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SEMINAR

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Use of the zebrafish model to study the evolution of tooth morphology and number and to investigate SSRIs induced bone loss *in vivo*

Cypriniforms, teleost fish that includes the zebrafish, display an impressive diversity in pharyngeal teeth, however little is known about the developmental mechanisms that generate such diversity Retinoic acid (RA) signaling controls the shape and number of pharyngeal teeth in Cypriniformes. By experimentally modulating the RA pathway in zebrafish we generated specific changes in teeth shape and number. Strikingly, relatively modest changes in RA levels generate adults with a sixth tooth in the first tooth row, when compared to the controls that contain only five teeth. Interestingly, similar variations are observed in another species, the goldfish, which harbor different adult pharyngeal teeth morphology. The specific changes in the tooth row that we observed after altering RA signalling is reminiscent of morphological changes observed in the wild in several species of Cypriniformes. Our analysis suggests that changes in the RA signaling pathway played an important role in the morphological diversification of the tooth row in fish. This suggests that, by allowing heterochronic variations, the RA pathway has the potential to alter reiteratively the morphological landscape during evolution.

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed treatments for depression and, as a class of drugs, are among the most used medications in the world. SSRIs increase the levels of serotonin in the synapse by blocking the activity of the serotonin transporter, which is responsible for returning serotonin into the presynaptic nerve ending. Concern for possible effects from SSRI treatment on bone metabolism has arisen as recent clinical studies have shown a link between SSRI use and a decrease in bone mineral density. Further studies have revealed that serotonin receptors and the serotonin transporter are present in human osteoblasts and osteoclasts. We previously showed that SSRIs induced apoptosis in these cells. SSRI use by mothers during pregnancy has also been associated with birth defects such as persistent pulmonary hypertension, seizures, and craniosynostosis. To determine possible effects from SSRI use on developing bone, we treated zebrafish with Citalopram and Sertraline during embryonic development. Here we show that SSRI treatments inhibit bone development. We observed decreased alizarin red staining in treated embryos. However, the decrease in mineralization observed was not associated with an increase in apoptosis. In situ hybridization on treated embryos revealed that rux2b and osterix expression was unaffected, while col10a1 was decreased. These findings will be confirmed in human osteoblasts and osteoclasts. Therefore, we propose that SSRIs inhibit bone development by affecting osteoblast maturation. These results may lead to further investigations into the safety of SSRI use during pregnancy and by people at risk for bone diseases.

Artwork by Ann Nee, DBS, NUS