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Molecular Control of Organogenesis, Cell Fate Specification and Cell Differentiation: Genetic and Experimental Studies in the Mouse

Akademisk avhandling

Som för avläggande av odontologie doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i föreläsningssal 3, Institutionen för odontologi, Medicinaregatan 12E, Göteborg, den 18 januari 2019, klockan 13:00

av Maha Abdelghaffar Abdelgawwad El Shahawy

Fakultetsopponent:
Manuel Mark, Professor
Strasbourg universitet, Frankrike

Avhandlingen baseras på följande delarbeten

I. Reibring CG, El Shahawy M, Hallberg K, Kannius-Janson M, Nilsson J, Parkkila S, Sly WS, Waheed A, Linde A, Gritli-Linde A. Expression patterns and subcellular localization of carbonic anhydrases are developmentally regulated during tooth formation. *PloS One*. 2014 May 1;9(5):e96007.

II. El Shahawy M, Reibring CG, Neben CL, Hallberg K, Marangoni P, Harfe BD, Klein OD, Linde A, Gritli-Linde A. Cell fate specification in the lingual epithelium is controlled by antagonistic activities of Sonic hedgehog and retinoic acid. *PLoS Genet.* 2017 July 17; 13(7):e1006914

III. El Shahawy M, Reibring CG, Hallberg K, Neben CL, Marangoni P, Harfe BD, Klein OD, Linde A, Gritli-Linde A. Sonic hedgehog signaling is required for *Cyp26* expression during embryonic development. *Manuscript*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR ODONTOLOGI

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Avdelningen för oral biokemi, Institutionen för Odontologi, Sahlgrenska akademin, Göteborgs universitet, Sverige, 2019.

Abstract

Deciphering the mechanisms controlling normal development sheds light onto the etiopathogenesis of congenital malformations and diseases, and knowledge of the expression patterns of proteins and/or their encoding genes is necessary to understand developmental pocesses. Good models to study developmental processes, such as morphogenesis, tissue patterning, cell fate specification and cell differentiation include developing teeth and tongue.

Carbonic anhydrases (CAs) are involved in several physiological processes and diseases, yet which of these enzymes are produced, and which cells express them during odontogenesis is unknown. To fill in this knowledge gap, we used biochemical and molecular analyses in developing mouse teeth. We revealed dynamic expression patterns of eight CAs during tooth formation, and showed that CAs are not produced solely by cells involved in enamel and dentine secretion and biomineralization. Furthermore, we showed that CAXIII protein was enriched in LAMP1/2-expressing vesicles, suggesting lysosomal localization, and that CAIII expression was confined to root odontoblasts. Our data suggest developmental regulation of CA expression, and that CAs participate in several biological events inherent to tooth-forming cells (study I).

The Hedgehog (Hh) and retinoic acid (RA) pathways play key roles during embryogenesis and tissue homeostasis. Both pathways are active in same or adjacent tissues. However, whether these pathways interact is largely unexplored. Furthermore, whether Sonic Hedgehog (SHH) signaling triggered by SHH, a Hh ligand, controls tongue development *in vivo* is unknown. To address these issues, we generated and studied mice genetically lacking SHH signaling (studies II and III). We revealed that in the developing tongue SHH abates RA activity through the RA-degrading enzymes CYP26s, and that epithelial cell fate specification is regulated by antagonistic SHH and RA activities, wherein SHH inhibits, whereas RA promotes taste placode and minor salivary gland formation. Furthermore, we showed that SHH signaling is required to prevent ectopic Merkel cell specification in the lingual epithelium (study II). We also revealed interactions between the Hedgehog and RA pathways in other embryonic structures (study III). Our findings (studies II and III) show that properly calibrated SHH and RA activities are crucial for adequate development, and are expected to be of interest, as deregulation of Hh/SHH signaling leads to congenital malformations and neoplasia.

Keywords: Carbonic anhydrase, *CRE/LoxP*, Glands, Merkel cells, Metaplasia, Patterning, Retinoic acid, Sonic Hedgehog, Tongue, Tooth

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