A Metaproteomic Approach to the Study of Pathogenesis of Periodontitis

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Current Opinions in Periodontology

The following interesting commentary provides the author's opinion regarding the etiology and pathogenesis of periodontal diseases. The Editor of the Journal of the International Academy of Periodontology will welcome formal responses from individuals who may have differing points of view. Letters to the Editor from IAP members providing their perspective are encouraged and may be submitted as described in the Instructions to Authors.

Our understanding of the etiology and pathogenesis of periodontitis has dramatically improved over the last three decades. The primary etiological role of dental biofilm has been well established; a number of periodontal pathogens have been identified and characterized; and wide arrays of virulence factors and pathogenic mechanisms have been determined. It has also become clear that tissue damage in periodontitis is mostly the result of destructive host immune responses rather than a direct bacterial assault, and many of these have been elucidated. To our disappointment, however, this seems to have little clinical significance so far as periodontitis continues to be treated as a non-specific infection, and to impose a high level of morbidity and an economic burden to societies (Loesche and Grossman, 2001). This makes the pathogenesis of periodontitis a hot research topic, not only to oral researchers but also researchers from other disciplines, especially as the evidence linking periodontitis to several systemic diseases continues to grow.

The last decade has witnessed increasing recognition of dental plaque as a bacterial community and typical microbial biofilm (Marsh, 2004). Furthermore, cultivation-independent techniques have recently revealed that certain as yet uncultivable species are probably also involved (Dewhirst *et al.*, 2000; Sakamoto *et al.*, 2002). It has also become evident that host responses potentially involved in periodontitis are much more complex than previously thought (Demmer *et al.*, 2008). These major developments have opened up new areas of research that could eventually fill in the gap in our knowledge, and have necessitated exploring novel approaches to employ in the study of the pathogenesis of periodontal diseases. Currently, metagenomics is such an approach that is being advocated by the National Institute of Dental and Craniofacial Research (NIDCR).

Metagenomics provides information on DNA sequences, regulatory elements and genes of a microbial community as a single entity. It is therefore a useful tool for identification of uncultivable species, construction of whole genomes, screening genes for potential novel virulence factors, exploring metabolic pathways, and determining the effect of community perturbations on health (NIDCR website). However, with metagenomics there is always a possibility of missing some sequences, especially for low abundance species, and encountering genes with unknown functions. In addition, metagenomics provides little information about the importance of the different genes and their functional expression within the microbial community (Wilmes and Bond, 2006), which is probably more relevant to the pathogenesis of periodontitis.

Metaproteomics is a new approach that has been recently introduced for the study of some ecosystems and provides quantitative information on the total protein profile of a microbial community (Wilmes and Bond, 2006). It, therefore, represents an invaluable tool for investigating protein expression in human microbial communities. Indeed, it has already been employed to study intestinal microbial communities in infants (Klaassens *et al.*, 2007). I hereby propose applying this approach to the study of pathogenesis of periodontitis. No doubt, it is an extremely difficult task to elucidate all functional proteins in a complex microbial community such as dental biofilm, and it would therefore be necessary to focus only on parts of the expressed proteome.

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Comparative studies would be the right choice in this respect. It is possible, for example, to compare protein expression by members of pathogenic microbial complexes, e.g., the red complex, in the planktonic, monospecies and multispecies biofilm states. A more realistic, but challenging, approach would be to perform comparative proteomic profiling of dental biofilm in health and disease. That would provide comprehensive information on functional expression of known as well as novel pathogenic determinants of cultivable and as yet uncultivable periodontal pathogens as members of a microbial community rather than individual species.

It must be re-emphasized at this stage that although bacteria are no doubt the primary cause of periodontitis, it is also well established that host's reaction to bacterial challenge plays an equally, if not more, important role in the pathogenesis of periodontitis (Page and Kornman, 1997; Preshaw *et al.*, 2004). Therefore, meaningful progress in the understanding of periodontal pathogenesis can probably not be achieved unless research efforts are directed at elucidation of both microbial and host components. Fortunately, the metaproteomic approach proposed above is also applicable in this respect.

Metaproteome of a subgingival sample will not only include microbial proteins but also host proteins that represent reaction of the gingival tissue as a whole to dental biofilm. In addition, it is also possible to obtain a "pure" proteome of the gingival tissue itself in parallel. By comparing profiles in health and disease, it will probably be possible to identify individual host proteins, pathways, and even networks that are involved in the pathogenesis of periodontitis. At that stage, it will also be possible to integrate risk modifiers, such as smoking and genotype, to assess how they influence the bacterial and host response components. As such, metaproteomics represent a valuable tool to study inputs (microbial factors and risk modifiers) and outputs (host responses) in a functional module within a biologic systems model as proposed by Kornman (2008).

Proteomics is very challenging compared to other technologies such as genomics and transcriptomics, and many difficulties should be expected along the way. However, the information obtained ultimately should improve our understanding of the pathogenesis of periodontitis, hopefully in a way that is clinically tangible.

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