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Squamous Cell Carcinoma – Similarities and Differences among Anatomical Sites

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Abstract

Squamous cell carcinoma (SCC) is an epithelial malignancy involving many anatomical sites and is the most common cancer capable of metastatic spread. Development of early diagnosis methods and novel therapeutics are important for prevention and mortality reduction. In this effort, numerous molecular alterations have been described in SCCs. SCCs share many phenotypic and molecular characteristics, but they have not been extensively compared. This article reviews SCC as a disease, including: epidemiology, pathology, risk factors, molecular characteristics, prognostic markers, targeted therapy, and a new approach to studying SCCs. Through this comparison, several themes are apparent. For example, HPV infection is a common risk factor among the four major SCCs (NMSC, HNSC, ESCC, and NSCLC) and molecular abnormalities in cell-cycle regulation and signal transduction predominate. These data reveal that the molecular insights, new markers, and drug targets discovered in individual SCCs may shed light on this type of cancer as a whole.

Keywords

Squamous cell carcinoma (SCC); Non-melanoma skin cancer (NMSC); Head and neck squamous cell carcinomas (HNSCC); esophageal squamous cell carcinoma (ESCC); Non-small cell lung cancer (NSCLC); epidemiology; risk factors; molecular characteristics; prognostic markers; targeted therapy

1. Introduction

Squamous cell carcinoma (SCC) is an epithelial malignancy that occurs in organs that are normally covered with squamous epithelium which includes several different anatomic sites, including the skin, lips, mouth, esophagus, urinary tract, prostate, lungs, vagina, and cervix. Of these anatomic sites, there are four which make up the majority of SCC cases: non-melanoma skin cancer, head and neck cancer, esophageal cancer, and non-small cell lung

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cancer. Given the range of tissues in which it arises, SCC represents the most common cancer capable of metastatic spread in the US and worldwide [1]. Despite advances in diagnostic methods and combined treatment modalities, the survival rate has not improved significantly over the last 30 years [2] due in part to a lack of reliable early diagnostic biomarkers and a limited number of molecularly targeted therapeutic strategies.

Numerous genetic alterations have been described in SCC sub-types, although the molecular mechanisms contributing to tumor initiation and progression are still poorly understood. SCCs share many phenotypic and molecular characteristics with each other [3–5], thus molecular insights, new markers, or drug targets discovered in individual SCCs may shed light on this type of cancer as a whole. In this article we will review SCC as a disease by describing the most common anatomic types of SCC with regard to their epidemiology, pathology, and risk factors. We will also review the current understanding of the molecular characteristics and prognostic markers. And finally, we will focus on targeted therapy and new approaches to studying SCC.

2. Epidemiology and Pathology

2.1. Non-melanoma skin cancer

Non-melanoma skin cancer (NMSC) is the most common cancer in humans [6], which includes SCC and basal cell carcinoma (BCC), and has shown a dramatic increase in Caucasians in the last few decades. Although BCC is most prevalent, SCC has the higher mortality due to metastases and high incidence [7]. The number of skin cancers diagnosed in the United States outnumbers all other cancers combined, and it is estimated that one in five Americans will develop skin cancer at some point in their life [8]. Most skin SCCs show relatively benign behavior and can be cured by local surgical and dermatologic methods. However, some of these lesions can have a locally invasive and aggressive course. The rate of metastasis is 0.3% to 3.7%, with an overall 5-year survival rate of less than 30% when systemic disease develops [9].

2.2. Head and neck squamous cell carcinomas

Head and neck squamous cell carcinomas (HNSCC) make up the vast majority (more than 90%) of head and neck cancers and rank as the sixth most common cancer worldwide [10], with 45,660 new cases of HNSCC diagnosed in 2007 and 35,720 new cases reported in the US during 2009 [11]. They are a group of tumor entities that arise from squamous mucosal surfaces, including nasal cavities, paranasal sinuses, oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx. In contrast to the declining overall incidence of HNSCC, which is mainly due to smoking prevention and cessation [12], oropharynx carcinoma shows a rising incidence, particularly among individuals less than 45 years of age, suggesting some nontraditional behavioral and environmental factors play a key role in its epidemiology. HNSCC has a 75% overall 5-year survival rate if detected early [13]. Despite advances in detection and treatments over recent decades, most patients present with metastatic disease at the time of diagnosis, reducing the overall 5-year survival rate to 35% [14]. Late diagnosis, formation of additional primary tumors, and metastases largely contribute to this poor survival rate [15].

2.3. Esophageal squamous cell carcinoma

Esophageal cancer (EC) ranks as the eighth most common cancer, with the sixth highest mortality in the world [16, 17]. As the predominant histological subtype of esophageal cancer, esophageal squamous cell carcinoma (ESCC) contributed 80% of all esophageal cancers worldwide. ESCC is characterized by extreme diversity in geographical distribution and high mortality. The "Asian esophageal cancer belt" region shows much higher incidence

than other areas of the world. For example, Linxian and surrounding counties in China [18]. Despite advances in diagnostic methods and combined treatment modalities, the majority of tumors are diagnosed at advanced stages and the overall 5-year survival rate is only 40% [19]. Although relatively less common in the United States than in other countries, there were still 15,560 new cases and 13.940 deaths reported in 2007, which was the sixth leading cause of death from cancers among American men that year [20]. In the US, ESCC occurs more commonly in African American than Caucasian patients and more commonly in men than women, although the prevalence in women has been increasing steadily [21]. The majority of ESCC patients present with advanced metastatic disease, with the overall 5-year survival of these patients being <10% [22].

2.4. Non-small cell lung carcinomas

Lung cancer is the leading cause of cancer death in the United States and most other countries [23], with approximately 30% being SCC [24]. Lung cancers are divided into small cell (SCLC) and non-small cell lung carcinomas (NSCLC) based on their histology and cellular origin. Non-small cell lung cancer (NSCLC) accounts for approximately 80–85% of all cases of lung cancer and is the most common cause of death in men and second only to breast cancer in woman [25]. NSCLC are classified into four histologic subtypes: squamous cell carcinoma (SCC), adenocarcinoma (ADC), large cell carcinoma, and sarcomatoid carcinoma. Anatomically, about 70% of SCC present as central lung tumors [26], whereas adenocarcinomas generally present as peripheral lung tumors [24]. A recent large, randomized phase III trial showed that platinum-based chemotherapy combinations yield a median survival time of only 8–11 months, a 1-year survival rate of 30–45%, and a 2-year survival rate of 10–20% [27, 28]. The overall 5-year survival rate for lung cancer is less than14% [29].

