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Androgen receptor in salivary gland carcinoma: A review of an old marker as a possible new target

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The role of the androgen receptor (AR) as an immunomarker for diagnosis of salivary gland duct carcinoma (SDC) is well known. Other non-squamous cell head and neck cancers (NSCC-HN), including a small subset of salivary gland cancers (SGCs), can also express AR. With the increase in effective and powerful new generation of anti-androgen agents and drugs administered orally, more targetable AR-driven NSCC-HN, such as subsets of SGCs, should be investigated for possible expression of AR. In this review, we focus on SGC subtypes, which could express AR and describe the main androgen deprivation therapy (ADT) strategies.

KEYWORDS
abiraterone, androgen receptor, enzalutamide, head and neck, immunohistochemistry, non-squamous cell carcinoma, salivary gland carcinoma

1 | INTRODUCTION

Salivary gland carcinomas (SGCs) are relatively rare, constituting 0.2% of all cancers and 5%-9% of all head and neck cancers.[1] The World Health Organisation (WHO) continues to revise classification of SGC subtypes, which spans a vast histological diversity.[2] Despite rarity and diversity, the current treatment for all SCG, regardless of histological subtype or grade, is usually by surgical resection and adjuvant radiotherapy, which provides an overall 10-year survival rate of 70%, however is poorly suited to the late presenting and rapidly progressive subtypes.[3] There is a significant challenge in these rare cases as anatomical location and rapid extension complicates ability to resect, and metastatic or recurrent disease can only be offered un-standardised palliative chemotherapy eliciting an overall response rate of just 10%-30%.[4]

Androgen receptor (AR) is expressed in some subtypes of SGC such as salivary duct carcinoma (SDC) (Figure 1), carcinoma ex pleomorphic adenoma, basal cell adenocarcinoma (BCAC), mucoepidermoid carcinoma (MEC), adenoid cystic carcinoma (ACC), acinic cell carcinoma (AcCC) and adenocarcinoma not otherwise specified (ACNOS).[5,6] AR is consistently identified as the most prevalent receptor in all these tumours and particularly is expressed in up to 98% of SDCs.[6,7] This is a promising discovery for a therapeutic treatment target, particularly since SDC which represents less than 2% of all SGCs[7] is one of the most rapidly progressing subtypes with distant metastases developing in 50%-75% of patients.[8,9] Recent research findings indicate that androgen-deprivation therapy (ADT) for SDC may elicit more than twice the current response rate of chemotherapy whilst offering lower toxicity.[10,11] The aim of this review is to outline current data with regard to the expression of AR in a range of SGCs and to discuss the therapeutic implications of AR positivity.

2 | BIOLOGY OF ANDROGEN RECEPTOR

Androgens (male sex hormones) are produced by the testis and present a wide spectrum of functions such as male development including secondary sexual characteristics, erythropoiesis stimulation and

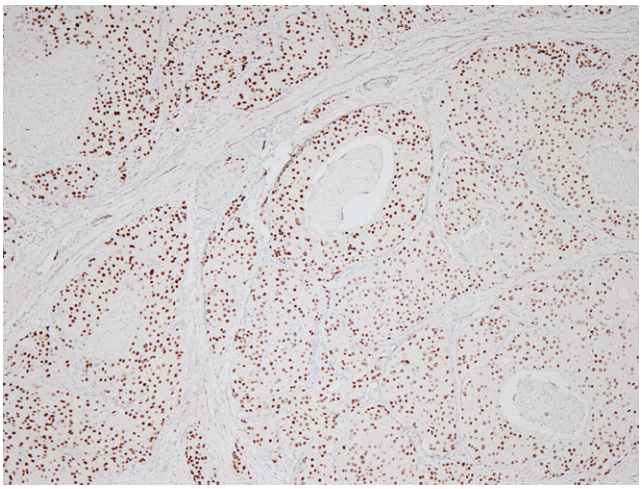

FIGURE 1 Immunohistochemistry with androgen receptor shows diffuse and intense nuclear positive staining

increasing the density of bone.[12] From a physiological point of view, the different functions of androgens are obtained stimulating AR.

