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Role of the microbiome in the normal and aberrant glycemic response

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SUMMARY

Multiple studies in the recent years suggest that the microbiome is critically important for normal host functions, while impaired host microbiome interactions contribute to the pathogenesis of numerous common disorders. Of these, much attention is recently given to the involvement of the microbiome in the pathogenesis of impaired glucose tolerance, type II diabetes mellitus (T2DM), and other metabolic disorders comprising the 'metabolic syndrome', including obesity, non-alcoholic fatty liver disease and their complications. In addition, alterations in the microbiome have been linked to the pathogenesis of type 1 diabetes mellitus (T1DM), an autoimmune disorder affecting the glycemic response, of distinct pathogenesis than T2DM. In this chapter we will discuss the roles of the microbiome in regulating the normal and impaired glycemic response in both mice and humans, and outline examples of underlying mechanisms by which the microbiome is contributing to diabetes mellitus. We will further discuss means by which the microbiome can be manipulated to develop future therapeutic interventions for hyperglycemia and its adverse effects.

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1. Microbiome alterations in type 1 and type 2 diabetes mellitus

The term 'diabetes mellitus' denotes two distinct metabolic disorders that share the common feature of chronic hyperglycemia and impaired glycemic response due to defects in insulin secretion, sensitivity or both. Type 1 diabetes mellitus (T1DM), is an autoimmune condition involving the destruction of beta cells in the pancreas, consequently leading to impaired production of insulin, rendering patients entirely dependent on exogenous insulin. T1DM accounts for ~5–10% of diabetes mellitus cases, and is characterized by abrupt onset in children and young adults. In contrast, type 2 diabetes mellitus (T2DM, previously termed non-insulin dependent diabetes mellitus) is characterized by impaired insulin sensitivity of target tissues (muscle, liver, adipose tissue), leading to impaired glucose uptake into peripheral tissues, a condition termed 'insulin resistance'. During most of the course of T2DM, insulin secretion is increased due to pancreatic beta cell compensation for insulin resistance, and only at late stages of T2DM pancreatic insulin secretion is impaired, leading to exogenous insulin dependency. Due to the gradual nature of this process, T2DM is mostly but not exclusively observed in adults [1]. Despite the differences in epidemiology and pathogenesis, the microbiome is suggested to play a role in the manifestation or progression of both T1DM and T2DM as outlined below.

T1DM. In addition to the existing mechanistic knowledge regarding the pathogenesis of T1DM, gut microbiome alterations also seem to be a feature of this autoimmune disorder. The classical murine model for T1DM is the non-obese diabetic (NOD) polygenic mutant mouse, in which animals develop spontaneous insulitis and consequently depletion of insulin production at about 12 weeks of age. When these mice additionally lack MyD88 (an adaptor for multiple receptors that recognize microbial patterns), they are protected from the development of T1DM, suggesting that microbial stimuli may be involved in disease pathogenesis in this model. Interestingly, deriving these mice as germ-free (GF) or treating them with broad-spectrum antibiotics leads to robust development of T1DM. Moreover, recolonizing NOD GF mice with a defined microbiota reduced the incidence of diabetes, suggesting that certain microbiome compositions may play a protective role in the development of T1DM [2]. This observation and follow up studies have led to the development of the 'balanced signal' hypothesis, in which various members of the microbiome may promote T1DM while others have an inhibitory function [3–5]. T1DM-promoting microbial composition may be induced by early exposure to antibiotics [6] (as discussed in the next section). The downstream microbiome effects on host susceptibility to T1DM may involve microbial-mediated alterations in host sex hormones [7,8], induction of host immune reactivity, mainly the Th17 response [9,10], as well as other, yet unidentified factors.

Support for the conclusions obtained in the above murine models can be found in human trials. In a small-scale prospective case–control study performed in eight children, a significant microbial dysbiosis was apparent early after the onset of autoimmunity, with increase of **Bacteroidetes** (and more specifically, the genus ***Bacteroides***) and consequent reduction of **Firmicutes** noted in new onset T1DM cases [11]. Other studies suggested that butyrate producing bacteria may be also reduced in T1D patients [12], possibly leading to altered mucin synthesis and compromised intestinal integrity, leading to systemic influx of microbial antigens inducing autoimmunity. Similar taxonomic differences were reported in a different cohort of children [13]. A recent longitudinal study with 33 infants determined that microbiomes of subjects who progress to T1D are characterized by significant reduction in alpha diversity even before the onset of clinical symptoms. In the children who progress into T1DM, several correlations were determined between distinct microbial taxa and serum or fecal metabolites that were previously associated with diabetes, suggesting that these microbe-metabolite relationships may cooperatively impact T1DM pathogenesis [14]. Despite this increasing number of reports, our knowledge regarding the role of the microbiome in T1D remains mostly descriptive. Further research is needed to fully understand the contribution and the function of the microbiome in the manifestation of T1DM.

T2DM. Multiple studies suggested an association between compositional and functional microbiome alteration ('dysbiosis') and the risk of developing metabolic syndrome-associated pathologies such as obesity, T2DM, non-alcoholic fatty liver disease and hyperlipidemia. In mice, induction of insulin resistance may be induced by alteration of the microbiome, mediated by changes in diet and immune dysregulation, as further discussed in the next section.