

BURLEIGH DODDS SERIES IN AGRICULTURAL SCIENCE

Understanding gut microbiomes as targets for improving pig gut health

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Understanding gut
microbiomes as targets for
improving pig gut health

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Introduction

The pig production sector faces many challenges, including the need to improve feed efficiency to reduce emissions from manure, finding alternative methods to prevent the onset of diseases affecting swine, as well as ensuring that the welfare of pigs is consistent with consumer and regulatory agencies' expectations. This volume offers a comprehensive coverage on the wealth of research on the porcine gastrointestinal tract, its key role in pig health and nutrition, as well as its implications for improving feed efficiency and growth.

The book is split into three parts. Part 1 focuses on the gut microbiome and pig gut health, focusing on aspects such as microbial ecosystems as targets for improving pig gut health as well as the metabolic and microbiological services that are delivered by the pig gut microbiome. Chapters in Part 2 address analysing the pig gut microbiome, discussing how microbial communities are characterised in the pig gastrointestinal tract, understanding the relationship between the microbiome and the pig gastrointestinal tract as well as the development of the gut microbiome. Part 3 of the book highlights the techniques to optimise gut function by manipulating gut microbiomes. Chapters review the use of prebiotics, dietary fibre and exogenous enzymes to optimise gut function in pigs. Chapters also address improving gut function to prevent dysbiosis, post-weaning diarrhoea and pathogen colonisation. A review of microbial protein metabolism in the monogastric gut is also provided.

Part 1 The gut microbiome and pig gut health

Part 1 of the book opens with a chapter that focuses on microbial ecosystems as targets for improving pig gut health. Chapter 1 begins by examining the evolutionary drivers for intestinal colonisation by microorganisms, the primary drivers for initial colonisation in animal intestines and the evolutionary pressure to transmit between hosts. The chapter then goes on to discuss the increasing complexity of using gut bacteria as microbial ecosystems and the role of the host in modulating and responding to microbial ecosystems. It focuses on aspects such as the spatial compartments in the intestine as well as the age of the host. A section on the various methods for assessing microbial ecosystems is also provided, focusing specifically on the empirical and rational approaches currently available to assess harm and benefit. These discussions are supported by current studies, which are then followed by a review of how host-microbial ecosystems can be manipulated. The chapter concludes by emphasising the importance of developing knowledge on microbial ecosystems.

The next chapter discusses microbial services of intestinal microbiota, specifically focusing on the metabolism of carbohydrates and bile salts. Chapter 2 begins by discussing carbohydrate metabolism by swine intestinal microbiota, concentrating on gastric microbiota and primary digestion in the stomach, rapid uptake of carbohydrates in the small intestine and microbial degradation of dietary carbohydrates in the hindgut. The chapter then goes on to examine the metabolism of bile acids, focusing on biosynthesis and the enterohepatic circulation of bile acids, bacterial transformation, lipid digestion and how bile acids act as signalling molecules. The chapter also discusses bacterial bile salt hydrolase in animal production, bile acids and intestinal health and the factors that can impact the bile acid profile. The chapter concludes by highlighting how metabolic services are key contributors to more efficient use of feed and better animal health.

The final chapter of Part 1 examines the microbiological services delivered by the pig gut microbiome. The gut microbiome plays a fundamental role in regulating pig health and growth. Understanding the functions performed by the microbiome is vital when considering it as a target to improve pig health and growth, a pursuit driven by the increasing regulation of traditional means of disease control and growth promotion. Chapter 3 explores the structure, diversity and functions of the pig gut microbiome, focusing on the role of the resident bacterial communities. It examines their relationships, interactions, and contributions to the host, ranging from the production of antimicrobial substances and prevention of pathogen colonisation to improvement of nutrient digestibility and the production of volatile fatty acids and vitamins. The chapter also reviews bacterial communication and the antibiotic resistome of the pig gut, outlining how they may be targeted/manipulated to reduce antibiotic resistance and promote improved gut health.

