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Review

Salivary gland cancer stem cells

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SUMMARY

Emerging evidence suggests the existence of a tumorigenic population of cancer cells that demonstrate stem cell-like properties such as self-renewal and multipotency. These cells, termed cancer stem cells (CSC), are able to both initiate and maintain tumor formation and progression. Studies have shown that CSC are resistant to traditional chemotherapy treatments preventing complete eradication of the tumor cell population. Following treatment, CSC are able to re-initiate tumor growth leading to patient relapse. Salivary gland cancers are relatively rare but constitute a highly significant public health issue due to the lack of effective treatments. In particular, patients with mucoepidermoid carcinoma or adenoid cystic carcinoma, the two most common salivary malignancies, have low long-term survival rates due to the lack of response to current therapies. Considering the role of CSC in resistance to therapy in other tumor types, it is possible that this unique sub-population of cells is involved in resistance of salivary gland tumors to treatment. Characterization of CSC can lead to better understanding of the pathobiology of salivary gland malignancies as well as to the development of more effective therapies. Here, we make a brief overview of the state-of-the-science in salivary gland cancer, and discuss possible implications of the cancer stem cell hypothesis to the treatment of salivary gland malignancies.

Introduction

Salivary gland cancer is a relatively rare yet deadly disease. On average, 3300 new cases are diagnosed every year in the USA. Due to limited mechanistic understanding of the disease and lack of effective regimens for chemotherapy, surgery is still the main treatment option of these patients. As a consequence, treatment for these tumor is generally accompanied by significant morbidity and debilitating facial disfigurement. Malignant tumors are generally fatal. This is reflected in the 5-year survival rate that drops drastically from 78% for stage I tumors to 25%, 21%, and 23% for stages II–IV, respectively.[1] Of much concern is the fact that the survival of patients has not improved over the last 3 decades, which is in contrast with the significant improvement in survival observed in other glandular tumors. Such data suggest that focused research efforts on the understanding of the pathobiology of these tumors could lead to significant improvements in patient survival and quality of life.

Mounting evidence supports the existence of a sub-population of tumorigenic cells that possess stem cell-like characteristics in many tumor types (e.g. breast cancer, pancreatic cancer, head and neck squamous cell carcinomas). These cells, termed cancer stem cells (CSC), are capable of self-renewal and also to differentiate into cells that make up the bulk of the tumor. Cancer stem cells are resilient cells that play a major role in resistance to chemotherapy and radiation therapy in other cancer types.[2–4] While such studies are unveiling the mechanisms of resistance to therapy in other malignancies, very little is known about the resistance of salivary gland tumors. Indeed, one of the most pressing clinical issues in salivary gland cancer is the poor response to therapy.[5] It is certainly possible that low proliferation rates contribute to resistance to therapy in a group of salivary gland tumors but another possibility is that cancer stem cells play a role in the resistance to therapy observed in these tumors. Characterization of stem cells in these tumors might lead to the identification of novel pathways that could be targeted to sensitize these tumors to chemotherapy.

Salivary gland structure and function

Salivary glands play an essential role in protection and maintenance of health in the oral cavity, lubrication of food, taste of food, and speech. Saliva is produced in secretory cells called acini. There are three different types of acini and each is characterized by the composition of the cell secretions. Serous cells release saliva that is abundant in several proteins but lacks mucin protein. Mucous cells secrete saliva-containing mucin proteins attached to carbohy-

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drates.[6] Seromucous cells secrete a combination of both mucous and serous saliva. Once the saliva is secreted from these cells, it is transported through intercalated ducts, small excretory ducts, and then through a larger excretory duct that opens into the mouth.[6] Excretory ducts are lined with columnar epithelium, cuboidal cells surround the intercalated ducts, and columnar cells make up the striated duct. As the saliva passes through these ducts, additional proteins, such as Immunoglobulin A and lysozyme, from the ductal cells are secreted into the saliva. Myoepithelial cells contract and help secretory cells release the saliva and also promote salivary flow through the ducts.

Salivary glands are subdivided into the major and minor glands. The major salivary glands consist of three pairs of glands that are located around the oral cavity. The largest are the parotid glands that are located in directly below the ears along the jaw. Saliva is exported from the gland directly across from the crowns of the second maxillary molars via the Stensen's duct, a 5 cm duct connecting the gland to the oral cavity. Secretions from the parotid glands are exclusively serous. The sublingual gland is located underneath the floor of the mouth and are the smallest of the major salivary glands. These glands open to the oral cavity via 8–20 excretory ducts and secrete only mucous saliva.[6] The submandibular glands are also located in the floor of the month but are adjacent to the mandibular bone. Saliva is secreted via the Warthon's duct that opens into the floor of the mouth. This gland secrets seromucous saliva but contains a higher percentage of serous acini then mucous acini. The oral cavity also contains 600–1000 minor salivary glands that can be found on the tongue, inside of the cheek, lips, floor of the mouth, and the hard palate.[6] Secretions from these glands are predominately mucous with the exception of von Ebner's glands, which are exclusively serous.