2.5. Overall comparison

Overall 5-year survival rates for the four major SCCs are among the lowest of the major cancers. NMSC has an advantage over the other SCCs, as it is presented on the skin surface and not an internal organ; therefore, the chance of early detection is much greater and it is often cured by dermatologic and local surgical methods. For all of the major SCCs, including NMSC, a common theme of late diagnosis, formation of additional primary tumors and metastases are associated with the poor survival rates presented above. Regional recurrence after surgical resection is also a contributing factor as is seen more commonly in NSCLC SCC than other histologic subtypes because SCC is able to spread by extending through periobronchial tubes which allow them to directly invade mediastinal lymph nodes and other mediastinal structures [26, 30]. Even thought NMSC has an early detection advantage over the other SCCS, repeated exposure to risk factors will influence severity of disease progression and recurrence as equally as observed in the other major SCCs.

3. Risk Factors

The incidence of SCC shows marked variation in its distribution, suggesting that personal habits, environmental exposures, infections, and ethnicity all play a role in the etiology of SCC (Table 1), with several of these risk factors influencing prognosis (Table 2).

3.1. Non-melanoma skin cancer

Unlike other types of squamous cell carcinoma, NMSC is primarily caused by chronic long-term UV solar radiation exposure [31], in conjunction with the patient's skin type. Fair-skinned individuals who always burn and never tan are at a much higher risk for developing skin SCC than those with darker-skin [32], and it has been demonstrated that both sun exposure earlier in life and intense sun exposure appear to heavily predispose the

populations to skin cancer [32]. Furthermore, human papilloma viruses (HPV) may be involved in the multi-step process of skin carcinogenesis as a co-factor with UV-radiation [33], especially in patients with poor immune status such as organ transplant recipients [34]. And, smoking tobacco may double the risk of skin cancer [35], thus although the effect is not as great as in other SCCs, smoking plays a role in the development of NMSC.

3.2. Head and neck squamous cell carcinomas

Contrary to NMSC, alcohol and tobacco use are the most common risk factors for HNSCC in the US, although they have not been associated with survival [36]. Moreover, alcohol and tobacco are likely synergistic in causing cancer of the head and neck [37]. Cigarette smokers have a lifetime increased risk for head and neck cancers which is 5- to 25-fold increased over the general population [38], and smoking cessation does not eliminate the risk of cancer development [39]. In addition, environmental exposure to tobacco smoke also increases the risk of developing HNSCC, even for individuals who have never actively smoked [40]. Heavy alcohol consumption is also an independent risk factor for HNSCC, particularly for cancers of the hypopharynx [41]. Moreover, smokers and alcohol drinkers are at risk for the development of second primary oral cancers [42]. Interestingly, even in the presence of alcohol consumption or tobacco use, a high intake of fruit and vegetables may prevent the development of a quarter of HNSCC and possibly one half of oral and oralphyrengeal SCC [43]. Causation has been shown with viral infection for HNSCC and the association varies based on the site of the tumor. For example, human papilloma virus (HPV), in particular HPV16, shows the highest distribution in the tonsils [44], while Epstein-Barr virus (EBV) infection is associated with nasopharyngeal cancer. HPV is associated with 20–25% of HNSCC, and individuals with HPV-positive tumors have a better overall survival compared to those with HPV-negative tumors [45, 46]. Specifically, the presence of HPV-16 is now recognized as a highly favorable prognostic indicator for patients with HNSCC [45]. Betel quid chewing, a common habit in some regions of Asia and some Asian communities in the western world is considered a regional risk factor for cancers with a poorer prognosis [36]. In addition, oral health, acid reflux disease and environmental exposures (nickel refining, textile fibers, and woodworking) are also related to HNSCC tumorigenesis.

3.3. Esophageal squamous cell carcinoma

Similar to HNSCC, smoking and alcohol ingestion are major etiologic factors for the development of ESCC [47]. Studies have shown that ESCC risk is increased approximately three- to seven-fold in current smokers [48–50] and three- to five-fold in heavy alcohol users [50–53], with additional associations between esophageal irritants such as lye ingestion, rapidly consumed high-starch diets without fruits and vegetables, and radiation therapy [47]. There also may be a causal relationship between ESCC and previous diseases such as achalasia, head and neck cancer, and Plummer-Vinson syndrome [54]. Pickled vegetable intake and micronutrient deficiency (such as zinc) may contribute to ESCC formation in some parts of China, especially in light of laboratory experiments demonstrating that high tissue zinc concentration is strongly associated with a reduced risk of developing ESCC in experimental animals [55, 56]. There are also other potential but as yet unsubstantiated risk factors like PAHs and acetaldehyde related to ESCC in China [57], with HVP-16 and HPV-18 reported to be risk factors [55, 58]. In the US, ESCC incidence is highest in African Americans and males. Interestingly, one cohort study of ESCC and esophageal adenocarcinoma (EA) found decreased risk of ESCC, but not EA, was associated with higher intake of both fruit and vegetables [59].

3.4. Non-small cell lung carcinomas

The causal relationship between smoking and lung cancer is well established with a 10- to 20-fold increased risk of lung cancer in smokers compared with never smokers [60] and is

the major risk factor for the development of NSCLC SCC [61, 62]. In the US, smoking is estimated to account for 87% of lung cancer cases (90% in men and 85% in women) [63]. The lifetime risk of developing lung cancer is approximately 17.2% for male smokers and 11.6% for female smokers, and this risk is significantly lower in nonsmokers: 1.3% in men and 1.4% in women [64]. Healthy ex-smokers have been shown to have a similar gene expression pattern in normal bronchial epithelium as non-smokers, indicating that most smoking-induced gene expression changes revert to normal levels after smoking cessation [65]. Aside from smoking, NSCLC is also related to genetic factors [66], radon gas [67], asbestos [68], and air pollution [69]; with Radon exposure reported as the second major cause of lung cancer after smoking [67]. There is a synergistic effect between tobacco smoking and asbestos exposure in the formation of lung cancer [68], and more recently HPV [70], JC virus [71] and cytomegalovirus [72] have been reported as additional potential risk factors for NSCLC.

3.5. Overall comparison

Tobacco smoking and HPV infection appear to be carcinogenic causes for all four sub-types. In addition, several risk factors are shared among the major SCC types. HNSCC and ESCC share the most factors, consistent with their histological relationship, including alcohol consumption dietary factors, and ethnicity. Unlike the other SCCs, UV exposure is the major risk factor for NMSC. Although numerous etiologic factors for SCC are known, the exact roles and molecular mechanisms of action have not been fully elucidated.

