The microbiota's funnel effect: How multiple factors independently converge in changing the microbiota

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Abstract: *The science of the microbiota, by revealing the complexity of interactions between the world of microorganisms that colonize us and that of human cells, represents the dawn of a new paradigm in biomedical and psychological sciences. It allows for a more complex yet more promising perspective on human health and disease compared to previous approaches. Scientific literature has now identified specific lifestyle-related factors (nutrition, environmental physical-chemical quality, psychological well-being, etc.) that significantly influence the composition of the microbiota. This paper introduces the concept of the "funnel effect" of the microbiota to describe the convergent and partially independent nature of these factors (nutrition, physical activity, psychological well-being, sleep quality, social support, environmental physical-chemical quality, circadian rhythms) on the composition of the intestinal microbiota, thereby impacting the overall health of the human organism. The "funnel effect" of the microbiota has some highly relevant clinical implications, emphasizing the need for an integrated psycho-neuro-endocrine-immunological approach, in contrast to the highly specialized and molecularly focused approach that is currently widely adopted.*

Key words: *Microbiota, PNEI paradigm, Nutrition, Physical activity, Psychological well-being, Epigenetic.*

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Introduction

At the end of the last century, the massive Human Genome Project aimed to fully map human DNA with the ambition of understanding and potentially solving any human disease. This optimistic expectation stemmed from the theoretical concept of the so-called "central dogma of molecular biology", which posits that a gene (part of the genotype) corresponds to a specific protein (phenotype) and that there can be no informational flow from the phenotype to the genotype – only a unidirectional flow from the gene to the protein structure (Bottaccioli F. & Bottaccioli A.G., 2017; Gottlieb, 2000). Paradoxically, the success of the Human Genome Project in fully sequencing human DNA marked the end of the "central dogma of molecular biology" because it exposed the theoretical inadequacy of this concept considering the data emerging from genetic analysis and the complexity of human bio-psycho-social interactions. A striking example is the fact that a complex organism like a human possesses a genetic heritage of "only" about 25,000 genes, compared to wheat, which has around 150,000, and that the percentage of coding genes is limited to approximately 2% of the entire human genome.

As often happens in the history of science, the partial failure of the ambitious Human Genome Project, on one hand, led to an increasing awareness of the explanatory inadequacy of the "central dogma of molecular biology" in relation to human phenotypic complexity. On the other hand, however, it laid the foundation for two major revolutions – still ongoing – in the scientific landscape. The first revolution concerns epigenetics, the study of factors (both hereditary and non-hereditary) that modify an organism's phenotype without altering the DNA sequence. In other words, it involves studying the flow of information from the environment to the DNA, thereby influencing the expression of the genotype. The second revolution is represented by microbiota science, which examines the trillions of microorganisms (bacteria, fungi, viruses, protozoa) that colonize our bodies.

The effects of microbiota

Thanks to the genetic analysis technologies developed for the Human Genome Project, significant progress has been made in studying the microbiota and understanding the extent to which interactions among its microorganisms affect human cells. This emerging field of study has begun to uncover the astonishing complexity and significant impact of the microorganisms inhabiting our bodies in shaping human health and quality of life. Strengthening this broader perspective – one that includes the microbiota's influence on human bio-psycho-social well-being – there is now substantial evidence showing that the microbial ecosystem colonizing us pro-

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foundly affects complex functions such as nutrient absorption, immune system regulation, and neurodevelopment. It modulates systems like the stress axis and even influences cognitive, emotional, and motivational aspects. The interaction between the microbiota and intestinal permeability plays a particularly crucial role in modulating the immune system and the epigenetic impact on the human host. This makes it a key factor in the development of chronic inflammatory diseases, which have become a true "epidemic" in industrialized countries (Fasano, 2020).

The remarkable influence of the microbiota has shed light on the etiopathogenesis of conditions such as celiac disease, obesity, and ulcerative colitis, as well as psychological disorders, including anxiety, depression, and various psychopathologies such as autism spectrum disorders and schizophrenia (Caio *et al.*, 2019; Cheung *et al.*, 2019; Foster & McVey Neufeld, 2013; Garrett *et al.*, 2007; Li & Zhou, 2016; Mangiola *et al.*, 2016; Rodrigues-Amorim *et al.*, 2018; Sharon *et al.*, 2019; Simpson *et al.*, 2021).

