarasin, 1993; Pierceall, Goldberg, Tainsky, Mukhopadhyay, & Ananthaswamy, 1991) are all frequent events in cSCC. Interestingly, they occur relatively early rather than late in skin SCCs, and many are found in adjacent ‘normal’ tissues (Durinck et al., 2011; South et al., 2014), consistent with ‘field cancerization’ (Braakhuis, Tabor, Kummer, Leemans, & Brakenhoff, 2003; Leemans, Braakhuis, & Brakenhoff 2011). Field cancerization was initially described in HNSCCs, where it has been frequently observed that local secondary tumours could occur at the site of surgically removed primary tumours (sporadic non-familial cases), suggesting a cancerous ‘field’ of pre-malignant tissues or mutations in the peritumoral epithelia (Slaughter, Southwick, & Smejkal, 1953). The key idea behind this concept is also shared with the model of multi-step carcinogenesis (Fearon, Hamilton, & Vogelstein, 1987; Fearon & Vogelstein, 1990), such that peritumoral tissues are no longer considered “normal”, but often contain several early tumorigenic genetic events (Tomasetti, Vogelstein, & Parmigiani, 2013). Besides HNSCCs (Califano et al., 1996), field cancerization has also been observed

in many other carcinomas including lung (Franklin et al., 1997), esophagus (Prevo, Sanchez, Galipeau, & Reid, 1999), urinary tract (T. Takahashi et al., 1998), cervix (Chu, Shen, Lee, & Liu, 1999) and vulva (Rosenthal, Ryan, Hopster, & Jacobs, 2002). TP53 mutations are also known to occur in a patchy fashion (Garcia et al., 1999)(Tabor et al., 2002; Tabor et al., 2001; van Houten et al., 2002), involving the otherwise normal epithelial mucosa of these abovementioned tissues, and most notably in the skin epidermis (Brash & Haseltine, 1982; Brash et al., 1991; Chao, Eck, Brash, Maley, & Luebeck, 2008; Jonason et al., 1996; Klein, Brash, Jones, & Simons, 2010; W. Zhang Remenyik, Zelterman, Brash, & Wikonkal, 2001; Ziegler et al., 1994). Besides epithelial cancers, analogous examples have been found in haematological malignancies, known as pre-leukemic clones in bone marrow (Challen et al., 2011; Corces-Zimmerman, Hong Weissman, Medeiros, & Majeti, 2014; Laurie et al., 2012; Shlush et al., 2014). Of importance, clonal haematopoiesis is directly associated with the risk of therapy-related myeloid neoplasms (K. Takahashi et al., 2017). Recent examples include the 'normal' eyelid skin (Martincorena et al., 2015), and esophageal mucosa (Martincorena et al., 2018; Yokoyama et al., 2019). In the case of esophagus, the frequencies of cancer driver mutations could be even higher in normal than cancer (Martincorena et al., 2018), and may occur as early as infancy (Yokoyama et al., 2019). Mechanistically, differentiation imbalance in single esophageal progenitor cells (Alcolea et al., 2014), aberrant signals from the mesenchyme (Hu et al., 2012), clonal selection during regeneration (M. Zhu et al., 2019), or cell competition during embryonic development (Ellis et al., 2019) are all pertinent possibilities that could lead to field change in normal tissues.

