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Manuscript assessment report

Dear Author,

It was a pleasure working on your document. Do go through my changes and comments in the edited file. In this document, I have provided my assessment of the manuscript in terms of its language and presentation, strength of the core argument, and submission readiness. Where relevant, I have also provided recommendations for improving the manuscript. Should you have any questions on the report, do let me know.

Best regards,
Your editor

Table of Contents

Language, presentation, and writing

Overview

This study on the role of Sox21 in ameloblast differentiation presents some interesting findings and discusses their implications on the development of teeth and hair. The manuscript was distinctly structured into the Summary, Introduction, Results, Discussion, and STAR Methods sections, as required by *Cell*. While the content provided under each section was exhaustive, its streamlining was crucial to ensure that the reader is only presented with information that is directly relevant to the objective of the study. The findings of the study were well supported by the data. Since *Cell* caters to a relatively broader readership, it would help to include some information on how these findings are relevant across various disciplines. For example, since the morphogenesis of ectodermal organs like teeth and hair is highly conserved, would the findings of this study be valuable for the development of therapies for ectodermal dysplasia?

Focus area: Conciseness in academic writing

While it is important to provide sufficient context and background information to help readers understand the rationale of the study, excessive information can be difficult to maneuver through and assimilate. In this manuscript:

The Introduction provided excessive background information regarding Sox proteins and the development of ectodermal organs, owing to which the section lacked focus and direction. The Results section typically does not contain references to previous studies; however, in this manuscript, the Results provided unnecessary background information and discussed the observations, which made the section extremely long, distracting the reader from the core results. The word count of the original document also exceeded the word limit specified by *Cell.*

I recommend the following to address this focus area:

Recommendation 1. Keeping the research problem in mind, begin the introduction by discussing the broader aspects of the research problem (In brief, describe Sox proteins and their role in cell differentiation and organ development), gradually moving to the focus of the research problem (Introduce Sox21) and what is known and yet unknown about it (Discuss published contributions of Sox21 to the development of teeth and skin; you can focus on the contributions of Sox21 rather than on the stepwise developmental process for teeth and hair), which will bring you to the rationale (Lack of information regarding the molecular mechanisms underlying ectodermal organ determination) and objective (The role of Sox21 in the development of teeth and its potential role in the development of hair) of the study. I have followed this recommendation to restructure the Introduction section and have included comments to indicate instances where additional information would be required to ensure a logical and smooth flow of ideas. Elimination of unnecessary content will allow for the inclusion of essential content, e.g., Shh and Anapc10 were studied to meet the objective, but there is no mention of these molecules in the Introduction. In contrast, several other molecules involved in the development of skin and teeth were mentioned in the introduction but not later in the text.

Recommendation 2. The Results section must be used to merely state the results in a logical manner. Inclusion of introductory information before presenting the results of each experiment is unnecessary, since you have already set context for the study in the Introduction. Similarly, the Discussion section is dedicated to discussing the results in the context of previous studies; hence, discussing the results in the Results section itself would be counterproductive, as the Discussion section would appear lackluster. I have moved the background information from the Results to the Introduction and Discussion sections based on their suitability to these sections and deleted repetitive information. Text discussing the results was moved to the Discussion.

Focus area: Highlighting the significance of the study

The significance of the study findings, their implications in the field at large, and multidisciplinary relevance are important criteria for publication. Although the findings of this study were unique and very interesting, they were not sufficiently highlighted in the Summary and Discussion. Moreover, for journals like *Cell* that cater to the research fraternity across multiple disciplines, discussing the multidisciplinary relevance of the findings is crucial to presenting the impact of the research.

I recommend the following to address this focus area:

Recommendation 1. The Summary must discuss the significance of the findings and end with their implications. I have rephrased and reorganized certain sections of text in the Summary and Discussion and framed the cover letter to highlight the significance of these findings and pique the interest of researchers in the field of experimental biology; however, the implications of the study findings have not been included in the manuscript. I have provided some suggestions on how this information can be included.

