



## Commentary

## Understanding the role of the R-spondin 2-LGR4 system in tongue squamous cell carcinoma progression


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Squamous cell carcinoma (SCC) is a major type of solid cancer that is derived from squamous cells and may develop in several parts of the body. Head and neck (HN) SCC represent a high proportion of the total SCC cases, indeed HNSCC is the eighth most common malignancy [1] and is a major cause of death worldwide. Sadly, HNSCC patients have low five-year survival rate of around 50% [3]. It is unfortunate that this percentage has not essentially improved over the last few decades. This is still the challenging fact, in spite of considerable advances in our knowledge of SCC progression, and also the introduction of new therapies such as the use of targeted (cetuximab), and immuno (pembrolizumab and nivolumab) therapies. These facts highlight the need for further studies in this field, especially to understand more about the mechanisms underlying SCC cancer progression and to reveal novel molecules which could be targeted for therapeutic purposes.

In *EBioMedicine*, Zhang et al. studied the role of the R-spondin 2-LGR4 system in tongue (T) SCC as an example of SCC both in general, and HNSCC specifically [9]. Studying this system in TSCC is of profound importance mainly because 1) the R-spondin 2-LGR4 system had not been studied before in TSCC, and 2) there are conflicting results about its role in other solid cancers, such as colon, breast, and gastric cancer ([2,4,6,8,10]. The role of R-spondin 2 in colon cancer represents a clear example of these contradictory results, as it was reported to enhance cancer progression by enriching LGR5<sup>+</sup> stem cells; but at the same time suppress cancer progression through inhibiting Wnt/ $\beta$ -Catenin signalling leading to a reduction in cancer cell proliferation and metastases formation [4,6,10]. This current article by Zhang et al. provides an in depth view about the enhancing role of the R-Spondin 2-LGR4 system in TSCC progression [9]. The evidence provided in this article are quite strong, especially since it covers several aspects of tumour progression, includes patient tissue samples, and *in vitro* and *in vivo* experiments. It is important to note that the authors showed that a high Rspo2 expression associated significantly with lymph node metastasis. This is an

especially important finding since one of the major problems for TSCC patients is the tendency for early metastasis of the disease to the regional lymph nodes followed by dissemination of the cancer and distant metastases formation. This observation could, together with the up-regulation of the epithelial-mesenchymal transition (EMT) properties by Rspo2, function as a driving force for the migratory and invasive behaviour of TSCC, as suggested by the authors.

Combining together all of the data provided in this article, it is clear that the Rspo2-LGR4 system participates in TSCC progression through five different ways. It enhances proliferation, migration, invasion, EMT and stem-like properties of cancer cells. The study also represents an important advance in understanding the molecular mechanism behind the role of the Rspo2-LGR4 system in TSCC progression, as the authors investigated the signalling pathways underlying this system. Supported by previous publications, the authors were able to prove that the Rspo2-LGR4 system works through the Wnt/ $\beta$ -catenin signalling pathway [7,8].

One of the main questions which remains unanswered and requires further profound study is the role of the Rspo2-LGR4 system in metastases formation of the SCC cells - this needs to be tested *in vivo*. In the newly accepted article by Zhang et al. a murine ectopic tumour xenograft model was used to demonstrate the effect of Rspo2-LGR4 system on tumour growth and cell proliferation [9]. Neither local invasion nor metastases formation were studied here, probably due to the limitations of this model which does not usually allow cancer cells to spread or enable metastatic growth. It will be interesting to analyse metastasis *in vivo* by using, for example, a murine orthotopic xenograft model where TSCC cells are injected into the tongue and carcinoma cells in neck lymph nodes are analysed. Additionally, a novel zebrafish larvae model could be used where TSCC cells are injected into the perivitelline space and metastatic cells are also detected in the tail.

From a clinical point of view, the current work reveals a novel molecule and a possible target for therapeutic purposes. Although the translational process from *in vitro* testing to clinical use is very long and has a high rate of failure - only 5% of compounds showing efficacy in *in vitro* tests were licensed following clinical trials [5] - the current study provides a stable base aiming to provide a new targeted therapy for TSCC patients.

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## Author disclosure

The authors declare no conflicts of interest.

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