4. Molecular Characteristics and Prognostic Markers

The development of clinically evident SCC is a multistep process involving the accumulation of multiple genetic alterations modulated by genetic predisposition, known risk factors, and other unknown environmental influences. The alterations are typically oncogene activation, including recessive oncogenes [73] and tumor suppressor gene (TSG) inactivation via mutations, loss of heterozygosity, deletions, or other mechanisms (e.g. methylation and miRNA modulation of gene expression) [74]. Molecular profiling studies that began with single or relatively small groups of genes or proteins have now progressed to large-scale and high-throughput methods using DNA-, RNA-, and protein-based approaches. These large-scale methods analyze thousands of genes at one time and have led to a better understanding of the complexity of gene abnormality patterns of SCC and have accelerated the discovery of novel genes involved in SCC pathogenesis. In addition to conventional prognostic factors [75], these molecular characteristics are becoming increasingly valuable as biomarkers in adjunct prognostic tools. There are numerous molecular markers that have been identified in SCC, and in this section we compare and contrast the major molecular abnormalities and their prognostic value among the four major SCCs.

4.1. Molecular markers common to NMSC, HNSCC, ESCC, and NSCLC

Different patterns of molecular changes and their role in prognosis have been shown between the four major SCCs; however, several key similarities are present including abnormalities in TP53, p63, Ki-67, CCND1, EGFR, and COX2 (Table 2, Table 3).

TP53—TP53 is one of the most important tumor suppressor genes in humans [76] and functions as a transcriptional regulator that controls the expression of genes involved in the cell cycle, DNA repair, apoptosis, and senescence. Under stress conditions, p53 is activated and triggers a variety of cellular responses needed to maintain the integrity of the genome, thus the protein has been designated a guardian of the genome. p53 mutations can lead to inactivation of p53 and have been found in a broad spectrum of human cancers [77], including NMSC, HNSCC, ESCC, and NSCLC. Inactivation of p53 is considered a critical

step in the development of NMSC [78]; however, TP53 mutation has not been correlated with aggressiveness of SCC, indicating the involvement of subsequent molecular events that determine tumor behavior [79]. TP53 alterations and its loss of function is a characteristic early change in HNSCC [80]. In HNSCC, it has been observed that *TP53* mutations that occur within the core domain completely blocking DNA binding are linked to accelerated tumor progression, reduced therapeutic responsiveness, and decreased patient survival compared to tumors that harbor less disruptive TP53 mutations [81, 82]. In ESCC, p53 mutation has been frequently identified [83, 84] and its function positively correlated with MDM2 and p14(ARF) expression [85]. Overexpression p53 has also been significantly correlated with poorer prognosis for ESCC [86]. In NSCLCs, TP53 mutations have been detected in 40–90% of resected tumors [87–89], with disruption of the TP53 pathway frequently observed in SCC [73]. TP533 mutations can produce chemotherapy resistance [90]; however, the specific type of mutation and sensitivity to chemotherapy agents has not been identified [88, 91]. As described, TP53/p53 abnormalities are present in all four major SCCs, but to date is only considered a prognostic factor for HNSCC and ESCC.

p63—p63, a member of the p53 family, is critical for the development of stratified epithelial tissues such as epidermis [92] and is usually limited to the proliferative (basal layer) compartment of the epithelium [93]. p63 expression has been reported to be a strong predictor of poorly differentiated NMSC [94]. Whereas, expression of p63 is frequently (>95%) observed in HNSCC and associated with increased survival [95–98]. Hence, p63 may be involved in squamous cell carcinoma formation through various paths. p63 alteration is also seen in ESCC and reduced expression of p63 has prognostic implications for patients [99]. In NSCLC SCC, p63 is used to differentiate SCC from adenocarcinoma because a diffuse strong p63 and CK5/6 immunoexpression is essentially restricted to SCC [24]. Interestingly, in NSCLC high expression of CCND1 [100] and CD24 [101] are associated with a worse clinical outcome, while expression of p63 [102] and BCL-2 [103] have a positive prognostic value. In contrast to TP53, p63 abnormalities in the four major SCCs are considered prognostic for SCC.

Ki-67 (MKI67)—Ki-67 is a cell proliferation index marker typically increased in tumors is related to rapid growth and recurrence in NMSC [104]. In HNSCC, co-expression of p21/Ki-67 is a strong negative prognostic factor [105]. In patients with stage II and III advanced ESCC, a significant correlation has been identified between Ser392 phosphorylation of p53 and high levels of Ki-67, lymphatic invasion, and poorer prognosis [106]. Similarly, one cohort study found 97% of NSCLC samples expressed Ki-67 and overexpression was associated with significantly shorter survival [107]. Similar to p63, Ki-67 abnormalities are prognostic for the four major SCCs. But in contrast to p63, Ki-67 abnormalities all appear to be indicative of poor prognosis in all four major SCCs.

CCND1—CCND1, a cell cycle regulator, acts by phosphorylating and inactivating the retinoblastoma protein [108]. In NMSC, CCND1 is involved in the early development of SCC via abnormal tissue organization and differentiation [109], with overexpression frequently seen in keratinocyte carcinogenesis [110–112]. Interestingly, CCND1 overexpression coupled with TP53 mutation has been correlated with poorer prognosis in NMSC [110–112]. In HNSCC, CCND1 polymorphism (GG) in exon 4 has been shown to be an independent prognostic indicator of disease-free interval [113]. In ESCC, CCND1 is overexpressed in 23 to 73% of tumor samples [55, 114] and is significantly correlated with poorer prognosis [115, 116]. Contrary to CCND1 in ESCC, the absence of CCND1 immunoexpression in NSCLC is associated with worse prognosis [117]. Similarly to p63, CCND1 is associated with poorer prognosis in NMSC, ESCC, and NSCLC, but is conversely associated with improved prognosis in HNSCC.

