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2025 FaceBase Community Forum

Poster Session Presenters

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Ameloblastin Multitargeting Domain Influences Ameloblast Gene Expression During Enamel Formation

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Background: Ameloblastin, the second most abundant enamel matrix protein, contains a multitargeting domain (MTD) that plays a crucial role in its interactions and multiple functions. MTD facilitates ameloblastin self-assembly, co-assembly (amelogenin-ameloblastininteractions), and binds to ameloblast cell membranes. We developed two novel mouse models with targeted mutations within this region to investigate the functions of distinct regions within the MTD on enamel formation. **Methods**: Two engineered mouse models, AmbnΔK74-L79and AmbnΔL76-P86, were generated by deleting amino acids 74-79 and 76-86 in the mouse ameloblastin sequence. Micro-computed tomography (μCT) was performed on 7-week-old mutant and WT mandibles to determine enamel mineral density. RNA-sequencing was performed to determine differentially expressed genes between the mutants and WT. **Results**: While both AmbnΔK74-L79 and AmbnΔL76-P86 mutants had phenotypes, the AmbnΔL76-P86 had a more severe outcome, with the entire length of the incisor affected. Seven-week-old AmbnΔL76-P86 mutants had reduced enamel volume and mineral density. Preliminary RNA-sequencing data suggests an upregulation of maturation stage genes such as *Odam*, *Amelotin,* and *Kallekrein-4* in the AmbnΔK74-L79 animals. Analysis of AmbnΔL76-P86 mutants, functional analysis of the differentially expressed genes and Ingenuity Pathway analysis will follow. **Conclusion**: Mutations in the MTD of ameloblastin leads to enamel hypomineralization and hypomaturation. We suggest that the domain regulates signaling pathways critical to normal enamel development in addition to contributing to the characteristics of extracellular matrix structure. **Funding support:** This research was funded by NIH/NIDCR grant R01-DE013414 and R01-DE027632 to JMO.

FaceBase: Data Resources for Craniofacial and Dental Development, Molecular Genetics, and Genomics

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FaceBase (facebase.org), established in 2009, provides a freely available repository of data for the scientific community on dental, oral and craniofacial (DOC) development and diseases as well as in other anatomically or biologically relevant regions. FaceBase is a trusted source of research and educational resources across the translational spectrum on humans and model organisms.

FaceBase is a highly scalable, Cloud-based (STRIDES) data sharing and analysis hub. Cloud storage provides extremely robust, cost-effective, virtually unlimited capacity and improves accessibility while ensuring long-term sustainability. FaceBase embraces TRUST (Transparency, Responsibility, User-focus, Sustainability, Technology) principles throughout to ensure the integrity of FAIR (Findable, Accessible, Interoperable, Reusable) data resources. FaceBase supports the full translational spectrum of research through enhanced data curation procedures for clinical and public health data while strengthening basic research data handling. FaceBase provides resources to help the community meet the new NIH Data Management & Sharing (DMS) requirements.

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Spatial Transcriptomics and Lineage Analysis for Craniofacial Mesenchymal Fate Determination

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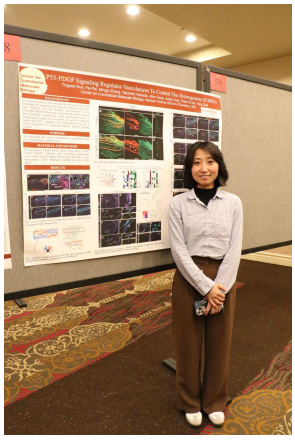
The differentiation of post-migratory cranial neural crest cells (CNCCs) into distinct mesenchymal lineages is essential for proper craniofacial development. Here, we combined single-cell RNA sequencing (scRNA-seq) with a seqFISH-based spatial genomics approach to generate high-resolution, spatially resolved gene expression profiles of the developing palate and other craniofacial regions in mouse embryos. We systematically defined mesenchymal cell types by linking their transcriptomic profiles to spatial identities. Integrative analysis of spatial transcriptomic data from E12.5 to E15.5 further revealed that mesenchymal lineage specification occurs at or prior to the onset of palatogenesis. The raw and processed scRNA-seq data from embryonic palatal tissue (E12.5, E13.5, E14.5, E15.5, and E18.5), along with the corresponding seqFISH data from anterior and posterior embryonic head regions (E12.5, E13.5, and E15.5), have all been deposited in FaceBase under DOIs 10.25550/62-QZ1A and 10.25550/62-Y0VT, respectively.