It is important to note that the emergence of the new paradigm, which positions the microbiota as a key player in our health, has been driven precisely by research demonstrating how the microbiota influences neurobehavioral and psychological dimensions – such as anxious or depressive states, sociality, and risk perception (Allen *et al.*, 2017; Ann *et al.*, 2024; Bercik *et al.*, 2011; Bravo *et al.*, 2011; Carloni *et al.*, 2021; Chen *et al.*, 2019; Cheung *et al.*, 2019; Cryan & Dinan, 2012; Cryan & OMahony, 2011; De Palma *et al.*, 2015; Farmer, Randall & Aziz, 2014; Koenig *et al.*, 2011; Ottman *et al.*, 2012; Wu *et al.*, 2021) and how certain phenotypic characteristics of these dimensions can even be transferred from one organism to another through the so-called «microbiota transplantation» (Chinna Meyyappan *et al.*, 2020; Collins *et al.*, 2013; Cryan & Dinan, 2012; Kelly *et al.*, 2016).

It has long been known that the mind can influence intestinal well-being (also because this is intuitively evident from an experiential perspective), but the study of the microbiota has also demonstrated the existence of the opposite causal direction, in which intestinal microorganisms exert an effect on psychosocial dynamics.

The significant impact of the microbiota on the human organism includes endocrine and immunological dynamics, as well as neural and psychological ones, thus affecting the entire complexity of human bio-psycho-social interactions. This is one of the reasons why it would be more appropriate to refer to the "microbiota-gut-brain-mind axis" rather than the reductive, yet widely used, term "microbiota-gut-brain axis", which erroneously considers the mind and brain to be entirely coincident (Agnoletti, 2023a).

The impact of microbiota interaction on human cells is remarkable, considering that the total mass of bacteria alone is estimated to be between 0.2 kg and 1 kg (70% of which are located in the gut), the number of bacteria is estimated to be equal to or greater than that of human cells, and most importantly, the genetic content of bacte-

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ria alone is approximately 100 to 1.000 times greater than that of humans (Sender, Fuchs & Milo, 2016a; Sender, Fuchs & Milo, 2016b).

Given the symbiotic relationship between microbiota and human cells, the microbiome – the collective genetic heritage of the microorganisms that make up the microbiota – represents a variable component of the human genome. In fact, due to its significantly larger genetic contribution compared to the human genome, the microbiota plays a crucial epigenetic role in relation to human cells, making it fundamental in determining human well-being, health, and longevity (Chang *et al.*, 2014; Claesson *et al.*, 2012; Cornuti *et al.*, 2013; Dalile *et al.*, 2019; Kumar *et al.*, 2014; López-Otín *et al.*, 2013; Ottaviani, 2011).

Understanding epigenetic dynamics is essential to grasp the complex interaction between the microbiota and human cells because studying the factors that influence genetic expression allows us to conceptualize the entire microbiota ecosystem as an extra-genetic factor ("extra" in relation to human DNA) that further extends the adaptive capacity of human cells. The additional genetic contribution of the microbiota enables the human holobiont organism (represented by the collaboration between human cells and microorganisms) to adapt more effectively to different environmental conditions, providing clear evolutionary advantages (Agnoletti, 2023b; Gasbarrini, Dionisi & Gasbarrini, 2019; Fasano, 2022). The nature of the genetic contribution of the microbiota represents the greatest factor of interindividual diversity. In fact, while human interindividual genetic heritage is approximately 99,9% identical, the genetic diversity of the microbiota between two individuals can reach as high as 80-90% (Gasbarrini, Dionisi & Gasbarrini, 2019).

The genetic diversity of the microbiota is primarily determined by environmental factors and only marginally by the host's human genetics (Rothschild *et al.*, 2018). Therefore, we can assert that almost the entire contribution of the microbiota to human cells is due to environmental factors rather than human genetic content. Human fitness is thus highly dependent on the epigenetic role of the microbiota, as it significantly expands the body's ability to adapt to variable contexts, such as the food we eat, the physical activity we engage in, the physicochemical quality of the environments we frequent, and the psychosocial stress we experience. Despite these variations, the microbiota still ensures the homeostasis of key physiological systems, including blood pressure, heart rate, blood volume, hydration, pH, bone density, and more.

For the purposes of this discussion, it is important to note that the currently available literature has clearly demonstrated that factors such as:

- Nutrition (Putignani & Dallapiccola, 2016; Valitutti, Cucchiara & Fasano, 2019; Zhang & Zuo, 2018),
- Physical activity (Allen *et al.*, 2018; Aragón-Vela *et al.*, 2021; Mohr *et al.*, 2020),
- Sleep quality (Neroni *et al.*, 2021; Sen *et al.*, 2021; Smith *et al.*, 2019),

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- Circadian rhythms (Bermingham *et al.*, 2023; Thaiss *et al.*, 2014; Voigt *et al.*, 2016),
- Physicochemical environmental quality (De Filippis *et al.*, 2024; Estevinho *et al.*, 2024; Mousavi *et al.*, 2022),
- Perceived social support (Cryan *et al.*, 2019; Kim *et al.*, 2021; Winter *et al.*, 2018),
- Psychological well-being (Chang *et al.*, 2024; Ge *et al.*, 2022; Ilchmann-Diounou & Ménard, 2020), influence the composition of the microbiota, thereby modifying its adaptive contribution – both epigenetic and non-epigenetic – to the entire organism, ultimately affecting human health and quality of life. For the purposes of this discussion, it is particularly interesting to note that the currently available scientific literature does not highlight the dominance of one factor over the others in influencing the microbiota. Instead, it describes a dose-dependent quantitative effect for each of them.

