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EDITORIAL

## Healthy axis: Towards an integrated view of the gut-brain health

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### Abstract

Despite the lack of precise mechanisms of action, a growing number of studies suggests that gut microbiota is involved in a great number of physiological functions of the human organism. In fact, the composition and the relations of intestinal microbial populations play a role, either directly or indirectly, to both the onset and development of various pathologies. In particular, the gastrointestinal tract and nervous system are closely connected by the so-called gut-brain axis, a complex bidirectional system in which the central and enteric nervous system interact with each other, also engaging endocrine, immune and neuronal circuits. This allows us to put forward new working hypotheses on the origin of some multifactorial diseases: from eating to neuropsychiatric disorders (such as autism spectrum disorders and depression) up to diabetes and tumors (such as colorectal cancer). This scenario reinforces the idea that the microbiota and its composition represent a factor, which is no longer negligible, not only in preserving what we call "health" but also in defining and thus determining it. Therefore, we propose to consider the gut-brain axis as the focus of new scientific and clinical investigation as long as the locus of possible systemic therapeutic interventions.

**Key words:** Microbiota; Gut-brain axis; Dysbiosis; Symbiosis; Person-centered medicine; Personalized medicine

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**Core tip:** The interest for gut-microbiota is rapidly increasing due to its impact on many physiological and pathological functions. In particular, gut-brain axis, in which commensal microorganisms' impact, in interplay with immune and endocrine systems,

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might be a tool and a focus of both scientific investigation and therapeutic interventions. Accordingly, here, by focusing on some examples of multifactorial conditions, such as obesity, we advocate for a redefined health account, in eco-systemic terms, in order to promote a new way of considering the detection of and the approach to diseases. A healthy axis could become part of a more effective perspective towards both person-centered medicine and personalized medicine.

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## INTRODUCTION

The term microbiota usually refers to the community of different microorganisms populating specific ecological niches within the human body (*e.g.*, in the gastroenterological system, the gut microbiota), thus forming a mutually advantageous relationship, often called symbiosis, with the host<sup>[1]</sup>. Especially in the gut (the most investigated area), microbiota contributes to the maintenance of its integrity, taking part into energy harvesting from food, constituting the first barrier against pathogens and modulating the immune responses<sup>[2]</sup>.

The composition of gut microbiota (GM) is quite complex and can undergo changes (more or less radical) in response to both exogenous (*e.g.*, life style and habits, interactions with pathogens and/or chemicals, environmental agents) and endogenous factors (such as genetic profile)<sup>[2-4]</sup>.

Notably, the number of microorganisms living in the intestines outnumber the cells of our organism. Additionally, more than 1000 bacterial species reside in the human gut, primarily situated within distal ileum and colon, predominantly belonging to Bacteroidetes and Firmicutes phyla<sup>[1]</sup>. Nevertheless, as already mentioned, the composition could be highly variable, dynamic, and susceptible to rapid changes in response to external factors or perturbations in health.

In fact, an increasing number of studies suggests that the microbiota (and especially the GM) plays a role in shaping a vast number of physiological functions of the human organism.

For example, the dysbiosis, a structural and compositional imbalance in intestinal microbial populations, can contribute, either directly or indirectly, to both the onset and development of various pathologies. This allows us to put forward new working hypotheses on the origin of some multifactorial diseases: From eating to neuropsychiatric disorders (such as autism spectrum disorders and depression)<sup>[5]</sup>, up to diabetes and tumors (such as colorectal cancer)<sup>[6-8]</sup>.

This scenario reinforces the idea that the microbiota and its composition represent a factor, which is no longer negligible, not only in preserving what we call "health" but also in defining and thus determining it<sup>[9]</sup>.

Indeed, from the perspective of the gastroenterologist, the increasing relevance of the microbiota impact in the understanding some pathological disorders, offer also a chance to reconsider the boundaries of current clinical analysis, towards the embrace of a more systemic mindset on both health and disease, with an eye to therapeutic interventions<sup>[9]</sup>.

