Commentary

A New Perspective of an Old Villain: Revisiting Biomarkers of Caries Development

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With a multitude of factors driving its onset and progression, dental caries remains a major public health challenge in the globe. Despite a better understanding of the aetiopathogenesis of dental caries, health-econometrical models have shown that sugar-related dental diseases are associated with a global burden of 172 billion US dollars (Meier et al., 2017), and that the number of untreated permanent and deciduous caries incident cases can be as high as US$ 742 million in a given year (Kassebaum et al., 2017).

While the involvement of multiple bacterial species in the etiology of dental caries cannot be overlooked, *Streptococcus mutans* has been consistently associated with the initiation and development of caries (Gao et al., 2014). Clinical studies have shown that early colonization of the oral cavity with *S. mutans* is associated with a high risk for developing early childhood caries (Teanpaisan et al., 2007), albeit the mechanisms that allow early colonization and persistence of *S. mutans* in the oral cavity are poorly understood. The paradigm of *S. mutans* colonization in the oral cavity is its ability to bind to the tooth enamel using sucrose-dependent and, to a lesser extent, sucrose-independent mechanisms. In the presence of sucrose, secreted glucosyltransferases (Gtfs) serve the dual roles of priming the tooth enamel surface with glucans for adhesion by surface glucan binding proteins (Gbps), and developing an extracellular polysaccharide superstructure that anchors the biofilm and supports matrix-delineated pH microenvironments (Bowen and Koo, 2011). On the other hand, sucrose-independent mechanisms are mediated by a small number of surface adhesins, which recognize and bind to specific constituents of the salivary pellicle and components of the extracellular matrix (Nobbs et al., 2009).

In *EBioMedicine*, Esberg et al. (2017) argued that the sole detection of *S. mutans* in whole saliva is a poor predictor of individual susceptibility to caries and proposed, instead, that the presence of sucrose-independent colonization mechanisms might be better predictors of caries risk. Based on a 5-year follow up study with 12-year old Swedish children, the authors investigated whether the presence of surface adhesins associated with sucrose-independent mechanisms in clinical isolates of *S. mutans* could predict caries development. Among the adhesins screened in the study was SpaP, which presents three variants (A, B and C) based on the occurrence of clustered amino acid substitutions

that are linked to distinct virulence expression behaviors, and the collagen and laminin-binding protein Cnm that is found in approximately 15% of *S. mutans* strains (Avilés-Reyes et al., 2017). The authors found that SpaP variant B and Cnm subtypes are associated with increased caries incidence and therefore may be useful markers of individual susceptibility to caries. In fact, *S. mutans* strains harboring both SpaP biotype B or Cnm showed increased binding to salivary DMBT1 and collagen as well as increased acid tolerance. Notably, expression of Cnm has been shown to contribute to adhesion and invasion of oral cell lines, binding to dentinal surfaces, implantation of oral biofilms and, ultimately, to caries severity in a rat model (Miller et al., 2015). Thus, Cnm appears to be associated with *S. mutans* niche expansion and persistence as Cnm$^+$ strains have the capacity to colonize multiple niches in the oral cavity such as soft tissues that may serve as bacterial reservoirs for early colonization and reinfection.

The study by Esberg et al. shows that although sucrose-independent mechanisms may not be viewed as major determinants associated with caries development, they may serve as biomarkers for determining the overall individual susceptibility to disease breakthrough. Future studies will be required to conclusively determine the relative roles of the two mechanisms in caries development and dependence on the individual host. Specifically, additional cohort studies are warranted to establish the prevalence of carriage of these adhesion subtypes in different populations and age ranges worldwide, particularly in high income countries where socioeconomic confounding variables are less apparent.

It is also worth noting that the findings by Esberg et al. (2017) can have implications beyond the scope of oral cavity, as reports by our group and others have shown that Cnm$^+$ isolates are associated with systemic infections, such as infective endorcaditis (Freires et al., 2017), and, possibly, haemorrhagic stroke (Nakano et al., 2011) and cerebral microbleeds (Miyatani et al., 2015). To determine whether the presence of Cnm may also serve as an indicator of individual susceptibility to extra-oral infections is another topic that deserves further investigations.

In several healthcare systems, one of the variables included for caries risk assessment consists in determining the number of salivary *S. mutans* counts by microbiological methods. While a positive correlation between *S. mutans* counts and caries development has been long suggested (Thibodeau and O'Sullivan, 1999), the simple count of salivary *S. mutans* failed to explain the increased caries increment observed by Esberg et al. (2017) and other authors (Zhang et al., 2007). Other approaches have been used for caries risk assessment, including

computer-based algorithms. The findings by Esberg et al. reinforce the need for a shift in the assessment of caries risk towards an approach that considers the presence of specific virulence factors in the risk/prediction model. A better understanding of the infective mechanisms associated with caries can ultimately facilitate the development of new measures for caries assessment, treatment and prevention.

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Conflicts of Interest

The authors declare no conflicts of interest.

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