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Introduction to the special issue on orofacial clefts (OFCs)

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The face that you see in the mirror each morning is likely the product of precision in cell behavior, balanced molecular regulation, and a nurturing environment relatively free from toxins or teratogens. Dr. Chengji Zhou and team from UC Davis provide us with 4 comprehensive reviews on aspects of orofacial clefts (OFCs) to bring us up to date on how our face develops and what happens when these processes are disrupted. Drs. Yulai Zhou and Julian Little and team from Universities of Ottawa and Dundee and Duke-evaluated the data that folic acid supplementation may effectively prevent OFCs. The study of OFCs could provide a better understanding of developmental programs common to morphogenesis of a variety of embryonic structures as well as in identifying therapeutic strategies specific to OFC prevention.

OFCs are the most common of craniofacial birth defects and one of the most common of all birth defects, affecting on average 1 in 700 newborns worldwide (Mossey & Modell, 2012). OFCs include the failure of the upper lip and/or palate (the roof of the mouth) to close properly during development, leaving a gap or gaps that often require surgical closure. Aside from the psychosocial consequences of OFCs that are not trivial (Al-Namankany & Alhubaishi, 2018; Broder et al., 1994; Hunt et al., 2005), difficulties in eating, speaking, and breathing can result from OFCs (Goswami et al., 2016). These individuals also have higher risk for ear infections and dental issues.

In humans, orofacial formation is mostly active from the 4th through 6th week of embryonic development (Schoenwolf et al., 2014). Face formation occurs in mice at embryonic day 8-14.5 (Tamarin & Boyde, 1977), in zebrafish during 36–48 hours post fertilization (hpf) (Swartz et al., 2011), and in chicken at incubation 3-6.5 days (HH stages 20-29) (Abramyan & Richman, 2018).

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The typical face is the result of several primordial tissues growing in concert and fusing at just the right time and place (Figure 1). These tissues are largely derived from or orchestrated by neural crest cell (NCC) progenitors in communication with surrounding epithelia. The NCCs proliferate and migrate while receiving and sending signals (Helms et al., 2005). After migration, they differentiate into a wide range of cell types. The cranial NCC derivatives form mounds of mesenchymal tissues covered by epithelial cells that are called prominences or processes that fuse with each other in a stereotyped way to form orofacial structures and separate oral and nasal chambers. Each step occurs with bilateral symmetry. Ji et al. (in this issue) explain and explore many cellular events that are involved in the development of the normal face and which ones are disrupted in OFCs.

In view of the complexity of face development, it is not surprising that networks of genes and factors have been implicated in its malformation. Reynolds et al. (in this issue) clarify this complexity and provide comprehensive tables of the conditions and associated or candidate genes.

OFCs can be found as isolated defects or as part of syndromes. The genetic causes of syndromic OFCs are easier to track than isolated OFCs. For example, 68% of individuals with Van der Woude syndrome and 97% of families with popliteal pterygium syndrome have mutations in the interferon regulatory factor 6 (IRF6) gene (1q32.2-q32.3) that transcribes a transcription factor involved in many developmental processes including epidermal development (de Lima et al., 2009). It is expressed in the orofacial epithelial cells to maintain epithelial integrity and prevent ectopic epithelial fusions during palatogenesis.

“Modern sequencing technologies have accelerated our ability to identify specific sequences and variants that are linked with clefts, and at least 350 candidate genes have been identified through association studies in human OFC patients alone.” (Reynolds et al., in this issue).

However, the genomic DNA sequence needs no change at all to initiate OFCs. Regulating access of transcriptional machinery to DNA sequences can be powerful in itself. The epigenetic causes of OFCs are presented by Garland and colleagues (Garland et al., in this issue). Epigenetics has a significant impact on OFC pathogenesis. Conformational changes to the DNA after methylation allow or prohibit binding of the transcriptional machinery. Other epigenetic factors include histone modifications and non-coding RNAs (such as miRNA), which also play important roles in OFC etiology.

Embryos are highly vulnerable to environmental factors such as maternal smoking, alcohol intake, poor diet, overheating, and exposure to drugs and pollutants. These environmental factors can cause developmental disorders including OFCs and can also have transgenerational consequences (Garland et al., in this issue). Embryonic face development is not only vulnerable to *in utero* exposure, but also affected by exposures to the mother and even the father before pregnancy. Maternal and paternal environmental effects can be transferred as epigenetic marks that can manifest as OFCs in the embryo without direct *in utero* exposure. While we know that some of these negative environmental factors can be eliminated, others cannot be avoided. Can the research help to protect us from OFCs by other avenues such as with the use of preconceptional and prenatal supplements?

Drs. Yulai Zhou, Julian Little and collaborators from the Universities of Ottawa and Dundee and Duke (in this issue) provide a set of meta-analyses to determine the relationship between different indicators of folate intake/status and OFCs. Since the last such analysis published in 2008 (Johnson & Little, 2008), 56 papers published in the years 2007 to 2020 were identified. Based on the 2008 study, the conclusion was that there was an 18% decline in the risk of CL/P (cleft lip/cleft palate) associated with the use of folic acid containing supplements, but no significant reduction in CP (cleft palate). They also reported a reduction of about 23% in CL/P risk with intake of multivitamins. The updated findings (Zhou Y et al., in this issue) suggest that taking multivitamin supplements that include folic acid during periconception may prevent CL/P, reducing the risk by 40%, and CPO (cleft palate only), reducing the risk by 19%. Folic acid supplementation alone did not seem to help. The update differs from the 2008 study in that study participants were from a wider range of countries, broadening the socio-economic variability. Comparison across these meta-analyses illustrate the difficulties inherent in these types of analyses and the need for more studies to get a clearer picture of just what is needed to prevent OFCs. Nonetheless, the good news is that supplements appear to be effective in preventing some OFCs.

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Figure 1.

Major types of orofacial clefts (OFCs) in humans include unilateral/bilateral cleft lip with or without cleft palate (CL/P) and cleft palate only (CPO) (see details in Fig. 1, Ji et al. in this issue). Orofacial formation involves various cellular actions such as epithelial-mesenchymal interactions, which are regulated by several key morphogenetic signaling pathways, including Bmp/Tgfb, Fgf, Retinoic acid (RA), Shh, and Wnt, and are also regulated by epigenetic factors such as DNA methylation of intragenic CpG islands, microRNAs (miRNAs), and gene-environmental interactions (GXE). Disruptions of any of these factors may cause OFCs.