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Beyond the Joint: What's Happening in the Gut

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Abstract Rheumatoid arthritis and celiac disease belong to the autoimmune disease family. Despite being separate entities they share multiple serological and genetic aspects. Celiac disease associated serum bio-markers are observed in rheumatoid arthritis. Contrary to their specific HLA pre-disposition, the diseases share multiple non-HLA loci. Those genes are crucial for activation and regulation of adaptive and innate immunity. Recently, light was shed on the interaction between host genetics and microbiota composition in relation to celiac disease and rheumatoid arthritis susceptibility, connecting bugs and us and autoimmunity. The present editorial updates and clarifies those aspects.

Keywords: *celiac disease, rheumatoid arthritis, serology, genetics, gut-joint axis, bio-marker*

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1. Introduction

Sur LM et al. deserve congratulations for summing up the recent serological and genetic aspects relating celiac disease (CD), juvenile arthritis and rheumatoid arthritis (RA) [1]. Their review sets up the stage to expand on the various aspects shared between those entities, thus reinforcing the gut-joint axis [2]. A question arises: Does the gut events contribute to the articular inflammation? The present editorial will discuss some of those aspects.

2. Shared Serological Markers

The pathogenic role played by specific autoantibodies is far from being elucidated [3]. CD related non-auto and autoantibodies and RA specific autoantibodies have been described in RA and CD, respectively. The occurrence of anti-Gluten antibodies was more common in RA patients, than in controls, with the exception of a few studies [4,5,6]. Anyway, they are not specific, nor sensitive for CD diagnosis and follow-up [7,8]. The more specific and recommended IgA-anti tissue transglutaminase (tTg) autoantibody was found even in RA [9,10]. Furthermore, the presence of RA related autoantibodies in CD patients is increased. IgM rheumatoid factor positive patients had a higher incidence of anti-tTg antibodies [11]. In fact, higher jejunal mucosal production of rheumatoid factor occurs in untreated CD, suggesting that the active immune stimulation to gluten might be involved in mucosal rheumatoid factor synthesis [12]. Reinforcing the ties between the two entities is the observation that the percentage positivity for anti-tTg antibodies is significantly higher in RA patients than in controls (11% compared to 2%, respectively) [13], but not substantiated in a more recent study [14]. Quite interestingly, IgA anti-tTG antibodies were positive in 33% sera of RA patients and a significant correlation between serum and synovial fluid anti-tTG levels was detected [15]. This correlation allowed the authors to hypothesize that anti-tTg antibodies could be synthesized in the site of arthritic lesions. Not surprisingly, silent CD can be detected by anti-tTg antibodies in juvenile rheumatic diseases [16]. The newer CD bio-marker, namely, the anti-neo-epitope tTg, when checked in RA patients, was most recently shown to have lower false positivity than the IgA-tTg one [17].

3. Shared Genetic Markers

Being autoimmune diseases, both are polygenic and inter-related. The genetic aspects of CD and RA are complex individually and much more when inter-combined together [18,19,20,21]. Up to date, around 66 and 50 candidate genes/susceptible loci have been proposed for CD and RA, respectively [18]. Lerner et al [18] summarized recently the relevant non-HLA alleles associated with shared susceptibility to RA and CD and their functions. Those non-HLA shared genes implicate downstream signaling events common to both diseases, resulting in altered T-cell activation and differentiation. Thus, pointing to the critical role of antigen presentation via MHC class II molecules to the TCR and subsequent activation and differentiation of T-cells, involving adaptive and innate immunity pathways, shared between CD–RA immuno-genetics pathways [22,23].

4. The Gut-joint Axis

Multiple observations strengthen the gut–joint axis in rheumatologic and gastrointestinal diseases. It appears that autoimmune inflammation starts in the gut mucosa, years prior to the onset of detectable joint manifestations

suggesting that RA and spondyloarthritis are a gut initiated inflammatory state [18,24,25]. Gut inflammation is associated with age, sex, disease activity and degree of MRI inflammation on sacroiliac joints, and is predictive for disease course, therapeutic decision-making and prognosis [24,25]. Specific alterations in gut bacteria have been shown to enhance or attenuate susceptibility to experimentally induced arthritis and, in humans, increased relative abundance of various microbes in RA/CD and spondyloarthropathy/ inflammatory bowel disease patients have been detected [18,24]. Taking in account common dysbiota, the wide potential of luminal post-translational modification of naïve peptides, the increased intestinal permeability and the multiple communications between the gut and joints by the blood vessels, one can foresee how the two compartments are interrelated [18].

