Genetics Of The Salivary Gland Adenoid Cystic Carcinoma - A Brief Overview

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Abstract

Adenoid cystic carcinoma (ACC) is one of the common aggressive variants of malignant salivary gland tumours. ACC is characterized by local spread, perineural infiltration, and distal metastases. Surgery with or without adjuvant radiotherapy is the treatment of choice. Inadequate molecular insights into signaling that triggers carcinogenesis and invasiveness in ACC together with no representative cell lines available for testing are major blocks to the discovery of more treatment options with better outcomes for this insidious cancer. Common tumour suppressor genes and oncogenes that are known to play essential roles in the pathogenesis of cancers in other organs are seen to be less prevalent in salivary gland cancers. Genes that take part in the carcinogenesis of ACCs are suspected to be unique. More research with goals to identify signaling mechanisms triggering in cancer genesis and spread to improve therapeutic insight is essential. In the short review article, we have tried to summarize all known genetic changes that have been studied and known to be involved in the carcinogenesis of ACC. This would save as a basis for more research to be done in this area with the objective of developing newer targets for treatment.

INTRODUCTION

ACC is one of the common variants of malignant salivary gland tumours and is known for its unpredictability and aggressive nature amongst the head and neck cancers. Subtle local invasion and tendency to perineural infiltration and distant spread to bone and lung are notable features that are characteristics of ACC [1, 2]. ACCs are usually treated with surgical resection with or without adjuvant radiotherapy. Inadequate molecular insights into signaling that triggers carcinogenesis and invasiveness in ACC together with no representative cell lines available for testing are major blocks to the discovery of more treatment options with better outcomes for this insidious cancer [3, 4]. More research with goals to identify signaling mechanisms triggering in cancer genesis and spread to improve therapeutic insight is essential. Common tumour suppressor genes and oncogenes that are known to play essential roles in the tumorigenesis of cancers in other organs are seen to be less prevalent in salivary gland cancers. So alterations in unique regulatory genes of the cell cycle are expected to trigger tumorigenesis in ACC [5, 6].

C-KIT

c-kit is seen in the long arm of chromosome 4 and codes for

tyrosine kinase transmembrane receptor, KIT [7-9]. When c-KIT binds with its corresponding ligand, it triggers signaling pathways leading to cell division and maturation [10, 11]. c-KIT has previously related to tumorigenesis of mast cell tumour, lung cancer, gastrointestinal stromal tumour, germ cell tumour, haematological malignancies, and others [12-16]. Many studies reported immunoreactivity for c-kit protein in more than 50% of the cells in most of ACCs [17-19]. Further, many studies on ACC have shown c-kit protein expression in tumour cells showing solid, tubular, and cribriform patterns of ACC [20-22]. The pattern of c-KIT expression on immunohistochemistry is diffuse that might be the reason for previous studies that showed contradicting results. The understanding of the role of the c-kit in tumorigenesis in ACC is not yet complete. Studies show that although c-kit expression is seen in ACC, it is found to be non-phosphorylated, resulting in the belief that it is unlikely to have an essential carcinogenic role in ACC [23]. The high expression of c-kit in ACC may represent a role for c-kit inhibitors as a possible therapeutic treatment for this tumour. Tyrosine kinase inhibitors that work for gastrointestinal tumours of the stomach were not found to be effective for ACCs. this might be because of the non-phosphorylated form of c-kit and lack c-kit mutations in

ACCs [24-28]. Further research studies directed to identify pathways of c-kit involvement in pathogenesis might lead to the discovery of newer therapeutic targets of ACC.

MYB

Many studies have reported translocation (6, 9) in ACCs of head and neck and also of the breast [29-30]. This translocation attaches the MYB gene and the NFIB gene that results in a chimeric transcript. The deleted region of the MYB gene is seen to bind with micro-RNA molecules that customarily suppress the expression of MYB, and the opposite is true for fusion [29]. Studies report that MYB activation via gene fusion or other pathways is an important event in tumorigenesis of adenoid cystic carcinoma, regardless of the location of the tumour. MYB could be a helpful novel biomarker for the diagnosis of ACC. MYB and its downstream pathway effectors could also be potential therapeutic targets. Further research focused on discovering the transcriptional targets of MYB-NFIB and MYB in ACC is essential so that new potential target therapies could be developed that may enhance the outcome of ACC patients [31].