While "field cancerization" suggests malignant recurrence originates from peritumoral tissues, the idea "tumors are wounds that never heals" postulates that cancer has its roots in chronic wounds (Balkwill & Mantovani, 2001; Coussens & Werb, 2002; Dvorak, 1986; Ge & Fuchs, 2018; Ge et al., 2017; Schafer & Werner, 2008). Indeed, transcriptional similarities have been widely observed between wounds and tumors in various tissues (Chang et al., 2004; Iyer et al., 1999; Lambert et al., 2014; Pedersen et al., 2003; Riss et al., 2006). Skin is an excellent model to study both wound healing and carcinogenesis. The epidermis harbors highly abundant, well-defined and genetically accessible adult stem cells, responsible for appendage (hair follicles, nails, sebaceous, eccrine and apocrine glands) regeneration, wound repair and tumor development (Balmain & Yuspa, 2014; Benitah, 2012; Blanpain & Fuchs, 2014; Chuong, Cotsarelis, & Stenn, 2007; DeStefano & Christiano, 2014; Ge & Fuchs, 2018; Gurtner, Werner, Barrandon, & Longaker, 2008; Hsu, Li, & Fuchs, 2014; Khavari, 2006; C. Lu & Fuchs, 2014; Millar, 2002; Paus & Cotsarelis, 1999; Rompolas & Greco, 2014; Schepeler, Page, & Jensen, 2014; Takeo, Lee, & Ito, 2015; Wabik & Jones, 2015; Watt, 2014). Historically, organotypical cultures of human skin (proto-type of nowadays organoids) have been the front runner in regenerative and translational medicine due to its effective treatment of burn patients (Gallico, O'Connor, Compton, Kehinde, & Green, 1984; Rheinwald & Green, 1975). *In vivo* lineage tracing in GEMMs has revealed the cell-of-origin for cSCCs (Lapouge et al., 2011; White et al., 2011). Recent work in the skin has dived deeper into functional significance underlying the observed similarities between wounds and cancer, shedding light on the role of adult stem cells in driving wound repair and cancer progression (Ge et al., 2017).

Many types of skin chronic wounds may predispose patients to cSCCs, and precursor lesions may develop into cSCCs (Alam & Ratner, 2001). Chronically injured skin, including regions affected by non-healing ulcers (Enoch, Miller, Price, & Harding, 2004; Kerr-Valentic, Samimi, Rohlen, Agarwal, & Rockwell, 2009), sinus tracts, osteomyelitis, radiation dermatitis, or vaccination scars, and chronic inflammatory disorders including discoid lupus erythematosus, lichen sclerosus, lichen planus, dystrophic epidermolysis bullosa (Bastin, Steeves, & Richards, 1997), and lupus vulgaris, are all predisposing factors of cSCCs. Actinic keratosis is a classic precursor lesion of cSCC (Callen, Bickers, & Moy, 1997), along with other potential precursor lesions or SCC variants including epidermodysplasia verruciformis, Bowen's disease and Bowenoid papulosis, erythroplasia of Queyrat, keratoacanthoma, and verrucous carcinoma (Alam & Ratner, 2001). SCCs of other organ sites also have similar precursor lesions, such as oral leukoplakia (Mao et al., 1996) potentially progressing into HNSCC, and Barretts esophagus (Rustgi & El-Serag, 2014; Spechler & Souza, 2014) developing into EAC and/or rarely, ESCC.

Besides chronic wounds, various therapeutic agents may also increase the risk for development of cSCCs, a common secondary malignancy. These disease-predisposed individuals or skin regions may harbor cancerous fields or non-healing wounds, providing a conceptual explanation of increased cancer incidence and severity. cSCCs are known to frequently arise in 15-30% patients receiving the BRAF inhibitors such as vemurafenib, dabrafenib or sorafenib (Arnault et al., 2009; Belum, Fontanilla Patel, Lacouture, & Rodeck, 2013; F. Su et al., 2012). This is likely due to the paradoxical MAPK-pathway activation upon BRAF inhibition (Hall-Jackson et al., 1999; Hatzivassiliou et al., 2010; Heidorn et al., 2010; Poulikakos, Zhang, Bollag, Shokat, & Rosen, 2010). Interestingly, HRAS mutations are relatively infrequent in primary tumors, but become highly enriched in BRAF inhibitor treated tumors (Oberholzer et al., 2012; South et al., 2014), pointing to a predominant role for HRAS in driving secondary cSCCs. Indeed, mouse models of cSCCs are particularly addicted to HRAS activating mutations and high level of pERK signaling (Balmain, Ramsden, Bowden, & Smith, 1984; Burns, Jack, Neilson, Haddow, & Balmain, 1991; Quintanilla, Brown, Ramsden, & Balmain, 1986; Quintanilla et al., 1991).

