

KIR2.1 POTASSIUM CHANNELS AND BONE MORPHOGENIC PROTEIN IN CRANIOFACIAL DEVELOPMENT. KS Swenson (Ph.D., GS), Y Ozekin, T Isner, E Bates, Department of Pediatrics, University of Colorado | Anschutz Medical Campus, Aurora, CO.

It is well known that craniofacial development relies on signaling molecules such as Bone Morphogenic Protein (BMP). More recently, it has become apparent that ion channels are also critical for craniofacial development. However, how ion channels contribute to canonical developmental signaling remains mysterious. Loss of the K⁺ Inwardly Rectifying Channel Kir2.1 (*Kir2.1^{KO/KO}*) phenocopies loss of BMP2/4 signaling from the cranial neural crest cells (cNCCs) of mice. Kir2.1 is also required in the cNCCs for secondary palate closure. Furthermore, BMP signaling is reduced in the developing palate of *Kir2.1^{KO/KO}* mice. To understand how Kir2.1 contributes to BMP signaling, we knocked out one copy of Kir2.1 and turned on a constitutively active BMP receptor in the cranial neural crest. We then quantified changes in craniofacial development. In *Kir2.1^{KO/+}* mice that express a constitutively active BMP receptor (*caBMPRIa/+*) in the cNCC, we found an exacerbation of phenotypes including a shortened premaxilla, shortened nasal bones, widened fontanelle, and decreased mandible height and length. Mice lacking one copy of Kir2.1 (*Kir2.1^{fl/+}*) and one copy of the BMP4 ligand (*BMP4^{fl/+}*) in the cNCC showed a tendency towards rescuing the craniofacial defects of the *BMP4^{fl/+}* in the cNCC alone. *BMP4^{fl/+}* alone show craniofacial defects at embryonic day 18.5, as noted by increased fontanelle area, decreased mandible length, and decreased mandible height. While the *Kir2.1^{fl/+}; BMP4^{fl/+}* also showed craniofacial phenotypes, they are less severe. Data from our lab shows that depolarization can induce BMP4 release. Loss of Kir2.1 should depolarize cells and could lead to a constant release of BMP4. Together, these results suggest a negative feedback loop in BMP4 signaling in which constant release of BMP4 is detrimental to the efficiency of BMP4 signaling.