Metabolome in Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is a systemic autoimmune disease, clinically characterized by poly-articular involvement with chronic synovial inflammation culminating in bone erosions and disability. Metabolomics is an emerging science that is part of the omics group (e.g., proteomic, transcriptomics, etc.). It allows the identification of small molecules, known as metabolites, in a biologic system, catching the alteration of the metabolic status of different tissues and fluids that mirror the cellular perturbation occurring during disease.

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1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease, clinically characterized by poly-articular involvement with chronic synovial inflammation culminating in bone erosions and disability [1].

RA is considered a multistep disease [2]. In the preclinical phase of the disease, genetic predisposition and environmental triggers increase susceptibility to the onset of RA, resulting in the activation of the immune system outside the joint compartment, mainly in the mucosal surfaces. Despite the typical joint involvement in established RA, the pathogenesis of the disease likely begins far from joint structures, in the lungs, periodontium, or intestine [3]. In a second phase, the immune response is amplified systemically, with an expansion of the autoantibody repertoire. Finally, the synovial compartment becomes the target of a local inflammatory response that culminates in clinically evident synovitis [4].

2. Metabolome in RA

Metabolomics is an emerging science that is part of the omics group (e.g., proteomic, transcriptomics, etc.). It allows the identification of small molecules, known as metabolites, in a biologic system, catching the alteration of the metabolic status of different tissues and fluids that mirror the cellular perturbation occurring during disease.

Metabolic pathways can be influenced by various agents such as the surrounding environment, lifestyle, and exposure to microbiota imbalance. In this regard, links between diet-related metabolites and changes in the microbiome have been extensively investigated [5]. In turn, the body's metabolic homeostasis influences the immune response [6], making metabolomics helpful not only to understand pathogenesis pathways, but also to improve early disease detection and therapeutic chances [6].

Nowadays, in the “omics era”, numerous metabolomics assays of peripheral blood, tissues, and urine in patients with RA have been conducted, and many techniques have been employed to characterize metabolomics. Metabolomics is based on two main high-throughput technologies: nuclear magnetic resonance (NMR) and mass spectrometry (MS). After the acquisition of experimental data, multivariate statistical analysis is performed in order to identify the patient’s metabolic profile. MS is more sensitive, but requires sample pre-treatment through separation of individual constituents using liquid chromatography or gas chromatography; this results in greater variability and lower reproducibility. In contrast, NMR does not require sample pre-treatment, yielding more reproducible NMR despite lower sensitivity. In both cases, a plot is obtained that identifies the different metabolites representing the metabolome of a specific sample [7].

Metabolomics has been applied in various fields of medicine, as it has enabled the identification of new possible biomarkers through new methods. This justifies the growing interest in its application in the study of rheumatic diseases.

A recent study demonstrated a correlation between inflammation in the early stages of immune diseases, as detected using C reactive protein (CRP) levels, and the serum/urinary metabolome. The most abundant metabolites present in the samples included glucose, amino acids, lactate, and citrate [8]. In 2013, Young et al. showed a relationship between the early inflammatory stages of RA and the levels of specific metabolites such as low-density lipoproteins, lipids, lactate, glucose, methylguanidine, amino acids, and their derivatives [9]. Nevertheless, inflammation has been related to metabolites derived from oxidative stress processes, the urea cycle, and catabolism protein [10], raising the profile of the urinary metabolome, which, so far, has been studied mainly to evaluate and predict pharmacological response [11] and to accelerate the diagnostic process [12].

However, no differences in metabolites were found between RA patients in the early stage and advanced stage, or between the seropositive and seronegative forms.

Interestingly, a negative correlation was identified between the levels of CRP and citrate, which can be explained by the metabolic reprogramming process resulting from the activation of the immune response [13]. Once innate immune cells such as macrophages and DCs are activated, the glycolysis and pentose phosphate pathways are upregulated, while the citrate pathway, oxidative phosphorylation, and fat acid oxidation are reduced. However, the increase in glycolytic flux can lead to an accumulation of citrate and succinate in the mitochondria, which, once transported to the cytosol, is broken down to form substances necessary for the activation of macrophages and DCs [14].

Conversely, a positive correlation between CRP levels and succinate was highlighted. This finding is consistent with the ability of succinate to stimulate IL-1ß production during the inflammatory process and, furthermore, post-translational processes such as succinylation are able to sustain inflammation [15].

Despite the positive association with glucose and lactate, serum CRP levels correlated negatively with pyruvate levels. Several mechanisms could justify elevated glucose levels during an inflammatory response in order to

satisfy the increased cellular demand [16]. Mainly, the activation of glycolysis and the reduction of pyruvate to lactate are both pathways required for the perpetuation of the immune response [17].

Since the establishment of the inflammatory response requires adequate bioavailability of metabolites to meet the cellular demand necessary for clonal expansion and cytokine production, some metabolites are, therefore, considered potential biomarkers that can predict the onset of the disease and, simultaneously, potential therapeutic targets [18].

However, it should be considered that the major cell lines adapt to different metabolic conditions: T cells reduce glycolysis and prefer anabolic reactions, while macrophages, on the other hand, store glucose in favor of cytokine production. The reason why major cell lines rely on different pathways could be related to the reprogramming of immune cells, influenced by the inflammatory environment.

The different metabolic adaptations mirror the main roles of the involved cell lines. T cells mainly perform a regulatory and memory function. Macrophages predominantly act as effector cells [19]. Anabolic reactions seem to be the exclusive prerogative of T lymphocytes, in particular of naive T lymphocytes and memory cells, while macrophages have developed an adaptation in a hypermetabolic sense and this imprinting is already present in undifferentiated monocytes [18].

Metabolic signature can predict arthritis onset in its early stages and can influence autoantibodies' production, also according to genetic susceptibility.

Studies of genome-wide association (GWAS) highlighted the presence of many loci associated with metabolite levels, which are involved in various metabolic pathways, indicating the genetic influence on the metabolome. These pathways include amino acids, lipid metabolism, carnitines, fatty acid metabolism, intermediates of purine and pyrimidine metabolism, glucose homeostasis, vitamin, and cofactor levels; the genetic polymorphisms of genes linked to these metabolic pathways in RA have been described [20][21].

Specifically, GWAS studies have identified approximately 100 genetic loci implicated in the etiopathogenesis of RA [22].

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