A group of aggressive cSCCs are known to develop in organ transplantation recipients, heavily associated with immune-suppression (Berg & Otley, 2002; Boukamp, 2005; Euvrard, Kanitakis, & Claudy, 2003; Rangwala & Tsai, 2011). This is particularly prominent in renal (Birkeland et al., 1995; Bouwes Bavinck et al., 1996; Dantal et al., 1998; Hartevelt, Bavinck, Kootte, Vermeer, & Vandenbroucke, 1990; Jensen et al., 1999; Lindelof, Sigurgeirsson, Gabel, & Stern, 2000; Ramsay, Fryer, Hawley, Smith, & Harden, 2002) and heart (Jensen et al., 1999; Veness et al., 1999) transplant recipients, and occur at moderate rates among hematopoietic stem cell transplant recipients (Dargent, Kornreich, Andre, & Lespagnard, 1998; Hasegawa et al., 2005; Leisenring, Friedman, Flowers, Schwartz, & Deeg, 2006; Lishner et al., 1990; Rizzo et al., 2009). Although recipients of solid organ transplants are known to have 3-4-fold increased risk of developing malignancies in general, their risk for cSCCs is particularly noticeable with up to 250-fold (Harwood et al., 2013; Pelisson, Soler, Chardonnet, Euvrard, & Schmitt, 1996; Penn, 2000). cSCCs from these patients are also more aggressive (Euvrard et al., 1995; Lott, Manz, Koch, & Lorenz, 2010; Veness et al., 1999), and exhibit different characteristics than the general population,

including altered rates of oncogenic mutations and HPV infections (Pelisson et al., 1996), poor prognosis and increased incidence of metastasis (Carucci et al., 2004; Martinez et al., 2003; Wells & Shirai, 2012). Of note, the fact that incidences of SCCs and BCCs are completely reversed in this subset of patients compared to the general population, and additionally the up-to-100 fold increase of SCCs in the anogenital regions (Boukamp, 2005; Euvrard et al., 2003) strongly implicates these patients' specific susceptibility to squamous cancers rather than a non-discriminative predisposition of all skin cancer incidences. Changing immune suppressive agent and/or dose (Dantal et al., 1998; Guba, Graeb, Jauch, & Geissler, 2004; Otley, Coldiron, Stasko, & Goldman, 2001; Otley & Maragh, 2005) significantly altered the course of cSCC development in these patients, suggesting a direct mechanistic link between cSCCs and immune modulation. In this regard, the use of a combination of oral methoxsalen, cyclosporine, and UVA radiation for the treatment of psoriasis and other chronic dermatoses is associated with an elevated risk of cSCC (Forman, Roenigk, Caro, & Magid, 1989; Marcil & Stern, 2001; Stern et al., 1984). Interestingly, the calcineurin inhibitor cyclosporine as an immune-suppressant not only inhibits skin resident Langerhans cells (Borghi-Cirri et al., 2001; Dupuy, Bagot, Michel, Descourt, & Dubertret, 1991) and dendritic cells (Abdul, Charron, & Haziot, 2008; Sauma et al., 2003), but also directly acts on tumor epithelial cells in a cell-autonomous manner (Han, Ming, He, & He, 2010; Hojo et al., 1999; Walsh et al., 2011; X. Wu et al., 2010) to promote tumor progression. Many other immune-suppressive drugs include tacrolimus (another calcineurin inhibitor), azathioprine and mycophenolate mofetil (inhibitors of purine synthesis), rapamycin analogs (mTOR inhibitors), monoclonal antibodies against TNF α and IL-12/IL-23, or glucocorticoid have been under intensive studies in their relationship with non-melanoma skin cancer development (Euvrard et al., 2003; Rangwala & Tsai, 2011).

Finally, cSCCs are also among the top secondary tumors observed in chronic lymphocytic leukemia (CLL) patients (Adami, Frisch, Yuen, Glimelius, & Melbye, 1995; Manusow & Weinerman, 1975; Mehrany, Weenig, Pittelkow, Roenigk, & Otley, 2005; Onajin & Brewer, 2012), a low-grade clonal B-cell lymphoproliferative disorder, accounting for 25% of all leukemias in developed countries. In contrast to solid organ transplant recipients where cSCC rate is exceptionally high, in CLL patients, BCCs and HNSCCs are also similarly elevated (Wong et al., 2008). Metastasis and mortality due to cSCCs are found to be increased in these patients (Mehrany, Weenig, Lee, Pittelkow, & Otley, 2005). Immune-dysregulation has been proposed to contribute to development of these second malignancies. Intriguingly, neoplastic B cells may infiltrate cSCCs and compromise anti-tumor T cell responses (Dargent et al., 1998; Smoller & Warnke, 1998). Besides immune dysfunction, the confounding factors of chemo- and radiation therapies as well as common genetic alterations have also been suggested, although a direct causal relationship is yet to be established (Mehrany, Weenig, Lee, et al., 2005).

