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Viewpoint

Holobionts: emerging strategy for interventions against infectious diseases, metabolic disorders & cancer

Human gut harbours up to 100 trillion microbes and these interact with the host to provide benefits in terms of nutrition, development and immunomodulation. Abundance and diversity of microbes in an organism probably contribute to the evolution of specific host microbe interactions leading to survival of the fittest, both for the host as well as for the microbe[1]. Such interactions have led to the formation of a hologenome that comprises the genetic information of holobiont (host and its associated microbiota) together as a single unit. The phenotype of host is, therefore, not just because of its own genes but those of its associated microbiota as well. The hologenome theory of evolution readily explains our understanding of forces for selection of such interactions during the evolution[1,2].

A recent study on gut immune maturation after colonization with a host specific microbiota revealed the crucial importance of the host microbiota for the development of a normal healthy immune system[3]. In this study, human gut microbiota and mouse gut microbiota were used to stimulate immune maturation of mouse. It was found that although human gut microbiota appeared to be similar at the phylum level to the mouse gut microbiota, yet species and the strain differences contributed to the incomplete maturation of mouse gut immune system. Further, mice colonized with human microbiota exhibited increased susceptibility to *Salmonella* infection. It was likely that co-evolution of host and microbiota favoured specific host microbiota interactions conferring this specificity. Therefore, it is not only the microbiota which adapts according to the host but the host also acquires 'changes' to allow the microbiota to stay inside. In another recent study[4], it was shown that $CD71^+$ cells suppressed the immune system to reduce inflammation during the initial colonization of microbiota in the infant gut after parturition. While this suppression renders the infants highly vulnerable to infection it also provides them the protective benefits of gut microbiota colonization. Manipulating these cells could be strategically exploited to design new interventions to curb neonatal infections and effective vaccinations, as well as normal gut development in premature babies/caesarian section infants who fail to acquire normal gut microbiota from the birth canal.

Some recent studies have added a new dimension to our understanding of the involvement of microbiota in various non-infectious diseases like rheumatoid arthritis[5], neuro-developmental disorders[6], diabetes[7], obesity[8], ageing[9] and cancer[10] including modulating cancer treatment[11,12]. While a direct correlation between expansion of a specific gut bacteria *Prevotella copri* with increased susceptibility to arthritis in human patients has been shown[5], an association between human gut bacteria *Bacteroides fragilis* and the amelioration of autism spectrum disorder (ASD) in a mouse model, as a consequence of the modulation of the levels of several host metabolites by the bacteria, has been reported[6]. Altered gut microbiota is found to be associated with the risk of colorectal cancer[10], and a strong link between altered gut microbiota and prediction of diabetes with a geographically distinct gut microbiota composition has been shown[7]. Further study by Duca *et al*[8] linked the presence of unfavourable gut microbiome with the host susceptibility to obesity by observing germ free mice becoming obese upon transfer of microbiota from obese prone rat.

Besides the microbiota influence on metabolism, its involvement in normal physiological process like ageing has also been reported in an invertebrate *Drosophila* fly model recently[9]. The anti-cancer immune effects of

cyclophosphamide could be modulated by the intestinal microbiota in a mouse model[12]. That the modulation of tumour microenvironment by the commensal gut microbiota also helped in controlling response to the anti-cancer therapies is an observation of profound clinical importance[11].

Pathogenic enteric and gut microbiota share similar niche factors but differ in the outcome of their colonization[13]. That gut microbiota takes both shelter and nutrition from the host, the question remains as to how pathogenicity among gut microbial strains occurs. An understanding of the mechanisms behind the adaptation of some pathogenic bacteria to a particular host range during the course of evolution may help not only in identifying the origin of pathogenicity but also the evolution of pathogenicity[14]. Carrier animals/ human hosts for certain microbial diseases, such as Typhoid Mary[15], are interesting examples where even though they harbour the pathogenic bacteria they show no symptoms. In such cases the role of gut microbiota in prevention of infection in the host cannot be ignored. The struggle for niche sites between pathogenic and

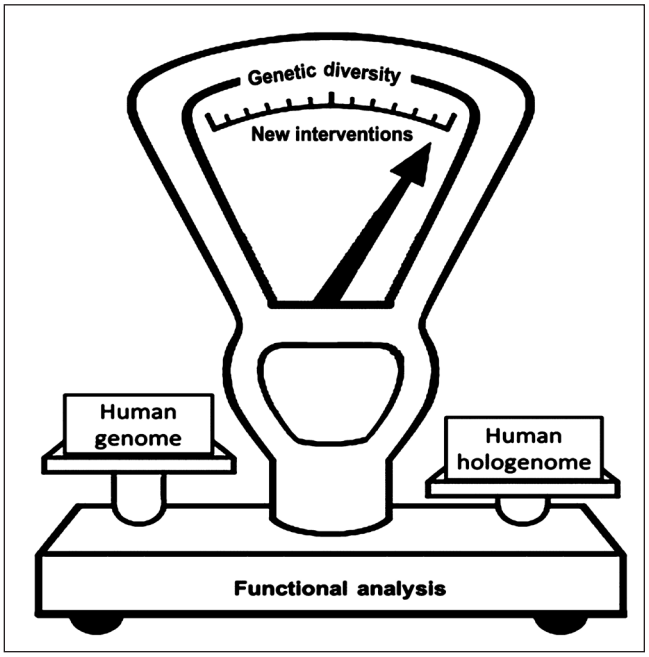

Fig. 1. Functional analysis of human hologenome is more challenging than that of human genome alone due to greater genetic diversity providing more avenues for interventions in the context of human diseases.