EGFR—EGFR is present in the cell membrane as a monomer and is activated by ligand binding to the extracellular domain [118]. Mutations that lead to EGFR overexpression have been associated with a number of cancers. For example, some studies identified EGFR overexpression in metastatic SCC of the skin [119–121]. EGFR was also shown to be up-regulated/overexpressed in 90% of HNSCCs and associated with local recurrence and poor survival [122, 123]. Overexpression of EGFR [124, 125], is significantly correlated with poorer prognosis for ESCC. SCCs demonstrate most of the genetic abnormalities commonly present in NSCLCs, except for *KRAS* and *EGFR* gene mutations, which are more frequent in adenocarcinomas [73, 126]. Overexpression of EGFR, p53 [127–129] and Her2 [130, 131] has shown conflicting results in NSCLC and their use as prognostic markers require further study [132–136]. However, two prognostic proteins in NSCLC have been identified and are used together. NSCLCs having both IGFR-1- and EGFR-positive immunoreactivity represent a subpopulation capable of developing aggressive clinical behavior [137]. Again, similarly to p63, EGFR is associated with poorer prognosis in NSCM, HNSCC and ESCC. But due to conflicting reports, the use of p63 as prognostic marker in NSCLC needs to be investigated further.

COX2—COX2 (PTGS2) is an enzyme that functions in protein metabolism by increasing prostaglandin synthesis and plays a role in tumorigenesis. The expression of COX-2 is upregulated in many cancers and its product, PGH_2, is converted by prostaglandin E2 syntheses into PGE_2 which in turn can stimulate cancer progression [138]. For example, in NMSC, high expression of COX-2 has been found in AK, SCC and BCC [139] and COX-2 expression increases during progression from AK to SCC [140]. Overexpression of COX2 has also been shown in HNSCC, and some *ex vivo* studies have demonstrated that COX-2 is overexpressed in ESCC and premalignant lesions [141, 142]. Statistically significant COX-2 overexpression has also been found in 28.9 % of NSCLC SCC [143]. Overexpression of COX-2 and upregulation of the prostaglandin pathway plays a significant role in SCC and blockade of the process has strong potential for cancer prevention and therapy. However, to date, COX2 has not been identified as a prognostic marker of SCCs.

4.2. Other key molecular markers shared in several SCCs

In addition to the shared cell cycle regulation (TP53, p63, Ki-67, and CCND1), signal transduction (EGFR), and protein metabolism (COX2) molecular abnormalities, several other molecular abnormalities of gene expression, protein expression, gene mutation, and epigenetic regulation and their respective prognostic values have been characterized in SCCs (Table 2, Table 3). Key markers shared in two or three of the major SCCs involve several classes of genes including signal transduction (VEGF), transcription factor (SOX2), cell adhesion (CDH1), and extracellular matrix degradation (MMPs). Additional markers affecting only one of the SCCs can be found in Table 2 and Table 3.

VEGF—VEGF is an important signal transduction protein involved in both vasculogenesis and angiogenesis. Four subtypes have been described (A, B, C, and D). VEGF alteration is involved in HNSCC and ESCC. In oral SCC, it was reported that overexpression as measured by immunohistochemistry of subtypes A and B were correlated with tumor angiogenesis and subtypes C and D with metastases and poor prognosis [144]. In ESCC, VEGF (VEGF A) expression has historically ranged between 24–93% [145], and recently elevated immunoexpression has been reported in 55% of ESSC tissues (n= 108) [146]. Overexpression of VEGF has been significantly correlated with poorer prognosis of ESCC [145].

SOX2—A recently discovered lineage-survival oncogene, SOX2, has been shown to be important in HNSCC, ESCC, and NSCLC. Lineage survival oncogenes are activated by

somatic mutations and thus may play an important role in carcinogenesis. The genomic amplification of the SOX 2 embryonic stem cell transcription factor located on chromosome 3q26.33 was first reported in ESCC and NSCLC [147]. SOX2 has been associated with poor prognosis in ESCC [148], but its use as a prognostic marker in NSCLC has not yet been elucidated. In HNSCC (oral), high protein expression of SOX2 has been found to correspond to copy number gain in 52% of oral SCC tumors [149]. miR-145 is involved in regulating SOX2 [150]; however, its role as a prognostic factor in SCCs is still unknown.

Our group has recently characterized SOX-2 protein expression related to the pathogenesis of NSCLC SCC [151]. By assessing SOX2 mRNA expression in various published datasets against the previously characterized OCT4/SOX2/NANOG signature, we were able to effectively separate SCCs from adenocarcinomas. In this study, we further characterized SOX immunoexpression of NSCLC tissues and identified SOX2 protein expression pattern in SCC development (hyperplasia, dysplasia, and carcinoma *in situ*) [151].

CDH1 (E-cadherin)—CDH1 belongs to the cadherin family of Ca 2+ -dependent cell-cell adhesion molecules which induce and maintain intercellular connections. CDH1 has been implicated in carcinogenesis due to reduced expression [152] and promoter hypermethylation [153]. In NMSC, down-regulation of CDH1 is linked to increased potential for tumor invasiveness and distant metastasis and the frequencies of CDH1 promoter hypermethylation appear to be correlated with a more advanced stage of squamous carcinogenesis in skin [153]. In ESCC, tumors with reduced CDH1 expression invade deeper, have more lymph node metastasis, and have more lymphatic invasion than tumors with preserved CDH1 expression [154]. Disorganized CDH1 expression was also reported to be a feature of advanced ESCC [152].

MMPs—Matrix metalloproteinases (MMPs) are a family of zinc-containing endopeptidases that degrade various components of the extracellular matrix, and have been strongly implicated in multiple stages of cancer progression including the acquisition of invasive and metastatic properties. MMPs are altered in NMSC, HNSCC and ESCC. In NMSC, MMP-2 and MMP-9 immunoexpression is associated with NMSC pathogenesis and is an indicator of cutaneous cancer invasion and progression [155]. Expression of MMPs has been identified in both the epithelial and stromal elements of HNSCC [156], with MMP2 and MMP9 showed an association with invasive potential [157, 158]and poor outcome [159]. Gu *et al*. evaluated the expression of MMP1, MMP7, MMP9, and MMP13 in ESCC tissues from 208 patients and found that MMP7, MMP9, and MMP13 may be involved with early stage ESCC, and their coexpression predicted poor outcome for ESCC patients [160]. These data are consistent with the previous finding that expression of MMP-7 and MMP-9 may be a good marker for the presence of lymphatic metastasis in ESCC [161]. Moreover, our group identified MMP3 and MMP10 as potential early diagnosis biomarkers for ESCC. Both enzymes showed a tumor increase at both the transcriptional and proteomic levels [162].

