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PROBIOTICS, PREBIOTICS & NEW FOODS: NOVELTIES FROM THE 11TH INTERNATIONAL MEETING

L. Capurso[1], F. Franceschi[2]

[1]Department of Gastroenterology, San Filippo Neri Hospital, Rome, Italy
[2]Emergency Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

Corresponding Author: Lucio Capurso, MD; email: lcapurso@libero.it

Abstract – The 11th International meeting Probiotics Prebiotics & New Foods was held in Rome, at Università Urbaniana, from September 12th to 14th 2021. The congress has been attended by 570 people from 36 countries (Algiers, Argentina, Australia, Austria, Belgium, Bosnia – Herzegovina, Brazil, Canada, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Israel, Italy, Japan, Lithuania, Morocco, Netherlands, Poland, Portugal, UK, Romania, Russia, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, Spain, Sweden, Swiss, Ukraine, USA).

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The picture showed in the brochure of the meeting (Graphical Abstract) represents Ceres, the Roman goddess of agriculture, fertility and crops, who gave the name to the word "cereal". According to FAO[1], cereals represents about 43% of the global supply of food energy and this is the reason why it is very important to highlight their role, together with botanicals, especially those rich in fiber and polyphenols, in modulating the host gut microbiota, fighting dysbiosis with increased intestinal permeability and contributing to the development of the *holobiont*[2]. In order to explain how cereals and botanicals may influence cell functions, we have to remind that eukaryotes and prokaryotes produce extra-cellular nano-vesicles that contain mRNAs and other molecules that they use to communicate with each other[3]. Plant foods contain also many types of microRNAs resistant to digestion, able to be absorbed into the blood of individuals who consume those foods: the exosome-like nanoparticles (ELNs) from edible plants, such as ginger, are preferably taken-up by intestinal bacteria of the microbiota and influence intestinal barrier function and permeability[4]. Many plants may also produce specific hormones capable of influencing the human gut microbiota composition and the gut barrier, fighting dysbiosis and increased intestinal permeability. Based on all these concepts, the aim of this congress was to highlight the role of probiotics and prebiotics and new foods, as well as the effect of some specific nutraceuticals and botanicals in human health.

R. Marabelli in his lecture highlighted the concept of holobiont, which may be the base of "One's Health", a collaborative, multisectoral, and transdisciplinary approach with the goal of achieving optimal health outcomes, recognizing the interconnection between people, animals, plants, and their shared environment.

Graphical Abstract. Figure of the brochure of the meeting "The 11th International meeting Probiotics Prebiotics & New Foods", Rome, Italy.

E. Ghelardi[5], in his lecture, illustrated the importance to develop an easy system to culture gut microbiota species *in vitro,* for studying the dynamics of the bacterial community without interference of mammalian components. For this purpose, an interesting model of three-dimensional reticular structure of electrospun gelatin scaffolds able to promote bacterial adhesion and facilitate microbial survival after removal from the human host, has been presented. This method appears suitable for studying gut microbiota composition and production of metabolites and to show how these parameters are modulated in response to different factors (e.g., nutrients, drugs, probiotics, infecting agents) either in healthy or in pathological conditions.

Similarly, L. Putignani[6-8], F. Del Chierico[6-8], S. Levi Mortera[7] and P. Vernocch[6-8] suggested, in their lectures, that metagenomic, metabolomics and metaproteomics are crucial methods to study system biology and to integrate and obtain more complex information.

WM de Vos[11] chaired the session "Next Generation Microbial Therapeutics" in which J. Doré pointed out the importance of reconstruction of host-microbes symbiosis by full ecosystem microbiotherapy.

A. Brochot presented very interesting animal data on the activity of *Akkermansia muciniphila,* both live or in pasteurized form. *Akkermansia is able to* improve gut barrier and immunity*, to* decrease cholesterol, blood glucose and diabetes, limiting fatty liver disease[9,10,11] inflammation and obesity,. Based on those results *A. muciniphila* may be considered as the first next-generation beneficial bacteria with significant health effects in humans approved by the EFSA[12].

