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Letter to the Editor Open Access

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 (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

1. Rutter M (2005) Incidence of autism spectrum disorders: changes over time and their meaning. Acta Paediatr 94: 2-15.
2. Blumberg SJ, Bramlett MD, Kogan MD, Schieve LA, Jones JR, et al. (2013) Changes in prevalence of parent-reported autism spectrum disorder in school-aged U.S. children: 2007 to 2011–2012. National Health Statistics Reports 65: 1-12.
3. Zeidán-Chuliá F, Rybarczyk-Filho JL, Salmina AB, de Oliveira BH, Noda M et al. (2013) Exploring the Multifactorial Nature of Autism Through Computational Systems Biology: Calcium and the Rho GTPase RAC1 Under the Spotlight. Neuromolecular Med 15: 364-383.
4. Zeidán-Chuliá F, Gursoy UK, Könönen E, Gottfried C (2011) A dental look at the autistic patient through orofacial pain. Acta Odontol Scand 69: 193-200.
5. Casanova MF (2007) The neuropathology of autism. Brain Pathol 17: 422-433.
6. Williams EL, Casanova MF (2010) Autism or autisms? Finding the lowest common denominator. Bol Asoc Med P R 102:17-24.
7. Popoff MR, Bouvet P (2009) Clostridial toxins. Future Microbiol 4: 1021-1064.

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8. Bolte ER (1998) Autism and *Clostridium tetani*. Med Hypotheses 51: 133-144.
9. Finegold SM, Molitoris D, Song Y, Liu C, Vaisanen ML, et al. (2002) Gastrointestinal microflora studies in late-onset autism. Clin Infect Dis 35: S6-S16.
10. Parracho HM, Bingham MO, Gibson GR, McCartney AL (2005) Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. J Med Microbiol 54: 987-991.
11. Busch C, Aktories K (2000) Microbial toxins and the glycosylation of rho family GTPases. Curr Opin Struct Biol 10: 528-535.
12. Linseman DA, Laessig T, Meintzer MK, McClure M, Barth H, et al. (2001) An essential role for Rac/Cdc42 GTPases in cerebellar granule neuron survival. J Biol Chem 276: 39123-39131.
13. Tashiro A, Minden A, Yuste R (2000) Regulation of dendritic spine morphology by the rho family of small GTPases: antagonistic roles of Rac and Rho. Cereb Cortex 10: 927-938.
14. Finegold SM (2008) Therapy and epidemiology of autism--clostridial spores as key elements. Med Hypotheses 70: 508-511.
15. Shaw W (2010) Increased urinary excretion of a 3-(3-hydroxyphenyl)-3-hydroxypropionic acid (HPHPA), an abnormal phenylalanine metabolite of Clostridia spp. in the gastrointestinal tract, in urine samples from patients with autism and schizophrenia. Nutr Neurosci 13: 135-143.
16. Petrof EO, Claud EC, Gloor GB, Allen VE (2013) Microbial ecosystems therapeutics: a new paradigm in medicine? Benef Microbes 4: 53-65.
17. Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, et al. (2013) Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. Proc Natl Acad Sci U S A 110: 9066-9071.
18. Hansen CH, Krych L, Nielsen DS, Vogensen FK, Hansen LH, et al. (2012) Early life treatment with vancomycin propagates Akkermansia muciniphila and reduces diabetes incidence in the NOD mouse. Diabetologia 55: 2285-2294.
19. Pequegnat B, Sagermann M, Valliani M, Toh M, Chow H, et al. (2013) A vaccine and diagnostic target for *Clostridium* bolteae, an autism-associated bacterium. Vaccine 31: 2787-2790.