Gene mutations—Gene mutations other than those in TP53, EGFR, and CCND1 have also been shown to be important in SCCs, with a large proportion of mutations having been identified in NSCLC and to a less extent HNSCC. Functional inactivation of p16 through deletion frequently occurs in HNSCC [163]. Chromosome 3p contains numerous TSGs (e.g. ALS2CL, EPHA3 and CMYA1) and the loss of heterozygosity in this region may contribute to SCCs, including HNSCC [164] and NSCLC [165]. Activating RAS mutations occur in approximately 15% to 20% of NSCLC, with a majority of them being KRAS [166], however these mutations are rare in SCC [167]. Although, c-MET, TTF-1, LKB1, BRAF and PIK3CA are often mutated or amplified in NSCLC [167].

Methylation—The epigenetic mechanism of methylation has been shown to modulate of gene expression in SCCs. Since its discovery as a cyclin-dependent kinase inhibitor in 1993, the tumor suppressor p16 (INK4A/MTS-1/CDKN2A) has gained widespread importance in cancer [168]. Like NMSC, gene methylation has also been identified in HNSCC, ESCC, and NSCLC to varying degrees. p16 inactivation often occurs via methylation in both HNSCC [163] and ESCC [169]. This silencing of p16 in ESCC has been shown to lead to deregulation of cell proliferation and consequent genomic instability [169]. Different patterns of gene methylation have been found in the major histological types of NSCLCs, with LKB1 and RASSF1 being the most important in NSCLC SCC. Inactivation of the TSG LKB1 by mutation and deletion is a relatively frequent event in SCC (19%) of the lung [170]. But, RAS association domain family 1 gene (RASSF1) is the most frequently hypermethylated gene in NSCLC. RASSF1A methylation has been correlated with worse prognosis in surgically resected NSCLC patients and was confirmed as an independent prognostic factor by multivariate analysis [171].

miRNAs—miRNAs are a class of small (~18–24 mer) nucleic acids that negatively regulate gene expression. Through their targets, miRNAs are known to play important roles in cell differentiation, proliferation, and apoptosis, and altered miRNA levels result in the aberrant expression of gene products that may contribute to cancer biology [172, 173]. An emerging number of studies have shown that miRNAs can act as oncogenes, as tumor suppressor genes, or sometimes as both [174]. High-throughput analyses have demonstrated that miRNA expression is commonly dysregulated in human cancer [173]. However, considerable disagreement remains with respect to the miRNA signature for specific cancer cell types, which appears to depend largely on the analytical platform [173].

Dysregulation of miRNAs have been identified in HNSCC, ESCC, and NSCLC and not NMSC. However, Drosha, an important enzyme in the miRNA machinery, has been found to be overexpressed in NMSC; thus giving strength to the hypothesis of miRNA involvevement in NMSC carcinogenesis [175]. In HNSCC, overexpression of miR-211 has been associated with invasive potential [176]. In addition to miR-211, miRNA profiling has revealed four upregulated miRNAs (miR-21, -31, -18, and -221) and 13 down-regulated miRNAs (miRNA-133a, -133b,-125a, -138, -139, -200c, -26b, -302b, -302c, -342, -371, -373, -375) associated with HNSCC [177]. Moreover, the ratio of miR-221:miR-375 showed a high discriminatory potential, with a sensitivity of 92% and specificity of 93% in distinguishing tumor from normal tissue, suggesting that this simple molecular marker may hold significant clinical potential as a diagnostic tool [178]. miR-21 has also been reported in ESCC and found to induce cell proliferation and invasion [179]. Our group evaluated ESCC related miRNAs by comparing microdissected cells involved in normal differentiation and tumorigenesis and confirmed that miR-21 was overexpressed in tumors (Zhu, *et al*, submitted). miRNAs have been shown to regulate several important pathways in NSCLC and have been correlated with disease outcome in NSCLC [180–182]. Of interest, a five miRNA signature (let-7a, miR-221, miR-137, miR-372, and miR-182) has been identified in NSCLC that predicts treatment outcome [182]. In that study, patients with high risk scores in their miRNA signatures showed poor overall and disease-free survivals compared with patients with low risk scores [182]. Loss of expression of miRNA-128b, putative regulator of EGFR, correlated with response to targeted EGFR inhibition in primary NSCLC [183]. miRNA is an area of very active research that will have an impact on pathogenesis and therapy as more is learned about the role of miRNAs in SCC.

Numerous molecular abnormalities in gene expression, protein expression, gene mutation, and epigenetic regulation have been characterized in SCC (Table 3), with several of these markers associated with disease prognosis (Table 2). Commonalities in molecular changes present in the four major SCCs are predominantly found in cell cycle regulation and signal

transduction. Although not all of the described molecular abnormalities are shared in all four of the SCCs, many are shared in at least two or three of the SCCs. The comparison of molecular characteristic similarities and differences in SCC provide insight not only into the relationships between NMSC, HNSCC, ESCC, and NSCLC, but to SCC as a whole. And this insight into SCC can putatively be translated to improved disease control and treatment. Currently, drugs targeting several of these gene and pathway abnormalities are being used in the treatment of SCC.

5. Targeted Therapy

Targeted therapy is a type of treatment that uses drugs that identify and attack specific cancer cells without harming normal cells and has been extensively investigated in recent decades, both as a single modality therapy and in combination with cytotoxic treatments such as radiotherapy or chemotherapy. With the growing understanding of molecular genetics of SCC, targeted therapies now offer expanded treatment options for patients that have clinically significant benefits. The targets that are currently considered the most relevant in SCCs fall into one of the following categories: cell-cycle regulation, signal transduction, growth factor receptors, angiogenesis, and protein degradation.

Similar to the fact that there are few prognostic markers for NMSC, there are currently no targeted drugs developed for NMSC. Although not developed as a targeted therapy, Diclofenac, a dual inhibitor of COX-1 and COX-2 with higher selectivity for COX-2, has been investigated and reported to be effective for patients with AK, a precancerous syndrome of skin [184].

Several targeted therapies are being investigated for HNSC, ESCC, and NSCLC with many of the molecular targets being shared among the three SCCs (Table 4). Targeted therapies have been extensively investigated in HNSC and NSCLC, especially EGFR TKIs and their mechanisms of resistance.

