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Editorial

Gut Microbiome and Suicidal Ideation: An Inscrutable Link?

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"Existence is quite weird - Man is a little germ that lives on an unimportant rock ball that revolves about an insignificant burning star on the outer edges of one of the smaller galaxies, and it is this funny tiny microbe, growing on this planet, which is way out somewhere, who has the ingenuity by nature of this magnificent organic structure to realize its own presence and to evoke the whole universe".

-Alan Watts

With the advancement in highly efficient parallel DNA sequencing technology, mass spectrometers and computational tools, the subject microbiology has undergone disruptive transformations in the study approaches where it extend its focus from the properties of single types of microorganisms in isolation to the operations of entire communities. Our current understanding that our genomic DNA drives the growth, development and behaviours is being counter questioned on the grounds that it's not just our own DNA that governs us but also the DNA of millions of microbes that live almost everywhere in the human body are constantly linked with playing key roles in human health and pathophysiology of diseases. Interestingly, if we consider in terms of the total number of unique genes in human, it is estimated that the microbiome community that natively resides in the ecological niche of our body exceeds our own genes by 10 folds. Nevertheless, human body has been considered as a super-organism as it is composed of over 10 times more microbial cells than our body cells [1].

In the quest of unravelling the secretes of microbiome driven inscrutable mechanisms regulating the human health and pathophysiology of several human aliments, the research window of 'microbiome and human health' has gained significant momentum in the main stream of human disease research and is evolving in logarithmic fashion across the world [2]. As on today, there is no global acceptance about the molecular mechanisms of microbiome driven human health, behaviours and regulation of variety of human aliments. Several notable research institutes and Pharma industries have undertaken series of research project in this direction, for example, NIH had initiated a multidimensional "The Human Microbiome Project" during 2007 to 2016, which resulted in getting answer for numerous questions about the microbiome-human body interactions [3]. A leading genomics research organization, like J Craig Venter Institute has undertaken over dozens of research projects and programs that are focused on this emerging research area with a basic aim of identifying and characterizing the human microbiome in relation to health and diseases [4]. Nevertheless, over 1000 clinical trials are associated with word 'Microbiome' at ClinicalTrials.gov.

In the mainstream of microbiome studies, gut microflora has attracted unprecedented interest since past decade owing to their evolving link with human health and behaviours in general and their inscrutable underpinnings in the causation of depression and thereby suicidality and suicidal ideation. The emerging experimental evidence has established a gut-brain axis that revolves around the human health in general and behaviours in particular. It is this reason why the 'Brain in Stomach' analogy is used to describe this aspect [5]. In the course of evolution, the human gut microbiome has co-evolved with its host for millennia and, therefore, it has strong associations and affiliations with several biological activities like digestion, nutrition, detoxification, body defense, maturation of the host immune system,

and disease. As a result a large number of microbes with high degree of diversity can be found in the mammalian gut [6]. There is emerging evidence that links the gut bacteria with brain function, and this novel finding can be explored to a new set of interventions to target mental health conditions and suicide risk. The literature that accumulated in the recent past has mounted evidence that describes the gut commensal microflora as a significant modulator of psychological disorders including anxiety and depression [7]. The situation warrants investigations because there exists population wise variations in the gut microbiome profile.

Major Depressive Disorder (MDD) is a common, often recurrent, heterogeneous neurological disorder responsible for significant disability and economic burden which in majority of cases has remained a cause for suicidal ideation. The molecular mechanisms underlying the pathophysiology of MDD are implicated with immune, endocrine and neurotransmitter dysregulation. Pre-clinical animal model studies have demonstrated that the complex and dynamic gut microbiota can modulate brain development, function and behaviour by recruiting the same neuroimmune, neuroendocrine and neural pathways of the brain-gut-axis which are dysfunctional in MDD [8]. Amongst the array of metabolites that has been described to be correlated with suicidal ideation, serotonin has been extensively attributed in suicidal behaviours. More precisely, abnormalities in the serotonergic system have been widely implicated in suicidal behaviour and suicide. For example, although it cannot be considered a global reality but in general it has been observed that low levels of 5-hydroxyindoleacetic acid (a measure of serotonin) and increased expressions of platelet 5HT2A receptors are strongly associated with suicidal behaviours [9].

How serotonin is related with gut microbiome? The fact is that, about 90% of the body's serotonin (5-hydroxytryptamine, 5-HT) is produced in the gut region and the recent report states that gut microbiota regulates maturation of the adult enteric nervous system via enteric serotonin networks [10]. Owing to this suspicious link, American foundation for suicide prevention has investigated suicidality risk in concert with distal gut microbiome, and CNS serotonin [11]. Depression a major cause of suicidality has been found to be associated with altered gut microbiota composition and decreased gut microbiota richness and diversity [8]. In an interesting preclinical model studies designed to understand whether the gut microbiota implicated in the pathophysiology of depression, the fecal microbiota transplantation (FMT) experiment was carried out, wherein the FMT from depressed animals was transferred to a microbiota-depleted rat model. Surprisingly, it was observed that FMT induced depression related behavioural & physiological changes in antibiotic treated recipient rats [12]. This clearly indicates that gut microbiome activity is associated with behaviours in general and depression in particular.

In summary, there is substantial emerging evidence which pinpoints the inscrutable involvement of gut microbiome in modulating the depression and there by the suicidal ideation. Identification of suicidal associated unique signatures of gut microorganisms in concert with the levels of well-established suicidal maker Serotonin will pave the way for establishing the significance of gut microbiome as biological marker of suicidality and will help the suicide sensitive population to undergo treatment before commission of suicide.

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