COUPLING PACLITAXEL-INDUCED DYSFUNCTIONS WITH GUT-MICROBIOTA ALTERATION: EFFECT OF DIETARY TREATMENT WITH THE POSTBIOTIC SODIUM BUTYRATE

L.Turco[1,2], B. Mateu[1,3], L. Coretti[1,3], C. Cristiano[1,3], M. Cuozzo[1], R. Russo[1,3], F. Lembo[1,3]

[1]Department of Pharmacy, University of Naples Federico II, Italy.
[2]Department of Precision Medicine, University of Campania Luigi Vanvitelli, Italy.
[3]Task Force on Microbiota Studies University Federico II of Naples, Napoli, Italy.

Keywords: Gut microbiota, chemotherapeutics, sodium butyrate, eubiosis.

Objectives: Paclitaxel (PTX) is a broadly used chemotherapeutic agent though its use is limited by debilitating side effects involving both gastrointestinal and behavioural dysfunctions. To explore the possible role of dysbiosis on worsening peripheral and central side effects due to anti-cancer treatment, we profiled gut microbial communities under PTX treatment. Furthermore, we tested the effect of sodium butyrate (BuNa) dietary treatment on shaping gut microbiota profiles to assess its potential to alleviate PTX-induced comorbidities by promoting gut eubiosis.

Methods: Adult CD1 male mice received intraperitoneal injections with PTX (8 mg/kg) or vehicle every two days for a week. A group of mice was also treated with BuNa (0.23 mg/mL/day) in drinking water for 30 days before receiving PTX. All the experimental groups underwent behavioral analysis and biochemical investigations of gut barrier integrity and definition of gut microbiota profiles at 7 days after PTX or vehicle administration. Specifically, caeca were collected for gut microbiota analysis and V3-V4 16S rDNA amplicon sequencing was performed. Demultiplexed paired-end reads from MiSeq were analyzed using the Quantitative Insights Into Microbial Ecology (QIIME2, version 2021.4) and the linear discriminant analysis effect size (LEfSe) method. The microbiota network of interactions was studied in all groups by applying Spearman co-occurrence network using the CoNet plugin for Cytoscape (3.9.0).
Results: PTX treatment perturbed microbiota composition mainly influencing Bacteroidetes/Firmicutes ratio and impacting on specific microbial taxa belonging to Bacteroidetes phylum, namely *Odoribacter splanchnicus*, *Muribaculum intestinale*, *Prevotella stercorea*, and *Alistipes senegalensis*. BuNa administration restored the altered balance between Bacteroidetes and Firmicutes and was able to modulate the levels of bacterial genera involved in SCFAs production. In particular, BuNa administration induced a new metabolic network of microbial assemblages, sustained by the acetate- and butyrate-producing *Clostridium saccharolitycum*.

Conclusions: PTX-induced pathophysiological alterations were clearly accompanied by gut microbiota changes. BuNa treatment defined a new gut microbiota signature by reducing bacterial genera able to promote intestinal dysbiosis and inflammation such as *Prevotella* and increasing bacteria involved in SCFAs production. On this basis, BuNa-promoted gut eubiosis may represent a beneficial adjuvant possibly involved in the improvements of peripheral and central side effects during chemotherapy cycles.