5.1. Growth Factor Receptor Antagonists

EGFR—EGFR is a member of the ERBB family of transmembrane tyrosine kinase receptors [132]. EGFR and their receptors are involved in signal transduction and tumor growth, thus blockade of these systems provides a therapeutic approach, through neutralizing ligands, inhibiting ligand binding, or blocking the tyrosine kinases of the receptors. Examples of EGFR inhibitors include monoclonal antibodies against the extracellular domain of the receptor (e.g., cetuximab and panitumumab) and receptor tyrosine kinase inhibitors (TKIs) that target the intracellular domain (e.g., gefitinib and erlotinib). EGFR inhibitors have been applied in HNSCC, ESCC and extensively in NSCLC clinical trials. In HNSCC, patients with locally advanced disease have been shown to benefit from the addition of EGFR inhibition (for example, cetuximab) to radiotherapy [185]. But, EGFR targeted therapy trials conducted in HNSCC to date still show various disadvantages such as low efficacy and significant toxicity [186]. In ESCC, inhibition of EGFR-TK by erlotinib is promising through inducing growth inhibition and cell cycle arrest in human esophageal cancer cells and enhancing the antineoplastic effects of other targeted agents [187]. Cetuximab and panitumumab are currently being investigated in NSCLC. Phase II trials showed that cetuximab improved survival in-chemo-naïve patients with advanced cancer [188, 189] and panitumumab is currently in phase II trial [190].

EGFR TKIs gefitinib and erlotinib were the first two targeted agents recently approved for the treatment of NSCLC in the United States and several markers have been identified that predict response in NSCLC patients. These EGFR TKIs produce responses in approximately 10% of NSCLC patients having progressed with prior chemotherapy [191–193]. But in those

patients who benefit from gefitinib or erlotinib the responses can be dramatic and may last for longer than a year, with favorable response being associated with activating mutations in the EGFR tyrosine kinase domain (exons 18 to 21), increased gene copy number, and increased protein expression [191–194]. Even though targeting EGFR mutated NSCLCs with gefitinib or erlotinib has been effective, most of these patients acquire resistance to the EGFR TKI therapy [195, 196] in an average of 6–12 months [197]. Interestingly, smokers presenting with NSCLCs are generally resistant to EGFR-TKIs [198, 199], which may have implications in other targeted therapies of this class because SCC is the predominant histologic subtype associated with smokers. In an effort to counteract EGFR TKI resistance mechanisms, an initial study has shown TKI resistant NSCLC cell lines can be treated by administering PI3K-mTOR and MEK signaling inhibitors simultaneously with EGFR TKIs [200]; but, to date this has not been tested in NSCLC patient populations.

Other growth factor receptor antagonists—IGF-I acts though the IGF receptor 1 (IGF- R1) to promote cell survival and cell proliferation [201]. It plays an important role in normal growth and has anabolic effects in adults normally. But IGF-I has been implicated in cancers [202] as its anti-apoptotic properties allow cancerous cells to resist the cytotoxic effects of chemotherapeutic drugs or radiotherapy. A recent clinical trial reported that combining the fully humanized anti–IGF-IR monoclonal antibody A12 with radiation to treat HNSCC resulted in more pronounced antitumor activity than either agent alone [203]. In NSCLC, early clinical trials showed an acceptable safety profile together with pharmacodynamic evidence that IGF-RI can be successfully targeted [204]. And, biomarkers of the IGF-IR pathway were shown to be key elements in development and monitoring of anti-IGF-RI therapy in NSCLC [205]. Recently, phase II study data has suggested that co-administration of an anti-IGF-IR antibody with chemotherapy improves the response rate and progression-free survival [204].

HER3 (ERBB3), a gene encoding a member of the epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases has emerged for HNSCC targeted therapy within the past four years [206, 207]. Several laboratories are designing antibodies that will block HER3 heterodimerization with EGFR or HER2 to prevent signaling to PI3K/Akt [208].

5.2. Cell-Cycle Regulation

Although cell-cycle regulation contains the most molecular abnormalities in SCC (Table 3) and subsequently numerous potential therapeutic biomarkers, currently only one marker, CCND1, has been exploited. Mutations, amplification and overexpression of CCND1 are frequently observed in a variety of tumors, including SCCs, and may contribute to tumorigenesis. Flavopiridol, the first cyclin-dependent kinase inhibitor in human clinical trials, was reported as a targeting drug for HNSCC [209]. Flavopiridol has also been shown to decrease CCND1 expression in ESCC cell lines and was subsequently found to induce radiosensitivity [210] and may have application to the other SCCs.

5.3. Signal Transduction

Signal transduction was the second most common group of molecular abnormalities in the four major SCCs (Table 3). Of which, both of mTOR and MET have been identified in HNSCC and NSCLC as molecular targets. mTOR is a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription. It is activated by Akt and blocks apoptosis to increase the proliferative potential of cancer cells. Several mTOR inhibitors are currently under investigation in HNSCC [211]. In an ongoing phase II trial, combined inhibition of mTOR with everolimus and gefitinib was evaluated in patients with stage IIIB/IV NSCLC [212]. Bortezomib is a small-molecule proteasome inhibitor that has shown encouraging results in a phase II trial,

and a phase III trial of gemcitabine/carboplatin ± bortezomib in advanced stage NSCLC is in progress [213].

C-MET is the cell surface receptor for hepatocyte growth factor (HGF), also known as scatter factor [214]. Binding of the receptor to its ligand, hepatocyte growth factor, induces receptor dimerization that triggers conformational changes that activate MET tyrosine kinase activity which then have profound effects on cell growth, survival, motility, invasion and angiogenesis [215]. Dysregulation of MET signalling has been shown to contribute to tumorigenesis in a number of malignancies and hence can serve as a potential drug target. Zucali, et al. found that activated cMET appeared to be a marker of primary gefitinib resistance in NSCLC patients and suggested cMET may be a target for treatment [216]. In NSCLC, several phase II/III tiral with PF-02341066 either as monotherapy or in combination with EGF-R inhibitors are currently underway [217].

In addition, preliminary data from a phase II trial testing of sorafenib, a potent inhibitor of the Raf-1, B-Raf, VEGFR-2-3, and PDGFR-B pathways, in metastatic or recurrent HNSCC were recently reported [218]. Sorafenib treatment for NSCLC is being evaluated in several phase III studies [217].

5.4. Protein Degradation

Cox-2 has been implicated in apoptosis resistance, angiogenesis, decreased host immunity and enhanced invasion and metastasis, and, thus is involved in critical aspects of carcinogenesis [219]. COX-2 selective inhibitors, a form of non-steroidal anti-inflammatory drug (NSAID) that directly targets COX-2, has been shown to reduce the occurrence of cancers and pre-cancerous growths [220] and is in clinical trials for both ESCC and NSCLC [219]. Histone deacetylase inhibitors (HDIs) have been shown to block the activation of COX2 transcription [221]. In recent years, there has been an effort to develop HDIs for cancer therapy and they have demonstrated activity in patients with advanced solid tumors in phase I trials as well as in patients with relapsed NSCLC [222]. Since COX2 dysregulation was also shown in all of the four major SCCs, HDIs should be investigated for SCC as a whole.