AR as oestrogen receptor (ER), progesterone receptor (PR) and glucocorticoid receptor (GR) is a member of the nuclear hormone receptor family of transcription factors.[12,13] The canonical signalling pathway of AR is composed of different phases: binding of androgens to AR, dissociating from heat-shock proteins, translocating to the nucleus with formation of AR homodimers, binding to androgen response elements (AREs) within the promoter region of AR target genes, recruitment of coactivators and transcription of target genes.[14] This pathway can interact with other oncogenic signalling pathways such as AKT/mTOR/PI3K, EGFR, HER2/Neu, Wnt[15-21] which are involved in promoting growth and resistance in different malignancies, including salivary gland carcinomas.[22] Targeting AR-signalling pathway, due to its multitude of effects, might have beneficial effects in target therapy of SGCs.

2.1 | Mucoepidermoid carcinoma (MEC)

MEC accounts for 29%-34% of all SGCs frequently affecting the parotid gland.[23] Typically, the cellular composition of MEC includes epidermoid cells, mucocytes and intermediate cells.[23] Histopathologically, MECs are classified as low intermediate and high-grade tumours.[24] Low-grade MECs are often cystic with the presence of high number of mucocytes and are unlikely to metastasise. Intermediate-grade tumours have comparatively equal number of mucous and squamous cells. High-grade MECs consist of solid islands of squamous and intermediate cells, with high rate of recurrence.[24-26] The 5-year overall survival (OS) for the low-grade MEC is between 92% and 100%.[25] In intermediate-graded tumours, OS is 62%-92%, while 0%-43% in high-grade tumours.[25] Generally, MECs have 90%-98% cure rate but it will vary depending on the stage and grade of the tumour, with surgical resection of involved gland and adjuvant radiotherapy being the first-line treatment currently.[26]

2.2 | Adenoid cystic carcinoma (ACC)

Adenoid cystic carcinoma is accountable for 22% of SGCs[27] and affects more minor salivary glands. It is histologically subdivided into three subtypes: tubular, cribriform and solid. ACC frequently has a poor long-term prognosis and presents late distant metastasis approximately in 24%-55% of cases.[28] The 20-year OS is 21%-23% and 10-year OS is 39%-55%.[28] Surgical excision followed by postoperative radiotherapy is the first-line treatment for ACC.[27]

2.3 | Salivary duct carcinoma (SDC)

Salivary duct carcinoma are rare and highly aggressive tumours which have poorer survival rates than other SGCs.[29] SDC occurs mainly in the parotid gland[29]and usually have a rapid progression. SDC shares some similarities with breast carcinoma and morphologically is composed of cuboidal and polygonal cells creating ducts and nests, often with comedonecrosis.[30] SDCs have a very poor prognosis because of high metastatic rate.[29]

2.4 | Basal cell adenocarcinoma (BCAC)

Basal cell adenocarcinoma is a slow growing malignancy and is considered the malignant counterpart of basal cell adenoma because of infiltrative pattern with perineurial/vascular invasion. BCACs constitute 1%-2% of salivary gland carcinomas and mostly arise in the parotid gland. Minor salivary glands are rarely involved. BCAC shows solid, trabecular, tubular, membranous growth patterns and may show palisading pattern. It consists of two cell types: small cells with scant cytoplasm and dark nuclei and polygonal cells with eosinophilic/amphophilic cytoplasm and clear nuclei. BCACs are locally destructive, often recur, and only occasionally metastasise.[31]

Several studies examined the molecular basis of SGC and were able to uncover potential molecular targets that could aid a novel therapeutic approach for these tumours.[10,32,33]

2.5 | Androgen deprivation therapy (ADT)

Androgen receptor is a hormone receptor that regulates cell growth and differentiation in some human tissues.[34] It is found that overactivity of the AR signalling pathway is a vital oncogenic driver in several cancers including prostate and a subgroup of breast cancers.[35,36] ADT can be accomplished by direct inhibition of AR (antiandrogen therapy) or downregulation the signalling output of gonadotropin-releasing hormone (GnRH) receptors, thereby reducing testosterone serum levels (chemical castration).[37,38]

Multiple immunohistochemistry studies assessed the expression of AR signalling in different SGCs. It was found that AR overexpression is more commonly associated with SDCs, with reports of 64%-98% of cases showed AR immunreactivity.[7,39-43] In contrast to SDCs, only a small subset of MEC and ACC has a detectable weak AR expression (5%-15%) which may be irrelevant to the oncogenic process.[39]

