Unravelling the role of the gut microbiota in rare diseases: a new chance for treatment of Duchenne Muscular Dystrophy

Hilal Kalkan[1], Ester Pagano[2*], Debora Paris[1*], Elisabetta Panza[2], Mariarosaria Cuozzo[2], Claudia Moriello[1], Fabiana Piscitelli[1], Armita Abolghasemi[3], Elisabetta Gazzerro[4], Cristoforo Silvestri[3], Raffaele Capasso[5], Andrea Motta[1], Roberto Russo[2], Vincenzo Di Marzo[1,3#] and Fabio Arturo Iannotti[1#]

[1]Endocannabinoid Research Group, Institute of Biomolecular Chemistry (ICB), National Research Council (CNR), Pozzuoli (NA) 80078 IT

[2]Department of Pharmacy, University Federico II of Naples Italy

[3]Institut Universitaire de Cardiologie et de Pneumologie de Québec and Institut Sur la Nutrition et Les Aliments Fonctionnels, Centre NUTRISS, Université Laval, Quebec City, G1V 0A6, Canada

[4]Unit of Muscle Research, Experimental and Clinical Research Center Charité Universitätsmedizin and Max Delbrück Research Center, 13125 Berlin, Germany

[5]Department of Agricultural Sciences, University of Naples Federico II, Via Università 100, 80055 Portici (NA), Italy.

Background:

Duchenne muscular dystrophy (DMD) is the most frequent form of genetic disorder characterized by an irreversible degeneration of skeletal muscles. Therefore, the identification of novel translational approaches aimed to halt or reverse disease progression remains an important unmet need.

Methods and Results:

We found that in mdx mice, a validated model of DMD, the disease is associated with a significant alteration in the gut microbiota composition compared to healthy controls. Along with microbiota perturbation, plasma levels of related metabolites including short-chain fatty acids (SCFAs) and ketone bodies (KBs) were altered. Supplementation with sodium butyrate (NaB) rescued muscle strength and autophagy and also prevented inflammation associated with excessive endocannabinoid signalling at CB1 receptors to the same extent as deflazacort (DFZ), the standard palliative care for DMD. In LPS-stimulated C2C12 myoblasts, we demonstrate that NaB exerts anti-inflammatory effects, promotes autophagy and prevents dysregulation of microRNA targeting the CB1 receptor gene in a manner depending on the activation of GPR109A and PPARγ receptors.

Conclusions and Significance:

We highlight the translational value of the gut microbiota-endocannabinoid system crosstalk as a novel disease-modifying approach in DMD that may have benefits also in other muscular dystrophies.

Keywords:

Gut microbiota, Endocannabinoid system, Duchenne Muscular Dystrophy, Autophagy, microRNA (miRNA)

Thematic Area:

~~o Frontiers in Microbiome Research~~
- Microbiome: from Research to Clinics

Infrastructures:

Facilities available at ICB (Liquid Mass Spectrometry – LC-MS; Nuclear Resonance Spectroscopy – NMR; Molecular and Cell Biology facilities and Equipment)