Recommendation 2. The Discussion lacked a strong "take home message." I have included comments suggesting the inclusion of additional information in the last paragraph highlighting the important findings and their implications, the multidisciplinary relevance of the findings (I have suggested discussing the possible clinical significance of the findings since you had discussed the importance of the Sox21-Anapc10 axis in certain syndromes in the introduction), and the scope for further studies.

Strength of the core argument

Overview

The ideas in the manuscript appear to be a tad disconnected. The title focuses on the induction of hair formation in the dental epithelium and highlights this finding as important and unexpected, but the Results and Discussion sections do not lend the same level of significance to this finding. These sections, in fact, focus largely on the role of Sox21 as an ameloblast marker and its contribution to the development of teeth. The Summary does not clearly state the rationale and objective of the study before delving into the methods and findings of the study, which could leave readers grasping at straws trying to understand what the study aimed to achieve. While the Discussion includes references to previous studies to provide information regarding various molecules and their roles, it has not been discussed whether the findings of the study corroborate or contradict those of similar previous studies. The Discussion appears to be redundant with the Results, which *Cell* specifically discourages. The Discussion also lacks information regarding the limitations and implications of the study.

Focus area: Ensuring correspondence among the ideas presented in the different sections of the manuscript

Along with ensuring that the manuscript sections are well structured and impactful, it is important to ensure that the ideas presented in the different sections are connected, allowing the reader to move seamlessly from one section to the next. Since the focus of the study seems to shift from section to section, it would be important to first identify the focus of the study: was it the general role of Sox21 in the development of teeth or the ability of ameloblasts to lose their dental identity to transdifferentiate into hair cells? Accordingly, the title may need to be revised as "Sox21-mediated regulation of ectodermal organ determination" or "Sox21-Anapc10 axis influences ameloblast

identity." The Summary and the rest of the manuscript would then have to be structured in line with the title, ensuring correspondence among the title, rationale, study objective, and conclusion.

I recommend the following to address this focus area.

Recommendation 1. Sections showing a shift in focus have been highlighted through comments. I have also provided suggestions for the rationale and objective statement to be included in the Summary. The order of the sections in the results has been altered to ensure that related topics focusing on the role of Sox21 in the development of teeth are grouped together, separate from those focusing on the influence of the Sox21-Anapc10 axis on ameloblast identity.
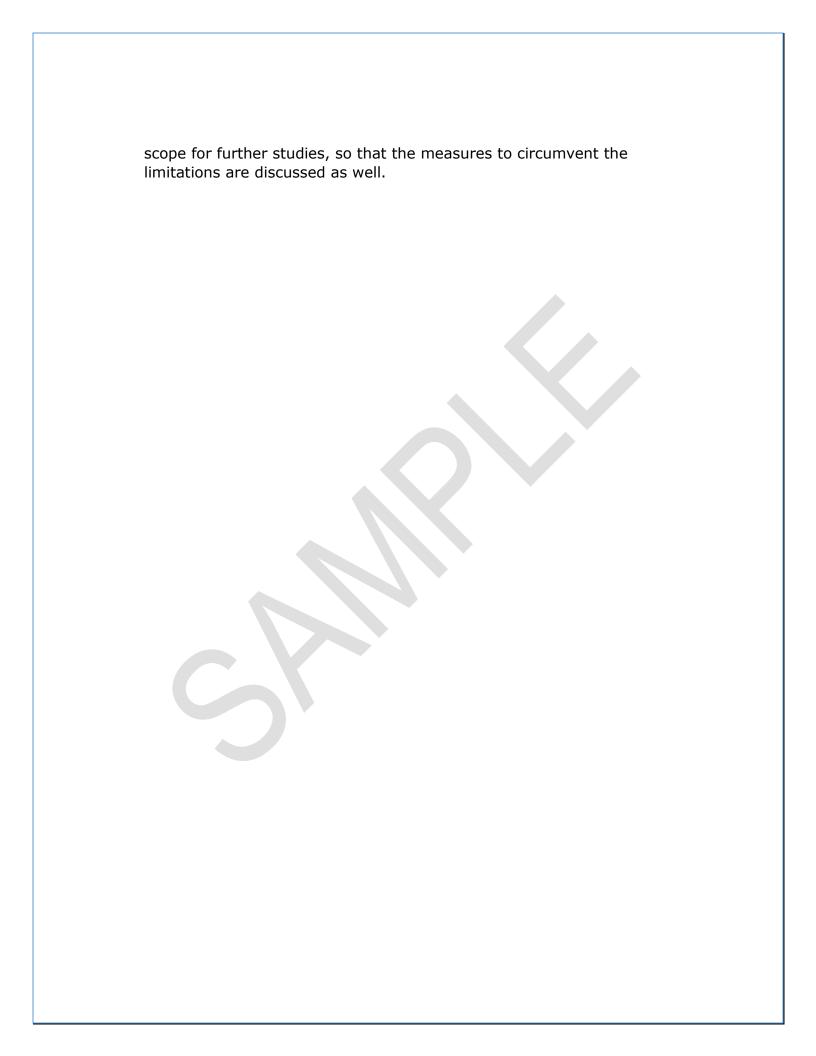
Focus area: Writing a compelling Discussion