A study of ADT in AR-positive SDC has shown that ADT appeared to clinically benefit five out of ten cases and two of them had partial response.[43] Therefore, this approach proves to be with more effective outcomes than chemotherapy.[43] In addition, ADT has generally less adverse effect than chemotherapy, which may lead to enhanced clinical outcomes in patients.[43]

A case of complete remission, confirmed by CT scan, of an AR-positive adenocarcinoma in the parotid gland has been reported; the 73-year old patient received a complete anti-androgen blockade and monthly triptorelin and bicalutamide.[44]

3 | ONCOLOGY DRUGS

3.1 | Chemotherapy

The present treatment for metastatic or recurrent SGCs is chemotherapy for which a standard regime has not been defined; however, 5-fluoricil, doxorubican, cyclophosphamide and cisplatin combinations (CAP) have shown some of the highest response rates of 45% in small-scale studies.[45,46] The rates of temporary complete remission are just 20% and disease-free progression time with CAP has a median of 11 months although this needs to be individually balanced against drug toxicity and quality of life.[47-52] There is a wide variety in results due to the lack of treatment standardisation and disease rarity but chemotherapy has been used in palliation of aggressive SGC since the 1980s with minimal success and development.

3.2 | Androgen-deprivation therapy and complete androgen blockade

Common androgen receptor antagonists are bicalutamide, flutamide and enzalutamide, which are both AR competitive inhibitors, and abiraterone which irreversibly inhibits the steroidal enzyme CYP17A1 blocking its conversion of 17-hydroxyprogenolone to dehydroepiandrosterone, therefore reducing serum androgen levels. Common GnRH agonists are triptorelin and goserelin, which similarly to abiraterone, act to reduce AR activation by reducing serum androgen via luteinizing hormone (LH) downregulation. Reduction in serum androgen reduces AR-mediated tumour proliferation, invasion and metastasis,[52] which is a mechanism that has been applied to treatment of prostate cancer since the 1940s and continues to be developed and applied to the treatment of breast, ovarian and colon cancers.[53]

Trials of AR targeted drugs have typically involved a regime, which most commonly combines bicalutamide and triptorelin to provide a complete androgen blockade (CAB). This CAB combination has been used at doses of 50-80 mg oral bicalutamide every day and 3.75 mg IM every 28 days until progression or toxicity occurred, which induces a median disease-free progression period of 11 months and an overall response rate of 65%[9,10] whilst higher daily doses of 150 mg Bicalutamide has induced sustained complete remission of both MSGT and brain metastases in isolated cases.[7,53] As with chemotherapy, tested regimes and results are varied and there is almost always eventual continuation of disease progression; however, figures for response are more promising than current treatments, and importantly produce less side effects, toxicity and greater pain reduction.[7]

A number or mechanisms are currently being explored in regard to ADT/CAB resistance in prostate cancer including mutations in the Forkhead box protein A1 (FOXA1) transcription factor, involved in AR transcription, and mutations in the fatty acid synthase (FASN) enzyme, which controls fatty acid synthesis and may promote tumour growth.[54-56] These mutations may be applicable to AR-positive SGCs[29] in addition to research investigating splice variants in AR ligand binding domains, which has shown to cause ADT resistance in prostate cancer.[57-61] Whilst resistance currently seems inevitable, CAB may provide a safer alternative or addition to chemotherapy, which both offer improvement to quality of life in SGC palliative care.

4 | CONCLUSION

Besides surgical resection and radiotherapy of SGCs, there are currently no other effective treatments; therefore, alternative methods are being investigated. Radiotherapy has potential debilitating side effects of permanent dry mouth. Surgical resection is still considered first-line and best potential outcomes; however in frail candidates who may not be suitable for anaesthetics now stand a chance of a reasonable disease-free survival with oral androgen antagonists such as abiraterone and enzalutamide. SGCs are rare, making randomised clinical trials difficult to recruit. As the androgen receptors antagonist has successfully carried out mature safety profile in the large prostate cancer cohort, the use of Phase 2, single-arm, open label AR-SDT could be justify. This would be one of the most promising approaches in some subtypes of salivary gland cancers.

However, to discover new therapeutic methods with high efficacy, it is vital to develop further understanding of AR in SGC.

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