## STUDY ANALYSIS

It is known that biological functions are modulated by the interaction with the environment. However, the very notion of symbiosis and its implications challenge the mainstream view concerning the sharp distinction between external and internal factors<sup>[10]</sup>. Since decades, ecologists warned us that the environment is not just a container or simply a background in which biological species live and exist. The relationship between the host and its microbiota does not simply take place within the environment. It rather constructs it. Furthermore, at the microbiota level, both commensal and non-commensal microbe species take part (either cooperating or struggling among each other's) to specific niches construction, thus constituting a crucial node of that intricate ecosystem that is the human body. If we accept an

ecological view of health, it seems reasonable to reconsider clinical approaches in a more organismic (*i.e.*, the body is more than the sum of its parts/organs) and systemic way<sup>[10,11]</sup>.

Indeed, novel studies confirm that the gastrointestinal tract and nervous system (particularly the encephalon) are closely connected by the so called gut-brain axis, a complex bidirectional system in which the central and enteric nervous system interact with each other, also engaging endocrine, immune and neuronal circuits<sup>[1,4,12]</sup>. Indeed, the articulation of these relationships and the functions of this axis are also modulated by the gut microbiota, thus pushing to reconsider the idea that microbial activity is circumscribed only to the intestines. Because of that the concept of microbiota -gut-brain axis has been introduced to highlight the relevance of this interplay in the development of both metabolic and neurological conditions, thus challenging a sharp taxonomy of diseases, primarily based on organ situation<sup>[9,10]</sup>.

In line with these conjectures, the obesity is somehow paradigmatic since it is definitely a metabolic disorder, but it can be seen also from a psychopathological angle<sup>[13]</sup>. This fact, combined with the view of some scholars<sup>[14]</sup> who claim, challenging the reductionist approach of a vast part of contemporary biomedical research, points out that causal trajectories are neither linear nor one-way in the life sciences. It is crucial to recognize that the way by which diseases and disorders are classified, understood and therapeutically addressed, is more often the result of disciplinary interests and history rather than “carving nature at its joints”.

Indeed, recent data indicate a relevant relationship between microbiota composition and the obesity development. This connection should be surely evaluated as a dynamic interplay between microbial activities and human physiology but also be seen considering usual obesity-associated (*e.g.*, anxiety and depression) “comorbidities”<sup>[13]</sup>.

This healthy axis perspective aims at reconsidering this frame by arguing that an ecological, systemic view on health should stop seeing the problem in a mere “additive sense”, by privileging one side (*i.e.*, obesity) over other factors (*i.e.*, comorbidities). Rather, the entire question, obviously without simplifying or neglecting specific issues associated with localized phenomena, should be seen as a “network disease”.

Therefore this suggests that clinical approaches, if not coordinated, should always be performed in the awareness that therapeutic interventions can rarely neglect the presence of different (either cooperating or in contrast) forces acting on the system, *i.e.*, our healthy state.

On the practical side, such an approach implies a twofold change. On one hand, both researchers and clinicians should be more aware that the their way approaching a particular condition is partial and runs the risk of neglecting important factors pertaining to other specialists. Thus, an open attitude towards integration should be encouraged. On the other hand, disciplinary boundaries are not always a direct responsibility of single researchers but rather reflect the way scientific programs are designed and thought at the institutional level, which often mirrors political and economic factors. Therefore our aspiration is that science, at a regulatory level, would become more open, inclusive, fostering the need of promoting a more systemic and integrated perspectives<sup>[9]</sup>. I hope that this might also further, among researchers, the importance of conceptual issues and terms once central within the life sciences (such as “organism”) and now lost within disciplinary boundaries<sup>[15]</sup>. Of course, science is also the difficult combination of innovation and caution. New ideas are important but in order to be “scientific” something more is needed.

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## CONCLUSION

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The increasing studies about the microbiota impact in human healthy generated a great enthusiasm, but runs also the risk of a big hype<sup>[16]</sup>. The idea that microbiota could be the new “Holy Grail” of biology is not only wrong and reductive but it also contradicts the systemic and ecological perspective we support. This is why, in the light of the well know adversities in settling precise causality in biology, it is fundamental to recall extreme caution, avoiding the seducing idea of a privileged point of view that will explain anything else<sup>[9]</sup>.

Bearing this in mind, the importance of microbiota-gut-brain axis should be considered, primarily as a methodological stance, in order to develop new systemic procedures. We hope that this perspective would promote a more satisfactory and definite framework for person-centered medicine<sup>[9,17]</sup>, whereas healthy axis will become not only a research tool but also an active locus for therapeutic interventions.

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