

Hibernation on the Gut Microbes of Mammalian Animals

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Hibernating mammals confront seasonal and harsh environmental shifts, prompting a cycle of pre-hibernation feeding and subsequent winter fasting. These adaptive practices induce diverse physiological adjustments within the animal's body. With the gut microbiota's metabolic activity being heavily reliant on the host's diet, this cycle's primary impact is on this microbial community. When the structure and composition of the gut microbiota changes, corresponding alterations in the interactions occur between these microorganisms and their host. These successive adaptations significantly contribute to the host's capacity to sustain relatively stable metabolic and immune functions in severe environmental conditions.

mammals

metabolism

hibernation

gut microbiota

homeostasis

1. The Effects of Hibernation on the Host's Gut Microbiota Diversity

The diversity of gut microbiota involves the richness of species and the distribution of relative abundance of microorganisms ^[1]. Different types of bacteria possess different abilities to break down and absorb substrates, leading to their diverse metabolites. Thus, the significance of diversity in the gut microbiota stems from its influence on host health and overall biological balance. The dysregulation of the gut microbiota has the potential to result in a range of metabolic disorders ^{[2][3][4]}.

Hibernating species like the 13-lined ground squirrel, Daurian ground squirrel, greater horseshoe bat, and brown bear have undergone thorough studies concerning their gut microbiota ^{[5][6][7][8]}. Due to winter fasting, the host experiences a sharp reduction in degradable substrates available for gut microbiota, which can impact the variety and composition of the gut microbial community ^[9]. Previous research has suggested that results from the 16S rRNA gene sequencing of DNA extracted from cecal contents of 13-lined ground squirrel ^[10] can support the fact that community diversity changes in the hibernator gut microbiota. During hibernation, the Shannon index and Simpson index were significantly decreased compared to other periods, indicating a noticeable reduction in alpha diversity compared to the active phases ^[10]. In the summer, the predominant phyla in the ground squirrel's gut microbiota were Bacteroidetes, Firmicutes, and Verrucomicrobia, with the latter being primarily represented by *Akkermansia muciniphila* (*A. muciniphila*) ^[11]. The relative abundance of Firmicutes, including Lactobacillaceae and classes Lachnospiracea, reduced during hibernation, displaying an almost total absence of Operational Taxonomic Units (OTUs) categorized to obtain taxa, and the same applies to the phylum Mollicutes ^[10]. In general, the diversity of gut microbiota of 13-lined ground squirrels significantly decreases during hibernation ^{[10][11]}. In the study

on Daurian ground squirrels, they were divided into three groups: the pre-fattening period, hibernation period, and active period. In terms of alpha diversity, the Shannon index of the fattening and hibernation phases was significantly lower than that of the active phase [12]. The results of the biological analysis indicated that during the pre-fattening period, as Daurian ground squirrels continued to consume food, the dominant microbial communities in their cecum tended to stabilize, which was accompanied by a decrease in the overall microbial abundance. Conversely, the hibernation period was characterized by fasting, which led to a scarcity of nutrients required by the gut microbes, resulting in a reduction in the abundance [12]. Carey et al. found that in the emergence period, as the 13-lined ground squirrels increased their food intake and had access to a more diverse food source, the abundance of gut microbiota reached its highest level [13]. Moreover, in the investigation of hibernating brown bears, a reduction in gut microbiota diversity has been observed [7]. Stool samples were collected from brown bears during both the hibernation and active periods of the same year. Through 16S rRNA analysis and sequencing, the findings indicated a noteworthy reduction in gut microbiota diversity during hibernation as opposed to the active period. The predominant bacterial phyla with elevated relative abundance during hibernation encompassed Proteobacteria, Firmicutes, Bacteroidetes, and Actinobacteria [7]. By utilizing DNA extraction and 16S rRNA sequencing technology, 1750 OTUs resulted from the gut microbiota of 39 bats. By analyzing the alpha diversity, the diversity within the gut microbiota was significantly greater in late summer as opposed to that in early winter. Moreover, the Shannon index of the gut microbiota during early summer exhibited a notably lower value compared to the winter period [8].