Future studies of integrated molecular profiling and characterizations of cSCCs, both primary and secondary malignancies as discussed above, will be important to further provide deep mechanistic understanding of squamous carcinogenesis. Of particular biological and therapeutic relevance would be to compare cSCCs to SCCs from other organs, as well as to clinical cases of skin wounds and chronic inflammatory dermatoses, aiming to reveal the

functional significance behind squamous lineage convergence in the context of cancer as a non-healing wound.

4. Cancer drivers of the squamous lineage and their context dependency

As cancer genomic studies continue to provide deep insights into cancer drivers, functional studies using GEMMs, patient derived xenograft and organoid models, combined with well-characterized cancer cell line cultures {Behan, 2019 #18069}{Tsherniak, 2017 #18070}{Barretina, 2012 #9639}{Ghandi, 2019 #18071}, together offer comprehensive toolkits to define and refine cancer genes. No models are perfect, but all are useful and complementary to each other. A combination of these mouse models and human samples offers functional validation and drug screening platforms, while providing opportunity for in depth mechanistic dissection of driver programs, a prerequisite knowledge to truly advance cancer therapy.

Many pathways have been repeatedly revealed to be essential for SCCs across various sites, including cell cycle, squamous differentiation and developmental genes, oxidative stress regulators, and epigenetic factors (Dotto & Rustgi, 2016). Here we focus our discussion on frequent alterations that differentiate SCCs from the rest of cancer types (Figure 2). Notably, for driver genes universally altered in many cancers, often the mutation outcomes and mechanisms of action are distinct among cancer types, raising the critical issue of context dependency (Schneider, Schmidt-Supprian, Rad, & Saur, 2017). Studies using various pre-clinical GEMMs and cellular models have revealed pathways known to be important for squamous fate specification and differentiation, and provided unprecedented insights into carcinogenesis mechanisms and as well as putative therapeutic targets.

4.1 The 3q26-3q28 amplicon in SCCs

As discussed above, SCCs exhibit a characteristic copy number alteration event, namely frequent co-amplification of numerous oncogenes at 3q26-3q28 (Bass et al., 2009; Freier et al., 2010; Hussenet et al., 2010; Long & Hornick, 2009; Maier et al., 2011; Yuan et al., 2010). Below, we review some of the known examples of SCC drivers residing within this region.

One of the defining factors for squamous lineage specification is TP63, residing at 3q28 (Figure 2). TP63 belongs to the same family of transcription factors as TP53, and was initially discovered to bind to TP53 responsive elements (Bian & Sun, 1997; Zeng, Levine, & Lu, 1998). TP63 is highly expressed in the basal layer of stratified squamous but not single-layered epithelia (A. Yang et al., 1998), and is crucial to maintain the proliferative potential of epithelial stem cells and prevent differentiation (Carroll et al., 2006; King et al., 2006; King et al., 2003; Koster, Kim, Mills, DeMayo, & Roop, 2004; Liefer et al., 2000; Okuyama et al., 2007; Parsa, Yang, McKeon, & Green, 1999; Pellegrini et al., 2001; Senoo, Pinto, Crum, & McKeon, 2007; X. Su, Cho, et al., 2009; Truong, Kretz, Ridky, Kimmel, & Khavari, 2006; Yugawa et al., 2010). TP63 mutation is the most common genetic basis for the congenital ectrodactyly, ectodermal dysplasia, and facial clefts (EEC) syndrome (Brunner, Hamel, & Van Bokhoven, 2002). Mice lacking TP63 failed to develop stratified epithelia and epithelial appendages, such as teeth, hair follicles and mammary glands. TP63

along with several other transcription factors are potent enough to reprogram wound fibroblasts into skin epithelial cells (Kurita et al., 2018).