5.5. Angiogenesis

Although VEGF alteration has not yet been shown to be directly involved in NMSC and NSCLC, VEGF expression in generally is commonly seen in tumors due to its involvement in vasculogenesis and angiogenesis. Furthermore, VEGF may cause a cell to survive, move, or further differentiate through various molecular mechanisms, thus VEGF is a potential target for the treatment of cancer, including SCCs. Anti-VEGF therapies have capitalized upon this potential and have proven to be important in the treatment of certain cancers using monoclonal antibodies (bevacizumab) and orally-available small molecule VEGF TKIs (sorafenib). In SCC, sorafenib has been used in clinical trials of HNSCC and NSCLC [223, 224]. Bevacizumab, the first commercially available angiogenesis inhibitor, has been tested in HNSCC and NSSCLC [225, 226]. Interestingly, improved outcome has been shown using bevacizumab in combination with the combination chemotherapy of paclitaxel carboplatin in patients with advanced NSCLC, but is contraindicated for SCC due to safety risks [226]. This contraindication for SCC is due to grade 5 hemoptysis in SSC patients and identification via multivariate analysis of SCC as an individual significant risk factor [226]. As such, bevacizumab in combination with paclitaxel carboplatin is now only used with non-squamous NSCLCs.

Advances in understanding the molecular pathogenesis of SCC has provided a unique opportunity to attack SCC by targeted therapy. Examination of molecular abnormalities in

tumors has become increasingly important. Similarly, the development of molecular "signatures" (e.g. mRNA expression profiles) from tumors that provide information on the prognosis and predict the response of individual patient's tumors to specified therapy would be a major step forward. For a targeted therapy to truly be effective, we must also have biomarkers to precisely predict or monitor tumor response or resistance to cytotoxic and targeted agents [227]. Unfortunately, to date, no good clinical or biological markers to predict outcomes of targeted therapy have been identified.

6. New Approach to Studying Molecular Abnormalities in SCC

In an effort to advance the molecular profiling and subsequent understanding of SCC as a whole, new methodologies are being developed using specific anatomic site SCCs with the goal of applying these novel approaches to the characterization of molecular abnormalities in other SCCs. Our group utilized a microdissected normal basal-tumor gene expression comparison to identify pathways and genes that could be putative therapeutic targets for ESCC (Yan *et al*. submitted). In other words, we contrasted the expression profile of a normal dividing cell population against its counterpart transformed cell population in a search for growth-related genes that are unique to cancer and not part of the standard cell growth machinery per se [228]. The data showed that gene expression in normal differentiated cells was markedly different from normal basal cells and tumor; whereas, tumor and normal basal cells were more closely related. Tumor cells showed a general decrease in differentially expressed genes relative to normal basal cells as opposed to differentiated cells that exhibited the opposite trend. The results identified two highly dysregulated networks in normal differentiation and tumorigenesis; DNA repair pathways were involved in normal and pathological growth; and some individual cell differentiation related pathway and genes were uniquely expressed in basal cells compared to differentiated cells. Furthermore, using our 'biologic filter', 12 genes were identified as being unique to the normal basal-tumor comparison and could potentially be therapeutic targets for treating ESCC.

In a separate study, we have focused on characterizing targeted-therapy related molecular biomarkers from NSCLC ever-smokers versus never-smokers, using microdissected paired tumor/normal cells and a novel qRT-PCR with pre-amplification method developed by our group (Yan *et al*. submitted). The data provided potentially useful information in guiding an individual treatment approach for lung cancer.

Although these strategies have been developed in ESCC, these novel methodologies can be applied to other SCCs to identify potential therapeutic targets directly related to tumorigenesis. We hope that these new approaches to studying SCC will also elucidate markers for prognosis and lead to effective therapies for SCCs of all anatomical sites.

7. Conclusion

Despite improvements in diagnosis and therapy, mortality and morbidity rates for some forms of SCC remain high. Early diagnosis is of course important in preventing this cancer and reducing mortality, and in parallel to improving screening and diagnostic efforts, there is a significant need to develop novel therapeutic agents for patients with advanced disease. SCCs demonstrate a wide range of epithelial tumors that vary in their anatomic sites. These tumors show varying degrees of relationship to risk factors, with HPV showing the greatest relationship.

Modern molecular genetic analysis allows us to probe beneath the phenotypic surface to the underlying etiologic molecular abnormalities of SCC and a number of molecules that contribute to the complex events of carcinogenesis and cancer progression in these cancers

have been identified. The molecular lesions found in SCC tumors share common elements and characteristic changes, with molecular abnormalities of cell-cycle regulation and signal transduction predominating SCCs as a whole.

Encouraged by the development of methodologies for isolation of cells from small histologic lesions, such as laser microdissection, combined with techniques to perform genomic studies from minute amount of DNA, RNA and protein, several groups, including ours, have made substantial progress on unveiling the molecular and genetic abnormalities of SCCs. The development and application of new molecular genetic methods for analysis of SCC tissue specimens will help delineate the significant molecular abnormalities responsible for SCC development and progression. Additional studies are needed to further improve our understanding of the similarities and differences among the various SCCs, toward improvements in diagnosis, prognosis and therapy.

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Table 1

Risk factors of SCC.

Risk factor	NMSC	HNSCC	ESCC	NSCLC
Personal habits				
Tobacco smoking	●	●●●	●●●	●●●●●
Alcohol consumption		●●●	●●●	
Dietary factors		●[a]	●[b]	
Oral health		●		
Environmental exposures				
UV light	●●●●●	●		
Occupational exposure (nickel refining, textile fibers, woodworking)		●		
Radon gas				●
Particulate matter				●
Asbestos				●
Viral infections				
HPV	●	●	●	●
EBV		●		
JCV				●
Other diseases				
Acid reflux disease		●		
Achalasia			●	
Plummer-Vinson Syndrome			●	
Ethnicity		●[c]	●[d]	

● = common factor
●●● = major factor
●●●●● = predominant factor

[a] Betel nut chewing

[b] High-starch diet without fruits and vegetables, or pickled vegetables

[c] African American

[d] African American, male

Table 2

Prognostic indicators and markers of SCC.