Due to the fasting behavior during hibernation, the scarcity of dietary substrates leads to a reduction or even disappearance of certain microbial groups that cannot adapt to extreme conditions [14]. Only a small fraction of these groups possess the ability to switch metabolic substrates or metabolize host-derived substrates during hibernation [15], enabling them to survive in this period. Overall, the diversity of the mammalian gut microbiota during hibernation is significantly decreased compared to that during the active periods. During hibernation, the increase or decrease in specific microbial populations in the host's gut collectively contributes to a reduction in gut microbiota diversity. This alteration might assume a pivotal role in helping the host adapt to the scarcity of food and fluctuations of the environment during the winter, maintaining relative homeostasis.

2. The Effects of Hibernation on the Structure of the Host's Gut Microbiota

The taxonomic changes in the microbiota of 13-lined ground squirrels were closely linked to the substrate preferences of important species in the mammalian gut microbiota [16]. Hibernation is associated with the decline in the abundance of specific taxa, like Lachnospiracea, that typically thrive on dietary plant glycans. Conversely, it leads to a rise in the proportion of taxa that excel in breaking down host-derived substrates, like *A. muciniphila* [11] [17]. Certain Bacteroides, exhibiting metabolic adaptability, can dynamically shift their foraging preferences between dietary and host-derived substrates based on availability, and also exhibit an increase in abundance. The breakdown of mucin by bacteria such as *A. muciniphila* leads to the liberation of sulfates. This process might be a plausible explanation for the observed elevation in the increase in the abundance of sulfur-reducing *Desulfovibrio*

in hibernating 13-lined and Arctic ground squirrels when contrasted with its level in the summer [10][18]. A study about Daurian ground squirrels revealed notable alterations in the structure and capacity for functions within the gut microbiota during hibernation. Specifically, the relative abundance of the phylum Bacteroidetes increased, while the phyla Firmicutes and Verrucomicrobia decreased in relative abundance in the Daurian ground squirrel gut microbiota [6]. PICRUSt analysis of gut microbiota showed that, during hibernation, the significant enrichment of pathways associated with carbohydrate metabolism and pentose phosphate occurred. In contrast, the control group exhibited enrichment in pathways linked to lipid biosynthesis and isoprenoid biosynthesis [6]. These results suggested a metabolic shift within the gut microbiota of Daurian ground squirrels in hibernation, favoring the breakdown of polysaccharides [19] and carbohydrates, ensuring an adequate energy supply for the host, and supporting their survival during the hibernation period [6][20]. The 16S rRNA sequencing analysis of brown bear feces across different seasons, along with unweighted UniFrac analysis, revealed distinct patterns in the gut microbiota composition [7]. As winter sets in, compared with summer, the relative abundance of Bacteroidetes has a notable surge, while the abundance of Actinobacteria and Firmicutes diminishes. These shifts in the makeup of the brown bear's gut microbial community during winter are primarily attributed to the absence of nutritional resources during the hibernation period. The ability of Bacteroidetes to adapt to host-derived polysaccharides in the absence of external substrates, combined with the substrate preferences of Firmicutes, contributes to the discernible alterations in the gut microbiota structure during the winter months [7]. Furthermore, the greater horseshoe bat serves as a small mammal model for studying hibernation-related mechanisms. In a study utilizing 16S rRNA amplicon sequencing and PICRUSt to predict the diversity, composition, and function of gut microbiota at different periods, results indicated that, during late summer, there was notably greater diversity observed in the gut microbiota compared to the winter season [8]. During hibernation, there was a significant reduction in the proportion of Proteobacteria and Firmicutes, while Bacteroidetes showed a significant increase. In the gut microbiota of the greater horseshoe bat, Proteobacteria took center stage, accompanied by relatively lower proportions of Bacteroidetes and Firmicutes [8]. Conversely, in the gut microbiota of other mammals like ground squirrels and brown bears, Bacteroidetes and Firmicutes were the major players, while Proteobacteria made up only a small fraction. Furthermore, there was no occurrence of an elevation in Verrucomicrobia, including *Akkermansia muciniphila*, during the hibernation phase in brown bears, which is different from small mammalian hibernators. While the primary gut microbiota varied among bats and certain other mammals, there appeared to be commonalities in the transformations of their gut microbiota during hibernation [8].

