Program/Abstract # 91

Gain-of-function in Ras signaling perturbs dental development in mouse and human

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Gain-of-function in Ras signaling perturbs dental development in mouse and human

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The control of inner ear morphogenesis by Sprouty and Tbx1 genes in mouse models of 22q11.2 deletion syndrome

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Ras/MAPK signaling is critical in animal development, and RTK signaling, which activates Ras signaling, is known to play an important role in tooth development. Our previous work has shown that increasing Ras/MAPK signaling by inactivating Sprouty genes adversely affects tooth morphogenesis. Here, we directly examined the effects of activating Ras/MAPK signaling in both humans and mice. Costello Syndrome (CS) is caused by a heterozygous de novo germline mutation in HRAS that results in constitutive active Ras protein. We examined a cohort of CS patients and identified a number of craniofacial and dental anomalies. We found that a large majority of patients presented with pronounced enamel hypoplasia. Microcomputed tomography of exfoliated primary teeth from CS patients showed a significant decrease in enamel thickness compared to controls. We next examined the CS mouse model and found that the mice also had an enamel defect. Further inspection revealed disorganization of the ameloblasts in the mouse incisor. We are currently studying cell proliferation and polarity of the ameloblasts in the mutant mouse incisors. In addition, we are using an ameloblast-like cell line to determine the effects of increased Ras/MAPK signaling on the behavior of the cells.

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Program/Abstract # 93

The Role of FGF Gradients in the Regulation of Early Limb Growth

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While molecular biology can identify the molecular components regulating tissue growth, by itself it can not explain how embryos determine their shape and size. FGFs, which control cell proliferation, differentiation, migration and survival, are key molecules in embryonic morphogenesis. In this paper, we use a reaction-diffusion model for morphogen diffusion and a Glazier-Graner-Hogeweg multi-cell model to simulate numerically the role of FGF4 and FGF8 in regulating the early growth of the vertebrate limb. FGF diffusion, decay and secretion, and cell growth in response to FGF concentrations, determine the shape and size of limbs, and hence more generally, of tissues and organs during embryonic development. Physiologically reasonable values for FGF secretion, diffusion and decay grow a simulated limb with correct shape, size and antero-posterior asymmetry. We show that the limb mainly expands by growth of the distal domain which has high FGF concentrations and that the distalized expansion locks the region of high FGF concentration into the distal tip. We conclude that the interaction between growth and FGF gradients dominates regulation of the proximo-distal and antero-posterior outgrowth of the limb and the FGF distribution.

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