The Living Textbook of Diabetes
DIAPEDIA

Microbiome and type 1 diabetes

The human microbiome (the collective of microorganisms, which inhabit the human body) and changes therein (often referred to as microbial dysbiosis) is emerging as a potential player in the development of type 1 diabetes mellitus. This section discusses the human microbiome and its potential involvement in type 1 diabetes through its central roles in energy metabolism and modulation of the immune system.

Glossary

Microbiota: Communities of microorganisms comprising bacteria, archaea, eukaryotes (e.g. fungi, protists) and viruses.

Microbiome: The entirety of microorganisms, including their genes, functional gene products and metabolites, found in a given habitat, e.g. the human host, at a given point in time.

Dysbiosis: An imbalanced intestinal microbial community characterized by quantitative and qualitative changes in the composition of the microbiota itself, in its modified metabolic activities or in the local distribution of its members[1].

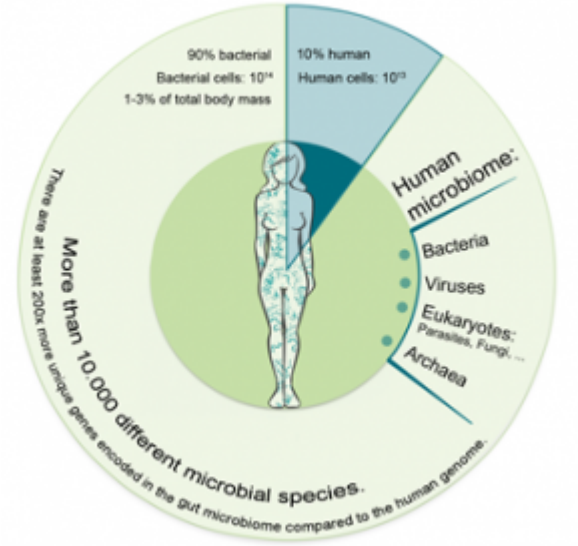
Classical views

Type 1 diabetes is an autoimmune disease, which leads to the destruction of insulin-secreting beta cells in the pancreas and thereby to the dependency on external supplies of insulin in order to regulate glucose metabolism. Regarding the factors that trigger the destruction of the beta cells, it is generally accepted that **genetic predisposition** is a major contributing factor. However, **environmental factors** are also thought to contribute significantly to the development of autoimmunity. In this context, the '**threshold hypothesis**' has been proposed as a model for type 1 diabetes by simultaneously considering the contributions of genetic and environmental determinants for developing the disease[2]. Many scientific studies have focused on such environmental factors, which range from viral infections, lack of breast-feeding after birth to even the consumption of cereals in early childhood [3][4]. However, so far, none of these have been found to be strongly associated with type 1 diabetes. Nevertheless, the marked potential that exists within the immediate environment as a trigger or regulator of autoimmunity remains accepted amongst scientists and medical practitioners alike. In this context, the "environment within", i.e. the gastrointestinal tract and its microbiota, is attracting more and more attention in relation to its possible role in the origin and development of type 1 diabetes because of its **central roles in energy metabolism and modulation of the immune system.**

The human microbiome

The **human microbiome** represents the entirety of microorganisms, including their genes, functional gene products and metabolites, found in and on the human body at a given point in time. Microbial colonisation of the human body is not limited to the gastrointestinal tract, even though this organ contains the highest density

of microorganisms. Each and every body surface in contact with the environment is exposed to the microbial world. It is estimated that overall an adult body forms the scaffold for around **10^{14}** microbes, a number ten times greater than the number of human cells constituting the body [5]. The human body comprises many different habitats ranging for example from the

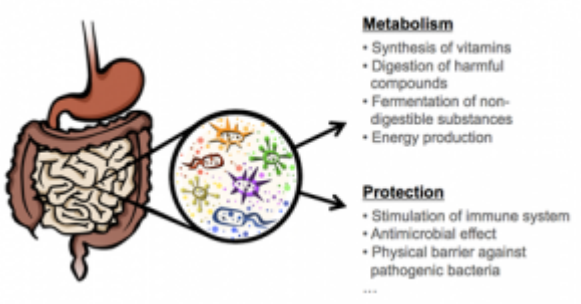


palms of our hands to the nasal cavity. Within their respective niches, human-associated microorganisms can lead many different lifestyles, which in turn leads to extensive microbial diversity. Current estimates suggest that the gastrointestinal tract alone may harbour between **1,000 and 36,000 different bacterial species** [6][7]. In addition to bacteria, which comprise the majority of microorganisms, archaea, fungi, parasites and viruses are also part of the general microbiota, which have co-evolved with the human organism and form a symbiotic relationship with it.

The **gastrointestinal tract** is an essential organ, whose primary functions are the digestion and absorption of food and nutrients. The gastrointestinal tract is heavily colonised by microorganisms and it harbours more than one kilogram of bacterial mass or approximately **2% of our body mass** [6]. **Microorganisms** within the gastrointestinal tract were first discovered by Antonie van Leeuwenhoek in 1683. Fast forward to the early twentieth century when the Russian Nobel Prize laureate **Ilya Ilyich Mechnikov** (also seen as Élie Metchnikoff) was the first to realize the positive health effects of certain microorganisms in the gut. He coined the term **dysbiosis** (also known as dysbacteriosis) to describe aberrations in the microbial communities in the gut, which may trigger a range of diseases including diabetes mellitus [8]. Gut dysbiosis and **immune dysregulation** frequently coincide and can occur as a result of one another [1]. Following on from his work, Mechnikov suggested to exchange harmful bacteria in the gut by beneficial ones and was thereby the first scientist to suggest the use of **probiotics** [9].

