Oral Oncology 97 (2019) 135–136

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Letter to the editor

The relevance of Fas/Fas ligand axis in the tumor microenvironment of salivary gland adenoid cystic carcinoma

ARTICLE INFO

Keywords:
Salivary gland carcinoma
Adenoid cystic carcinoma
Granzyme
Tumor-infiltrating lymphocytes
Tumor microenvironment
Fas ligand
Checkpoint inhibitors
CD8 T cells
PD-L1

Adenoid cystic carcinoma (ACC) is a salivary gland neoplasm characterized by poor prognosis and a high rate of local recurrence. Even though ACC is a relatively rare tumor, the treatment options are relatively limited and therefore, ACC represents a largely challenging cancer to be treated. The standard treatment protocol is currently based on radical surgery followed by radiotherapy and chemotherapy, if indicated. However, both local recurrence and distant metastases were previously found and documented in patients even many years after completing the treatment of the primary tumor [1].

Through the last decade, immunotherapy has changed the course of oncology and led, in a number of malignancies, to a switch from palliative care to complete long-lasting remissions. Nevertheless, the efficacy of immunotherapy does largely depend on the presence of tumor-infiltrating lymphocytes (TILs) and moreover, on the functional properties and phenotypic markers of TILs.

In many cases, TILs do not exhibit immune molecules that serve as optimal targets for a broad number of immunotherapeutic approaches. For that reason, some patients and some malignancies do not respond to immunotherapy. In those patients/malignancies, researchers are currently focusing on possible modifications of the tumor microenvironment that could sensitize the tumor to different immunotherapies, such as checkpoint inhibitor therapy or adoptive cell immunotherapy [2,3].

Recently, Mosconi et al. published a study investigating expression patterns of TILs residing in ACC of salivary glands. The study consisted of 36 individuals who had undergone surgical treatment for ACC between years 2005 and 2015. We believe that this histopathological analysis of immune-related markers in salivary gland ACC is of major importance. The authors performed a detailed analysis of molecules PD-1, PD-L1, PD-L2, CTLA-4, and HLA-G in tumor-infiltrating CD8 T cells and NK cells. The markers PD-1, PD-L1/2 and HLA-G were specifically chosen by the authors to determine the level of cell inhibition and to open a discussion of potential targets for the treatment with checkpoint inhibitors. This has been the first study investigating immune checkpoint molecules in ACC of salivary glands. Furthermore, CD83 and CD1a molecules have been investigated in order to capture intratumoral dendritic cells and T cells responsible for the presentation of glycolipids and lipopeptide antigens to dendritic cells. Finally, granzyme B, an enzyme responsible for the apoptosis of tumor cells triggered by CD8 T cells has been studied [4].

The research group revealed that increased CD8 T cell density in salivary gland ACC was associated with less recurrence and longer survival [4]. This conclusion, along with the results of immune microenvironmental research in other solid tumors, supports the urge to investigate new approaches increasing CD8 T cell numbers in the tumor or at least to decrease the loss of CD8 T cells [2,3]. Mosconi et al. also presented that the positivity of HLA-G and PD-L2 was seen in most of the cases, the positivity of CTLA-4 and PD-1 in few cases, and PD-L1 was negative in all of the cases [4]. These observations brought new insights into current limitations in the treatment of salivary gland ACC, especially with anti-PD-L1 drugs.

The analysis we would like to comment on, is the measurement of granzyme B in the tumor samples. The authors accurately referred that the effectiveness of antitumor immune response depended on the activation of CD8 T cells [4]. Regarding this matter, we would like to add that even though the cytotoxic ability of CD8 T cells presented by perforin-granzyme is a well-established mechanism of apoptosis induction, it is the Fas/Fas ligand axis that serves as a major system that both, CD8 T cells and NK cells use to eliminate neoplastically transferred cells [5]. The mechanism of action via Fas ligand expressed on TILs is one of the major cancer killing strategies [2,5] and it would be, therefore, extremely valuable to demonstrate the expression of Fas/Fas ligand on both TILs and tumor cells in ACC of salivary glands. Fas and/or Fas ligand expression on TILs has already been described to be a prognostic marker in multiple cancers [5,6] and we presume, that this area should also be explored in such challenging cancer as salivary gland ACC.

Abbreviations: ACC, adenoid cystic carcinoma; TILs, tumor-infiltrating lymphocytes

https://doi.org/10.1016/j.oraloncology.2019.08.015
Received 9 August 2019; Received in revised form 14 August 2019; Accepted 16 August 2019
Available online 24 August 2019

Since salivary gland ACC has been recently described to be a MAGE expressing type of cancer [7], we would like to highlight a study by Zhu et al. pointing at Fas/Fas ligand axis in MAGE-type induced tumors. The authors clarified, that the apoptosis of TILs by Fas/Fas ligand is one of the main factors responsible for a resistance to cancer immunotherapy. They further explained, why interrupting the Fas/Fas ligand axis could increase the CD8 T cell numbers and promote the efficacy of check point inhibitors [2].

We strongly support the TILs exploration in salivary gland ACC and would like to encourage the authors Mosconi et al. to further investigate the potential markers of TILs apoptosis. While defining the exhaustion/activation profile of TILs in salivary gland ACC together with determining the predictive role of increased CD8 T cell density represent new advancements in the field, it might be of importance to discuss also potential approaches to prevent the loss of tumor-infiltrating CD8 T cells. This could be achieved by a wider phenotypic profiling of both TILs and tumor cells in salivary gland ACC including the analysis of Fas/Fas ligand expression.

In summary, we would like to thank the authors Mosconi at al. for being the first to provide a detailed analysis of salivary gland ACC TILs and to open the discussion of checkpoint inhibitor treatment. We would largely appreciate the elucidation of a potential role of Fas/Fas ligand axis in the salivary gland ACC microenvironment and, therefore, encourage the authors to provide a follow-up study.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Declaration of Competing Interest

The authors Martin Kuchar, Zuzana Strizova, Michal Votava and Jan Plzak declare that there is no conflict of interest regarding the publication of this article. The manuscript has been approved for publication by all authors and is not currently under review or submitted to another journal.

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