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Extra Intestinal Manifestations of CD: Common Pathways in the Gut- remote Organs' Axes

Aaron Lerner[1,2,*], Torsten Matthias[2]

[1]B. Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
[2]AESKU.KIPP Institute, Wendelsheim, Germany
*Corresponding author: aaronlerner1948@gmail.com

Abstract Genetic and environmental risk factors for celiac disease are well established, however, the precipitating events leading to development of celiac disease and associated conditions remain enigmatic. Being a multi-faced, multi-organ disease and the multiple extra intestinal phenotypes of celiac disease, further more add to its complexity. The present editorial summarizes the potential mechanisms connecting gut eco system events to remote organ manifestations and dysfunctions in celiac disease. It is suggested that nutrients, the microbiome/dysbiome interplay, the local post translational modification of naive proteins, the leaky gut and the leaked immunogenic or toxic molecules or complexes and the circulating pro-inflammatory immune cells and cytokines are at the basis of the gut-remote organ pathologies, in CD.

Keywords: *celiac diseases, potential mechanisms, gut eco system*

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1. Introduction

Although some genetic (HLA-DQ2\8) and environmental (gluten) risk factors for celiac disease (CD) are well established, the precipitating events leading to development of celiac disease remain enigmatic. The multi-faced phenotypic presentations, the plethora of extra intestinal manifestations and its changing epidemiology and incidence, make CD a very challenging condition. It has been shown that the classical intestinal clinical picture of malnutrition, chronic diarrhea and nutritional deficiencies are disappearing and extra intestinal presentations are emerging. Skin, endocrine, musculo-skeletal, hepatic, cardiologic, rheumatic, hematological, gynecological, fertility, dental, geriatric, immunological, neurological and behavioral abnormalities are often described [1-9]. Nowadays, we are witnessing an epidemiological shift in the disease phenotype toward a more advanced age, and increased prevalence of latent, hypo symptomatic or asymptomatic presentations [1]. The late decade's increase in autoimmune diseases incidence, including CD, opens the long standing debate between the driving force of the genetics vs environmental changes as being dominant [10,11]. For sure, CD is neither a solved problem nor a "closed case" and the future will bring us many new revelations. In view of the growing list of extra intestinal manifestations associated with CD, the recent extended updated review, in the present volume [12] and the increased knowledge of the luminal and intestinal eco-events, affecting the whole body, the present editorial will summarize the common pathways in the gut- remote organs' axes that potentially operate in CD.

Abbasi and Allameh Seyed should be congratulated for taking the task of overviewing the extra intestinal manifestations in CD [12]. The list is long, dynamic and constantly expanding. Since our last review, dating 1992, a lot were added [2] and even some others, not mentioned in Abbasi et al, can be added now: Rheumatoid arthritis, spondyloarthropathy, psoriatic arthritis, inflammatory bowel disease, helicobacter pylori positive or negative lymphocytic gastritis, osteopenia, osteoporosis, learning disabilities, hypotonia, myositis and hypercoagulability [3,6,8,13-18].

2. Common Potential Pathways Connecting Gut Eco Events to CD Extra Intestinal Manifestations

2.1. Nutrition

The association between nutrients and the risk of developing autoimmune diseases was proposed in decades ago and was reviewed recently [19,20]. Despite our increasing knowledge, little is known about the interplay of diet and gut microbiota in human immune-mediated diseases. Dietary milk, carbohydrates, fats, protein, fiber, fruit, vegetables, animal proteins, sodium chloride and aluminum were studied as potential etiological factors in Crohn's disease. Cow milk, fruit and berry juices, and n3-PUFA were studied in type 1 diabetes. Even multiple sclerosis incidence

was positively associated with the consumption of milk, animal fat and meat, total energy intake and resulting obesity.

Comparable pattern of dietary risk factors was also suggested by in rheumatic arthritis and in some additional autoimmune disease. Contrarily to induction, many nutrients were suggested to act as anti-inflammatory [6]. These include, at list in rheumatoid arthritis, fish oil, primrose oil, black cumin, fenugreek, liquorice, coriander, tomato, carrot, sweet potato, broccoli, green tea, rosemary, hazelnut, walnut, wheat germ and dates. In celiac disease, long chain ω-3 fatty acids, plant flavonoids and carotenoids were shown to modulate oxidative stress, inflammatory mediators and gene expression. More so, phytonutrients such as lycopene, quercitine, vitamin C and tyrosol were shown to protect against the cytotoxic effects of gliadin [6].