Trp53 Coordinates with Hippo Signaling During Tooth Root Development

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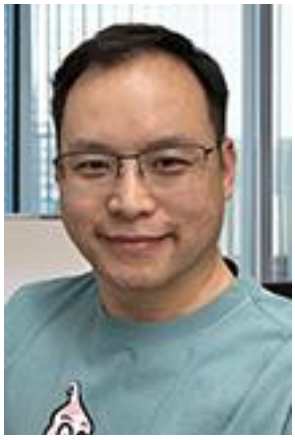
Background: Cranial neural crest cells (CNCCs) play an essential role in craniofacial development and function. These cells have the ability to differentiate into multiple cell types, contributing to diverse craniofacial structures, including bones, cartilage, and connective tissue. Despite their significance, the mechanisms governing the cell fate decisions of post-migratory CNCCs remain largely unknown. Transcription factors play a central role in orchestrating these developmental processes by regulating gene expression programs. P53 is a well-known master regulator, extensively studied in cancer biology for its role in controlling cell growth and apoptosis. However, its role in postnatal development, particularly in craniofacial development, is less understood. **Methods:** The transgenic mouse model used in this study was *Gli1-CreER;Trp53*$^{fl/fl}$. Techniques used in this study included immunohistochemistry, RNAscope, CUT&RUN-seq, bioinformatic analyses, and cell culture. **Results:** In this study, we used the mouse molar as a model to investigate the role of P53 signaling in tooth development, revealing that P53 not only regulates key processes in tooth development but also interacts with the transcription factor Arnt to modulate Hippo signaling. This coordination influences the expression of *Gli1* during the postnatal development of CNCCs. We demonstrated that the interplay among the P53, Hippo, and hedgehog signaling pathways is essential for regulating tooth root development. These insights provide a deeper understanding of how these pathways converge to regulate postnatal craniofacial development. **Conclusions:** These findings suggest that P53 plays a broader role in developmental biology beyond its established functions in cancer, potentially influencing other aspects of postnatal tissue formation and regeneration. **Acknowledgement of research support:** This study was supported by funding from the National Institute of Dental and Craniofacial Research, National Institutes of Health (R01 DE022503, R01 DE012711 and U24 DE034163 to Yang Chai).



Dysregulated chondrocyte formation as a novel mechanism of lambdoid synostosis

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Craniosynostosis affects approximately 1 in 2,500 infants, with lambdoid synostosis being a rare subtype involving premature fusion between the parietal and occipital bones. Its underlying mechanisms remain poorly understood due to its rarity and lack of suitable models. Previously, we reported that Pdgfra overactivation leads to premature coronal suture fusion in mice. In this study, we found that mesodermal expression of an autoactivated PdgfraK allele induces lambdoid synostosis, establishing PdgfraK/+;Mesp1Cre mice as a relevant disease model. Histological analysis revealed excessive cartilage formation prior to suture fusion, implicating chondrocytes in the process. To test this, we activated Pdgfra in chondrocytes using Col2a1Cre, which also resulted in lambdoid synostosis. This confirmed that dysregulated chondrogenesis contributes to the condition. Spatial transcriptomics (10X Visium) revealed that Pdgfra activation promotes chondrocyte proliferation and differentiation toward endochondral ossification. These findings were validated by immunostaining and proliferation assays. Two types of cartilage are involved in calvarial development: one undergoes endochondral ossification, while the other is typically resorbed. Our results suggest that Pdgfra activation alters the fate of the latter, redirecting it toward ossification and leading to premature suture fusion. This study presents a novel model for lambdoid synostosis, identifies chondrocyte abnormalities as a key pathological factor, and elucidates how Pdgfra signaling regulates this process.

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