Mechanistically, TP63 directly targets key squamous lineage genes, for example the keratin gene KRT14 (Candi et al., 2006), a tetraspan membrane protein and cell adhesion regulator Perp (Ihrie et al., 2005), and an extracellular matrix gene Fras1 (Koster et al., 2007), all characteristic of stratified epithelia (Figure 2). It also targets master epidermal morphogenesis signals such as JAG1 in the Notch pathway (Sasaki et al., 2002), and determinants of epidermal terminal differentiation IRF6 (Moretti et al., 2010; Richardson et al., 2006) and ZNF750 (Sen et al., 2012). Other major epidermal morphogenesis genes shown as direct P63 targets include AP-2gamma (Koster, Kim, Huang, Williams, & Roop, 2006), IKKa (Koster et al., 2007), microRNA miR-205 {Tucci, 2012 #5371}, ROS regulator REDD1 (Ellisen et al., 2002). Genome-wide search of TP63 targets in human and mouse epithelia further expanded squamous lineage defining target network of TP63, solidifying its active suppression of ectopic mesenchymal lineage, and interaction with other epigenetic regulators (Bao et al., 2015; Fan et al., 2018; Kouwenhoven et al., 2010; Medawar et al., 2008; Romano, Birkaya, & Sinha, 2006; Romano et al., 2012; Shalom-Feuerstein et al., 2011; A. Yang et al., 2006) (Figure 2).

Given its key role in squamous lineage specification and stratification of epithelial tissues (Crum & McKeon, 2010), it is not surprising that TP63 is one of the most well-established oncogenic drivers for squamous cancers and basal subtype carcinomas from stratified epithelia (Hoadley et al., 2018; Westfall & Pietenpol, 2004). TP63 is known to be frequently amplified in various SCCs (Hibi et al., 2000; Maier et al., 2011; Saladi et al., 2017; Schrock et al., 2014; Watanabe et al., 2014; X. Yang et al., 2011). Its molecular mechanisms have been linked to interaction with TP53 (Flores et al., 2005; Flores et al., 2002), P21 (Barbieri, Barton, & Pietenpol, 2003; Barbieri, Tang, Brown, & Pietenpol, 2006; Westfall, Mays, Sniezek, & Pietenpol, 2003) and YAP (Ehsanian et al., 2010; Saladi et al., 2017).

Adding to its complexity, TP63 has multiple isoforms due to both N- and C-terminal alternative splicing (Candi et al., 2006; Dohn, Zhang, & Chen, 2001; Ghioni et al., 2002; Helton, Zhu, & Chen, 2006; Jacobs et al., 2005; King et al., 2003; Laurikkala et al., 2006; X. Su, Paris, et al., 2009; Suzuki, Sahu, Leu, & Senoo, 2015; G. Wu et al., 2003). Two of these isoforms, known as Np63 and TAp63, respectively, have distinct functions. The former is the predominant isoform in the squamous lineage whereas the latter has a broader expression in the early ectoderm prior to stratification commitment, in stromal fibroblast (X. Su, Paris, et al., 2009) and neuronal (Jacobs et al., 2005) lineages. Whereas Np63 is key driver of squamous lineage or those of stratified epithelia, TAp63 appears to be highly expressed in non-squamous cancers including colorectal cancers and lymphomas (Bishop et al., 2012; Di Como et al., 2002; Nylander et al., 2002).

SOX2 is another transcription factor frequently amplified in SCCs, residing at 3q26. SOX2 is a master regulator of multiple lineages during development including embryonic stem cells, lung and neuronal lineages, and its aberrant expression and functional importance has been widely reported in many cancer types. Knocking out or overexpressing SOX2 in cultured SCC cancer cells suggests it is indeed a lineage survival oncogene (Bass et al.,

2009; Husenet et al., 2010). In vivo GEMMs further confirm its crucial function in LSCCs (Ferone et al., 2016; Y. Lu et al., 2010; Mukhopadhyay et al., 2014) and cSCCs (Boumahdi et al., 2014; Siegle et al., 2014). It is worth to note that some SCLCs also exhibit SOX2 amplification and are functionally dependent on its expression (Rudin et al., 2012). However, in SCLCs the SOX2 amplification may reflect the importance of its function in neuronal lineages rather than a squamous lineage.