P. Langella[13] lecture was dedicated to *Faecalibacterium prausnitzii,* a gram-positive bacillus*,* member of phylogenetic core and the most abundant (3.5-5% of the commensal bacteria) and ubiquitous commensal bacterium*,* major member of *Clostridium leptum* group cluster IV, very high butyrate producer and extremely O_2 sensitive microorganism. Interestingly, *F. prausnitzii* is decreased in IBD and is a predictive factor for Crohn Disease (CD) relapse in patients treated with infliximab, while its anti-inflammatory effects appear to be mediated by butyrate.

L. Laterza[14] addressed the problem of multistrain probiotics, which are assembled based on the supposed synergistic effects of included strains, but these effects are very often not evaluated in human randomized controlled trials (RCTs), omitting those different strains could also display an antagonistic effect. In fact, beyond the theoretical synergistic effects exerted by different strains, multistrain products usually contain higher total concentration of bacteria compared to monostrain products with a possible higher dose-related effect. This is the reason why many physicians are attracted by those products, due to the supposed higher and pleiotropic efficacy compared to single strain formulations. Nevertheless, many unsolved questions remain to be determined, including the correct phylogenetic characterization of each strain, their mechanisms of action, the interaction among strains, their stability during shelf life, the viability, the metabolic activity and, last but not least, the overall safety of these products.

M. Koch[15] has also established this point in his lecture "evidence-based medicine and probiotics". AGA guidelines: a critique". He highlighted the need for more therapeutic trials using standardized methods and meta-analyses. Moreover, he has also pointed out that AGA guidelines on probiotics are too restrictive in two areas. The first is that quality of evidence for preventing *Clostridum difficile* diarrhea should be upgraded from low to moderate/high, while the second is that the quality of evidence for the use of probiotics in children acute gastroenteritis is disturbed by heterogeneity of the studies. Nevertheless, conclusions against probiotic use are hard to be understood, while the causes of heterogeneity should be better investigated. Future analysis should be dedicated to single specific probiotics, while a Bayesian analysis could help.

In the session "Gut microbiota, probiotics and vitamin D in IBD" SM Collins[16] discussed about the role of composition changes in microbiota in inflammatory bowel diseases (IBD) in relation to the gut-brain axis which have been reported in 70% of treatment-naïve patients with IBD and in 80% of patients with quiescent IBD. Moreover, when looking at the phylum level, very common findings are a reduction in Firmicutes and Bacteroidetes and a relative increase in Proteobacteria and a reduction in the concentration of *F. prausnitzii.*

F. Facciotti[17] pointed out in her lecture that all IBD patients are dysbiotic, but some of them are more dysbiotic than others. IBD develop as a result of an immune response of the gut-associated mucosal tissue against an altered enteric flora. On this view, the modulation of intestinal immune cell responses by eubiotic or dysbiotic microbiota are very important. For example, the involvement of the microbiota in regulating the balance between Th and Treg subsets is important as well as the promotion of colitis by IgA-coated bacteria. FMT restores microbial eubiosis in one third of patients with IBD with an increase of lamina propria mononuclear cells (CCR7neg, gut homing Tregs, CCR7-α4+, IL-10+CD4 cells) and a reduction of mucosal Th17 cell (CD4+CD161+CCR6+), IL-17+ CD4 cell, and CD8 cell populations.

C. Pagnini[18] reported an interim analysis of a double blind randomized clinical trial with *Lactobacillus* GG (LGG) in patients with mild-moderate activity ulcerative colitis (UC). In a pre-clinical study, LGG demonstrated adhesion to the colonic mucosa and inhibition of pro-inflammatory cytokines in UC. 58% of the patients had a clinical remission with a Partial Mayo mean reduction=0.6 points (p=0.004). No serious adverse events were described.