The clear cut nutrient of gluten is established in CD with a cause and effect relationship.

Nevertheless, the majority of studies have been equivocal or circumstantial and do not yet support any of these macronutrients as causal factors [20]. Several more specific nutritional factors like; vitamin A, D, selenium, zinc, omega-3 fatty acids and flavanols were associated with immune responses involved in ADs [20]. Like mentioned above, the exact role of diet as a risk factor in these conditions is less clear-cut.

Even the more beneficial nutrients like polyunsaturated fatty acids, plant fiber, fish oils or the intake of vegetables and fresh fruits are far from establishing causality in autoimmune diseases prevention or therapy [19,20]. It seems that the nutritional exposome is far from explaining human reactome. Glucose, salt, emulsifiers, organic solvents, gluten, microbial transglutaminase, and nanoparticles, extensively and increasingly used by the food processing industries, are breaches of the intestinal tight junction integrity and are potential activators of the autoimmune cascade [21]. Microbial transglutaminase, that imitate functionally the tissue transglutaminase, was most recently suggested and shown to be immunogenic in CD patients [22,23].The leaky gut as discussed below, is a well-known pathway that drives not only allergy, but also systemic autoimmunity and may potentially drive the CD associated autoimmune conditions and its extra intestinal phenotypes [24].

A special place should be devoted to gluten, when dealing with autoimmune diseases in general and more specifically, with CD. Gluten is a major constituent of human nutrition. Considering the parallel surge in world-wide gluten consumption and autoimmune diseases frequencies, it is suggested that gluten might have biological detrimental effects. In fact, gluten has multiple side effects, impacting human health, characterized by gluten dependent digestive and extra-digestives symptoms that may be mediated by immunological reactions and triggered by gastrointestinal inadequacy. In the intestinal ecosystem it impacts the microbiome and increases intestinal permeability. Gluten is immunogenic and cytotoxic, pro-inflammatory and activates the innate and adaptive immune systems. On the cellular level it increases apoptosis, decreasing viability and differentiation and impacts nucleic acids and glycoproteins synthesis. It has multiple systemic effects as pro-inflammatory, enhancer of oxidative stress and impacts epigenetic processes. On therapeutic level, gluten withdrawal in certain non-celiac ADs affected individuals (type 1 diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, autoimmune hepatitis and thyroiditis) may be beneficial to minimize gluten's disadvantageous effects in human. In summary, multiple food pro-inflammatory or oxidative ingredients can contribute to the autoimmunogenesis in CD, contributing to its extra intestinal manifestations development.

2.2. Microbiome/dysbiome Balance

The gut ecosystem with myriads of microorganisms and the high concentration of immune system cells can be considered as a separate organ on its own. The balanced interaction between the host and microbial cells has been shaped during the long co-evolutionary process. In dysbiotic conditions, however, this balance is compromised and results in abnormal interaction between the host and the microbiota.

Some members of the gut microbiota have been linked to specific autoimmune diseases.

Changing a single bacterial species and/or the entire commensal

Community can alter the outcome of a specific autoimmune disease, due to the Imbalance of pathological/protective immune responses [25]. The summary of specific microbial species in relation to define animal models of ADs and their functions, in relation to disease progression, was most recently reported [26]. In CD, increased diversity of Lachnoanaerobaculum, Prevotella, Actinomycetes and Lachnoanaerobaculum umeaense was found. Ones wander if the CD associated dysbiota is changed while extra intestinal condition are developing?

In addition, the gut microbiota produces a myriad of metabolites that affect host physiology and susceptibility to disease; however, the underlying molecular events remain largely unknown. Diet-induced changes in the composition the gut microbiome can modulate the induction of regulatory versus effector immune responses at the gut level and improve health outcome. Prebiotics, probiotics and dietary fiber are the main avenues for prophylactic and therapeutic intervention against gut inflammation [27]. Most recently the cross talks between diet-microbiota-metabolomics-gene function was further elucidated on an animal model and in CD [28,29]. It was shown that microbial colonization regulates global histone acetylation and methylation in multiple host tissues in a diet-dependent manner: consumption of a "Western-type" diet prevents many of the microbiota-dependent chromatin changes that occur in a polysaccharide-rich diet. Furthermore, supplementation of germ-free mice with short-chain fatty acids, major products of gut bacterial fermentation, was sufficient to recapitulate chromatin modification states and transcriptional responses associated with colonization [28]. These findings have profound implications for understanding the complex functional interactions between diet, gut microbiota, and host health.