All the factors considered influence one another to some extent (for instance, physical activity affects sleep quality, and circadian rhythms impact the metabolic effects of nutrition). However, each factor also maintains a certain degree of autonomy from the others due to its unique causal mechanism in shaping the microbiota. For example, the management of psychological stress and the physicochemical environmental quality are both factors that influence the microbiota, but they do so at least partially independently of each other, as they follow different causal pathways. The "sensitivity" of the microbiota to multiple factors is thus somewhat independent of the specific nature of the influencing factor itself. In other words, whether it is nutrition, psychological well-being, or physical activity, there will always be an impact on the composition of the microbiota. For instance, dysbiosis may initially stem from a nutritional deficiency, a psychological trauma, or excessive sedentary behavior, even though the causal dynamics linking nutrition, psychological states, and physical activity to the microbiota are at least partially independent of one another.

The fact that various factors converge in modifying the microbiota does not mean that their impact is the same in terms of intensity or frequency. Naturally, the causal pathway resulting from chronic sleep deprivation has a different impact on the microbiota compared to, for example, a single mild exposure to pesticides.

The funnel effect

Considering the diversity and partial independence of the different factors that influence the microbiota, it is equally interesting to highlight the common convergence in modifying the composition of this complex ecosystem that colonizes our body.

For these reasons, the authors propose the concept of the "microbiota funnel effect" to describe the characteristic convergence of the seven main factors identified in the scientific literature (nutrition, physical activity, psychological, sleep-related, so-

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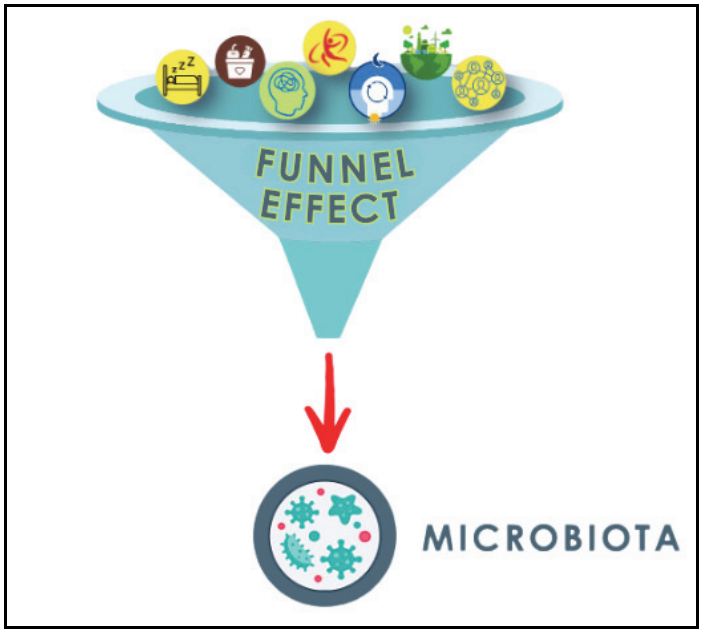
cial, environmental, and circadian), which, in a partially independent manner, contribute to altering the composition of the gut microbiota (see Figure 1).

Fig. 1. The Microbiota's Funnel Effect



The common convergence of the seven lifestyle-related factors on the microbiota has significant implications for peoples well-being and health, highlighting the need for a systemic and holistic approach to promoting well-being and treating suboptimal and pathological conditions.

From a clinical perspective, the "microbiota funnel effect" asserts that, given the high psycho-neuro-endocrine-immunological integration of the considered factors and the significant epigenetic impact of the microbiota on human cell function, the only way to ensure an effective clinical intervention is to adopt a systemic vision that includes a comprehensive evaluation of all factors. Continuing to use a specialist approach that analyses and treats only one (or even some, but not all) of these factors by decontextualizing it from the others is equivalent to adopting a reductionist perspective. This reductionistic approach, by failing to account for the convergent and partially independent nature described by the "microbiota funnel effect", proves to be clinically ineffective, particularly in addressing chronic conditions.

The concept of the "microbiota funnel effect" calls for a radical shift in clinical protocols, as it necessitates at least an initial comprehensive (but not generic) as-

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sessment of the individual factors involved and the patient's gut health (which includes the general state of the microbiota). For any professional whose goal is to enhance human health and well-being, the "microbiota funnel effect" represents a new paradigm that demonstrates the clinical necessity of a truly integrated, holistic, and scientific approach – essential for addressing complex issues involving the microbiota.

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