

Immunonutritional Bridge to Liver Health

José Moisés Laparra Llopis*

Molecular Immunonutrition, Instituto Madrileño de Estudios Avanzados en Alimentación, Spain

*Corresponding author: José Moisés Laparra Llopis, Director, Molecular Immunonutrition, Instituto Madrileño de Estudios Avanzados en Alimentación, Spain, Tel: (+34) 625141128; E-mail: J.Moises.Laparra@uv.es

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Introduction

Research efforts provided clear evidences of the straight relationship between immunonutritional factors and its interaction with gut microbiota and finally the immune system determining the gut-liver axis health and liver cancer [1]. Particularly, activators of the innate immune toll-like receptor (TLR)-4 signaling have been proved as essential mediators in hepatocellular carcinoma promotion. The lipopolysaccharide (LPS) of Gram-negative bacteria represents the prototypical activator of TLR4 inducing the expression of a variety of inflammatory mediators. Defined bacterial strains have shown potential to drive antitumor immune responses modulating immune checkpoint blockade [2,3]. In addition, several serine-type protease inhibitors with a potential use in treating diabetes and obesity [4] are present in several staple foods and exhibit structural motifs of strong activators of TLR4-driven innate immune responses [5]. Other cell surface clusters of differentiation such as CD44 and CD36 that respond to TLR4 signals and lipid mediators play important roles in leukocyte guidance and metastatic penetrance and tumor growth.

Innate immune signals engage biochemical tissue responses for neuroendocrine and physiological behavior. Thus, recent studies highlight the potential of immunonutritional TLR4 agonists to selectively modulate the production of lipid mediators normalizing lipotoxicity processes in hyperglycaemic animals [6]. Notably, there has been identified a positive effect of immunonutritional prebiotics normalizing the plasmatic levels of phospholipids such as N-acyl-phosphatidylethanolamine (agonist of the endocannabinoid system) in response to injured liver. Several lines of experimental data suggest that phosphatidylethanolamine becomes abnormally glycosylated under hyperglycemic conditions and plays an important role [7] in linking diabetes and cancer [8]. Some other different lipid mediators such as cholesterol esters and epoxyoctadecenoic acids have also been found to favor the development of aggressive liver cirrhosis and hepatocellular carcinoma [9].

Clinical trials support the beneficial effects of probiotics during a relatively brief-course supplementation in serum lipids and non-alcoholic fatty liver disease (NAFLD) scores [10]. NAFLD has become the most common liver pathology worldwide affecting an estimated 15-30% of most populations. Notably, modulation of intestinal microbiota can potentially influence either immune- or metabolic-based mechanism(s) affecting hepatic endoplasmic reticulum stress and lipidomic profile. This

occurs via some regulatory molecular pathways affecting fat storage [11] to commit macrophage function/activity (i.e., hepatic hepcidin production in response to intestinal dysbiosis, hypoxia, inflammation and oxidative stress) [12]. The species of microorganisms and their potential to regulate nutritional sensors in the gut controlling fat storage and partitioning into physiological cellular compartments are unknown. Here, a better understanding and the use of beneficial pre- and/or probiotics as important determinants of gut microbial diversity and function can greatly impact the immune function and, thereby the risk of developing NAFLD and associated comorbidities.

The conception of the gastrointestinal tract as a passive organ, with the sole function of mediating the absorption of nutrients, has evolved towards a dynamic perspective of the same providing innate immune signals that stem at intestinal level. This context has favored that enormous hopes are placed on immunotherapy, which implies all treatment capable of polarizing a more effective antitumor response of the immune system. Personalized nutrition and, moreover, immunonutritional-based precision intervention could have a significant impact on health to reduce the risk of metabolic and immune diseases and, particularly those associated to cancer promotion and/or progression. Over the last decade, there has been a continuous increasing progress in emergent immunotherapeutic approaches, to the extent that in 2013 immune oncology was granted the scientific breakthrough of the year.

In summary, there can be established straight links between nutrient sensors and their innate immune potential for modulating the severity of liver-related disorders to bridge innate immunity signaling and lipid metabolism. The latter will contribute the way for development of therapeutic applications based on personalized medicine, yet important questions such as how far and to what extent can the consequences of immunonutritional-related metabolic changes be modulated via targeted intervention. However, there remain key unanswered questions about immunonutritional active compounds that overall require a concerted effort to overcome the usually fragmented and compartmentalized approach to address their impact in the gut-liver axis health, immune function and cancer promotion.

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