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Bacterial species as partners and pathogens.
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BACTERIAL SPECIES AS PARTNERS AND PATHOGENS: SUMMARY OF THE SEMINAR AND THE DISCUSSIONS

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THE NOTION OF A BACTERIAL SPECIES

The 25th anniversary of the Old Herborn University Seminars (OHUS) provided an opportunity to delve into the concepts of bacterial species as friend and foe, as partners and pathogens. Many concepts have emerged and re-emerged during the past decade and have challenged our traditional notions of bacterial species. The definition of a bacterial species remains somewhat arbitrary despite advances in 16S rRNA gene sequencing, phylogenetic analysis, and bacterial genome sequencing. The cut-off value of 3% is still used frequently to distinguish bacterial species based on 16S rRNA gene sequencing data, but even this dividing line has been challenged for different genera and species. In this 2011 seminar, Pål Johnsen from the University of Tromsø discussed the nature and extent of sex and DNA transformation in bacterial species such as *Acinetobacter baylyi*, *Bacillus subtilis*, and *Escherichia coli*. Several bacterial species have developed sophisticated machinery for DNA uptake, and this facilitation of DNA transfer among microorganisms confounds phylogenetic analysis by permitting facile lateral exchange of genetic information (*Johnsen* et al., 2009). In addition to the contributions of sex to bacterial evolution and fitness, features that are potentially beneficial or deleterious to the host may be intermingled within one or several bacterial species. Individual species such as *E. coli, Clostridium difficile* and *Helicobacter pylori* may include a variety of strains that may be more or less virulent and perhaps beneficial to the host. Features such as quorum sensing may enhance intermicrobial communication in gut communities, and evolutionary pressures may be more relevant in the context of a single cell versus a community of microbes. In the single cell context, it may be difficult to reconcile the perceived importance of quorum sensing with the process of bacterial species evolution. The bacterial pangenome concept further challenges our ideas about bacterial species as partners and pathogens; a pangenome of any individual bacterial species may include pathogenicity and probiotic features present in different strains.

BACTERIAL CELLS AND COMMUNITIES

In the modern era of the microbiome and metagenomics, any consideration of bacterial species as pathogens or partners must include the concepts of microbial ecology. Leaving aside discussions regarding evolution, the idea of friendly versus pathogenic communities was presented by V. Young in

the context of Koch's postulates of infectious diseases. Mammalian intestinal bacterial communities consist of many diverse bacterial species, and these communities may protect the host against enteric infection. Freter's publication from 1955 (*Freter*, 1955) highlighted the adverse consequences and manifestations of a bacterial species as pathogen in the aftermath of communal destruction by antibiotics. Toxigenic *C. difficile* may ascend from status of colonizer to pathogen following the administration of specific antibiotics and corresponding effects on microbiome disruption. Recent evidence suggests that intestinal communities with relatively limited bacterial diversity may be predisposed to infections and chronic disease. The concept of disease-prone and pathogenic communities is emerging to accommodate ideas about pathobionts, symbionts, and the interplay between combinations of different bacterial species and the gut mucosa. Bacterial species may be partners if present in symbiont-dominated communities, and strains of the same species may be pathogens in disease-prone, pathobiont-dominated communities. The contextual information within bacterial communities may dictate to some extent whether bacterial species benefit the host or cause infection.

MICROBES AS PARTNERS

Beneficial microbes and probiotics are terms used to refer to friendly microbes and their role as partners in life. OHUS 25 spotlighted the potential roles of bacteria such as Segmented Filamentous Bacterium (SFB*), Lactobacillus reuteri* and *C. difficile* as friendly partners of mammalian hosts. Bacterial species may stimulate intestinal development and mucosal immunity, and provide signals that promote intestinal physiology and motility. Examples of these beneficial effects include the role of SFB in stimulating the differentiation of T lymphocytes and IgA-producing B lymphocytes (*Gaboriau-Routhiau* et al., 2009). *C. difficile* may regulate mitotic activity of mucosal cells, and microbe-derived biogenic amines may promote intestinal motility. An interesting connection is the description of the probiotic species *L. reuteri* and its role in promoting crypt cell proliferation and intestinal epithelial cell migration (*Preidis* et al., 2012). These examples reinforce the notion of bacterial species as partners with specific beneficial functions, depending on the strain of a bacterial species.

