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Review Article

Molecular pathology and potential therapeutic targets in esophageal basaloid squamous cell carcinoma

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Abstract: Basaloid squamous cell carcinoma (BSCC) is a rare and poorly differentiated variant of typical squamous cell carcinoma. Emerging studies show that genetic alterations are more frequent in BSCC than in conventional SCC, and some of which led to the identification of potential therapeutic targets in esophageal BSCC. Approximately half of the esophageal BSCC cases harbor either an *EGFR* mutation or amplification, and these occur in a mutually exclusive fashion. Therefore, the application of tyrosine kinase inhibitors may be beneficial to esophageal BSCC patients. This tumor is partly characterized by the activation of the Wnt and Hedgehog (HH) signaling pathways. Wnt signaling is activated by *SFRP2* promoter hypermethylation and HH signaling is activated by the frequent mutations in *PTCH1*. Increasing evidence shows that the Wnt signaling pathway is involved in cross-talk with other developmental pathways, including the HH pathway. Therefore, pharmaceutical therapy targeting both the HH and Wnt pathways would be quite effective in patients with esophageal BSCC with highly malignant potential. In this review, we discuss the pathology, prognostic factors, genetic alterations and potential therapeutic targets in BSCC of esophagus.

Keywords: Basaloid squamous cell carcinoma, molecular pathogenesis

Introduction

Basaloid squamous cell carcinoma (BSCC), first described as a laryngopharyngeal tumor by Wain et al [1], is a rare and poorly defined variant of typical squamous cell carcinoma (SCC). The majority of esophageal BSCC cases were previously diagnosed as adenoid cystic carcinoma (ACC). The incidence of esophageal BSCC is reported to range from 0.77% to 5.0% [2-6]. A recent large study comprising 142 cases of esophageal BSCC demonstrated its incidence as being 2% of all malignant esophageal neoplasms [7]. It is histologically characterized by solid nests with comedo-type necrosis, a lobular or trabecular architecture of crowded cells with scant cytoplasm and hyperchromatic nuclei [8]. These features are partly reminiscent of basal cell carcinoma (BCC) of the skin [8]. We and other groups have reported that esophageal BSCC is a distinctive invasive carcinoma characterized by poor survival [6-9]. This review describes the genetic alterations so far reported, as well as the prognostic factors and potential therapeutic targets in esophageal BSCC.

Molecular pathogenesis of esophageal basaloid SCC

The clinical symptoms and macroscopic features of esophageal BSCC are not different from those observed in conventional SCC of the esophagus [2, 8, 10]. Furthermore, BSCC shows diverse histological features, including a cribriform/pseudoglandular pattern [8]. Therefore, it is difficult to differentiate BSCC from conventional SCC, adenoid cystic carcinoma and small cell carcinoma, especially in small biopsy specimens. Only 12 cases were diagnosed as BSCC among 118 patients who received an endoscopic biopsy [7], and none of the histological specimens taken by esophagoscopy prior to surgery was diagnosed as BSCC [6]. Classically, BSCC has been confused with adenoid cystic carcinoma (ACC). It needs to be differentiated from ACC, especially from the solid variant with basaloid features, because these two tumors show apparently different clinical courses [5, 11]. ACC is a malignant tumor characterized by a proliferation of epithelial and myoepithelial cells that can occur in a variety of organs.

Because the *MYB-NFIB* gene fusion, resulting from a translocation t(6;9) (q22-23;p23-24) involving *MYB* on chromosome 6q and *NFIB* on chromosome 9p, has been identified in ACC [12, 13], these two tumors are distinct from each other and can be genetically differentiated. On the other hand, the molecular pathogenesis of esophageal BSCC remains unknown, though there are numerous features that distinguish it from conventional SCC. High-risk human papilloma virus (HPV) infection is recognized as an etiology in SCC of the head and neck, and HPV positivity in SCC of the head and neck regions has shown distinct clinicopathologic features, including basaloid morphology [14, 15]. However, it has been shown that high-risk HPV is negative in esophageal BSCC [9]. The expression of the cyclin-dependent kinase inhibitor 2A (p16) is less common in esophageal BSCC than in conventional SCC of the esophagus, whereas there is no difference in cyclin D1 expression [9]. Furthermore, bcl-2 expression and *c-myc* amplification are more common in esophageal BSCC than in conventional SCC [16]. TP53 expression has been observed in approximately half of the esophageal BSCC cases [4, 17, 18], and it has also been demonstrated that TP53 expression is less frequent in BSCC than in conventional well-differentiated (keratinizing) SCC [9]. We have observed significantly higher expression of TP53 in BSCC than in well-differentiated SCC (WSCC). However, this difference was not significant between BSCC and SCC forms other than WSCC [8]. The loss of heterozygosity (LOH) at the adenomatous polyposis coli (*APC*) and the mutated in colorectal cancers (*MCC*) locus was approximately twice as common in BSCC as in SCC [18]. The telomerase activity was reportedly observed in 95% of esophageal BSCC [10]. Telomeres shorten after each round of cell division, and the length of telomeres must be maintained to keep a limitless replicative potential. One important mechanism of telomerase activation is the recurrent mutations in the promoter regions of telomerase reverse transcriptase (*TERT*) [19, 20]. Recently, we have screened mutations in the *TERT* promoter in esophageal BSCC cases, though none of these cases contained *TERT* promoter mutations (unpublished data). Furthermore, approximately half of the esophageal BSCC cases harbored either an *EGFR* mutation or amplification, and these events occurred in a mutually exclusive fashion [8].