Part 2 Analysing the pig gut microbiome

Part 2 begins with Chapter 4 which focuses on the ecology and biotherapeutics of the gut microbiota in pigs. The chapter starts by reviewing the main methods used to analyse gut microbiomes, such as amplicon sequencing, omics techniques and cultivation. It then goes on to examine microbial diversity in the pig intestine, looking at ecosystem members and global diversity and functions. The chapter also highlights the main influencing factors of the gut microbiome and its interaction with the host, focusing on both the intrinsic and extrinsic factors. The chapter then summarises data on the structural and functional diversity of the microbial ecosystem. It also provides a case study to highlight the potential of cultivation applications based on the use of minimal bacterial consortia.

The subject of Chapter 5 is understanding the relationship between the microbiome and the structure and function of the pig gastrointestinal tract. The gut epithelium acts as a barrier to the gut environment. The integrity of the epithelial structure and function is thus critical for microbiome-host interaction. The gut microbiome can regulate the utilization and synthesis of mucin, the expressions of the intercellular junction complex, and the functioning of specific epithelial cells, such as enterochromaffin cells and stem cells in pigs. This chapter discusses how the pig gut microbiome modulates epithelial structure and function, highlighting findings that reflect the relationship between the gut microbiome, intestinal structure and function.

The next chapter focuses on understanding the development of the gut microbiome in pigs. Chapter 6 begins by discussing when the colonisation of the intestinal tract starts and whether piglets are born sterile. The chapter then goes on to discuss how the gut microbiome is a dynamic ecosystem over life, focusing on the early steps of microbiome establishment of new-born piglets, the evolution of the gut microbiome and what can be learnt from gene catalogues. The chapter also reviews the links between the evolution of the gastrointestinal tract, microbiome patterns and functionalities. It then discusses preparing for the weaning transition before reviewing individual variability of gut microbiome patterns.

Part 3 Techniques to optimise gut function by manipulating gut microbiomes

The first chapter of Part 3 addresses the use of prebiotics to optimise gut function in pigs. Chapter 7 summarises the current knowledge on effects of prebiotic oligosaccharides on porcine gut function and health. The chapter starts by reviewing the maintenance of gut health and functionality, then goes on to discuss the porcine gut microbiome. Definitions of prebiotics are also provided, which are then followed by a review of prebiotic di-oligosaccharides in pig nutrition. The modes of actions of those substances are discussed as well as aspects that need more investigation for future applications in diets for suckling piglets.

Chapter 8 examines the use of dietary fibre to optimise microbial gut function in pigs, with particular consideration of dietary cereal grains and legumes. The chapter examines interactions of dietary fibre components of pig diets with gastrointestinal tract microbiota. Carbohydrate composition of these feedstuffs are described, and their relationship to metabolic activity of the porcine intestinal microbiota and interactions with the host. Fermentable carbohydrates which act as substrates for microbial metabolism are described, followed by an assessment of cereals and legumes as potential modulators of

intestinal microbiota. Past work focused on purified extracts, but attention is now focussing on whole grains or their fractions such as brans, in terms of effects on microbial populations. Such studies are showing the positive consequences of mixtures of dietary fibre in the form of complex plant cellular structures, rather than single refined ingredients, to achieve beneficial health outcomes. Further work is also needed to define appropriate quantities and types of dietary fibre to achieve desired effects whilst minimising negative outcomes.

The subject of Chapter 9 is the use of exogenous enzymes to optimise gut function in pigs. Exogenous enzymes are used in pig diets to improve the availability and digestibility of some non-accessible nutrients. As result of this enhanced digestion, short fragments of these molecules may become available in the distal foregut and the hindgut and modulate microbiota composition, gut barrier integrity, and overall animal health. The chapter reviews the effects of different exogenous enzymes, such as carbohydrases, phytases, proteases and lipases, on nutrient digestibility, gut microbial ecology and barrier function and immunity of pigs at different. Exogenous enzymes are usually included into feeds as blends so they can complement each other's activities and further improve the accessibility to non-digestible structures. Exogenous enzymes used in feed manufacturing for more than 30 years, initially to improve the digestive function of non-digestible nutrients, more recently other indirect actions on the regulation of gut microbiota and gut health have gained interest.

