# Non-Photosynthetic Melainabacteria (Cyanobacteria) in Human Gut

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Gut microorganisms are comprised of thousands of species and play an important role in the host's metabolism, overall health status, and risk of disease. Cyanobacteria are the oldest organisms on earth, and their fossil record possibly tracked back to ~3.5 billion years ago. The emergence of the oxygenic photosynthesis of cyanobacteria was associated with the rise of oxygen in the earth's atmosphere (also known as the Great Oxygenation Event) ~2.1 billion years ago.

Keywords: human microbiome ; gut ; non-photosynthetic cyanobacteria ; Melainabacteria

## 1. Introduction

Cyanobacteria are the oldest organisms on earth, and their fossil record possibly tracked back to ~3.5 billion years ago [1]. The emergence of the oxygenic photosynthesis of cyanobacteria was associated with the rise of oxygen in the earth's atmosphere (also known as the Great Oxygenation Event) ~2.1 billion years ago [2]. Over the long evolutionary life, cyanobacteria have adapted to various changing environments and present high diversity in morphology, metabolism, and eco-physiology [3]. Cyanobacteria are ubiquitous and inhabit a broad spectrum of freshwater, marine, and terrestrial habitats, including extreme environments, e.g., hot spring, desert crusts, and polar zones. Cyanobacteria constitute the important primary producers and play a critical role in the global biogeochemical cycling of carbon and nitrogen [3]. They also attract attention due to their ability to form massive blooms that deteriorate water quality and threaten public health by producing toxic metabolites representing various chemical classes [4]. The discovery of the non-photosynthetic cyanobacteria Melainabacteria in the aphotic environments (e.g., lake sediment and aquifer as well as human and animal guts) [5][6][7][8] have advanced understanding into the breadth and complexity of cyanobacteria and are receiving the attention relating to the origin of oxygenic photosynthesis [9], redefinition of cyanobacteria [7][10][11], and also raised the new open questions regarding the ecological relevance of the non-photosynthetic cyanobacteria, e.g., Melainabacteria in these aphotic environments, particularly human gut.

## 2. The New Class Melainabacteria of the Phylum Cyanobacteria

The cyanobacterial 16S rRNA-like sequences have been previously detected in human gut samples [12][13][14], bovine rumen [15], termite gut [16], and another animal guts [17][18], implying the presence of non-photosynthetic cyanobacteria lineage in these aphotic environments. Di Rienzi et al. (2013), for the first time, assembled the complete genomes of non-photosynthetic cyanobacterium-like from human gut and groundwater, which were assigned to a new phylum Melainabacteria (Greek nymph of dark waters), sibling to the phylum Cyanobacteria because of the <85% sequence similarity with photosynthetic cyanobacterial members [5]. Later, Soo et al. (2014) expanded the coverage of the Melainabacteria members via assembling new Melianabacteria genomes from human and koala gut and bioreactor samples; they re-designated the Melainabacteria into a class within the phylum Cyanobacteria given the robust monophyly and shared traits with photosynthetic cyanobacteria [7]. This re-classification was supported by the genome phylogeny-based taxonomy [19]. The class Melainabacteria is divided into six major taxonomic orders (*Vampirovibrionales*, *Obscuribacterales*, *Gastranaerophilales*, and *Caenarcaniphilales*, SHAS531, and V201-46) based on the habitat and analysis of population genomes [7][9], the former and middle two are proposed to the microaerophilic and obligate anaerobic members, respectively, and the latter two orders have not been defined yet [6]. Soo et al. (2015) recently identified a predatory bacterium (*Vampirovibrio chlorellavorus*, previously known as proteobacteria) of green algae *Chlorella* to be the first cultivatable representative of non-photosynthetic cyanobacterial Melainabacteria through analyzing the genomes of lyophilized archive sample [20], the new *V. chlorellavorus* isolates were recently sequenced and characterized [21], they present the cocci cellular shape (0.3–0.6 µm in diameter) [22]. Utami et al. (2017) utilized the single-cell sorting and sequencing technology to assemble the genome of a melainabacterium (*Candidatus Gastranaerophilus termiticola* Tpq-Mel-01) from the termite gut [6], and they further utilized the fluorescence in situ

hybridization (FISH) technology to demonstrate that *G. termiticola* Tpq-Mel-01 grew in rod shape (1.0 µm by 0.5 µm in dimension).

So far, over 50 Melainabacteria genomes have been partially or wholly assembled from human and animal guts, bioreactor, lake water, and aquifer samples [5][6][7][9][20][21]; The *Gastranaerophilales*, *Caenarcaniphilales*, and *Vampirovibrionales* members have the relatively smaller genome size (1.6–2.7, 1.8–2.2, 2.8–3.0 Mbp, respectively) compared to the *Obscuribacterales* members (3.4–5.5 Mbp), and the *Obscuribacterales* and *Vampirovibrionales* members have relatively higher G+C content (49–55%) [7][21] compared to the other two order members (28–43%) [6][7], highlighting the genomic diversity of the Melainabacteria.