Recent scientific evidence suggests that the gastrointestinal microbiota plays a central part in **numerous**

human physiological functions. One example is that it acts as a physical and biochemical barrier against pathogens in the gastrointestinal tract. Synergistic and commensal microbiota in the mucosal layer act as competitors against invaders by occupying binding sites, restricting pathogenic bacteria from nutrients, and producing and stimulating the synthesis of antimicrobial agents [10]. On the other side, the microbiome has also been suggested to play an important role in triggering disease development through dysbiosis, for example in inflammatory bowel disease [11], type 2 diabetes [12] or obesity [13]. In the latter case, scientific studies observed that an obese-specific microbiota has an **increased capacity for energy harvest from diet** due to a shift in bacterial communities and underlying metabolic functions [14].



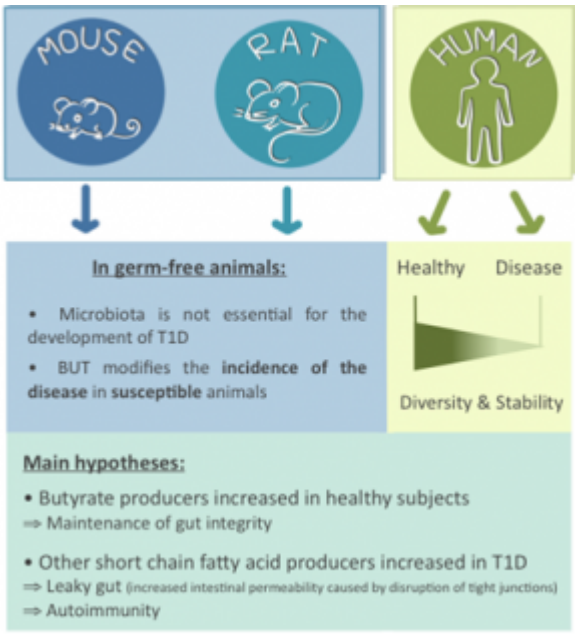
An essential supportive role played by the gut microbiota involves shaping of the **adaptive immune system**. As the gut microbiota are intimately linked to the development of the immune system [15], they may also play an important part in **autoimmunity** and thereby in the development of type 1 diabetes mellitus [16]. This idea is the basic concept of the '**perfect storm**' hypothesis, which considers three main components for the onset of type 1 diabetes, including a dysbiotic gut microbiota, genetic abnormalities in the regulation of mucosal immunity and increased impairment of the mucosal barrier (leaky gut). A **leaky gut** is characterized by an increased intestinal permeability caused by the disruption of tight junctions between epithelial cells, which in turn leads to an overstimulation of the immune system and potentially leading to auto immune destruction of islet cells [17].

Studies linking gastrointestinal microbiota and type 1 diabetes

Animal studies, which have used non-obese diabetic (NOD) mice and BioBreeding diabetes-prone rats as models, revealed that, when being raised germ-free, the animals still developed diabetes at high rates, indicating that the microbiome is not essential for the development of type 1 diabetes. However, the gut microbiota does **significantly modify the incidence of the disease** in susceptible animals [18]. Diet has been shown to play a well-established role in the development of type 1 diabetes in NOD mice [19]. Therefore, the microbial influence might be indirect and more related to dietary modifications as the composition of the diet has an influence on the enteric microbiota composition [20]. In particular, conventionally raised NOD mice lack an adaptor protein for multiple Toll-like receptors known to bind to microbial ligands. This protein is known to be a downstream signalling molecule in a specific pathway, which is involved in the innate immunity and plays also a role in type 2 diabetes mellitus. Interestingly, if these mice and rats are fed with antibiotics they fail to develop diabetes. A simple explanation for this finding might be that the used antibiotics select for certain microbial taxa that have the ability to prevent the autoimmune response in the mouse model [21][22].

A recent study in **humans** suggests that the gastrointestinal microbiota tends to reach a more or less stable state proportionally with an infant's age, whereas children who developed beta-cell immunity have a less diverse and stable gastrointestinal microbiota [23]. This finding suggests that the microbiome from diabetes type 1 children may be distinct from that of healthy children. This preliminary observation is currently the subject of intense additional scientific research.

It is important to note that none of the mentioned studies has been able to come up with a scientifically funded explanation how the gastrointestinal microbiota influence the progression of the immune system towards the destruction of pancreatic beta cells and thereby triggering type 1 diabetes. Nevertheless, some important hypotheses have been generated, which still need to be tested through extensive future research.



Conclusion

Studying the concrete relationship between gastrointestinal microbiota and type 1 diabetes is extremely challenging, as the gastrointestinal tract is a complex ecosystem, which has yet to be comprehensively characterised. This explains why the role of the human microbiota in the development of type 1 diabetes remains relatively unknown to date. Nonetheless, it has to be noted that the gastrointestinal microbiota has a profound impact on **energy metabolism and the immune system**. Therefore it is suggested to be one of the key players in the pathophysiology of diabetes mellitus. The increased prevalence of metabolic disorders and diabetes mellitus in the industrialised world and its mortal consequences are driving the demand for further investigations. Therefore, it is essential to gain proper understanding of the complex interactions between host and microbiome in relation to diabetes mellitus.

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Complexity

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