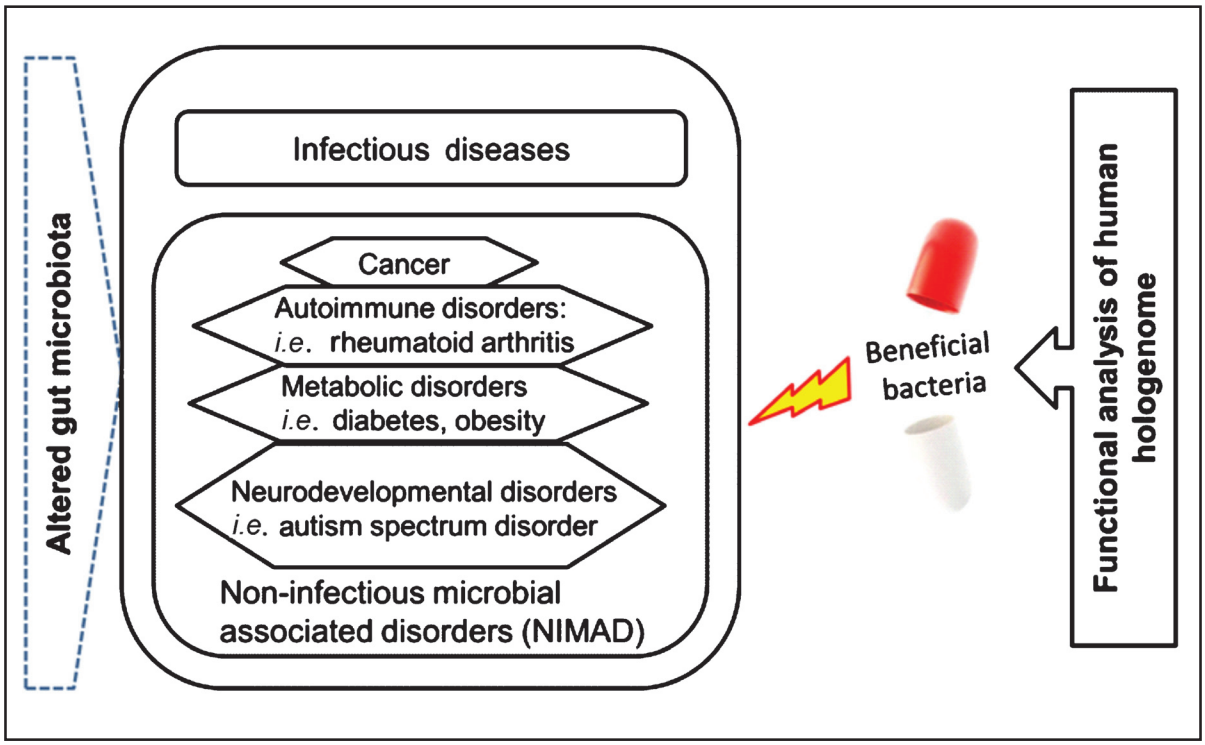

Fig. 2. Altered gut microbiota can lead to non-infectious microbial associated disorders (NIMAD). Beneficial bacteria colonization of gut can be used as a treatment/prophylactic strategy for these disorders. Functional analysis of human hologenome will help to identify the most beneficial microbiota for a particular disorder/disease.

gut microbiota may have also contributed towards the evolution of pathogenicity or symbiosis as competition for resources may have led to the origin of virulence in pathogenic strains. Pathogenic strains and normal gut microbiota contain pathogenicity islands and symbiosis islands, respectively, responsible for their respective activity[14,16]. Hologenome theory of evolution can further help us to understand the development of pathogenicity or symbiosis. Considering the hologenome theory of evolution, a microbe (bacterium/fungus/protozoan) may have many fates depending upon the immune status of the host. Immuno-compromised host can lead to transformation into a pathogen from a normal microbe/ commensal by reducing the selection pressure due to poor immunity. Further, transmission of hologenome variations can lead to potentiation of virulence in the subsequent host generations if they have a poor immune status. In another case, if the pathogen encounters a strong host immune response it can lead to either its elimination from host or formation of a carrier host. This type of a holobiont (carrier host and pathogen) will pass its hologenome to its progeny with fidelity. This progeny under the selective immune pressure may shed the genes responsible for virulence and again can revert to normal commensal in the subsequent host generations. Thus a disease can be interpreted as an interplay between the host, microbiota and pathogenic microbes.

While the examples cited earlier point to the possible microbial 'contribution' to many metabolic, non-communicable and inflammatory disorders, many such diseases perhaps deserve to be reclassified as "Non-infectious microbial associated disorders (NIMAD)". This also seriously questions the primary importance of human genome in genetic susceptibility and pre-disposition to various diseases. This argues for a shift in our focus on studying human genome alone to that of both human and the holobiont genome, to understand disease pathogenesis. Functional analysis of human hologenome with its huge diversity, several log more than the human genome, will pose a great challenge but will have potentially huge pay offs (Fig. 1) in term of designing new interventions to stop pathogenic bacteria from colonizing the host. Equally important strategy will be to enhance the colonization of beneficial bacteria to combat (Fig. 2) infectious and non-infectious microbial origin disorders - immunological, neurodevelopmental, metabolic disorders and even cancer.

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