Chapter 10 reviews improving gut function in pigs to prevent dysbiosis and post-weaning diarrhoea. The chapter begins by discussing eubiosis versus dysbiosis, focusing on how both of these conditions can affect the gut microbiota. The chapter then goes on to discuss how dysbiosis can occur during the post-weaning period, which is then followed by a review of how analysing microbiota composition can be used to predict post-weaning diarrhoea. Sections on the nutritional and dietary strategies to prevent dysbiosis in relation to post-weaning diarrhoea are also provided. The chapter also examines the host factors influencing gut function, before concluding with a section that emphasises the importance of future studies focusing on the key components of dysbiosis and eubiosis.

The next chapter considers improving gut function in pigs to prevent pathogen colonisation. Chapter 11 first highlights the main gut-related pathogens in pigs, such as *Escherichia coli*, *Salmonella*, *Brachyspira* and *Lawsonia intracellularis*. This discussion is followed by an analysis of pig genetics and how genetic variation can influence immune responses. The chapter then goes on to examine the management strategies affecting gut functionality and pathogen colonisation, focusing specifically on colostrum and milk intake, pre- and post-weaning feed intake and heat stress. Sections on the dietary strategies to improve gut functionality and prevent pathogen colonisation, such as feed size, protein and dietary fibre, dietary nitrate, organic and amino acids are also

provided. These sections are followed by a review of the dietary interventions for pathogen-specific defence. The chapter concludes by highlighting how understanding the physiology of resilience to disease in pigs is key to more sustainable production.

The final chapter of the book provides a review of microbial protein metabolism in the monogastric gastrointestinal tract. Chapter 12 first explores microbial protein metabolism in the hindgut of monogastrics. It then presents major end-products of microbial metabolism of amino acids, such as ammonia/ammonium, amines, hydrogen sulphide, short-chain fatty acids and branched-chain fatty acids. The production of phenolic and indolic compounds are also discussed. The use of bacterial protein metabolism as a target for improving host health is also reviewed, which is then followed by an assessment of the various factors that can affect protein metabolism in the hindgut. The chapter concludes by providing an overview of how the amount and composition of protein available in the microbiota of the host can change depending on the host's diet.

Chapter 1

Microbial ecosystems as targets for improving pig gut health

Mick Bailey, Laura Peachey, Sarah Lambton and Chris Stokes, University of Bristol, UK

- 1 Introduction
- 2 Increasing complexity: gut bacteria as ecosystems
- 3 The role of the host in modulating and responding to microbial ecosystems
- 4 Assessing microbial ecosystems
- 5 What will we need for the future of pig production?
- 6 Conclusions
- 7 Where to look for further information
- 8 References

1 Introduction

The last two decades have seen an explosion in microbiome research in humans, model organisms and domesticated species including livestock and companion animals. The term itself only came into use in primary publications after 2000, and the number of publications is still rising almost exponentially each year (Fig. 1). The field has seen, and continues to see, many revolutions in the way we think about microbiomes and their interactions with the host, and more and more aspects of the lives of humans and animals are now believed to be influenced, at least in part, by the type and function of the resident microbiome. This has created a clear potential for the development and deployment of nutritional and management interventions – probiotics, prebiotics, micronutrients and outdoor rearing – to modify aspects of metabolism, immunity, health and welfare.

A recent expert panel assessed our current concepts of what a microbiome is and what it does (Berg et al., 2020). However, the emphasis of the panel was still around definitions and, at only two decades old, the field is clearly still immature. What we do know is far exceeded by what we don't, and we are increasingly aware that pushing back the frontiers of our understanding is going to require technologies and resources which are currently only partly

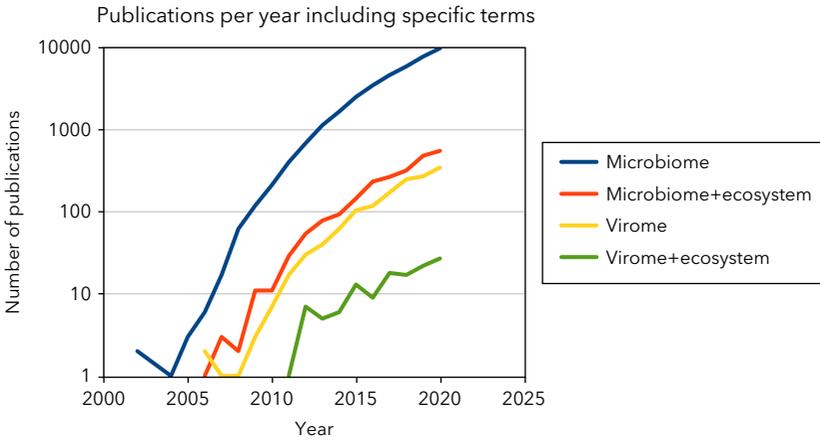


Figure 1 Number of publications per year recovered from Clarivate Web of Science, May 2021 (© Copyright Clarivate 2021) using the keywords identified in the legend to search TOPIC. Indexes searched were SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH and ESCI. Timespan searched was 'All years'.