A recent study has demonstrated that activation of the Wnt signaling pathway, shown by the nuclear accumulation of β-catenin, was observed in all cases of esophageal BSCC [21]. A mutation in the *CTNNB1* gene that encodes β-catenin was absent in this type of tumor, though 20% of cases harbored at least one mutation in either *APC*, *Axin1* or *Axin2* [21]. On the other hand, *SFRP2* promoter hypermethylation was observed in all esophageal BSCC cases, leading to the assumption that nuclear accumulation of β-catenin in esophageal BSCC is probably due to hypermethylation of the *SFRP2* promoter [21]. Our recent study also demonstrated frequent genetic alterations of *PTCH1,* leading to the constitutive activation of the Hedgehog signaling pathway (HHSP) in esophageal BSCC [22]. Germline loss-of-function *PTCH1* mutations in patients with Gorlin syndrome is an autosomal-dominant disease, and somatic mutations in *PTCH1* have been identified in more than 90% of sporadic BCC cases [23] and in ~20% of medulloblastomas [24]. Our findings were similar in esophageal BSCC, and *PTCH1* mutations were observed in 53.3% of cases. Interestingly, it has also been shown that epithelial HH ligand expression is an early event in mammary carcinogenesis of basal-like breast cancer that is associated with poor outcome with regard to metastasis and breast cancer-related death. It has also been shown that ectopic expression of the HH ligand in a mouse model of BLBC led to the development of rapidly growing, high-grade, invasive tumors [25]. These findings suggest that the activation of the HH pathway might be associated with basal cell morphology, and might contribute to the tumor's aggressive behavior. In summary, accumulating data suggest that genetic alterations are more common in BSCC than in conventional SCC, and the protein expression profiles are distinct between these two forms of SCC.

Prognostic factors in esophageal BSCC

The 1-, 3- and 5-year overall survival rates (OSRs) in 142 esophageal BSCC patients are 81.4%, 46.8% and 31.0%, respectively [7]. Another study of 26 patients found that the 1-, 3- and 5-year OSRs were 73.1%, 42.7% and 36.6%, respectively [6]. Furthermore, we have reported that the 3- and 5-year OSRs were 70.0% and 42.0%, respectively, and that the disease-free 3- and 5-year survival rates were both 45.0% [8]. We also noted that out of stage-

matched patients with BSCC, poorly differentiated SCC, moderately differentiated SCC, and well-differentiated SCC, BSCC patients demonstrated the worst cancer-related and disease-free survival rates. However, this difference was significant only when compared with WSCC [8], consistent with previous findings [6]. Furthermore, the median survival time and the 5-year OSR in patients with tumors located in the lower thoracic esophagus are significantly better than those in patients with lesions in the upper/middle esophagus [7].

It has been shown that there is no significant difference in tumor size, pT stage, pN stage, lymphovascular invasion, perineural invasion and patients' survival rates between esophageal BSCC and typical SCC [2]. In addition, another group has also reported almost similar findings regarding the frequencies of venous permeation and nodal metastasis, whereas lymphatic permeation was less frequent in esophageal BSCC [17]. We have observed that BSCC patients with ductal differentiation had significantly better OSRs than those without it, though this is not the case for disease-free survival rates [8]. In addition, it is also interesting to note that BSCC cases with lower expression of CK903 were associated with higher T stages and venous invasions [8]. Furthermore, lower expression levels of CK903 and CK14 were respectively associated with worse OSRs [8]. A high telomerase activity was significantly associated with a shorter survival rate in esophageal BSCC [10].

