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Title: **Secrets from the microbiome: molecular biology meets microbiology meets histopathology….meets *clinical biochemistry***

Short title: **Secrets from the microbiome**

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Secrets from the microbiome: molecular biology meets microbiology meets histopathology….meets *clinical biochemistry*

Abstract

The microbiome is the collective term used to describe the bacteria, viruses, fungi and archaea that reside on and in the human body. The majority of these organisms are found within the large bowel. Mounting evidence suggests that changes in the microbiome may be associated with the development of colorectal cancer, a disease which affects 1.3 million people a year worldwide. Using colorectal cancer as an example, this article presents the inter-specialty collaborative approach to microbiome research and discusses the key role that clinical biochemistry is likely to play.

Molecular biology meets microbiology….

The Microbiome

The microbiome is the collective term used to describe the bacteria, viruses, fungi and archaea that reside on the skin and within the aerodigestive, urogenital and gastrointestinal tracts. It comprises over 100 trillion organisms (outnumbering human cells within the body by a factor of ten), the majority of these organisms residing within the large bowel.

Until recently, the microbiome has been an overlooked entity, largely because 60%-80% of bacterial species could not be cultured. Advances in molecular biology, such as Next Generation Sequencing, have changed that. Bacteria are now typed by sequencing 16SrRNA, a highly conserved molecule with variable regions which permit species differentiation.[1] This allows study of the relative abundance and diversity of bacterial species. Metabolomics (the detection of bacterial metabolites within faeces, urine or blood) allows the function of the microbiome to be studied.

The International Human Microbiome Consortium has been established in order to advance this new field of research as quickly as possible. The microbiome develops from birth, dependent upon the

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method of delivery and antenatal feeding, and increases in diversity until an individual's signature microbiome is reached at approximately the age of three. The composition of the microbiome differs dependent upon location within the gastrointestinal tract (both anatomical position and luminal versus mucosa-adherent microbiome) and is influenced by external factors including diet, antibiotics, pregnancy and ageing.

The microbiome is vital to health; it is believed to influence the development of the gastrointestinal tract and the immune system, to metabolise food, drugs, mucus, bile salts and carcinogens, to synthesise vitamins, to influence energy release and to protect against pathogens. Studies suggest that disturbances of the microbiome (dysbiosis) may be implicated in diseases including gastrointestinal, metabolic and inflammatory/auto-immune disease.[1] Whilst further work is needed, the role that the relatively ignored microbiome may play in disease is exciting. It challenges current disease models, has the potential to shed light on idiopathic diseases and paves the way for novel treatment options including antibiotics, probiotics, prebiotics, diet, microbial therapeutics and faecal transplantation.

…meets histopathology…

Colorectal Cancer

Globally, colorectal cancer affects 1.3 million people a year. Within the UK, it is the fourth commonest cause of cancer and the second commonest cause of cancer deaths. Until recently, research has focused primarily on the genetic aberrations which cause colorectal cancer. However, the association between diet and colorectal cancer is well established. Might the microbiome underlie this association?

Whilst a plethora of studies have investigated this [2], they are limited by variations in methodology, often small sample sizes and an inability to prove causation (to date, no longitudinal study has been undertaken). However, despite these limitations, results of these studies suggest that there are

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significant differences between the microbiomes of healthy controls, patients with colorectal adenomas and those with colorectal carcinomas. In addition, there are significant differences between the microbiomes of people who come from countries with a low incidence of colorectal cancer and those from countries with a high incidence of colorectal cancer [3] and these differences in microbiome can be modified by diet.

…meets *clinical biochemistry*

With respect to colorectal cancer, the microbiome is of direct relevance to clinical biochemistry in three main ways:

NHS Bowel Screening Programme

The NHS Bowel Screening Programme launched in 2006. Adults aged 60-69 years are invited to complete a faecal occult blood test every two years. If the test is positive, colonoscopy is offered. Professor Stephen Halloran was involved in the development of this programme which is expected to save over 2,000 lives a year.

Studies are beginning to compare the sensitivity and specificity of the faecal occult blood test as a means of detecting colorectal adenomas and carcinomas to the sensitivity and specificity of changes in the microbiome. [4-6] Although considerably more work is required, there is the potential to integrate microbiome analysis into the existing bowel screening programme.

Metabolomics

Metabolomics (the detection of bacterial metabolites within faeces, urine or blood) is proving useful as a means of typing microbiomes and investigating their function. Metabolomics too has the potential to be applied to the bowel screening programme.

Drug metabolism

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Inter-individual differences in microbiomes give rise to inter-individual differences in drug metabolism. The current 'one-size fits all' approach to drug dosages may need to be revised, particularly for potentially toxic drugs such as chemotherapy. When prescribing medications in future, in addition to considering biochemical parameters such as renal and liver function, a patient's microbiome may need to be typed and considered.

Putting it all together: molecular biology meets microbiology meets histopathology meets clinical biochemistry

The microbiome is a fascinating new field of research with the scope to revolutionise our understanding and treatment of disease. It already challenges the current disease-centric, specialty-specific medical model by encouraging cross-speciality collaboration (as the somewhat lengthy title of this article demonstrates.)

Clinical biochemistry is set to be a lead player in the clinical application of microbiome research; the future potential for integration of microbiome data with existing clinical biochemistry investigations is exciting. In particular, there is the possibility of applying this to the bowel screening programme. Colorectal cancer statistics demonstrate that there is still a very real need to reduce mortality from this disease – understanding and exploiting the microbiome might be one way to do this.

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