Salivary gland cancer

Salivary gland cancers are rare accounting for 2–6.5% of all head and neck cancers with annual incidence of 2.2–3.0 cases per 100,000 people in the United States.[7–9] Tumors can originate in either the major or minor salivary glands. Approximately 80% of these tumors arise in the parotid gland, 15% arise in the submandibular gland, and 5% arise in the minor and sublingual salivary glands.[10] Males have a 51% higher rate of incidence over females, although both tend to develop the cancer within the fifth decade of life.[11] While little is known about the pathogenesis of salivary gland cancers, research has shown that radiation exposure is a risk factor and suggests that occupation exposures, viruses, UV light, alcohol, and tobacco may also be involved.[12–14] As much as 75% of salivary masses are benign. However, presentation of both malignant and benign tumors is similar making diagnosis and treatment very challenging. Malignant salivary gland tumors are markedly heterogeneous including 24 histologic subtypes, generating significant challenges in diagnosis, prognosis, and treatment.[9] The following discussion is centered on mucoepidermoid carcinomas and adenoid cystic carcinomas (Fig. 1), the two most common salivary gland malignancies.

Mucoepidermoid carcinoma

Mucoepidermoid carcinoma (MEC) is the most common salivary gland malignancy and represents approximately 5–15% of all salivary gland tumors and 30–35% of all malignant salivary gland tumors.[8,15–21] These tumors occur in both the major and minor salivary gland glands and are mostly comprised of epidermoid, mucous, and intermediate cells types. The epidermoid cells are polygonal in shape and characterized by keratinization and intercellular bridges. Mucous cells vary in size but all stain positively for mucin proteins. Intermediate cells are thought to functions as progenitor cells for epidermoid and mucous cells and are often basal-like in appearance. Mucoepidermoid carcinomas also contain a variety of other cell types including squamous, clear, columnar, and other uncommon cell types.[22–26] They are extralobular tumors and are believed to originate in the excretory duct.[22,24]

Diagnosis of mucoepidermoid carcinoma is based on the presence of both, histological and cytogenetic abnormalities. These tumors are categorized into three grades depending on the amount of cyst formation, the degree of cytological mutation, and the relative number of epidermoid, mucous, and intermediate cell types. Low-grade tumors tend to have a minimal amount of cytological mutation, a high population of mucous cell, and noticeable cyst formation. High-grade tumors contain large areas of intermediate and squamous cells that demonstrate increased mitotic activity. Intermediate-grade tumors manifest a combination of both low and high-grade characteristics. Additional unfavorable histologic factors include perineural invasion, necrosis, increased mitotic rate, angiolymphatic invasion, anaplasia, infiltrative growth pattern, and the presence of a cystic component.[27] However, this grading system is often variable making reproducibility difficult.[28] Low and intermediate-grade tumors are treated using surgical resections while treatment for high-grade tumors includes neck dissection and radiation therapy.[27] While surgical removal and radiation is often successful, a significant number of patients have a recurrence of the disease years later.[29] For these patients, few treatments options are available as mucoepidermoid carcinomas are highly chemo-resistant.[12] As a result, chemotherapy is used for patient palliation, although ineffective for actual treatment.[30] Improved understanding of the pathobiology of the disease leading to rationally designed targeted therapies are necessary to improve the outcome of patients with mucoepidermoid carcinoma.

The most common cytogenetic abnormality in mucoepidermoid carcinoma is a recurrent translocation between chromosomes 11 and 19 creating the CRTC1-MAML2 fusion protein. This translocation is found in 38–81% of mucoepidermoid carcinomas and is expressed in all cell types. CREB-regulated transcription coactivator 1 (CRTC1) protein activates transcription mediated by cAMP response element-binding (CREB) protein.[26,31] CREB activated genes regulate cell differentiation and proliferation.[32] Abnormal expression of these genes has been shown to lead to cancer development.[32] MAML2 is a coactivator for Notch transcriptional activity that regulates cellular differentiation and proliferation.[32,33] In the fusion protein, the intracellular Notch-binding domain of MAML2 is replaced by the CREB binding domain of CRTC1.[12]

Many studies have shown that presence of CRTC–MAML2 translocation has prognostic and diagnostic value.[12] Patients with tumors expressing CRTC1–MAML2 have a greater overall survival as well as a lower risk of recurrence and metastasis when compared with fusion-negative tumors.[34,35] However, there is a subset of high-grade tumors that express CRTC1–MAML2. Studies by Anzick and colleagues found that in these high-grade tumors expressing CRTC1–MAML2 and additional deletion or hypermethylation of CDKN2A was often found suggesting that the presence or absence of both of these abnormalities may serve as a better diagnostic marker.[36] The role this protein plays in the pathogenesis of mucoepidermoid carcinoma is not known, however, research suggests that this mutation occurs early on during tumor initiation.[12,27] Studies have shown that this translocation also appears in a subset of Warthin's tumors and may be linked to the development of these tumors to malignant MEC tumors.[34,35,37]

Adenoid cystic carcinoma

Adenoid cystic carcinoma (ACC) is the second most common malignant salivary gland cancer accounting for 10–25% of patients.[37–40] Tumors can occur in both parotid and submandibular