implemented, if at all. There is, then, a mismatch between the perceived potential of microbiome research to provide usable products to address issues of human and animal health, welfare and food security, and the amount of effort still required to rigorously understand the mechanisms by which any interventions might work. It is arguable that this has created a situation where interventions are being justified on the basis of incomplete understanding of mechanisms, with the potential for them either to be ineffective under a range of husbandry conditions, or to be effective but for a different reason, creating problems for further development.

The purpose of this collection of expert opinions is, firstly, to provide a snapshot of the current field as it applies to pig production, from the fundamental understanding of the molecular interactions between an animal and its microbiome, to the effectiveness and mechanisms of interventions intended to improve health, welfare and productivity. Secondly, though, it is intended to identify future directions for research, by identifying areas where our current understanding clearly has gaps. A consequence of this second aim is that it will propose novel ways of thinking about the field and make predictions about future changes in our thinking.

In this introduction, we will address the evolutionary and selective pressures which have shaped, and continue to shape, the relationships between intestinal microorganisms and the host, and what benefits each may accrue from those relationships. We will consider the historical development of our understanding of microbial ecosystems and the extent to which we can extrapolate from classical ecology to host-microbial ecosystems. We will discuss approaches

to dissecting the roles of microbiomes in delivering benefits to pig health, welfare and productivity. Finally, we will briefly suggest some future directions for research.

1.1 Evolutionary drivers for intestinal colonisation by microorganisms

The majority of free-living multicellular animals appear to be stably colonised by some form of commensal microbiome, suggesting that this characteristic is a fundamental component of complex life (but see Hammer et al., 2019). Similarly, many newly described species of bacteria are only found in association with host metazoa, suggesting that these relationships are evolutionarily ancient, at least as a general principle. Considerable work in the model species *Drosophila melanogaster* and *Caenorhabditis elegans*, together with a huge amount of effort in human, mouse and livestock microbiome research, is beginning to clarify the relationships between hosts and their microbiomes. This will provide us with considerable literature on which to base our assumptions and hypotheses. However, the first potential pitfall is probably the risk of conflating the evolution of hosts with the evolution of microbiomes. This is currently an area of significant debate, and it has been proposed that the 'holobiont', a complex of the genetic material of the host and its microbiome, should be considered as an evolutionary unit (Huitzil et al., 2018). Hosts evolve as a consequence of the effects of selection for fitness on heritable characteristics: the germline genes transmitted to offspring are, in the main, those of the parent. In contrast, there is no guarantee that selection for fitness in the microbiome will be transferred effectively to the host's offspring. Fitness in the microbiome may result in relative prolongation of lifespan of the host, or in numbers of the host's offspring, but there is no guarantee that those offspring will acquire the same microbiome as the parent, except where microbiomes are partly genetically-determined, or where the parent or extended family group continue to transfer organisms throughout the early lives of their offspring. In many of the species we deal with there do appear to be mechanisms for transmitting parental microbiomes through continued exposure to faeces, skin, milk, predigested food, etc. However, while those mechanisms may facilitate transfer from parents, they are also capable of transferring microbiomes from other individuals and even other species, and it is clear that even xenomicrobiomes can establish in a range of species including pigs (Seedorf et al., 2014; Wang and Donovan, 2015). In addition, robust evidence in many species including pigs clearly demonstrates that the initial microbiomes established in offspring are fundamentally different from those in adults, indicating incomplete transfer of parental microbiome (Mach et al., 2015). Interestingly, the process of weaning of piglets, or removal from the influence of the sow, results in one of the biggest changes in the

intestinal microbiome, raising the question of where the microorganisms' characteristic of the post-weaning period are acquired from.