The lecture of F. Cominelli[19] on "Gut Microbiota, Probiotics and Vitamin D" drew attention to the significant association between IBD and vitamin D deficiency and on the increased risk of clinically active disease, mucosal inflammation, clinical relapse, and low quality of life scores in patients with low levels of this vitamin. Unfortunately, there are no human studies evaluating the anti-inflammatory effect of vitamin D, its potential role in gut microbiota modulation and the possible synergistic effects between vitamin D and probiotics. However, experimental data in animal models, such those knock-out for vitamin D receptor (VDR-KO mice) suggests this possible synergistic effect, that may confer increased anti-inflammatory effects in the intestinal mucosa. Specific probiotic bacteria may increase circulating vitamin D levels and stimulate the mucosal expression and activity of VDR, which in turn may exert immunomodulatory effects. This may contribute to resolve or prevent dysbiosis, further favoring colonization of administered probiotic bacteria and butyrate-producing bacteria, with a consequent activation of the vitamin D/VDR axis. Vitamin D supplementation with 50,000 IU/week of ergocalciferol or 2000-4000 IU/day of cholecalciferol aiming to reach levels of 30 ng/mL, could potentially have a positive impact on disease activity. The mechanism of action is multifactorial but seems to involve regulation of the gut microbiome. VDR was identified as a human gene to shape the gut microbiome. However, the variations of the VDR gene in human with IBD are still unknown. Vitamin D/VDR deficiency could then be considered as a multifunctional susceptibility factor for IBD and appears to be important in the development and treatment of this condition. Further human clinical trials, with appropriate interventional design and aimed at evaluating the impact of vitamin D on the gut microbiota of IBD patients are now needed in order to confirm this hypothesis.

In the session "Gut Microbiota and Cancer" G. Capurso[20] addressed the topic "Microbiota and pancreatic cancer". He explained that case-control, cohort studies and recent meta-analyses reported an association between Periodontal Disease and Pancreatic ductal adenocarcinoma (PDAC) risk with a RR ranging from 1.5 to 2. Interestingly, there are functional similarities shared by pancreas and salivary glands, possibly creating a biological environment attractive to similar types of microorganisms. As periodontitis is caused by specific bacteria, mostly gram-negative and anaerobic, the salivary microbiota was investigated in PDAC patients and controls with findings of specific modifications in PDAC patients. Species, such as *Porphyromonas gingivalis, Actinomycetes, Streptococcus, Bacteroides, Bifidobacterium* and *Fusobacterium* were increased in PDAC patients. *Helicobacter pylori* infection with atrophic body gastritis and the use of proton pump inhibitors, both causes of hypochlorhydria, were also associated with PDAC risk with an estimated odds ratio of 1.75. May some oral microbes, relatively anaerobic, migrate to the pancreas under favorable conditions, such as decreased acidity and contribute to pancreatic carcinogenesis? The required route would be the duodenum in which there is a neutral pH, low O_2, mucus, bile and pancreatic juice, which may deeply influence microbiome composition lowering bacterial load and diversity and favoring a predominance of *Firmicutes* and *Proteobacteria*. Indeed, bacterial translocation from the gut lumen to the pancreas has been already demonstrated, while the duodenal and pancreatic microbioma are very similar; nevertheless, it seems to differ in PDAC patients compared to controls. Based on this rationale, paired salivary and duodenal microbiome have been investigated in 24 patients undergoing echo-endoscopy (EUS) for solid pancreatic lesion highly suspicious for PDAC and in 24 age and sex-matched controls undergoing gastroscopy for any reason (cancers, IBD, celiac disease were excluded). The results showed a lower alpha diversity (richness) according to OTUs in duodenal samples compared to salivary samples only in the cases and a higher beta diversity in duodenal samples compared to salivary samples both in cases and controls. The most significantly increased bacterial family in duodenal samples of cases *vs.* controls was Firmicutes *Erysiphelotrichaceae.* Among cases, Proteobacteria and *Pseudomonadaceae* were significantly more abundant in duodenal samples compared to saliva, while there were no significant differences among controls.