2.3. Post Translational Modification of Naïve Proteins

Post translational modification of proteins (PTMP) orchestrate many of the pathways associated with cellular

metabolism, and are thought to be a key regulator in autoimmunity.

Bacteria possess an amazing capacity for adaptation and survival strategies, including differential expression of transcriptome and proteome, variations in growth physiology, and in developmental behavior. PTMP contribute substantially to this adaptability and bacterial cell cycle regulation. On the other hand, the microbial PTMP has a paramount significance to the host. Their enzymatic apparatus is capable to transform naïve/self or non-self-peptides to autoimmunogenic ones. An extended list of enzymes originated from dysbiotic populations, capable of PTMP, was published recently [26].

A well-characterized example PTMP is the tissue transglutaminase (tTg) in CD. In CD, the auto antigen is tTg, capable of deamidating, or transamidating gliadin [30]. This PTMP occurs below the epithelium, resulting in neo-epitopes of gliadin docked on the tTg, inducing anti-tTg, or anti neo-epitope tTg autoantibodies. These are the well-known serological markers of celiac disease [31]. More recently, a family member of tTg, the microbial Tg that is heavily used in the food industry, has been shown as a potent inducer of specific antibodies in celiac disease patients [21]. Interestingly, the same food additive has been suggested as a new environmental trigger and potential inducer of celiac disease [22]. In fact, only celiac patients, and not controls, were shown very recently to mount specific antibodies against the cross-link complex between the microbial Tg and the gliadin [23]. PTMP can present a major luminal or intestinal event that potentially contribute to the extra intestinal phenotypes development or progression in CD.

2.4. Leaky Gut

Increasing knowledge, both functional, morphological and pathological, supports the concept of increased intestinal permeability as an intrinsic characteristic of several autoimmune diseases in both humans, cell-lines and animal models of the disease [32]. Often referred to as a 'leaky gut', its mechanistic impact on the pathogenesis of autoimmune diseases remains unclear. Is it a cause, consequence or coevolutional phenomenon? [32]. Data is accumulating that intestinal luminal environmental factors might perturbate the regulatory mechanisms of the tight junction, resulting in a leaky gut thus breaking equilibrium between tolerance and immunity to non-self-antigens. Nutrients, toxins, allergens, carcinogens, intestinal infections, dysbiotic bacteria, drugs, stress and the recently described industrial processed food additives, can breach the tight junction integrity [21,22,23,24]. In fact, tight junction dysfunction seems to be a major defect in CD and gliadin is one of the effective breacher of this apparatus [24,33]. Intestinal permeability is increased in many AD: Ulcerative colitis, Crohn's disease, CD, inflammatory joint disease, ankylosing spondylitis, juvenile onset arthritis, psoriatic arthritis, type 1 diabetes mellitus and primary biliary cirrhosis. Once again, pointing to the potential involvement of the leaky gut in CD extra intestinal manifestation induction. By conveying the luminal events' informations, through a dysfunctional tight junction, the pro-inflammatory cycle is induced and affect remote organ behavior [32]. The end result of the passage of those non-self-proteins, from the luminal compartment to the sub epithelial one, initiates the autoimmune cascade, thus contributing to peripheral organs' pathology in CD.

2.5. Pro-inflammatory Immune Cells and Cytokines

The richness of the mucosal milieu in immune components, cells and systems, blood and lymphatic vessels, entero-neuronal and endocrine network and mural endo-mesoderm cohabitation, constitute an ideal place to initiate, maintain and propagate the pro-inflammatory and/or the autoimmune cascade.

The mucosal committed immune cells, post translation modified proteins, pro inflammatory cytokines and lymphokines have the capacity to circulate via the local vessels, to bring the inflammatory and the autoimmune message to remote organs, thus creating a gut-extra intestinal organ axes [5,6,8,9,13,14,16,17,18,21,22,23,24,26,28,29,32].

3. Conclusion

Moreover, since dietary components, the metabolomic and proteinomic products of the dysbiota, the transformed neo-peptides can be transported systemically, they can act not only locally, but also in remote tissue, strengthening the pathophysiological interconnections between celiac gut and remote organs' manifestations. Understanding the complex relationship taking place in the celiac intestinal lumen and the cross-talks with the periphery, can bring new therapeutical strategies to help the CD populations.

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