THE ECOLOGY OF THE UNSEEN

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Abstract: On the global scale, humankind is having a profound impact on the ecology of assemblages of organisms which we can see with the naked eye. At the same time, we are also starting to learn about the impact of our collective, modern lifestyles on the ecology of the unseen, for example the microbes in our gut which are being affected by the overuse of antibiotics and unhealthy diets. However, we do not fully understand which functions the microorganisms fulfill as our knowledge so far is rather limited. In our own research, we see for example that 50-90 % of the molecules produced by microbes are completely unknown to Science but likely play important roles in key physiological processes. This means that we as humans are presently affecting key microbial processes in our bodies without fully understanding the possible repercussions. In addition, many of these molecules likely have bioactive properties and, thereby, represent an untapped resource for the development of new drugs. Therefore, it is important that we start charting out this great molecular expanse to ensure its stewardship for generations to come.

Keywords: Antibiotics, biomolecules, diet, disease, gut, health, microbial ecology, microbiome

1. Introduction

Biodiversity typically refers to the richness in the variety of plants and animals in a particular habitat. An elevated level is considered to be essential for the maintenance of key functions within ecosystems (Tilman *et al.*, 2014). Consequently, losses in biodiversity may greatly impact overall ecosystem functioning (Tilman *et al.*, 2014) and it is in this context that the topic is widely discussed on the global stage (Cardinale *et al.*, 2012). Humans are actively destroying many diverse habitats leading to irreversible losses in important genetic resources (Cardinale *et al.*, 2012). Through its actions, humankind is thereby greatly affecting ecosystem services and threatening its own well-being (Díaz *et al.*, 2006).

Losses in biodiversity are typically discussed in the context of the impact on macro-ecosystems, those ecological assemblages that we can see with the naked eye. Although we might nowadays be more or less accustomed to the idea of irreversible losses of resources through the destruction of such ecosystems, we are now also starting to learn about the impact of our collective lifestyles on the ecology of the unseen, in particular the microbes in our gut which are affected by many features of human civilization including the overuse of antibiotics, unhealthy diets, and unnecessary medical procedures (Blaser, 2018).

2. The gut microbiome

The collective of microbes in our gut, nowadays typically referred to as the “gut microbiome”, is comprised of a diverse set of organisms including distantly related species of bacteria, archaea and microeukaryotes (Gilbert *et al.*, 2018). In terms of cell numbers, the microorganisms colonizing the human body are at least as numerous as the human cells with constitute the body (Sender *et al.*, 2016). In terms of diversity, numbers vary but we generally assume that 1,000 species inhabit the gut (Gilbert *et al.*, 2018). The microbial communities in the gut form complex ecological networks and contribute essential functions to the human body, for example the digestion of food components which would otherwise not be usable by us (Karasov *et al.*, 2011).

3. Microbial dysbiosis and inflammation

Through the advent of modern molecular methods, we have been able to explore the human gut microbiome in unprecedented detail (Heintz-Buschart & Wilmes, 2018). Recent studies comparing healthy versus diseased individuals have shown that there are apparent differences in the gut microbiomes of people suffering from a whole range of diseases affecting different parts of the body ranging from metabolic diseases such as type 2 diabetes and obesity to neurodegenerative diseases such as Parkinson disease (Gilbert *et al.*, 2018). The apparent differences have been suggested to reflect a state of disequilibrium, also referred to as microbial dysbiosis, in a number of cases qualified by a loss in biodiversity, which in turn may be linked to a common feature of these diseases, that is inflammation (Blander *et al.*, 2017).

Under healthy circumstances, there is a constant stimulation of the immune system by microbial molecules but this does not culminate in an overreaction on behalf of the immune system (Blander *et al.*, 2017). The microbiome is thereby characterized by an equilibrium between beneficial bacteria and potentially harmful bacteria which are kept at bay (Carding *et al.*, 2015). Both the microbiome and the immune system are thought to be in a balanced state (Pflughoeft & Versalovic, 2012).

This balance can be upset by different factors, for example the administration of antibiotics, and may result in an overgrowth of potentially harmful bacteria (Carding *et al.*, 2015). Such bacterial communities, and the molecules produced by them, may lead to an overstimulation of the immune system culminating in inflammation (Blander *et al.*, 2017). Such disequilibria are currently associated with the chronic diseases highlighted beforehand (Flint *et al.*, 2012).

4. Biomolecules involved in immune system stimulation during the first days of life

Many different types of molecules produced by bacteria are involved in the stimulation of the immune system including DNA, RNA, proteins and metabolites (Pandey *et al.*, 2015). Differences in how much of a specific molecule is produced by specific bacteria can thereby have a real impact on the stimulation of the immune system and can trigger inflammation. Specific changes to the molecular pool induced by human intervention, i.e. lifestyle changes over the time since the industrial revolution, may thereby lead to differences in the stimulation of the immune system (Blaser, 2018).

5. Distilling the complex molecular soup in the gut

Overall, the molecules produced by the gut microbiome constitute a complex molecular soup (Fig. 1). The key exercise involves identification of the essential functional molecules link these to specific bacterial species (Roume *et al.*, 2015). We subsequently aim to understand what impact they may have for example on the human body in the context of health and disease, particularly in relation to immune system stimulation and the triggering of inflammation. In other words, what we need to be able to do is to recreate the recipe of the soup to later cook it and see whether it "tastes" right or not.