Interestingly, one of the genes co-amplifying with SOX2 is PRKCI, reported to functionally co-operate with SOX2 in LSCC (Justilien et al., 2014). PKC family members are known to be classical regulators of epidermal differentiation in response to calcium signaling and phorbol ester TPA (12-O-tetradecanoylphorbol-13-acetate) treatment (Hennings et al., 1980). However, this particular family member, PRKCI encoding PKC iota, is considered calcium insensitive and remains relatively under-characterized. It will be interesting to see whether functional interaction of PKC iota with SOX2 extends to other SCCs and whether there are yet unknown roles of PKC in SCCs.

Another known oncogene co-amplified with SOX2 at 3q26 is PIK3CA (Kozaki et al., 2006; Murugan, Hong, Fukui, Munirajan, & Tsuchida, 2008; Qiu et al., 2006; Redon et al., 2001; Woenckhaus et al., 2002). Even though PIK3CA is frequently mutated across many cancers, its mutational identity in SCCs is unique: PIK3CA E542K and E545K is enriched in CxSCC, HNSCC, and bladder cancer, and is very different from breast cancer and others (Cancer Genome Atlas Research et al., 2017), raising an intriguing possibility that a subset of PI3K pathway genes genetically or biochemically interact with these particular mutant PI3Ks in SCCs compared to other cancer types.

4.2 Regulators of squamous stratification

Several master development regulators important for squamous differentiation have been found to be significantly altered in SCCs; and, hence are *bona fide* drivers of squamous carcinogenesis.

NOTCH pathway genes are prevalently mutated in human cancers. NOTCH1 mutations in SCCs are loss-of-function type, implicating Notch1 as a tumor suppressor therein (Agrawal et al., 2011; Stransky et al., 2011; N. J. Wang et al., 2011). This is analogous to myeloid leukemia (Klinakis et al., 2011), but is in sharp contrast to lymphoid malignancies, where it is a well-established oncogene (Baldus et al., 2009; Di Ianni et al., 2009; Ellisen et al., 1991; Fabbri et al., 2011; Lee et al., 2009; Puente et al., 2011; Weng et al., 2004).

The tumor suppressive function of NOTCH in cSCCs has been well-corroborated by mouse models and cell culture studies. Skin epidermis-specific deletion of Notch1 leads to accelerated carcinogenesis in mice (Nicolas et al., 2003), possibly due to cell non-autonomous effect from the tumor microenvironment (Demehri, Turkoz, & Kopan, 2009). It is also consistent with NOTCH function in promoting cell cycle exit and squamous differentiation (Devgan, Mammucari, Millar, Briskin, & Dotto, 2005; Lefort et al., 2007; Lowell, Jones, Le Roux, Dunne, & Watt, 2000; Mammucari et al., 2005; B. C. Nguyen et al., 2006; Nickoloff et al., 2002; Rangarajan et al., 2001; Williams, Beronja, Pasolli, & Fuchs, 2011). Of note, clinical observations that patients treated with gamma-secretase inhibitor

(therefore blocking Notch ligand processing) frequently developed skin cancers (Extance, 2010), is in line with a tumor suppressive function of Notch in the skin epithelia. Functionally related to NOTCH, the transcription factor ZNF750 is a core component in epidermal stratification program directly regulated by TP63 (Boxer, Barajas, Tao, Zhang, & Khavari, 2014; Rubin et al., 2017; Sen et al., 2012), and appears to be frequently mutated in HNSCCs (Cancer Genome Atlas Network, 2015a; Gillison et al., 2019) and ESCCs (Cancer Genome Atlas Network, 2017; Lin et al., 2014; Sawada et al., 2016; L. Zhang et al., 2015).

NOTCH pathway mutations are also common in NSCLCs (Westhoff et al., 2009) and SCLCs (Cancer Genome Atlas Network, 2015b). Forced NOTCH expression in Notch-mutant SCLCs suppresses neuroendocrine signature, and extend survival of tumor-bearing mice (Cancer Genome Atlas Network, 2015b), supporting the tumor suppressive role of NOTCH in SCLC. Intriguingly, it has been recently reported the non-neuroendocrine NOTCH activated cells are slow-cycling and chemotherapy-resistant, providing trophic support to neuroendocrine tumor cells, where NOTCH inhibition combined with chemotherapy is effective in delaying disease relapse in pre-clinical models (Lim et al., 2017).

