

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 (Ca^{2+}) was shown to be its most relevant (central) node [3].

In addition to Ca^{2+} , 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 Ca^{2+} -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 (HPPHA), 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.

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