Current therapy and potential therapeutic targets

The current options to treat esophageal BSCC are mainly based on the experience obtained from the treatment of conventional SCC of the esophagus. Esophageal BSCC is currently treated with surgery, chemotherapy and radiotherapy, and standard treatment has not yet been established. Esophageal BSCC sometimes shows a quite aggressive clinical course with poor outcome, and an alternative, effective targeted therapy is therefore warranted. The most commonly used forms of chemotherapy for this type of tumor are the platinum-based regimens (cisplatin or carboplatin plus Taxol, cisplatin plus 5-Fluorouracil plus Etoposide, etc.). However, survival cannot be improved with these adjuvant therapies, including their combination with radiotherapy [7]. It has recently been shown that SCC with a basaloid histology in the lungs has a characteristic molecular profile related to its intrinsic resistance to cytotoxic chemotherapy [26], implying the possibility that the same mechanism underlying chemotherapy resistance might also exist in tumors with similar histology in other organs. Recently, a case of esophageal BSCC showing a durable and complete response to FOLFOX-4, comprising oxaliplatin, fluorouracil, and leucovorin, has been described [27]. This regimen was shown to be detrimental as the cisplatin plus fluorouracil by the PRODIGE 5/ACCORD 17 trial [28]. Furthermore, chemoradiotherapy with FOLFOX-4 has been shown to lead to higher overall esophageal cancer survival rates compared to cisplatin plus fluorouracil [29].

Regarding the possibility of molecular targeted therapy in esophageal BSCC, we have shown that the membranous expression of EGFR was significantly higher in BSCC than in conventional SCC forms, from well-differentiated to poorly differentiated types [8]. Furthermore, approximately half of the esophageal BSCC cases harbored either an *EGFR* mutation or amplification, and these were mutually exclusive [8]. EGFR tyrosine kinase inhibitors (TKIs) have already been used in the treatment of head and neck SCC (HNSCC), and Cetuximab (Erbitux®), a monoclonal antibody (mAb) against EGFR, is the only FDA-approved molecular targeting agent for the treatment of primary or recurrent/metastatic HNSCC [30]. It has been demonstrated that the administration of Cetuximab to treat patients with advanced local or recurrent/metastatic HNSCC has led to improved overall survival [30]. Therefore, the application of TKIs may be beneficial to patients with esophageal BSCC.

Pharmaceutical therapy targeting the HH pathway is a fairly recent concept, though the targeting of the HH signaling pathway (HHSP) as a form of anticancer therapy in esophageal BSCC is attractive, because *PTCH1* mutations are frequently observed in esophageal BSCC. Dysregulations in the HHSP are involved in malignant tumors, though the normal HHSP is also involved in cell growth and congenital development [31, 32]. It has also been shown that cyclopamine or synthetic HHSP inhibitors could be useful to inhibit HHSP in malignant tumors [33]. The main ligand that activates HHSP is

Sonic [34-36]. Sonic binds to its receptor, PTCH1, and inactivates it [34-36]. Without HHSP ligand signaling, PTCH1 remains activated and inhibits smoothened (SMO), keeping the transcription of HHSP target genes blocked. However, HHSP eventually enables the glioblastoma protein (GLI) activator, leading to the transcriptional up-regulation of target genes through SMO. Targeting the HHSP with SMO inhibitors is suitable for cancers with mutations in *PTCH1* and/or *SMO*. Several SMO antagonists have already been used to treat advanced BCC in clinical trials with impressive results [37, 38]. Pro-drugs with few side effects are also being developed, such as modulating cyclopamine containing a peptide cleavable by prostate-specific antigens targeted to prostate cancer [39].

Furthermore, the constitutive activation of the Wnt signaling pathway has been suggested in this tumor [8, 21], and this seems to be specific to BSCC, among the well to poorly differentiated forms of SCC. Therefore, molecular therapy targeted to the Wnt signaling pathway might be effective in treating esophageal BSCC. Molecular therapy targeted to the Wnt receptor, Frizzled (Fzd), has already been shown to have anti-tumor activity *in vitro* and *in vivo* [40-42]. Because the activation of the Wnt signaling pathway in BSCC is due to the downregulation of SFRP2 and to mutations in *APC* and *Axins*, these therapies also seem to be applicable to this type of tumor.

There is increasing evidence that the Wnt and HH signaling pathways cross-talk or intersect with the Notch and bone morphogenic protein pathways [43, 44]. The Wnt signaling pathway can also control Gli3 in the HH pathway [45], and HH can in turn antagonize Wnt signaling in the colon [46, 47]. Cross-talk between the Wnt and HH pathways has been also demonstrated in a gastric cancer cell line [48]. Furthermore, many studies have proposed several mechanisms underlying the resistance to molecular target therapies, including TKI. Over-activation of other ErbB family receptors, including HER2, has been shown as the common mechanism triggered by the EGFR-directed therapeutic antibody Cetuximab [49]. In addition, a recent study has also provided a rationale for co-targeting insulin-like growth factor 1 receptor and ALK in ALK fusion-positive lung cancer [50]. Furthermore, another study has reported cross-talk between KIT and fibroblast growth factor receptor 3, which promotes gastrointestinal stromal tumor cell growth and drug resistance [51]. Collectively, these findings highlight the importance to simultaneously block signaling pathways that are related to each other. Therefore, pharmaceutical therapies targeting both the HH and Wnt signaling pathways would be quite effective in treating esophageal BSCC.

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Disclosure of conflict of interest

None.

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