⊞ GUEST EDITORIAL

Early childhood caries prevention through a developmental origins model of the oral microbiome, host and oral environment, and sociodemographic influences

As the most common chronic disease in preschool children in the United States, early childhood caries (ECC) has a profound and lasting impact on a child's quality of life, is a significant human and economic burden, and disproportionately affects those in poverty. ECC is a multifactorial infectious disease, with onset and severity determined by response of the oral microbiome and host to the social environmental and health behavior context. Studies of the ECC oral microbiome, which are central to scientific and clinical advances, have been limited by *(1)* research designs without leverage to evaluate cause-effect relationships, *(2)* over-reliance on *Streptococcus mutans* and *Candida albicans* target candidates, and *(3)* lack of consideration of social determinants of health factors (eg, diet) and confounding factors (eg, stress physiology). Progress in advancing innovative therapeutic and preventative clinical approaches needed for accurate prediction and decrease in ECC onset requires a multidimensional analysis of the child oral environment and microbiome, and risk factors associated with psychosocial and economic disparities.

The oral microbiome and microbial interactions with the host oral environment are influential factors of human physiology and mediate critical aspects of oral health and disease, including nutrient metabolism and host immunity.[1] Transition from a healthy oral microbiome to a dysbiotic community, with differences in microbial composition and metabolism that promotes either health or disease, has emerged as a fundamental concept in the understanding of oral health and disease. The clinical and research focus on *S mutans* and *C albicans* as the only ECC-associated oral pathogens is out of step with current thinking on microbial disease and the emphasis on dynamic multi-microbial interactions within dysbiotic microbial communities.[2,3] A similar focus on the host factors associated with caries and microbial and host–microbial interactions of the ECC oral microbiome,[4] will yield correlations for prediction of ECC and design of novel approaches urgently needed for prevention and treatment.

Although deriving causal effects is decidedly challenging in clinical and observational studies, greater causal leverage would be derived from prospective longitudinal studies of mother–infant dyad cohorts. These cohorts would be composed of caries-free healthy controls and children with ECC onset during the study period, with maternal intraoral sampling at each trimester prior to birth and frequent intraoral sampling of the infant from birth through the first 6 years of infant life.[5,6] This developmental origins approach, which has clear parallels with the Developmental Origins of Health and Disease model, will enable characterization of prenatal maternal oral health, mother-to-infant seeding of the infant oral microbiome and temporal development of the infant oral microbiome, along with integration of maternal and infant exposures, and immune and metabolic markers of oral health and disease. Genome-wide association studies (GWAS) are also needed to examine host genetics on susceptibility to ECC and influence of the oral microbiome on modification of genetic susceptibility. Evaluation of maternal oral health and microbiome before and near birth and developmental timing of the infant oral microbiome relative to onset of ECC will identify the role of maternal seeding and potential windows of opportunity for intervention or preventive strategies for preclinical trials. In addition, there is a need to integrate microbiome-level analyses with social determinants of oral health; currently, these research agendas are largely distinct. Including sociodemographic and psychosocial factors alongside microbiome composition would offer novel, public health level data on the social context of ECC onset.

The proposed conceptual priorities mentioned above need to be matched with methodologic refinements. ECC studies require rigorous, standardized protocols for collection of maternal and infant oral saliva and plaque in sufficient quantity for analysis of the microbiome, serum and salivary immune markers, and maternal–infant genomic DNA for GWAS. Comparative metagenomic and metatranscriptomic analysis of the

oral salivary and plaque microbiome are needed to identify microbiome composition and diversity at the species and strain level, functions of each species, and ongoing metabolic activity microbiome community at the time of sample collection. Integration of this multidimensional data will provide a comprehensive picture of oral host–microbiome interactions, markers of oral mucosal immunity, and genomic variants that distinguish children who develop ECC from those who do not. Application of advanced computational approaches, including machine learning models, that assess all caries-related microbial, environmental, and demographic risk factors, will be used to build predictive models of ECC that identify critical points of intervention for preventative treatment.[7,8]

The longitudinal clinical cohort strategy and the multi-omics, multidimensional research approach proposed is urgently needed to address the public health crisis of ECC, especially within underserved and resource-poor communities. These studies will lead to the development of novel intervention strategies for oral care, illuminate understanding of the complex host–oral microbiome interactions, and identify unexplored therapeutic targets of ECC. There are additional exciting avenues of inquiry that will shape future work, including developments in discovery of spatial organization within the oral microbiome community and the metabolic organization that supports the exchange of diffusible signaling molecules and metabolites that contribute to caries formation.[9] Also on the horizon are studies on the oral virome, the community of viral (bacteriophage) predators and symbionts with the potential to reshape the ecology and function of the oral microbiome.[10]

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