LETTERS TO THE EDITOR

Ror2 may be downregulated in oral squamous cell carcinoma

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To the Editor:

The article by Masaki K. et al.[1] suggested that Ror2 expression in oral cancer was significantly higher than that in the normal oral mucosa. In their experiments, the normal tissue segments were from healthy volunteers. And in the Western blot figure, the 3 cases were not shown which region the tumor specimens were from. The normal tissue and the tumor specimens were from different person and different region of mouth. They did not even show whether the Ror2 expression in the gingiva, cheeks mucosa, tongue, and floor of the mouth was identical or not. Therefore, their normal tissue segments and tumor specimens may be not comparable.

According to our recent study, Ror2 was downregulated in oral squamous cell carcinoma (OSCC). We investigated protein level of Ror2 in 11 patients with moderately and poorly differentiated tongue OSCC. We used the adjacent epithelial of the tumor specimen from the same patient as the normal tissue. Therefore, our results are much more convincing.

Previous studies have shown that Ror2 was downregulated and served as a tumor suppressor in colon cancer and hepatocellular carcinoma.[2] And Ror2 also is a co-receptor of Wnt5a, they can form a complex to activate Wnt/planar cell polarity (PCP) signaling and inhibit Wnt/β signaling.[3] Wnt/PCP signaling plays a complex role in cancer development. At early stages of cancer, Wnt/PCP signaling inhibits cancer progression by antagonizing Wnt/β signaling. As tumor progress, Wnt/PCP signaling gets activated and promotes tumor cell migration and invasion and supports angiogenesis, contributing to metastasis in late stages of cancer.[4] It has been already identified that Wnt/β signaling is activated in oral cancer.[5]

Therefore, Ror2 may be serve as a tumor suppressor at the early stages of OSCC, but a promoter at the late stages. Thus our result of the downregulation of Ror2 in OSCC, at least in the early stages of oral cancer, will make sense. However, we did not get the upregulation of Ror2 in any case that we used in our experiment. Therefore, further studies should be performed to confirm whether the expression of Ror2 is upregulated at final stage of oral cancer to activate the Wnt/PCP signaling and promote the tumor spread, and whether the Ror2 expression in the gingiva, cheeks mucosa, tongue and floor of the mouth is identical.

This work was conducted in the laboratory of Maria A. Kukuruzinska at Boston University, USA, and supported by NIH grant 5RO1 DE015304 (to M.A.K.).

REFERENCES

1. Kobayashi M, Shibuya Y, Takeuchi J, et al. Ror2 expression in squamous cell carcinoma and epithelial dysplasia of the oral cavity. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2009;107:398-406.
2. Geng M, Cao YC, Chen YJ, Jiang H, Bi LQ, Liu XH. Loss of Wnt5a and Ror2 protein in hepatocellular carcinoma associated with poor prognosis. *World J Gastroenterol*. 2012;18:1328-1338.
3. Mikels AJ, Nusse R. Purified Wnt5a protein activates or inhibits beta-catenin-TCF signaling depending on receptor context. *PLoS Biol*. 2006;4:e115.
4. Wang Y. Wnt/Planar cell polarity signaling: a new paradigm for cancer therapy. *Mol Cancer Ther*. 2009;8:2103-2109.
5. Noguti J, DE Moura CF, Hossaka TA, et al. The role of canonical WNT signaling pathway in oral carcinogenesis: a comprehensive review. *Anticancer Res*. 2012;32:873-878.

http://dx.doi.org/10.1016/j.oooo.2012.12.018

Long-term dental and skeletal changes following surgically assisted rapid palatal expansion

To the Editor:

I think article by Vilani et al[1] in the December issue of your journal does not meet the level of research quality or methodological soundness that a meta-analysis should have. There are several significant problems:

1) The inclusion criterion of follow-up of at least 1 year after expansion should be interpreted with caution because it does not differentiate studies with patients who are still in orthodontic treatment from studies with patients whose orthodontic treatment is completed. So final dental changes (expansion and relapse) cannot be estimated with precision. Specifically, the studies of Koudstaal et al.,[2] Byloff and Mossaz,[3] and Berger et al.[4] are 12-month studies,

while the other studies have follow-up after the end of ortho treatment.[5-8]

2) The short-term data were pooled with longer-term data that ranged from 2 to 6 years at follow-up. Moreover, the observation time points differ among the studies. Three studies report the maximum expansion point at the end of the distraction period being their T2[2-4] while other studies report an expansion point taken at the end of ortho treatment.[5-7] The study of Kurt et al.[5] recruited in the Surgically Assisted Rapid Palatal Expansion (SARPE) group 4 patients who underwent orthopedic expansion that had failed.

