Modeling Late-Stage Dental Epithelium With Mouse Molar and Incisor Organoids

Objectives: In the last 15 years, 3D organoid technology has developed into a powerful asset to explore tissue biology and development, in health and disease. Organoid models more closely recapitulate phenotypical and functional characteristics of the tissue of origin than traditional 2D cell cultures, are highly and long-term expandable with preservation of their characteristics and can differentiate into specific tissue cell types following exposure to differentiation factors or co-culture with other cell types. Although current *in vitro* models have provided important insights into mouse tooth development and biology, *in vitro* models of the dental epithelium lack (the combination of) these benefits of tissue-derived organoids and are at most derived from one tooth type.
Methods: Here, we established organoid models from early-postnatal mouse molar and incisor, and further characterized and validated their differentiation capacity toward ameloblast-like cells.
Results: Mouse tooth organoids (TO) are long-term expandable, express dental epithelium stem cell (DESC) markers and recapitulate key properties of the dental epithelium in a tooth type-specific manner. Remarkably, TO, both of molar and incisor origin, display *in vitro* differentiation capacity toward maturation-stage ameloblast-resembling cells, reinforced in assembloids in which dental pulp stem cells and TO-derived cells are co-cultured. Single-cell transcriptomics supported this potential, and further revealed co-differentiation into junctional epithelium (JE)-resembling cells, as well as presence of odontoblast-/cementoblast-like cells in the assembloids. Finally, TO survive and show ameloblast-resembling differentiation *in vivo*, as observed after subcutaneous transplantation in mouse and grafting onto chicken chorioallantoic membrane.
Conclusions: In conclusion, the newly developed TO model provides a powerful tool to study fundamental aspects of the mouse dental epithelium such as tooth type-specific features, ameloblast/JE differentiation and epithelial-mesenchymal interactions. TO are expected to be instrumental in further unraveling tooth (patho-)biology and on the road toward eventual human biological tooth repair or enamel regeneration.

Division:
Meeting: 2023 IADR/LAR General Session with WCPD
Location:
Year: 2023
Final Presentation ID: 1122
Abstract Category|Abstract Category(s): Stem Cell Biology

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Support Funding Agency/Grant Number: Fonds Wetenschappelijk Onderzoek (G061819)
Financial Interest Disclosure: NONE

SESSION INFORMATION
Interactive Talk Session
Stem Cell Biology: Dental Epithelium in Tooth Development, Enamel Formation and Stem Cells in Bone Formation
Saturday, 06/24/2023 , 11:00AM - 12:30PM