Editorial
Host-pathogen interactions in bacteria

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Host–pathogen dynamics: it's complicated!

This set of three review articles on host–pathogen interactions begins with a discussion of emerging concepts on homeostasis of a specific microbiome, that of the gut, and how disruption of the microbial *status quo* can result in several syndromes (1). The following papers highlight research on host–pathogen interactions with two oral bacteria: the dynamics between *Treponema denticola* virulence factors and host proteins (2); and *Porphyromonas gingivalis* infection of a novel animal model that will ultimately shed light on pathogenesis and innate immune responses to the organism (3).

Research on the pathogenic infection of animal hosts began with whole animal studies (see (4) for a review of the work by Pasteur and Koch, and Riedel (5) for the work of Jenner on small pox vaccination), an approach that yielded many milestones in our understanding of infection and tremendous medical benefits for generations of humans. With the advent of bacterial genetics, and later molecular biology, the reductionist approach has held sway for the past 40 years with obvious triumphs such as the development of the field of cellular microbiology and whole genome sequencing of pathogenic (and non-pathogenic) microorganisms. More recently, the ability to isolate and amplify nucleic acids from small biological/clinical samples together with technological advances in high throughput deep sequencing enables us to look beyond which organisms are present in a specific ecological niche (i.e. the microbiome of the oral cavity, skin, gut, etc.) and ask 'what are they doing?' This is the key to understanding how a specific microbiome communicates with the host in both health and disease.

Because we and our microbiome have evolved together, we rationalize that the equilibrium between us results in health, and disruption of the homeostasis leads to disease. The constituent microbes in a microbiome do not act alone and alliances have evolved with each other, and with host proteins and cells. Recently, Brown & Whitely examined the metabolic relationship between the oral bacteria *Aggregatibacter actinomycetemcomitans* (*Aa*) and streptococci. Because they inhabit the same environmental niche, the gingival pocket, it was reasoned that *Aa* must derive benefits from this coexistence. Streptococci efficiently produce lactic acid from 6-carbon sugars and dietary sucrose, and it was established that *Aa* preferentially utilizes lactic acid as a carbon source over glucose, fructose, mannose, even at the cost of a lowered growth rate (6). Furthermore, *Aa* consumed the lactate produced from sucrose catabolized by *S. gordonii*. Microarray-based comparative transcription profiling was used to measure the *Aa* response to hydrogen peroxide, another metabolite produced by streptococci (7). Surprisingly, only two genes were significantly induced after exposure to sublethal concentrations of peroxide: *katA* whose product detoxifies peroxide to water and oxygen, and *apiA*, encoding a multifunctional outer membrane protein that also mediates binding to serum protein factor H, a complement regulatory protein, thus blocking and protecting *Aa* from being killed by the alternate complement pathway. Expression of both *katA* and *apiA* is activated by the OxyR transcriptional regulator. Finally, to test the biological relevance of these interactions, it was demonstrated that coculture with *S. gordonii* enhances virulence of *Aa* in a murine abscess model (8). Thus, many intermicrobe alliances that are based on nutritional dependencies may also affect host functions.

The literature is replete with examples of how microorganisms use host proteins for adherence to and, in certain cases, to promote their internalization by host cells. In turn, adherence to host cell surface proteins may trigger host innate immune responses such as production of antimicrobial peptides. This is not the only form of 'dialogue' between bacteria and host. It has long been established that bacteria communicate with each other via autoinducers (AI-1, AI-2, AI-3, and AIP) leading to the regulation of specific genes and pathways (9–12). A new participant was introduced into this conversation with the discovery that host cells communicate with commensal bacteria via the interaction of epinephrine/norepinephrine (host) and AI-3. This interkingdom dialog was first described by Sperandio et al. (13). Bacteria in the gut, including commensal *Escherichia coli* and pathogenic EHEC and EPEC strains, produce AI-3 (14); and mammalian hormones epinephrine and norepinephrine are also present in the intestine (15). EHEC and other pathogens sense the hormones through the QseBC two-component system, of which the QseC sensor histidine kinase is a receptor for and activated by epinephrine/norepinephrine (16). In the ensuing regulation cascade (17), QseC activates its cognate response regulator QseB and also KdpE and QseF to up regulate expression of virulence genes such as those involved in the production of flagella and motility (QseB); potassium uptake, osmotic protection, and the formation of attaching and effacing lesions (KdpE); and the SOS response (QseF) (18).

The themes of these two examples apply to the major oral infections, caries, and periodontal disease. The ecology and physiology that regulate the growth and persistence of these host-associated microbial

communities necessitate metabolic cooperativity. Microaerobic and anaerobic growth conditions favor cross-feeding and syntrophy (mutualism) because the disposal of metabolism-derived electrons is problematic in the absence of oxygen as an acceptor. What are the complex cross-feeding and syntrophic strategies that have evolved between anaerobes, microaerobes, and aerobes in the oral cavity? In the case of periodontitis, what triggers the disruption of the healthy homeostasis? Does the subgingival microbiota communicate with gingival epithelium via as yet unknown extracellular signaling systems?

Increased knowledge of the systems we study has shown them to be more complicated than we ever imagined but provokes a reluctant appreciation for the ingenuity of the discourse.

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Margaret J. Duncan, Guest Editor
'Host-pathogen interactions in bacteria'
The Forsyth Institute
Cambridge, USA
Email: mduncan@forsyth.org