An ideal discussion must include an introductory paragraph to re-orient the reader to the study before each result is discussed in the context of previous studies. Once the individual results have been discussed, the discussion must not merely end with the conclusion; it must describe the limitations of the study and present the way forward for this line of research.

I recommend the following to address this focus area.

Recommendation 1. The first paragraph of the discussion can be a short one, stating what the study aimed to do and the main findings. Now that this information has been summarized for the reader, he/she has the required context and information to understand the discussion of the individual results. I have suggested content for this introductory paragraph in the manuscript.

Recommendation 2. Please consider discussing whether the findings of previous studies corroborated or contradicted those of the present study. If the findings of previous studies contradict those of the present study, possible reasons to explain the observed discrepancy must be included.

Recommendation 3. While stating the limitations of the study may seem like a bad idea, it is important to list study design- or methodology-related factors that affected or influenced the interpretation of the results. These limitations can be connected to the

scope for further studies, so that the measures to circumvent the limitations are discussed as well.

Submission readiness

Overview

While it has been previously established that *Sox21* knockdown influences hair lipid composition, this study revealed that depleted *Sox21* expression caused ameloblasts to lose their dental identity and transdifferentiate into hair cells. This important and hitherto unreported finding renders this manuscript suitable for publication in *Cell*, which strives to publish manuscripts that present significant conceptual advances. However, as I mentioned before, it would be important to highlight the significance of the study findings and present their multidisciplinary relevance in sufficient detail to pique the interest of the journal editor. I have formatted the manuscript according to the requirements of *Cell* with respect to layout, naming and ordering of sections, and adherence to specified word limits and have included comments regarding formatting requirements that I could not address (e.g., preparation of the graphical abstract, author contributions, conflict of interest, and blurb for email alerts). The included keywords are relevant and suitable for indexing. With respect to the methodological information, while the required ethics statements and the major experimental methods were included, some sections lacked sufficient detail. The statistical information was clearly presented. The tables and figures prepared were relevant and cited in a sequential order in the manuscript; I have just added a few comments citing minor issues that need to be addressed prior to submission. The accuracy of the references and their correspondence with the in-text citations have been checked. I have prepared a cover letter that highlights the significance of the study findings and includes the declarations and statements required by *Cell*. Please add the implications of the study findings (significance of the findings to a broad readership) to the cover letter as well.

Focus area: Lack of sufficient detail in the methodological information

Journals actively promote the transparent reporting of methodological details of study designs, data collection, and analytical approaches to ensure that researchers worldwide can replicate the study and obtain robust and reproducible results.

I recommend the following to address this focus area.

Recommendation 1. Please include the total number of mice used for the study, along with their sex, average age and weight, and maintenance conditions (availability of food/water, housing conditions, exposure to light/dark conditions, relative humidity, and temperature). Information regarding the primers used and cycling conditions for qPCR is missing as well.