Further adding to the complexity of understanding Notch pathway deregulation in cancer, Notch signaling represents one of the classic developmental pathways where ligands and receptors may come from the same (autocrine) or the adjacent cells (paracrine) (Kopan & Ilagan, 2009; Kovall & Blacklow, 2010). On one hand, skin basal epithelial stem cells express the ligand Delta to induce neighboring cells expressing the Notch1 receptor to differentiate (Lowell et al., 2000). On the other, suprabasal cells express both ligand Jagged and receptor Notch to form a positive feedback loop and reinforce differentiation fate (Luo, Aster, Hassserjian, Kuo, & Sklar, 1997; Nickoloff et al., 2002; Rangarajan et al., 2001). Meanwhile, differentiated Notch-high cells actively suppress stem cell fate by inhibiting TP63 expression (B. C. Nguyen et al., 2006). In this regard, it is intriguing to notice that TP63 amplified and NOTCH1 mutated LSCCs exhibit minimal overlap (Hammerman et al., 2012), raising the possibility of direct genetic interaction between these two SCC drivers. Notably, one of the key Notch target and pathway regulator HES1 localizes to 3q29 region adjacent to TP63, is possibly co-amplified and functionally involved in SCCs. It will also be interesting to analyze at single cell level what type of signaling paradigm (autocrine vs paracrine) SCCs exploit to de-regulate NOTCH activity, especially in relationship with neighboring tumor parenchymal cells and tumor-stroma microenvironment.

MYC, a master oncogenic driver across many cancers and the founding member of oncogene amplification (Little, Nau, Carney, Gazdar, & Minna, 1983; Schwab et al., 1983), is amplified in SCCs (Rodrigo, Lazo, Ramos, Alvarez, & Suarez, 1996). Counterintuitively, MYC overexpression alone seems to be capable of both stimulating proliferation and promoting differentiation of the skin epidermis (Arnold & Watt, 2001; Gandarillas & Watt, 1997; Pelengaris, Littlewood, Khan, Elia, & Evan, 1999; Waikel, Kawachi, Waikel, Wang, & Roop, 2001; Waikel, Wang, & Roop, 1999). Notably, the incidence of MYC amplification in SCCs developing in renal transplant recipients is increased to 50% (Pelisson et al., 1996). MYC also appears to be important for SCC resistance to combined miR-21 antagonism and PI3K/mTOR inhibition (Darido et al., 2018). Intriguingly, GRHL2, a well-established

squamous stratification gene (Boglev et al., 2011) and functionally synergistic with MYC in reprogramming wound fibroblasts into epidermal keratinocytes (Kurita et al., 2018), is localized at 8q22 close to MYC at 8q24, and is potentially co-amplified with MYC. These together suggest context-dependent function of MYC across different tumor types, and hence, a foreseeable SCC-specific MYC oncogenic network.

Further speaking of context dependency, another recently reported SCC driver is KLF5 (Ge et al., 2017; X. Zhang et al., 2018). KLF5 promotes lineage infidelity in skin epidermal stem cells, and is functionally required for wound repair and cSCC propagation (Ge et al., 2017). Epidermal-specific KLF5 overexpression induced skin dysplasia (Sur, Rozell, Jaks, Bergstrom, & Toftgard, 2006; Sur, Unden, & Toftgard, 2002). While KLF5 appears to promote proliferation, its close family member KLF4, one of the induced pluripotent stem cell (iPSC) reprogramming factors (K. Takahashi & Yamanaka, 2006), is crucial for epidermal stratification and differentiation (Jaubert, Cheng, & Segre, 2003; Ohnishi et al., 2000; Segre, Bauer, & Fuchs, 1999). Interestingly, KLF5 is also frequently amplified or mutated in other cancers, including HNSCC, ESCC and LSCC (Campbell et al., 2016; X. Zhang et al., 2018; X. Zhang et al., 2016), salivary gland tumors (Giefing et al., 2008), uterine cervical adenocarcinomas (Cancer Genome Atlas Research et al., 2017), gastric cancers (Deng et al., 2012), and bladder cancers (Cancer Genome Atlas Network, 2014b). Indeed, KLF5 has a plethora of functions across epithelial tissues as well as the hematopoietic system (Dong & Chen, 2009; McConnell & Yang, 2010; Turner & Crossley, 1999), consistent with its wide involvement of human cancers. KLF5 function and targets likely differ in various cancer types, whereas its function in SCCs may significantly overlap. It will be crucial to integrate and leverage our current knowledge on squamous regulators to gain deeper understanding of the context dependency mechanisms of cancer drivers.

