Editorial

Small players with a big role: MicroRNAs in pathophysiology of cleft lip and palate

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Cleft lip with or without cleft palate (CL/P) and isolated cleft palate (CPI) are two of the most common congenital craniofacial birth defects in humans. These orofacial clefts (OFC) cause profound psychosocial distress as well as an enormous economic burden to the affected individual, their families, and the community. While genetic and environmental factors contribute to the complex etiology of OFC. Affected infants have an increased risk of death due to associated conditions, such as prematurity, respiratory and infectious diseases, and central nervous system disorders, while affected adults have been shown to have increased risk of cardiac disease, suicide, epilepsy, and various cancers.[1] Thus, it is considered a pressing public health problem. Thirteen loci (genomic positions) on various chromosomal regions and 20 genes associated with CL/P have been reported by linkage and association analysis. Nevertheless, the etiology of this disorder is still poorly defined. Recent studies indicate that disruption on microRNAs (miRNAs) activity may also play a role on the onset of these deformities.[2-4] miRNAs are approximately 22 nucleotide RNAs that regulate embryonic development by controlling post-transcriptional gene expression. During miRNA biogenesis, the RNase III enzyme *Dicer1* participates in the final step of miRNA processing by cleaving the precursor miRNAs and generating mature miRNAs, which as part of the RNA-induced silencing complex (RISC), interact with target sites within mRNAs and induce immediate cleavage or post-transcriptional repression.[5,6] A growing number of evidences support the importance of miRNAs in vertebrate and mammalian craniofacial development; however, studies focusing into the importance of miRNAs specifically in human craniofacial development are limited. The study of genetically engineered mouse models have yield important insight on a variety of human diseases and provided new opportunities to investigate the complex molecular and genetic factors underlying the pathogenic processes. In this issue of the journal, Barritt *et al.*, uses a mouse model to discuss the effect of conditionally deleting the human orthologue *Dicer1* gene in the mid-hindbrain boundary, which corresponds to the site of origin of the cranial neural crest (CNC) cells giving rise to craniofacial structures.

In mice, as in humans, the palatal region undergoes extensive growth and positional changes during craniofacial development. Around E10.5 (~5th week of embryonic development in humans), the primary palate starts developing from the frontonasal region, and by E16.5 (~10th week of embryonic development in humans), palatal outgrowth, shelf elevation, and fusion of lateral palatal shelves are complete. In the anterior two-thirds of the palate, CNC-derived tissue undergoes intramembranous ossification to form the hard palate;

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while in the posterior third, skeletal muscle develops in the soft palate.[7] The authors show that, in spite of a fully formed primary palate, secondary palatogenesis is disrupted in the *Dicer1* conditional knockout (CKO) mouse model. Evidences gathered on this study suggest that palatal clefting in the *Dicer1* CKO mouse is primarily caused by impaired palatal outgrowth and arrested bone differentiation resultant from decreased proliferation and increased apoptosis in the developing palatal shelves. The authors' findings support the premise that progenitor cells are less dependent on miRNAs than their differentiated progeny. Therefore, lack of *Dicer1* and, consequently mature miRNAs in the mid-hindbrain boundary would not impact the migration of CNC cells to the first pharyngeal arch, but rather impair the growth and differentiation of the resultant tissue and the formation of cartilaginous and bone structures associated with the craniofacial region. The evolutionary conserved nature of miRNA synthesis and structure among mouse and human, allied to the present results supporting their importance in mouse palatal development, emphasize the importance of further studies dissecting the potential contribution of *Dicer1* and specific miRNAs to the pathogenesis of human OFCs. Moreover, it has been documented that transcriptional regulation of Dicer is controlled by *TP63*.[8] Interestingly, *TP63* gene mutations are associated with various monogenic malformation syndromes manifesting cleft lip with or without cleft palate.[9-12]

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