The meta-analysis would have benefited from an objective of differentiating short-term and long-term dental and skeletal changes. Our prospective study[9] who include 38 consecutively treated patients with SARPE was an attempt to clarify these points.

Best regards,

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REFERENCES

1. Vilani GN, Mattos CT, de Oliveira Ruellas AC, Maia LC. Long-term dental and skeletal changes in patients submitted to surgically assisted rapid maxillary expansion: A meta-analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2012;114:689-697.
2. Koudstaal MJ, Smeets JB, Kleinrensink GJ, Schulten AJ, van der Wal KG. Relapse and stability of surgically assisted rapid maxillary expansion: an anatomic biomechanical study. *J Oral Maxillofac Surg*. 2009;67:10-14.
3. Byloff FK, Mossaz CF. Skeletal and dental changes following surgically assisted rapid palatal expansion. *Eur J Orthod*. 2004;26:403-409.
4. Berger JL, Pangrazio-Kulbersh V, Borgula T, Kaczynski R. Stability of orthopedic and surgically assisted rapid palatal expansion over time. *Am J Orthod Dentofacial Orthop*. 1998;114:638-645.
5. Kurt G, Altug-Ataç AT, Ataç MS, Karasu HA. Stability of surgically assisted rapid maxillary expansion and orthopedic maxillary expansion after 3 years' follow-up. *Angle Orthod*. 2010;80:425-431.
6. Magnusson A, Bjerklin K, Nilsson P, Marcusson A. Surgically assisted rapid maxillary expansion: long-term stability. *Eur J Orthod*. 2009;31:142-149.
7. Sokucu O, Kosger HH, Bicakci AA, Babacan H. Stability in dental changes in RME and SARME: a 2-year follow-up. *Angle Orthod*. 2009;79:207-213.
8. Anttila A, Finne K, Keski-Nisula K, Somppi M, Panula K, Peltomaki T. Feasibility and long-term stability of surgically assisted rapid maxillary expansion with lateral osteotomy. *Eur J Orthod*. 2004;26:391-395.
9. Chamberland S, Proffit WR. Short-term and long-term stability of surgically assisted rapid palatal expansion revisited. *Am J Orthod Dentofacial Orthop*. 2011;139:815-822.e1.

http://dx.doi.org/10.1016/j.oooo.2013.01.054

Long-term dental and skeletal changes following SARPE

In Reply:

We are grateful for the opportunity to start a debate on our systematic review and meta-analysis.[1] We appreciate the interest of Dr. Chamberland in our article[1] published in the December issue of this journal and we wish to discuss some aspects raised in his evaluation. His letter raised some interesting points worthy to be discussed by the scientific community.

As to the point raised that the follow-up of at least 1 year after expansion does not differentiate studies where orthodontic treatment was completed from those where it was not, leading to final dental changes imprecisely estimated, we believe that this inclusion criteria did not impair our results. Specifically, the study of Byloff and Mossaz[2] described a follow-up of at least 12 month post-surgery (after fixed appliance therapy) and Berger et al.[3] described a follow-up of 1 year after removal of the retention appliance before any additional orthodontic treatment. Only Koudstaal et al.[4] reported a follow-up of 1 year after treatment and did not specify if it was 1 year after expansion or 1 year after orthodontic treatment. The other studies[5-7] presented a follow-up after the end of orthodontic treatment. Most importantly, from all comparisons performed in the meta-analysis, only one presented any level of heterogeneity ($I^2 > 0\%$) among the studies, which means that this variable, which could be a confounder, in fact was statistically proved as not having influenced the results among the included studies.

As to observation time points differing among the studies, this variable was not considered a problem either as the heterogeneity among studies was very low, as mentioned before. And the heterogeneity measurement shows to what extent the results of studies are consistent.[8] The lower the heterogeneity, the more consistent the results are.

Our inclusion criteria also prevented us from including the interesting and contributive study from Dr. Chamberland[9] in our systematic review and meta-analysis, as we did not include studies where patients presented any history of another craniofacial surgery. In the referenced article, 28 patients were submitted to a second surgical phase. Additionally, the results from this study are very similar to the results from our meta-analysis, which further validate our data.

We would like to thank Dr. Chamberland for the opportunity of this discussion, but we cannot agree with him that our published article does not meet the level of research quality or methodological soundness that a meta-analysis should have. According to the Cochrane Handbook,[8] the process of undertaking a systematic review involves a sequence of decisions and while many of these decisions are clearly objective and non-contentious, some will be somewhat arbitrary or unclear because there is no consensus about them on the literature. In a systematic review or meta-analysis, the inclusion criteria for selection of studies are a prerogative of the authors and abiding by