EGFR

Epidermal growth factor receptor (EGFR) is a transmembrane receptor made of glycoprotein that has tyrosine kinase action. EGFR comprises a hydrophobic area that acts as a ligand-binding domain along with a cytoplasmic area that houses a tyrosine kinase domain [32]. EGFR is known to cause an increased rate of cell division, inhibit cell death, heighten tumour cell mobility, new blood vessel formation, and increase the life of cancer cells. Increased expression of EGFR has been related to advanced disease with increased metastatic potential and worse outcomes in many human cancers [33]. However, recent studies demonstrated the inverse relationship of EGFR expression and the severity of the disease pattern. EGFR expression is characterized in ACC as to be present strongly in myoepithelial cells and only weakly positive in ductal epithelial cells. Since myoepithelial cells are often absent in the advanced solid pattern of ACC, EGFR expression is found to be restricted to early disease patterns, tubular and cribriform only [34, 35].

Like many other epithelial malignancies, the expression of members of the EGFR family seen in ACC encouraged drug trials against ACC using tyrosine kinase receptor inhibitor drugs [49]. But unfortunately, the results were not favourable [36-38]. Combination therapy of tyrosine kinase

inhibitors along with platinum-based chemotherapy and radiotherapy showed some positive outcomes in ACC patients who had advanced metastatic disease [39]. Further studies need to be done to understand the role of EGFR in the tumorigenesis of ACC and identify target therapy for better patient outcomes.

RAS

Promoter methylation of the RASSF1A gene was seen to be related to the grade and the TNM stage of salivary gland ACC. Further studies showed RASSF1A promoter methylation in about 35% of all salivary gland ACCs [40] which is lower than other cancers such as lung, colon, and breast [41-43]. The pattern of this gene methylation exceptionally in the advanced stage of the disease suggests that the RASSF1A gene might have an important role in the carcinogenesis of ACC. Similar predictions were also recorded in bladder and kidney tumours [44, 45]. Other than promoter methylation, tumour suppressor genes can be rendered inactive by loss of heterozygosity (LOH) or point mutation. Although promoter methylation of RASSF1A is common in ACC, LOH has also been reported in about 18% of the cases [46]. About 12% of the cases, both promoter methylation and LOH were reported in ACCs rendering the gene inactive. This type of two-hit phenomenon is more efficient in tumorigenesis and has also been reported to cause cervical cancers in a lower percentage previously [47, 48]. However, promoter methylation of RASSF1A is more common in ACC than LOH and is found to be directly related to patient outcome. Thus RASSF1A gene promoter methylation may serve as a prognostic biomarker for predicting survival in ACC patients. Also, it is interesting to note that patients with both promoter methylation and LOH seem to have the worst outcome than the patients with either one of the abnormalities [49]. Further studies need to be done to uncover mechanisms of RASSF1A gene involvement in the carcinogenesis of ACC might lead to the discovery of newer therapies against this deadly disease.

CTNNB1

The CTNNB1 gene encodes the protein catenin that has an important part in the Wnt/-catenin signaling mechanism. This pathway is related to tumorigenesis of many human cancers. -catenin is found to have different functions depending on its varied location in the cell [50-52]. -catenin in the membrane promotes cellular adhesion while cytoplasmic and nuclear pooling of -catenin is related to cancer formation [50, 51]. Reduced -catenin and its cytoplasmic pooling that results in dedifferentiation,

increased invasiveness, and aggressive nature have been reported in salivary gland carcinomas [53, 54]. Over-expression of □-catenin in the membranes has been found to be related to the better overall outcome of patients with salivary gland ACCs [55]. However controversial results have been reported by some studies saying that no definitive pattern of expression has been implicated by □-catenin and hence do not have any role in tumorigenesis of ACCs [56]. Although possible roles of □-catenin in the aggressiveness of ACC have been suggested by many studies, it's biological importance and clinical relevance still remains unknown. Further research to discover the role of □-catenin could lead to newer insights into the molecular mechanisms and therapeutics options for ACCs [57, 58].

RUNX3

Human runt-related transcription factor-3 (RUNX3) is a recently recognized tumour suppressor gene associated with gastric cancer. It has also been reported to be a transcriptional screen of the downstream signaling pathway of transforming growth factor □ in apoptosis and hence its role in carcinogenesis is acknowledged [59]. Methylation of 5□-C-phosphate-G (CpG) island of RUNX3 gene is seen to result in inhibition of its expression and is related to the genesis of the stomach, liver, and oesophagal cancers, and also to overall patient survival [60-66]. The absence of RUNX3 gene expression has been reported in ACC but its mechanism is unknown. It is interesting to note that ACC expression was seen higher in early-stage disease with very low expression in advanced ACCs implicating its role in earlier stages of tumour development [67-70]. RUNX3 gene methylation is seen to have a direct association with patient prognosis and hence could be a prognostic biomarker for ACC leading to possible therapeutic implications [71].