5. Summary and perspectives

Over the past century, milestones leading to a cure in cancer have been progressively exciting, including the momentous advancement of surgical, radiation- and chemo-therapy, targeted molecular therapy, and most recently immunotherapy in cancer treatment. Pondering over the important lineage addiction phenomenon of cancer, it is also sobering to realize many of the lineage factors discussed above are not readily targetable. That said, signaling events leading to activation of these lineage pathways might serve as putative therapeutic targets.

Meanwhile, with effective treatments, many types of cancers are becoming a chronic disease, and the next challenge in cancer medicine would be to address the pressing issues of treatment toxicities, comorbidities and long-term survival of our cancer patients. One strategy is to exploit cancer specific targets while sparing normal adult tissues, based on our fundamental knowledge of cellular and molecular pathways governing adult tissue homeostasis. By dissecting how pathways of stress and wound repair are hijacked by cancer cells, one could also re-purpose therapeutic agents approved for management of other diseases to cancer patients. Furthermore, one of the most fascinating questions in cancer biology is to understand context dependency of cancer drivers. One ought to take advantage

of our knowledge in embryonic development and adult stem cells to dissect cancer vulnerability and lineage addiction across tissues and organs.

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Abbreviations:

SCCs	squamous cell carcinomas
HNSCCs	head and neck squamous cell carcinomas
ESCCs	esophageal squamous cell carcinomas
EACs	esophageal adenocarcinomas
NSCLC	non-small cell lung cancer
SCLC	small cell lung cancer
LSCCs	lung squamous cell carcinomas
LACs	lung adenocarcinomas
CxSCCs	uterine cervical squamous cell carcinomas
BCCs	basal cell carcinomas
cSCCs	cutaneous squamous cell carcinomas
GEMMs	genetically engineered mouse models

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Figure 1. Molecular convergence in squamous cell carcinomas (SCCs) across organ sites. SCCs occur frequently in head and neck (HNSCC), lung (LSCC), esophagus (ESCC), uterine cervix (CxSCC), and the skin (cSCC). Bladder and pancreas cancers have subgroups deemed squamous like carcinomas. Other organ sites develop rare SCCs including the breast, prostate, and thyroid. Based on integrative molecular analysis, HNSCCs, LSCCs, ESCCs and CxSCCs are divided into subtypes based on transcriptional signatures, each subgroup with distinct genomic alterations associated. Classical and basal subtypes are shared across SCCs. Not depicted here are mesenchymal subgroup of HNSCCs and ESCC3 subgroup of ESCCs.

A. P63 is a squamous driver gene within the SCC characteristic 3q26-3q28 amplicon

B. NOTCH exerts context dependent functions in squamous- versus non-squamous-lineages

Figure 2. Understanding context dependency of cancer genes with squamous drivers.

(A) The SCC-characteristic amplicon 3q26-3q28 is a prototypical example for understanding context dependency of cancer driver genes. Within this amplicon, TP63 – notably the deltaNp63alpha isoform – is widely involved in the development, homeostasis, and aging of stratified epithelia tissues, and is a canonical driver gene of squamous cancer. Its direct transcriptional targets include regulators of squamous lineage specification, proliferation and differentiation. It also directly suppresses ectopic mesenchymal lineage genes and interacts with epigenetic regulators to orchestrate lineage plasticity. (B) Other key squamous specification, maintenance and stratification genes are frequently altered in SCCs. Meanwhile, many of them have important functions outside squamous lineages. Their functions in these diverse tissues differ drastically dependent on the lineage context. NOTCH is oncogenic in lymphoid organs but tumor-suppressive in myeloid leukemia and squamous tissues, consistent with its function to promote proliferation versus stratification during the development of these two lineages, respectively. Several mechanisms may underlie such context dependency. Notch could provide cell-autonomous dependency of neuroendocrine lineage in SCLC, while non-autonomously drive slow-cycling and chemo-resistance in NSCLC. Notch coordinate with other squamous transcription factors such as P63, ZNF750 and HES1 to drive differentiation program. Notch signaling in both autocrine and paracrine fashion to impact the tumor parenchyma and tumor microenvironment.