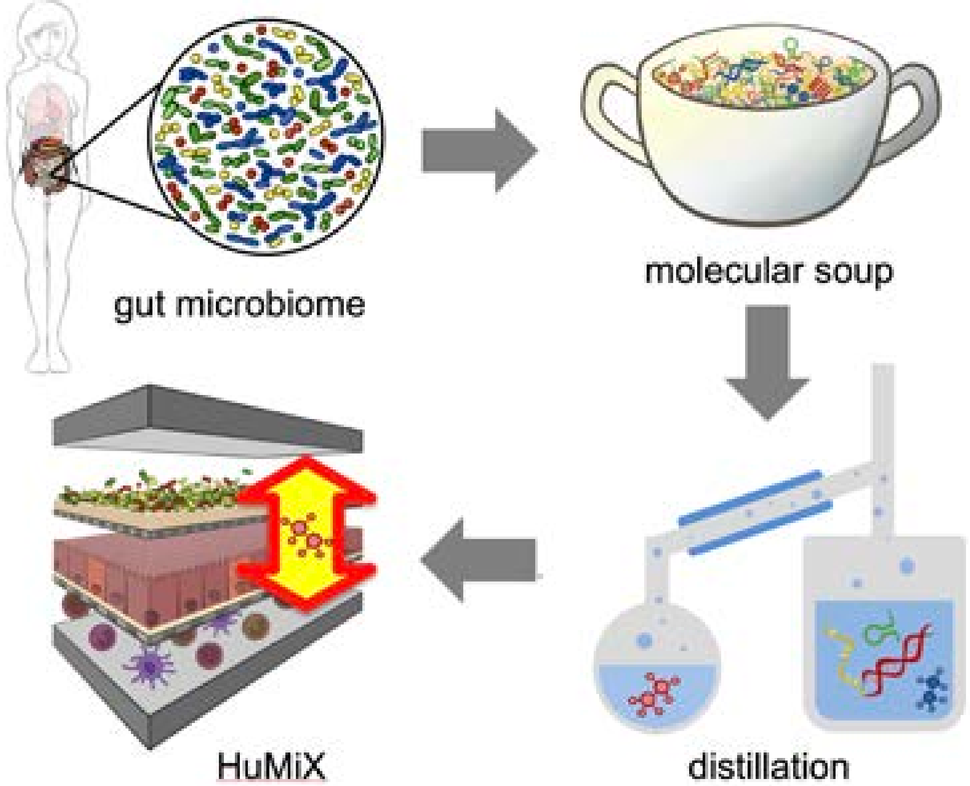

Figure 1: *Understanding the functional role of the gut microbiome for the discovery of new bio-active compounds. In a first stage, microbial communities from the gut are sampled. In a second stage, the molecular soup is obtained. In a third stage, the complex molecular soup is separated into its constituent biomolecular fractions comprising DNA, RNA, proteins and metabolites. In a fourth stage, microbial biomolecules of interest are investigated in the HuMiX model for their effects on human cells.*

To achieve this, we first need to separate (distill) the molecular soup into its constituent parts (Fig. 1). For this we have developed a suite of methods which facilitate the isolation of DNA, RNA, proteins and metabolites from for example human fecal samples (Roume *et al.*, 2015; Roume *et al.*, 2013a,b; Muller *et al.*, 2013; Shah *et al.*, 2018). These are then individually subjected to specialized analyses generating large volumes of data (Muller *et al.*, 2014). To make sense of the data, we have further developed computer programs to be able to link known molecules to the bacteria which produced them (Muller *et al.*, 2014; Laczny *et al.*, 2014, 2015; Narayanasamy *et al.*, 2016; Heintz-Buschart *et al.*, 2017).

Understanding the impact on the human host

To assess the impact of specific molecules produced by specific bacteria on the human body, most notably on the immune system, we have also developed HuMiX, a gut-on-a-chip system which allows us to obtain representative human read-outs without the need for animal experiments (Shah *et al*., 2016; Eain *et al*., 2017; Wilmes *et al.,* 2018). With HuMiX, we are able to study the molecular interactions between human cells and microorganisms from the gut (Fig. 1). We are for example able to study specific functions performed by specific bacterial species or communities in relation to their impact on human health and disease, how specific dietary components in the context of the gut microbiome affect human cellular pathways and how different drugs are metabolized differently depending on the gut microbiomes of individuals. Thereby, HuMiX represents an important research tool for unraveling the functional impact of microbiome-derived molecules on human physiology.

6. Outlook

Coming back to the notion of how losses in biodiversity are inextricably linked to potential losses in important resources, we need to be aware, that through our collective modern lifestyles, we are likely gradually eroding away a whole treasure trove of potential drugs and other resources which so far remain to be discovered. It is therefore important that we start thinking about how to catalogue this molecular space in order to ensure the stewardship of these resources for generations to come. Therefore, we need to systematically resolve and identify the different molecular contingents produced by the gut microbiome. Overall, this presents a grand research frontier with the potential to result in groundbreaking discoveries and impacts in Ecology, Medicine as well as other fields.

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