NTRK3

Tropomyosin receptor kinase C (TrkC) is a receptor tyrosine kinase. TrkC is encoded by NTRK3 and it binds to neurotrophin 3. Overexpression of TrkC is found to be associated with cancers such as melanoma, neuroblastoma, and breast cancers [72-74]. The role of TrkC in the normal development of the nervous system is well documented previously [75-78]. In cancers, TrkC, in the presence or absence of stimulation by neurotrophin 3, interferes with apoptosis signaling. Studies also report the possible role of TrkC/NTRK3 signaling pathways in the carcinogenesis of ACCs along with potential therapeutic advantages [79].

SOX 10

The transcriptional factor SOX10 seems to trigger stem cell-like characteristics in normal and tumour cells. The stem cell features are in a controlled state and are silent in normal tissue [80-82]. In melanoma, SOX10 serves as a biomarker of the stem cell-like CD27 positive cells [83, 84]. SOX10 was seen to be found usually during differentiation of salivary gland and increasingly expressed in most ACC cells. SOX10 could be a diagnostic marker for ACCs in a similar way it is used to differentiate normal melanocytes from melanoma. Sox10 is not only expressed in the normal myoepithelial cells and tumours of myoepithelial lineage but is also found in acinar cells, acinic cell cancers, and, rarely, in the basal cells of the intercalated duct of the salivary glands. Thus, Sox10 shows a wider specificity than TrkC and may be useful for the differentiation of other salivary cancers of acinar and intercalated duct origin. The expression of SOX10 as a basal-like breast carcinoma marker in ACC suggests that the tumour cells reveal the inert flexibility of normal stem cells [85] and encourages more research looking into the therapeutic and diagnostic significance of SOX10. Studies also show co-expression of SOX10 with other genes that largely increases the target size and improves the chances of treatment outcome. Recognition of newer transcriptional factors and signaling mechanisms related to SOX10 overexpression might help to identify specific biomarkers and prospective therapeutic targets [86].

AKT

The serine/threonine kinase AKT is a protein encoded by the AKT1 gene. AKT affects the mechanism of the phosphoinositide 3-kinase (PI3K)-AKT-mTOR signaling pathway. By doing so, AKT controls cell growth, division and survival. Once hyperactivated, AKT seems to play a major role in tumorigenesis. AKT also plays a role in new blood vessel formation and helps tumour development [87, 88]. Studies found genes involved in the PI3K-AKT-mTOR signaling pathway to play a role in the pathogenesis of ACC in about 30% of cases [89]. Phosphorylated forms of AKT and mTOR were seen increased in ACC tissue when compared to adjacent normal salivary gland tissue [90, 91]. Studies report controversial results regarding the presence of hyperphosphorylated AKT and its association with patient prognosis in AKT [90, 91]. The discord maybe because of the existence of different isoforms of AKT. Research should be directed towards isoform-specific target therapy for ACC against different isoforms of AKT [92].

BCL-2

Apoptosis is one of the main tumour preventing systems and is majorly controlled by the BCL-2 family of proteins [93]. Tumour cells often harbour deregulated BCL-2 protein that helps them to escape apoptosis initiated by decreased oxygen and genetic alterations [94]. Increased expression of anti-apoptotic BCL2 has been recorded in the tumours of the lung and brain [95, 96]. Decreased expression of pro-apoptotic BCL2 family protein known as BAX is recorded in cancer of the ovary, prostate and blood [97-99]. Whole-genome mapping of ACC showed involvement of the ATM gene in its carcinogenesis mechanism [100, 101]. Interestingly, BCL 2 like molecules are found to be one of the target molecules in the downstream signaling mechanism of the ATM gene in response to gene mutation [102]. Hence it is suspected that mutations in the ATM gene might result in dysregulated BCL 2 like molecules resulting in ACC formation. Also, the aberrant expression of proapoptotic proteins such as BCL-2 and BCL-xL has been reported in ACC. Further research regarding the role of the BCL-2 family of proteins and the genes responsible for their aberrant expression might pave the way for potential targeted therapy for ACC in the future [103, 104].

OTHER MUTATIONS

Mutations that were recently identified in ACC cases and are under research include PIK3CA, CDKN2A, SF3B1, SUFU, ATM, TSC1, NOTCH, SPEN and CYLD. Also, the discovery of three different activating gene alterations in the tyrosine kinase receptor FGFR2, similar to those recorded in endometrial and ovarian cancers, point towards possible therapeutic implications for a at least a small group of ACC cases [105].

CONCLUSION

Insights regarding genetic information are crucial to develop more targeted therapies is crucial especially for deadly cancers such as ACC of the salivary gland. In this short review, we have identified all the genes that are reported to be associated with ACC cases. Also, these genes and their encoded protein expressions are currently being researched with the objective of identifying newer targets for treatment.

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