Medical Xpress

Small molecule replacement therapy to rescue craniofacial defects

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Today at the 45th Annual Meeting & Exhibition of the American Association for Dental Research, researcher Shihai Jia, University of Utah, Salt Lake City, USA, will present a study titled "Small Molecule Replacement Therapy to Rescue Craniofacial Defects." The AADR Annual Meeting is being held in conjunction with the 40th Annual Meeting of the Canadian Association for Dental Research.

PAX9 and MSX1 are known to be associated with human cleft palate and tooth agenesis. Mice lacking Pax9 or Msx1 die at birth with cleft palate and tooth developmental arrest at bud stage, and Pax9+/-;Msx1+/- gene in mutant mice have defects in incisor and the third molar development. In this study researchers explored the therapeutic use of small molecules to rescue the craniofacial defects by manipulating signaling pathway involved in craniofacial development. This translational study provides novel candidates for the therapeutic treatment of the patients with craniofacial defects.

To increase Wnt signaling activities, the Dkk1 inhibitor WAY-262611 was injected into the tail vein of pregnant Pax9+/- mice, which had been mated with Pax9+/- or Msx1+/- males for Pax9-/- and Pax9+/-;Msx1+/- embryos, during the embryo developmental stage of palate and tooth formation. To modulate Eda/Edar signaling pathway, anti-Edar antibody was injected into the tail vein of pregnant Pax9+/- mice at embryonic day E9.5. The phenotypes were analyzed at E18.5 via whole mount view and HE stained sections. WAY-262611 treatment partially rescued palatal defects in Pax9-/- embryos, tooth buds advanced to the early cap

stage compared with developmental arrest at bud without treatment. However, correction of the craniofacial defects did not prevent postnatal death of Pax9-/- pups. Similarly, Pax9-/- embryos treated by anti-Edar antibody had fused palate shelves with tooth buds advanced to the early cap stage. In addition, both of the treatments could restore the 3rd molar formation in Pax9+/-;Msx1+/- mice. Neither WAY-262611 nor Anti-Edar antibody had negative effects on the mother or control littermates.

The small molecule WAY-262611 and anti-Edar antibody could rescue the craniofacial defects in Pax9-/- and Pax9+/-;Msx1+/- mice without any overt associated toxicities, suggesting that they have the potential to be used as safe therapeutic drugs for treating developmental abnormalities related to Wnt or Eda/Edar signaling deficiency.

More information: This is a summary of oral presentation #1497, "Small Molecule Replacement Therapy to Rescue Craniofacial Defects," which will be presented on Saturday, March 19, 2016, 8 a.m. - 8:15 a.m. at the Los Angeles Convention Center, room #408B.

Provided by International & American Associations for Dental Research