Our bacterial partners may be engaged in conversations with mammalian cells and organs. Interkingdom signalling provides opportunities to understand mutualism, commensalism and symbiosis in the host, and the expanding field of microbial endocrinology presents opportunities for understanding microbe-mammal crosstalk (*Lyte*, 2011). Growth of bacteria in the presence of neurochemicals such as catecholamines and dopamine may enhance the relative abilities of bacteria to colonize the GI tract and be our partners or pathogens causing enteric infections. Iron and iron siderophores may be an important consideration as catecholamines and other neurochemicals may scavenge iron from transferrin or ferritin. Intestinal bacteria may produce signals such as gamma-aminobutyric acid (GABA) and histamine that may have beneficial, although presently unknown, functions in the gastrointestinal tract (*Thomas* et al., 2012). GABA is a compelling tar-

get for studies of signalling in the enteric nervous system, and considerations of GABergic cells may include host-associated microbes. Conversely, intestinal bacteria such as *E. coli* may contain receptors for catecholamines and dopamine, and bacterial partner species may receive and alter their cellular behaviour based on the presence of host-derived signals.

MICROBES AS PATHOGENS

Bacterial species may cause infections by different mechanisms including invasion and toxin production. Bacterial species that may be friendly in one context may be pathogenic in a different context. An excellent example of the microbes discussed in OHUS 25 is *C. difficile*. This microbe may be functionally neutral and perhaps beneficial on the basis of regulation of cell proliferation in the intestinal mucosa. However, when bacterial communities are disrupted and depleted functionally by antibiotics, toxigenic strains of *C. difficile* may proliferate and become pathogens causing antibiotic-associated diarrhoea and colitis (*Chang* et al., 2008). Bacterial species as pathogens depend on intrinsic capabilities of disease-causing bacteria, in combination with the context of the microbiome. The bacterial species *C. difficile* serves as an excellent example of bacterial colonizer and infectious agent. Early in the first year of life, *C. difficile* is frequently present in infants and not associated with any disease phenotype. Is this species beneficial for early development and perhaps immune maturation? Toxigenic strains have the ability to cause disease in contrast to non-toxigenic strains of the same species, further emphasizing the importance of specific virulence genes and their regulation in bacterial genomes. Finally, the typical pattern of *C. difficile*-associated disease in the context of antibiotic treatment highlights the importance of the bacterial community in the outcome of bacterial species as partner or pathogen (*Chang* et al., 2008).

The pathogen *Helicobacter pylori* infects the stomach, and it tends to predominate in simpler gastric communities as discussed by Lars Engstrand in OHUS 25. Effectively, *H. pylori* diminishes the diversity of microbial communities in the stomach, resulting in a restricted community dominated by *H. pylori* and permissive for chronic disease caused by *H. pylori*. A pathogenic species such as *H. pylori* may be associated with different disease states such as peptic ulcer disease, atrophic gastritis and gastric cancer (*Giannakis* et al., 2008). These different disease states may depend on the combination of *H. pylori* strains with bacterial communities that differ in composition. For example, gastric bacterial communities with a greater abundance of *Prevotella* and *Streptococcus* species are present in the chronic condition of atrophic gastritis, and this disease state predisposes the human host to cancer. Our idea of the bacterial species as partner or pathogen is modified again by *H. pylori*, a species that is intimately associated with human history (*Linz* et al., 2007). This species may be an important example of "disappearing microbiota" proposed by Martin Blaser; these disappearing species (secondary to targeted antimicrobial therapy) may be associated with the onset of diseases due to their absence (*Blaser* and *Falkow*, 2009). For example, the elimination of *H. pylori* by antimicrobial agents may result in diminished predis-

position to gastric disease and increased predisposition to esophagitis. Bacterial species may be pathogenic at one site, and partners at a different anatomic site in the human gastrointestinal tract. Differences in composition and function of oesophageal and gastric microbiomes may contribute to different outcomes – bacterial species as partner or pathogen.

SUMMARY THOUGHTS

Our ideas regarding bacterial species are evolving rapidly in the era of the mammalian microbiome, metagenomics, and pangenomes. The individual bacterial species presented and discussed at OHUS 25 provide excellent examples of the challenges when we consider bacteria as our friend or foe. As we say in English, "it all depends." As our knowledge of the microbiome and microbial genomes expand, we hope to appreciate more fully the diversity of bacterial strains within a species and the contributions of bacterial neighbours in the microbiome. These dynamic interactions among microbes may determine the final outcome of bacterial species as partners or pathogens in an individual mammalian host.

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