Understanding mechanisms yields novel approaches to reduce radiotherapy-related xerostomia

Peter van Luijk, Johannes Albertus Langendijk, Robert Paul Coppes

Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Correspondence to: Peter van Luijk. Department of Radiation Oncology, University Medical Center Groningen, P.O. Box 30001, 9700 RB Groningen, The Netherlands. Email: p.van.luijk@umcg.nl.

Provenance: This is a Guest Correspondence commissioned by Executive Editor Zhi-De Hu, MD (Department of Laboratory Medicine, General Hospital of Ji'nan Military Region, Ji'nan, China).

Response to: Eisbruch A. Can xerostomia be further reduced by sparing parotid stem cells? Ann Transl Med 2016;4:S16.

Submitted Dec 04, 2016. Accepted for publication Dec 08, 2016.

doi: 10.21037/atm.2017.02.02

View this article at: http://dx.doi.org/10.21037/atm.2017.02.02

First, we would like to thank Dr. Eisbruch for his interest in and balanced discussion of our paper (1). The main finding was that stem cells that were previously identified to be responsible for the regeneration of salivary glands after a radiation insult (2), are predominantly localized in the major ducts of the gland. Moreover, we showed that sparing of that region leads to function loss proportional to the irradiated volume, which is consistent to the classically hypothesized parallel organization of the gland. However, if this region is irradiated, this results in global degeneration (1,3). Such response is more representative of an organ with serial organization. Though this may seem to contradict the commonly-reported association with mean dose to the parotid, it should be realized that in most data different dose metrics characterizing the dose to the parotid gland are strongly correlated. In our paper this can be recognized from the small difference in correlation coefficients between outcome and either dose to the stem cell or dose to the total gland. As such, solely modelling of retrospective clinical data is a weak test of the role of hypothesized organ structures in the response of the parotid gland. Therefore, in our study this hypothesis relies on a number of more specific radiobiological studies in mice, rats and patients. In addition, we fully agree with Dr. Eisbruch that prospective testing of the hypothesis that the stem cell region plays a crucial role in the response of the gland to non-uniform irradiation requires prospective testing. To this end we already initiated a prospective double-blind randomized controlled trial comparing parotid sparing IMRT to stem cell sparing IMRT (https://clinicaltrials.gov/ct2/show/NCT01955239). Combining both arms of the trial will yield data in which the correlation between dose to the whole gland and dose to its stem cell region is reduced, providing better insight in the question which dose metric is most critical for the response of the gland. At the time of writing this correspondence patient accrual is nearly complete (95 of the planned 102 patients.)

We are familiar with the work of Kwak *et al*. on the localization and proliferative behaviour of K14+ cells in the intercalated ducts (4). They found this to be a long-lived cell population that contributes to tissue homeostasis by proliferation. However, its role in restoration of homeostasis after induction of damage by e.g., radiation has not been elucidated. In contrast, stem cells residing in the excretory duct have been shown to be capable of such restoration and fulfil the criterion of durable self-renewal (2). Finally, the presence of multiple stem cell populations would not be unique and has been observed in e.g., lung as well (5). However, only stem cell populations that are distributed non-uniformly may offer opportunities for treatment plan optimization, indicating the specific relevance of a population localized in the excretory ducts.

Finally, we fully agree with Dr. Eisbruch that the parotid gland is not the only gland sparing of which is relevant to reduce the risk of inducing patient-reported xerostomia. However, the size of the submandibular and sublingual glands and location of their main ducts make stem cell sparing approaches challenging. Therefore, the findings

that *in vitro* expandable stem cells (6) representing a critical target localized in anatomical similar regions in different glands in various species (1,2) suggests that transplantation of stem cells may be a viable approach to rescue e.g., the submandibular gland (6,7).

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. van Luijk P, Pringle S, Deasy JO, et al. Sparing the region of the salivary gland containing stem cells preserves saliva production after radiotherapy for head and neck cancer. Sci Transl Med 2015;7:305ra147.
2. Lombaert IM, Brunsting JF, Wierenga PK, et al. Rescue of salivary gland function after stem cell transplantation in irradiated glands. PLoS One 2008;3:e2063.
3. Konings AW, Cotteleer F, Faber H, et al. Volume effects and region-dependent radiosensitivity of the parotid gland. Int J Radiat Oncol Biol Phys 2005;62:1090-5.
4. Kwak M, Alston N, Ghazizadeh S. Identification of Stem Cells in the Secretory Complex of Salivary Glands. J Dent Res 2016;95:776-83.
5. Hogan BL, Barkauskas CE, Chapman HA, et al. Repair and regeneration of the respiratory system: complexity, plasticity, and mechanisms of lung stem cell function. Cell Stem Cell 2014;15:123-38.
6. Maimets M, Rocchi C, Bron R, et al. Long-Term In Vitro Expansion of Salivary Gland Stem Cells Driven by Wnt Signals. Stem Cell Reports 2016;6:150-62.
7. Pringle S, Maimets M, van der Zwaag M, et al. Human Salivary Gland Stem Cells Functionally Restore Radiation Damaged Salivary Glands. Stem Cells 2016;34:640-52.

Cite this article as: van Luijk P, Langendijk JA, Coppes RP. Understanding mechanisms yields novel approaches to reduce radiotherapy-related xerostomia. Ann Transl Med 2017;5(3):63. doi: 10.21037/atm.2017.02.02

