LABORATORY OF

TRANSGENIC MODELS OF DISEASES

Transgenic model, metabolism, craniofacial development, protease, Ub ligase

Radislav Sedláček

BIOCEV

more information

e-mail

The work of the laboratory is dedicated to four research areas that are interlinked by technologies used, especially genome editing, and animal models studied to reveal gene functions in the complexity of the whole organism.

In the protease area, we particularly focus on kallikreins, metalloproteinases (MP), and ADAMs (a disintegrin and metalloproteinase). Regarding the kallikreins, we have created a number of mutants for *Klk* genes on the background of SPINK5, the major inhibitor of serine proteases, to reveal their complex network in the skin, especially in the development of the Netherton syndrome.

In the metabolism area, we study the role of CLUH, which is an mRNA-binding protein interacting with more than 400 mRNAs and also regulating mitochondrial functions. We aim to elucidate the importance of CLUH in adipocyte differentiation and mitochondrial biogenesis and cancer.

In the field of ubiquitylation-mediated processes, we have created a number of mutant mice with the aim to understand the role of ubiquitination in regulating the intestinal barrier function, craniofacial development, immunity, and to characterize the links with human inflammatory bowel disease. The work focuses on cullin-RING ubiquitin ligases involved in GIT homeostasis and pathological processes, since the cullin family has been largely associated with different types of cancer in GIT and thus represents a promising pharmacological target. We also study other U3 ligases using (non)-conditional mouse models, among them the role of Btbd3 in the skeleton, Rnf121 in the cardiovascular system, Rnf186 in the lung, Cul4a, Ddb1, Cul3, and others in the gastrointestinal tract. In the area of craniofacial development, we focus on the molecular mechanism driving the craniofacial development and unveiling the molecular regulation of development of mineralized tissues such as teeth and bones. The molecular mechanisms cover the differentiation events of mineral-producing cells, secretion, and maturation of extracellular matrix and finally the crystallization process of hydroxyapatite. We focus on the function of extracellular protein ameloblastin in the regulation of mineralization processes in tooth enamel formation and bone homeostasis process. We also study the function of FAM46A, which is mutated in patients with osteogenesis imperfecta. We generated a Fam46a knockout model to characterize the molecular mechanisms that underlie the observed phenotypic changes.

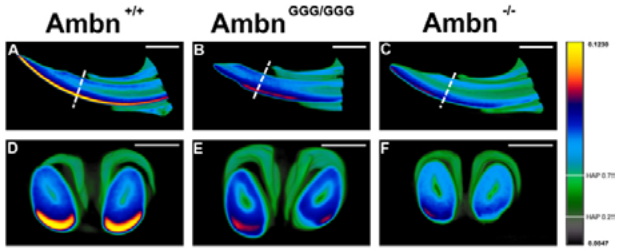

Figure 1. Dominant function of Ambn in formation of structured enamel

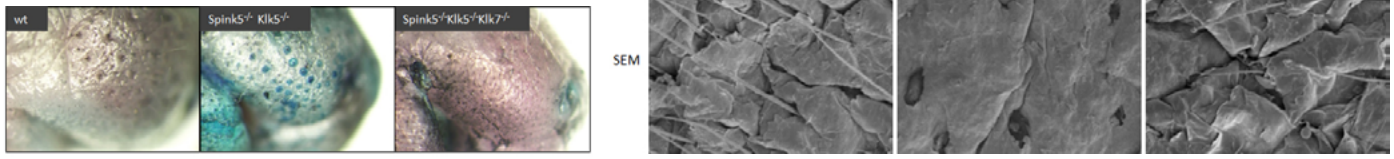

Figure 2. Unregulated activity of KLK7 causes severe epidermal barrier damage in time dependent manner

Selected publications:

1. Kasparek P, Ileninova Z, Zbodakova O, Kanchev I, Benada O, Chalupsky K, Brattsand M, Beck IM, Sedlacek R*(2017) KLK5 and KLK7 ablation fully rescues lethality of Netherton syndrome-like phenotype. *PLoS Genet*, **13**:e1006566.
2. Prochazka J, Prochazkova M, Du W, Spoutil F, Tureckova J, Hoch R, Shimogori T, Sedlacek R, Rubenstein JL, Wittmann T, Klein OD* (2015) Migration of founder epithelial cells drives proper molar tooth positioning and morphogenesis. *Dev Cell*, **35**:713-724.
3. Kaiser K, Gyllborg D, Procházka J, Salašová A, Kompaníková P, Molina FL, Laguna-Goya R, Radaszkiewicz T, Harnoš J, Procházková M, Potěšil D, Barker RA, Casado ÁG, Zdráhal Z, Sedláček R, Arenas E, Villaescusa JC, Bryja V* (2019) WNT5A is transported via lipoprotein particles in the cerebrospinal fluid to regulate hindbrain morphogenesis. *Nat Commun*, **10**:1498.
4. Wald T, Spoutil F, Osickova A, Prochazkova M, Benada O, Kasparek P, Bumba L, Klein OD, Sedlacek R, Sebo P, Prochazka J*, Osicka R*(2017) Intrinsically disordered proteins drive enamel formation via an evolutionarily conserved self-assembly motif. *Proc Natl Acad Sci USA*, **114**:E1641-E1650.
5. Balounová J, Šplíchalová I, Dobešová M, Kolář M, Fišer K, Procházka J, Sedlacek R, Jurisicova A, Sung HK, Kořínek V, Alberich-Jorda M, Godin I, Filipp D* (2019) Toll-like receptor 2 expression on c-kit+ cells tracks the emergence of embryonic definitive hematopoietic progenitors. *Nat Commun*, **10**:5176.

In the picture: 1. Raishbrook Miles Joseph | 2. Kašpar Petr | 3. Szczerkowska Katarzyna | 4. Mrázková Blanka | 5. Michalčíková Tereza | 6. Procházková Michaela | 7. Syding Linn | 8. Šlaufová Marta | 9. Kašpárek Petr | 10. Sedláček Radislav | 11. Turečková Jolana | 12. Sanchez Villalba Alvaro | 13. Slámová Monika | 14. Nováková Rozálie | 15. Buková Ivana | 17. Petrzselyová Silvia | 18. Aranaz Novaliches Goretti | 19. Procházka Jan