The implications for us are that studies in model species (*Drosophila*, *C. elegans*) and even mice and humans are probably of value to identify common, general mechanisms rather than detailed mechanistic information in pigs. Apparently similar components of a microbiome in humans and pigs are likely to have been independently acquired in the two species, rather than sequentially transmitted from the most recent common ancestor of pigs and humans. The presence of ancestral characteristics like eyes, which have a common evolutionary origin from a functional unit, allow us to make fairly sound assumptions about their function in pigs and humans. In contrast, because microorganisms undergo very frequent horizontal transfers (and are probably continuing to do so), pigs are likely to be dealing with organisms which are recent acquisitions from other species, including humans, where they may have evolved for millions of years. As an example, comparisons of the taxonomic complexity of 900 vertebrate species have demonstrated the presence of a surprisingly birdlike microbiome in bats (Song et al., 2020), almost certainly either convergent or horizontally transferred. Despite this, the homogenisation of microbiomes by horizontal transfer between species may actually make inferring across species possible but we need to be careful about how we do it – how confident can we be that a specific microorganism or group transferred to a new host species will function the same way, and that the host response will be the same? It seems likely that 'convergent' evolution/establishment of the function of microbiomes may be taking place, such that similar outcomes may be delivered by different microbiomes in disparate environments or that a similar microbiome may deliver a different outcome in those different environments or in different host genetics.

1.2 The primary drivers for initial colonisation of niches in animal intestines

In any biological system, organisms occupy niches because those niches provide resources which facilitate their survival and reproduction. This can be as simple as warmth, allowing the efficient progression of biochemical pathways without excessive expenditure of energy, or necessary substrates which avoid the need to encode and express the biochemical pathways necessary to make them. One of the earliest observations from studies of human and animal microbiomes has been the number of apparently unculturable bacteria. However, the definition of these organisms as 'unculturable' is being challenged, as targeted phenotypic culturing linked to large-scale whole-genome sequencing, phylogenetic analysis and computational modelling has begun to allow the culture of many of these organisms (Browne et al., 2016). There still remains the possibility

that some 'unculturable' organisms are simply engaging in a conservative strategy for growth and transmission through dormancy (Bodor et al., 2020). However, the demonstration of unexpected dependencies of these 'hard-to-culture' organisms on specific substrates suggests an adaptation to community living, and has a number of important implications for our understanding of microbiomes as ecosystems: their presence in such microbiomes indicates that other organisms are providing sufficient excess of substrates, either by synthesis (bacteria) or ingestion (the host) that they do not need the pathways themselves.

The critical inference for our understanding of the host-microbial interface is that many of the components of the intestinal microbiome are auxotrophs: that is, they are fully dependent on substrates provided by other members of the microbiome, with the presumption that most of them will, in turn, provide substrates necessary for other auxotrophic microorganisms. That is, that they constitute an ecosystem in which, as a minimum, different members contribute and use different biochemical substrates. This phenomenon of 'streamlining', where microbial genomes lose specific metabolic and regulatory functions and reduce genomic redundancy, is well documented in environmental microbial ecosystems and seems to be linked to maintaining large, genomically diverse populations (Giovannoni et al., 2014; Mondav et al., 2020). One interpretation of the evolution of streamlining has been that large, complex populations of microorganisms can afford to become genomically heterogeneous and therefore interdependent, but only providing they are transmitted as an intact unit. That is, that the population comprising multiple, complementary, streamlined organisms can be considered as a single, metabolically competent prototroph. While this may be possible, and even likely at a limited level, we have already discussed the observation that microbiomes which establish in early life in humans and in pigs are significantly different from those in adults, particularly in gestating and lactating females (Mach et al., 2015). Again, this suggests that there is a significant bottleneck between the mother and offspring which makes it unlikely that vertical transfer of intestinal microbiomes is capable of maintaining a sufficient population size to establish all the necessary components of the genomically heterogeneous, metabolically competent prototroph.

1.3 Evolutionary pressure to transmit between hosts

Expansion of a population of a single species of microorganism within a single host with a limited lifespan is essentially irrelevant unless that microorganism can ensure its transmission to the next generation. Selection pressure on microbiomes is essentially focused on successful transmission between individual hosts, and the colonisation of a sufficiently large population of hosts

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