Several mechanisms may be involved in the breaking of tolerance to self-antigens at the intestinal mucosa initiating rheumatologic manifestations in gastrointestinal condition or participating in rheumatologic disease [18,26].

1. Toll-like receptors, part of intestinal innate immunity, triggered by endogenous nuclear material aberrantly released during cell death, are associated with induction of autoimmunity. Anti-tTg antibodies are known to decrease apoptosis clearance and apoptosis generates citrullinated endogenous proteins in CD and RA, respectively.

2. Mucosal microbial constituents can lead to inflammation by molecular mimicry, generating autoantibodies.

3. Migrating mucosal neutrophils may induce tissue citrullination, induced by local peptidylargenine deiminases.

4. Activated neutrophil extracellular traps (NETs), can generate anti- citrullinated protein antibodies via release of citrullinated peptides.

5. Any local factor may lead to an altered balance between autoreactive and regulatory T cells.

6. Elevation of rheumatoid factor, even in the absence of arthritis, is associated with mucosal inflammation.

7. Emerging evidence indicates that blockade of TNF-α by biologics not only ameliorates rheumatoid inflammation, but can affect the secretion and action of gut hormones on appetite, body composition, energy expenditure, muscle catabolism and bone remodeling. A link between the gastrointestinal endocrine axis-immune system and joints may be established through the interaction of proinflammatory cytokines, including TNF-α and gut hormones. [27,28]

8. Additionally, some immunological pathways may be actively involved in the transition of autoimmunity from the intestinal mucosa to the joint: Citrullinated immune complex formation deposition, shared antigenic targets (tTg) in the joint or intestinal PAD, gut–joint epitope spreading, and migration of activated effector T cells from the gut to the joints, mimicking mucosal vaccine's effects on remote organs. Very recently, citrullination of the epithelial neutrophil-activating peptide 78/CXCL5 chemokine, resulted in activation of the monocyte-recruiting chemokine [29]. In fact, epithelial neutrophil-activating peptide 78/CXCL5 is expressed in intestinal inflammation, citrulline is preferentially synthesized in the gut epithelium and PADs reside in the local microbiome and the intestinal mucosa. This may explain how mucosal citrullinated chemokines recruit monocytes to inflamed joint tissue. Most recently, IL-17 and IL-22 were suggested to bridge between the gut and synovial fluid in ankylosing spondylitis [30].

The hypothesis of a food additive (like: microbial transglutaminase) inducing CD [31,32] is strengthened by the observation that the production of cross-reactive antibodies is strikingly increased in the gut of many RA patients. Their food related problems might reflect an adverse additive effect of multiple modest hypersensitivity reactions mediated, for instance, by food originated immune complexes promoting autoimmune reactions in the joints [33].

5. Conclusions

Human beings assemble and maintain a diverse but host-specific gut microbial community along the longitudinal axis of the intestines. However, due to genetic background and changing environment, the physiological microbiota can turn to dysbiota inducing major alterations in gut ecosystem. It is accepted that the rapidly changing environment impact autoimmune diseases susceptibility much more in the last decades. The gut-joint axis is part of the multiple gut-remote organ axes that play a pivotal role in systemic autoimmunity. The major contributors and drivers of this axis are the daily ingested nutrient, specific dysbiota, the luminal transformation of naïve peptides to immunogenic ones and the breached intestinal permeability associated with rheumatic as well gastrointestinal diseases. It is current knowledge that nutrition, the intestinal microbiota and their capacity of post-translational modification of peptides, the gut mucosal immune system, the leaky gut and the autoimmune pathology are deeply intertwined in rheumatic and gastrointestinal autoimmune diseases. Better understanding of the gut-joint axis might unravel novel predictive, preventive and therapeutic strategies to combat those diseases.

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