Clostridium Bacteria and its Impact in Autism Research: Thinking “Outside The Box” of Neuroscience

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With a prevalence of 1 in every 50 children in the United States and an incidence that seems to be increasing with time [1,2], there is concern worldwide (not only within the society but also among the scientific community) about the etiologic cause/s of autism. The literature is full of hypotheses dealing with numerous environmental factors and genes accounting for its apparently higher prevalence and associated neuropathology, respectively [3-5].

Considering this multifactorial scenario, elucidation of routes that could potentially serve as point/s of crosstalk between genetic and environmental contributions, may be a priority to better comprehend the pathological basis of the disorder [6]. With this goal, our group recently published a network model able to integrate 112 genes/proteins and 191 environmental factors, already reported in the literature together with potential candidates in the context of autism, where calcium (Ca²⁺) was shown to be its most relevant (central) node [3].

In addition to Ca²⁺, the Rho GTPase RAC1 was shown to be among the most central nodes within the in silico model with no previous autism-related report in the literature. Furthermore, genes belonging to the Ca²⁺-RHO family of GTPases interactome network revealed a differential gene expression in the cerebellum of autistic patients. Therefore, this family may indeed represent one of these points of crosstalk commonly altered in autism spectrum conditions.

A number of anaerobic bacteria are pathogenic to humans and their virulence is based on secreted toxins, which are mainly produced by species from the Clostridium genus [7]. Particularly, these are not invasive bacteria but their secreted active molecules can exert deleterious effects at a distance from the microorganism. Bolte [8] published a hypothetical paper postulating that a subgroup of children diagnosed with autism could be suffering from Clostridium tetani colonization of the intestinal tract and that the neurological symptoms were the direct result of in vivo production of tetanus neurotoxin.

Four years later, Finegold et al. [9] reported that autistic children had nine species of Clostridium not found in control children, whereas controls yielded just three species not found in children with autism. In an elegant study, Parracho et al. [10] demonstrated that the faecal flora of autism spectrum disorders (ASD) patients was enriched in Clostridium histolyticum group (Clostridium clusters I and II) of bacteria than that of healthy children; a particular bacteria group that are recognized to be toxin-producers. Ras and Rho family GTPases are specifically targeted by clostridial toxins [11].

For instance, specific inhibition of Rho, Rac, and Cdc42 by Clostridium difficile toxin B induces apoptosis of granule neurons [12] and can induce changes in spine and density morphology [13]. Thus, the centrality displayed by RAC1 in our in silico model of gene-environment interactions in the autistic context and the differential expression of the Rho family of small GTPases found in the cerebellum of patients [3] is consistent with reports supporting clostridial spores as key elements in the etiology of autism [14].

Moreover, higher concentrations of 3-(3-hydroxyphenyl)-3-hydroxypropionic acid (HPHPA), a compound produced by different species of the Clostridium genus, have been found in urine samples of children with autism and seems to be also increased. In this study, the authors postulated it as a probable metabolite of m-tyrosine (or a tyrosine analog) able to deplete brain catecholamines and lead to typical autism-related symptomatology [15].

Nowadays, a number of researchers are paying attention to “gut dysbiosis” or a state of imbalance in the gut microbial ecosystem that includes excessive proliferation of specific organisms and loss of others, as a potential cause for several diseases and disorders like autism, obesity, and even diabetes [16-19]. With these examples, our aim is to emphasize the use of multidisciplinary research approaches, in addition to neuroscientific ones, to unravel the etiological causes and pathological events associated to autism; perhaps, the best example of multifactorial disorder.

References

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