Some case-control studies reported an association between changes in the oral and duodenal microbiome composition and PDAC. It is then possible to hypothesize that microbes may colonize the pancreas coming from the duodenum, then altering the immune response and favoring tumor growth.

In the same session M. Libra[21] and S. Vivarelli[22] addressed the topic "Microbiota modulation in colorectal cancer". Gut microbiota changes during colorectal cancer (CRC) progres-

sion have been, in fact, described. This is a rationale for probiotics administration in CRC patients, in order to guarantee the establishment/preservation of an eubiotic microbiota and to increase compliance to therapies by reducing treatment-related adverse events. In patients with a highly compromised integrity of the gut barrier function, the administration of specific LGG-derived molecules, instead of living bacteria, might be a preferred strategy than the administration of live forms, especially to avoid blood translocation. In a pilot and *in vitro* study, LGG-supernatant (LGG-SN) decreases cancer cell viability in a concentration-dependent manner, shows a synergistic effect in combination with 5-FU or irinotecan and induces a G2/M phase cell-cycle arrest without the occurrence of apoptosis. In the future it will be interesting to identify all LGG-derived molecule(s) mediating an anti-cancer effect and to characterize the mechanism of action in a translational model (i.e., patients-derived tumor organoids).

The lecture by G. Cammarota[23,24] focused on *Clostridioides difficile* infection (CDI). CDI is increasing in incidence, recurrence and complication rates (including death), and represents a considerable burden for most healthcare systems of the westernized world[23]. A large and reliable body of evidence supports the use of fecal microbiota transplantation (FMT) as an effective treatment option for recurrent CDI. However, despite the excellent clinical outcomes, FMT for CDI is still under diffused, as recently assessed in a Europe-wide survey. Current barriers include the lack of expert centers, the bureaucracy issues, the issues related to donor screening. Stool banks may overcome these drawbacks and are advocated as an effective way to disseminate FMT in clinical practice[24].

Finally, F. Franceschi in his lecture illustrated the importance of an eubiotic vaginal microbiota and its cross-talk with the gut microbiota. The concept of eubiosis is opposite when considering vaginal and gut microbiota. In fact, while richness, diversity and relative abundance are key points for a healthy gut microbiota, all those characteristics are pathological for the vaginal side. Vaginal microbiota is composed by very few species, especially Lactobacilli, able to acidify the vaginal environment, which is an essential mechanism to protect the vagina from the colonization by other bacteria[25]. Five main vaginal community state types have been described, based on predominance of specific *Lactobacillus* species[25]. Type one is mainly characterized by the abundance of *L. crispatus*, type 2 by *L. gasseri*, type 3 by *L. iners*, type 4 by low concentration of Lactobacilli, type 5 by *L. jensenii*. Interestingly, type 4 is the one associated with vaginal dysbiosis and predispose women to the acquisition of sexual and non-sexual infections and cancer. Interestingly, since short chain fatty acids (SCFA) exert a positive role in the gut microbiota, their role in vaginal microbiota is undesirable. We know that there is an active cross-talk among gut and vaginal microbiota species but what we need to better understand whether specific gut microbiota enterotypes may favor or not vaginal dysbiosis[26]. This information is crucial in order to design appropriate and combined interventional strategies to modulate gut and vaginal microbiota in order to prevent infections and cancer.

CONCLUSIONS

Promoting a scientific knowledge on all above-mentioned topics is crucial for improving either prevention or treatment of many pathological conditions associated to dysbiosis in humans. Discussing those topics in a multidisciplinary environment is the key to improve collaboration and research.

Conflict of Interest

The authors declare that they have no conflict of interest.

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