## 3. Neurodevelopment and Neurodegeneration

Selected cyanobacteria can synthesize a non-essential neurotoxic amino acid, β-methylamino-L-alanine (BMAA) [23], which is suggested as a potential etiological factor of neurodegenerative processes and diseases (e.g., Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease, and dementia). This raises the question of whether such BMAA-producing microorganisms can be a part of the human intestinal microflora [14]. Therefore, it has been hypothesized that the BMAA-producing cyanobacteria are present in the human gut and are associated with the development of neurodegenerative diseases (e.g., ALS, Alzheimer's disease, and Parkinson's disease) in humans [24]. However, no clinical studies have been performed to confirm these hypotheses. Di Gioia et al. (2020) performed the first prospective longitudinal study analyzing the compositional gut microbiota difference between 50 ALS patients and 50 control subjects matched for sex, age, geographical origin, and eating habits [25]. In their double-blinded, placebo-controlled phase I pilot trial, the patients received either probiotic supplement or placebo to assess the impact of probiotic supplementation on the gut microbiota and disease progression. Interestingly, they observed that members of the Cyanobacteria phylum in the diseased group were significantly higher than those in the control group (0.3% vs. 0.2%, respectively; $p < 0.05$).

Such a differing pattern was also observed for the Gastranaerophilales members belonging to the non-photosynthetic cyanobacterial Melainabacteria ($p < 0.05$). Their findings supported the hypothesis of the potential role of gut cyanobacteria in the pathogenesis of neurodegenerative diseases [25][26]. More recently, a population study was conducted to investigate the impact of exposure to polycyclic aromatic hydrocarbons on neurodevelopment on the gut composition in 38 healthy three-year-old healthy children that had postnatal PAH exposure [27]. After adjusting for the urinary hydroxyl PAHs, the cyanobacteria abundance was negatively correlated with the neurodevelopment in adaptation, gross motor, and language [27]. These findings continued indirectly to support the hypothesis of the association of gut cyanobacteria and neurodevelopment disorder. Furthermore, more detailed studies are needed to evaluate it.

## 4. Gastrointestinal and Metabolic Diseases

When studying the association of the human gut microbiome with gastrointestinal and hepatic diseases, Lu et al. (2016) analyzed the adenoma mucosal biopsy samples and adjacent normal colonic mucosa from 31 patients with adenomas and 20 healthy controls. Significantly higher cyanobacterial abundance in the adenomatous tissue was found when compared to the healthy tissue [26]. Xiong et al. (2021) analyzed the fecal samples from 25 healthy infants in comparison to samples collected from 18 and 24 infants with acute gastroenteritis caused by rotavirus and human norovirus, respectively. Cyanobacteria members had a higher abundance in infants' gut with viral diarrhea compared to the healthy control group [28]. These two studies consistently implied the positive correlation between gut cyanobacteria and gastrointestinal disease. Sarangi et al. (2017) analyzed the fecal samples from 35 patients with cirrhosis and 18 healthy controls; and they observed a relatively lower cyanobacterial abundance in the patients with cirrhosis compared to the health controls (0.0% vs. 0.53%, $p < 0.05$) [29], suggesting the negative correlation between the gut cyanobacteria and cirrhosis. One should note that such studies are insufficient to imply causation. Further longitudinal studies are warranted to assess it.

In terms of metabolism-associated health and disease, Kaplan et al. (2019) analyzed the gut microbiome composition in the 1674 adults of Hispanic Community Health Study/Study of Latinos in the USA, and they observed that the cyanobacteria were significantly negatively associated with obesity [30]. Oduaran et al. (2020) analyzed the population of South Africa and observed a significant abundance of the Vampirovibrio members (non-photosynthetic cyanobacterial Melainabacteria) in the rural community Bushbuckridge when compared to inhabitants the highly urbanized area Soweto [31]. Chumpitazi et al. (2019) noticed that the fructan-sensitive children with irritable bowel syndrome have enriched cyanobacteria compared to the fructan-tolerant group, indicating the involvement of cyanobacteria in food digestion [32]. Cai et al. (2020) analyzed the gut microbiota composition in the patients with Wilson's disease (an autosomal recessive inherited disorder of chronic copper toxicosis), and they observed a higher cyanobacterial abundance in the patients with

Wilson's disease compared to the health controls (0.12% vs. 0.0%, $p < 0.05$) [33]. It appears that there is no consistently positive or negative correlation between gut cyanobacteria and metabolism-associated disease.

## 5. Other Diseases

Zhu et al. (2020) analyzed the gut microbiota composition in the patients with allergy rhinitis (AR) and showed that the cyanobacterial abundance in the AR patients was significantly lower than those in the non-AR group [34]. Zhang et al. (2018) observed a relatively higher gut cyanobacterial abundance in lung cancer patients than the healthy controls [35]. Sublette et al. (2020) analyzed the intestinal microbiota in the abstainers and continuing smokers and observed that the exhaled CO level in daily cigarette smokers correlated positively with the relative abundance of gut cyanobacteria [36]. These findings suggest the need for further studies elucidating the potential role of gut cyanobacteria in respiratory diseases. Shi et al. (2021) analyzed the gut microbiota composition of 30 Graves' disease (GD) patients without Graves' orbitopathy (GO), 33 GO subjects, and 32 healthy subjects and observed the significant difference in the gut cyanobacteria among the studied groups, implying the potential association of the changing gut cyanobacterial abundance with the Graves' disease and Graves' orbitopathy [37].

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