During hibernation, the dominant degraders (the predominant microbial communities) change, and the sub-degraders that utilize the enzymatic activities of the dominant degraders for metabolic activities (cross-feeding) [21] also experience alterations. For example, in hibernating ground squirrels, there was a sharp decrease in the abundance of *Lachnospiracea* [18], which prefers metabolizing plant polysaccharides [22]. Consequently, this results in a decrease in the abundance of *Lactobacillus* (a sub-degrader of lactose and plant monosaccharides). The fundamental reason for this is the insufficient substrate supply during the winter, which is inadequate to sustain their metabolic activities. The combined findings from the mentioned studies revealed significant alterations in the gut microbial composition among various species throughout hibernation [6][7][8][12]. A common trend observed was the decrease in the abundance of numerous taxa compared to the summer, with an increase observed only in

microbial communities capable of adapting to environmental impacts. This shift is primarily attributed to the scarcity of dietary substrates during winter. Furthermore, the enrichment of specific metabolic pathways during hibernation reflects the adjustment of energy and metabolic processes in mammals throughout this period [23]. In summary, changes in the configuration of the gut microbiota induced by hibernation may contribute to maintaining homeostasis through interactions with the host.

3. The Effects of Hibernation on the Metabolites of the Host's Gut Microbiota

The byproducts produced by the gut microbiota, particularly short-chain fatty acids (SCFAs) that provide energy and modulate the immune system, play a vital role in maintaining the homeostasis of the host's nutrient absorption, metabolism, immune system [24], and even nervous system [25]. During hibernation, changes occur in the diversity and composition of the host's gut microbiota, resulting in modifications to their metabolites [26], and further causing a series of adaptive changes in the host. The targeted metabolite analysis of the cecal contents of Arctic ground squirrels was conducted using gas chromatography–mass spectrometry (GC-MS). This research revealed seasonal changes in the concentrations of SCFAs in the intestine [18]. The results suggested a noteworthy reduction in the total SCFA concentration in the cecum of ground squirrels during winter, as opposed to its summer levels. This decrease is presumably attributed to the scarcity of substrates necessary for bacterial fermentation during the winter fasting period [18]. Taking into account the periodic arousals during hibernation in Arctic ground squirrels, it was observed that the overall levels of SCFAs were lowest during the torpid phase of hibernation, while during the arousal periods, there was an increase in SCFAs levels [18]. This phenomenon is hypothesized to be linked to the increase in body temperature during arousal phases. The elevation in temperature is believed to contribute to heightened bacterial enzyme activity and an upregulation of bacterial metabolism, which makes the level of SCFAs higher than that during torpor [27]. However, unlike these small hibernators, during hibernation, brown bears can sustain a body temperature of around 30 °C [28], excluding the possible influence of reduced body temperature on shaping their microbiota. Therefore, this phenomenon would not occur in brown bears. Further analysis of the experimental data uncovers changes in the mole ratios of some SCFAs during the hibernation period. In summer, acetic acid ranks highest in mole ratio, succeeded by butyric acid, with propionic acid registering the lowest concentration [18]. In the cecal metabolome, this changing trend can be linked to alterations in the abundance of mucin-degrading bacteria during the hibernation period. As mentioned earlier, the proportionate prevalence of *A. muciniphila* rises throughout the hibernation, while the *Lachnospiraceae* shows a significant decrease (the initial ones produce both acetic acid and propionic acid [29], while the latter ones predominantly consist of butyric acid producers [30]). Besides SCFAs, metabolites like tryptophan (Trp) and bile acids (BA) also play a role in influencing the metabolism of immune cells, contributing to immune suppression and the modulation of inflammatory responses [31].

The metabolites generated by the gut microbiota significantly impact the health of the host. These metabolites can potentially affect various organ systems associated with hibernation, including the intestines, the liver, white and

brown adipose tissues, and the brain [\[32\]\[33\]](#). Therefore, further research into the changes in the metabolites of gut microbiota during hibernation is essential for understanding other organs in hibernating animals.

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