PD-1/PD-L1 biology and immunotherapy in HPV-positive oral cancers

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HPV-infection related oral cancers are on the rise [2]. Conventional therapies (surgery, radiation and prophylactic vaccines) and some proposed nonconventional therapies (natural and synthetic antioxidants)-based treatments have limitations. In the light of recent advancement of immune checkpoints and their inhibitor molecule related cancer immunotherapies, we present updated information on the current status of PD-1/PD-L1 therapies in HPV mediated oral carcinogenesis. We limit the scope to oral carcinogenesis.

Oral squamous cell carcinoma is the sixth most common cancer that accounts for almost 5% of all malignancies worldwide [1,2]. It is predominately attributed to smoking and alcohol, but a subset has been demonstrated to contain anogenital HPV infections. Many studies have established that the high-risk HPVs, especially HPV type 16 (HPV16) are etiologically related to a subset of oral cancer cell [1–3]. Nonsmokers with less median age, harboring wild type p53 and wild type p16, well-differentiated epithelium and better survival/good prognosis are some of the best identified exclusive characteristic features of HPV infected oral cancers. After surgical options and radiation therapies in platinum-refractory oral cancers, traditionally EGFR-based monoclonal antibodies

are preferred by clinicians as a standard treatment regimen. But as usual, non-specific targeting has been identified as one of the major problems, warranting the need for newer approaches such as checkpoint inhibitor-based immunotherapies.

Even after four decades of HPV research, there are no specific therapies available for the effective treatment of HPV. However, virus-like particle (the major HPV virion protein L1)-based two prophylactic vaccines: quadrivalent Gardasil (HPV16/18/6/11) and bivalent Cervix (HPV16/18) are available. In 2014, the US FDA has approved a nonavalent vaccine against nine HPV types (HPV6, 11, 16, 18, 31, 33, 45, 52 and 58) but these vaccines are not commercialized well in developing countries [4–6].

PD-1/PD-L1 in oral cancers & HPV infections

Programmed death ligand 1 (PD-L1, B7-H1, CD274) overexpression is seen in many solid tumors, to safeguard cancer cells and also to simultaneously suppress the activity of PD-1 expressing adjoining tumor-infiltrating effector CD4/CD8 T cells [7].

Manipulation of the PD-1: PD-L1 interaction related pathways is one of the most recent and promising concepts of cancer immunotherapy, classified under checkpoint inhibitor therapies. Data from initial

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Phase I clinical trials of PD/PDL-1 immunotherapy in melanoma, renal cancers and lung cancers have placed it in the fastest growing category of cancer therapies [8]. Cancer immunotherapies have impacted not only the latest scientific research programs such as NCI Cancer Moonshot Program of US NIH but also the commercial landscape of cancer drug markets across the globe [8].

On average, investigators report that 50–90% of patients with oral cancer have shown PD-L1 overexpression [9,10]. But very little literature has been published correlating HPV positivity and oral cancer lesions with immune-checkpoint inhibitors. Two different studies by Lyford-Pike *et al.* and Upko *et al.* have shown that HPV-positive oral cancer cases overexpressed PD-L1 when compared with HPV negative cases [11,12]. They also established that HPV-positive cases possess PD-1 overexpressing CD8, CD4 and TILs in their tumor microenvironment. A constant exposure with tumor antigen increases the activity of PD-1 on the surface of T cells which eventually generates a population of exhausted and abnormal T cells with aberrant signals to fight cancer cells. More recently, Sun and colleagues demonstrated that PD-1 overexpression is a general phenomenon irrespective of HPV status in head and neck cancers including oral cancer [13].

Mechanistic outcomes of PD-1/PD-L1 interactions during carcinogenesis

Some of the mechanisms of PD/PDL-1 related immune escape of cancer cells are; induction of effector T-cell death [14], antiapoptotic signaling

by PD-L1 [13] and cytotoxic T-cell inhibition by direct interaction of PD-L1:CD80 [15]. Treatment with PD-1 dramatically increases the T-cell population and IFN- γ production in head and neck cancer patients, in whom PD-1 positive myeloid-derived suppressor cells were detected in peripheral blood [16].

This can explain the fact, why HPV-positive patients have better survival advantage linked to the immune-escape of HPV-positive cancer cells. However, we also previously demonstrated the role of NF- κ B/p21 axis in dictating the survival of high-risk HPV16-positive oral cancer cells [17] (Figure 1). Pai and colleagues have also shown that PD-1: PD-L1 interaction generates immune privileged site for the immunological escape and survival of HPV-positive cells [11]. Tumor cells and macrophages had increased PD-L1, while on CD8+ cells PD-1 overexpression was detected. Therefore, blockade of this interaction by check point inhibitors warrants a suitable therapeutic approach in head and neck cancers. Interestingly, when Ad5 [E1-, E2b-]-E6/E7 immunotherapy was combined with anti-PD-1 antibody, a reduction in tumor PD-L1 expression on tumor cells with reduced PD-1+ TILs were observed [18]. Tartour E and colleagues have demonstrated that PD-1-expressing tumor-infiltrating T cells are a favorable prognostic biomarker in HPV associated head and neck squamous cell carcinoma (HNSCC) [9].

Conclusion

So, far studies correlating HPV infections and oral cancers in context of PD-1: PD-L1

Figure 1. Model: implication of PD-L1 in HPV mediated oral carcinogenesis toward better prognosis.

interaction and checkpoint inhibitors are very few with varying results performed with different molecular tools. Preclinical studies are also lacking in this field. That can caution the rationale toward development of therapeutic intervention for the time being. But the experimental data based on PD-1: PD-L1 studies can be undoubtedly exploited to explain the biology of HPV-induced better prognosis of oral cancer patients.

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