	NMSC	HNSCC	ESCC	NSCLC
Risk factors				
HPV		●		
Molecular markers				
TP53/p53		●	●	
EGFR	●	●	●	
Ki-67	●	●	●	●
p63	●	●	●	●
VEGF		●	●	
SOX2			●	
Smad6/7			●[229]	
CDH1	●		●	
CD44v6		●[230]		
MMPs	●	●	●	
Trop2		●[231]		
EpCAM		●[232]		
HER2		●[233]	●[234]	
CCND1	●	●	●	●
CCND1 + p53 mutation	●			
Bcl-x			●[235]	
Bcl-2			●	●
Bax			●[236]	
p16			●	
CD24				●
IGFR-1 + EGFR				●
RASSF1A				●
miR-21			●	
miR-211		●		

Table 3

Molecular abnormalities in SCC.

Marker	Class	Function	Abnormality	NMSC	HNSCC	ESCC	NSCLC
TP53	CCR	Tumor-suppressor gene regulating cell-cycle progression and cell survival	GE, GM	●	●	●	●
pRB	CCR	Tumor-suppressor gene regulating cell-cycle progression and apoptosis	GE		●[237]		
p16	CCR	Tumor-suppressor gene regulating senescence and cell-cycle progression	GM, M		●	●	
PTEN	CCR	Tumor-suppressor gene controlling cell proliferation and apoptosis	GE		●[237]		
MKI67 (Ki-67)	CCR	Proto-oncogene regulating cell proliferation, increased from normal to pre-cancer	GE	●	●	●	●
CCND1	CCR	Proto-oncogene regulating cell-cycle progression	GE	●	●	●	
p63	CCR	A member of the p53 family of transcription factors	GE	●	●	●	●
p27	CCR	G1 arrest	GE			●[238]	
CD95	CCR	Death ligands	GE	● [239]			
FHIT	CCR	Negative regulation of progression through cell cycle	GE			●[240]	
Bcl-x	CCR	regulate programmed cell death	GE			●[235]	
Bcl-2	CCR	regulate programmed cell death	GE			●[103]	
Bax	CCR	regulate programmed cell death	GE			●[236]	
EGFR	ST	Transmembrane TK acting as a central transducer of multiple signaling pathways	GE, GM	●	●	●	●
VEGF	ST	Transmembrane TK that promotes the proliferation, migration, and survival of endothelial cells during tumor growth	GE		●	●	
HER2	ST	Cell membrane surface-bound receptor tyrosine kinase leading to cell growth and differentiation	GE		●[241]	●[234]	
Annexin I	ST	Cell surface receptor linked signal transduction	GE			●[242]	
RRas2	ST	Small GTPase mediated signal transduction	GE, GM			●[243]	
Smad6/7	ST	TGF beta receptor signaling pathway	GE			●[229]	
NKX2-1 (TTF-1)	ST	Regulates gene trancription	GE, GM				●
BRAF	ST	Protein kinase is involved in sending signals in cells and in cell growth	GE, GM				●
c-MET	ST	Membrane receptor that is essential for embryonic development and wound healing	GE, GM				●
PEDF	ST	Serine protease inhibitor	GE				●[244]
PIK3CA	ST	Phosphatidylinositol 3-kinase	GE, GM				●
LKB1	ST	Protein kinase regulates cell polarity and functions as a tumor suppressor	GE, GM				●
RASSF1A	ST	Encord protein mediated signal transduction	GE, M				●
CD24	ST	Encord protein mediated signal transduction	GE				●[101]

Marker	Class	Function	Abnormality	NMSC	HNSCC	ESCC	NSCLC
CD44v6	CA	Transmembrane glycoproteins that maintain tissue integrity by mediating contact between cells or between cells and the extracellular matrix	GE		●[230]		
CDH1	CA	Ca 2+ -dependent cell-cell adhesion molecule, induce and maintain intercellular connections	GE, M	●		●	
Trop2	CA	Cell adhesion, signal transduction	GE		●[231]		
EpCAM	CA	Cell adhesion, signal transduction	GE, GM		●[232]		
ALCAM	CA	Cell adhesion, signal transduction	GE			●[245]	
MMPs	EMD	A family of zinc-dependent proteolytic enzymes that degrade the basement membrane and other components of the extracellular matrix	GE	●	●	●	
COX-2	PM	Prostaglandin metabllism	GE	●	●	●	●
SOX-2	TF	Transcription factor	GE		●	●	●
AP-1	TF	Transcript factor	GE	●[246]			
PPARb/d	TF	Transcript factor	GE	●[247]			
CK-14	CK	Epidermis development	GE			●[248]	
CK-4	CK	Cytoskeleton organization and biogenesis	GE			●[248]	

CCR = cell-cycle regulation
ST = signal transduction
CA = cell adhesion
EMD = extracellular matrix degradation
PM = protein metabolism
TF = transcript factor
CK = cytokeratin
PK = protein kinase
GE = gene expression
GM = gene mutation
M = methylation

Table 4

Molecular targets for therapy in SCC.

Target category	Target	Drug example	Construction	NMSC	HNSCC	ESCC	NSCLC
Growth factor receptor	EGFR	cetuximab/panitumumab	Monoclonal Antibody		●	●	●
		erlotinib/gefitinib	tyrosine kinase inhibitors		●	●	●
	IGF-IR	IGF-IR antibody	Monoclonal Antibody		●		●
	HER3	HER3 antibody	Monoclonal Antibody		●		
Signal transduction	mTOR	everolimus	mTOR inhibitor		●		●
	MET	SU11274/PF-02341066	Small molecule		●		●
	Raf/VEGFR	Sorafenib	Small molecule		●		●
	Ras	reovirus	Virus		●[249]		
	MEK1/2	AZD6244	Small molecule		●[250]		
Angiogenesis	VEGF	bevacizumab	Monoclonal Antibody		●		●
	Raf/VEGFR	Sorafenib	Small molecule		●		●
Cell cycle	CCND1	Flavopiridol	Kinase inhibitor		●	●	
Protein degradation	Cox-2	Celecoxib/Meloxicam	Kinase inhibitor	●[a]		●	●
	Histone deacetylases	vorinostat	HDAC inhibitors				●
Mitosis	Polo-like kinases	BI 2536	PLK1 inhibitor				●[251]
	Aurora Kinase A/B	Aurora Kinase inhibitor	serine/threonine kinases inhibitor		●[252]		
Inducers of apoptosis	APO2	AMG655/conatumumab	Monoclonal Antibody		●[253]		●[254]
Cell adhesion molecules	CD44v6	CD44v6 antibody	Monoclonal Antibody		●[230, 255]		

[a] Diclofence