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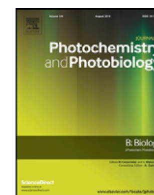

Spontaneous ultra-weak photon emission in correlation to inflammatory metabolism and oxidative stress in a mouse model of collagen-induced arthritis

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ABSTRACT

The increasing prevalence of rheumatoid arthritis has driven the development of new approaches and technologies for investigating the pathophysiology of this devastating, chronic disease. From the perspective of systems biology, combining comprehensive personal data such as metabolomics profiling with ultra-weak photon emission (UPE) data may provide key information regarding the complex pathophysiology underlying rheumatoid arthritis. In this article, we integrated UPE with metabolomics-based technologies in order to investigate collagen-induced arthritis, a mouse model of rheumatoid arthritis, at the systems level, and we investigated the biological underpinnings of the complex dataset. Using correlation networks, we found that elevated inflammatory and ROS-mediated plasma metabolites are strongly correlated with a systematic reduction in amine metabolites, which is linked to muscle wasting in rheumatoid arthritis. We also found that increased UPE intensity is strongly linked to metabolic processes (with correlation co-efficiency $|r|$ value >0.7), which may be associated with lipid oxidation that related to inflammatory and/or ROS-mediated processes. Together, these results indicate that UPE is correlated with metabolomics and may serve as a valuable tool for diagnosing chronic disease by integrating inflammatory signals at the systems level. Our correlation network analysis provides important and valuable information regarding the disease process from a system-wide perspective.

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1. Introduction

Rheumatoid arthritis (RA) is one of the most prevalent chronic autoimmune diseases, occurring in about approximately 1% of the population in Western countries [1,2]. RA manifests as a complex inflammatory syndrome that typically includes joint swelling, pain, and hyperthermia, as well as synovial hyperplasia and destruction of cartilage and bones in the joints. RA is considered a systemic disease that is caused by a variety of pathophysiological processes [3]. These processes are accompanied by increased levels of cytokines such as tumor necrosis factor α (TNF-α) and interleukins (IL-1β and IL-6) in the blood and interstitial fluids, activation of NF-κB pathways (to inhibit apoptosis in various immune cells), and systemic disruptions in inflammatory metabolite synthesis [4–6].

Experimental studies of RA—particularly the pathophysiological mechanisms of therapeutic interventions—are often conducted using animal models. The most commonly used model for RA is the collagen-induced arthritis (CIA) mouse model, which has pathophysiological processes and features similar to patients with RA [7–11]. In addition, advances in metabolomics technology, which now enable researchers to measure extremely low concentrations of metabolites in several pathways simultaneously [12], has facilitated the study of RA in considerably more detail, thereby increasing our understanding of the pathological mechanisms that underlie the disease [13]. We previously studied the differences in molecular profiles between CIA mice and control mice by examining differences with respect to inflammation and reactive oxygen species (ROS), analyzed using univariate and multivariate metrics [14]. In addition to the well-characterized inflammatory phenomenon, issues related to muscle wasting and energy expenditure

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are also present in RA [15–18], and this is reflected by the presence of amine metabolites in the plasma of CIA mice [19].

Differences between CIA mice and control mice were also observed with respect to the intensity of ultra-weak photon emission (UPE), which reflects differences in the organization of the system at a biophysical level [20]. UPE is a process that occurs in all living organisms and is the spontaneous emission of light with extremely weak intensity (10^1–10^3 photons/s/cm^2) in the UV, visible, and near-IR spectra [21]. Many studies have focused on the relationship between UPE and ROS production during metabolic processes [22–26]. Considering that ROS production is closely associated with inflammatory diseases and impaired metabolic processes, it is reasonable to expect that UPE is also associated with inflammatory disease and/or metabolic processes. UPE might therefore be used to help diagnose inflammation and inflammation-related diseases. UPE has been proposed for monitoring lipid peroxidation in cell membranes [27], and applications using UPE in human studies—and their potential relationship with ROS—were summarized by van Wijk [23]. Moreover, the putative relationship between UPE, physiological state, and metabolic processes has been proposed by several research groups [28–31]. Here, we performed an integrated analysis of the biochemical and biophysical differences between CIA mice and control mice, based on the hypothesis that a combined analysis would reveal unique insight into the biochemical and biophysical changes that occur during RA.

Network biology is an emerging field in biomedical research, and network biology tools are increasingly used to identify clusters of correlated parameters, to visualize or explore high-dimensional data, and to understand or interpret interactions that reflect part of a complex biological system [32,33]. Correlation networks have been used in “omics” studies to combine complex data sets, for example combinations of metabolomics, genomics, and/or proteomics data sets. Correlation networks are also used to support the biological interpretation of large data profiles and to differentiate disease phenotypes [34–37]. Here, we expanded the systems-based approach of correlation-based analyses in order to examine the relationship between metabolomics profiling and UPE data. Using this correlation network analysis, we visualized systematic perturbations in bio-photons, inflammatory processes, and ROS-related mediators. This approach may be used to facilitate the diagnosis of disease and/or to discriminate between disease syndromes, particularly with respect to complex chronic diseases such as RA and type 2 diabetes mellitus.

2. Materials and Methods

2.1. Animal Study Samples, Modelling, and Ethics Statement

CIA was induced by the intraperitoneal injection of type II collagen and lipopolysaccharide in adult (6–7 weeks of age) DBA/1 J male mice as described previously [38]; the CIA and control (Ctrl) groups contained 10 mice each. The injections were performed on days 0, 14, 28, 42, and 56; UPE intensity was then measured in each paw (day 70th), and blood was collected into pre-cooled EDTA tubes (BD Vacutainer, Plymouth, UK) immediately after UPE measurements. The blood samples were centrifuged at 3000 × *g* for 10 min, and then stored at −80 °C until metabolic measurements were performed [14]. All animal experiments were performed in compliance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health, Bethesda, MD). All animal care and experiments were approved by the Tohoku Institute of Technology Research Ethics Committee, Sendai, Japan.

2.2. Instruments and Data Acquisition

2.2.1. UPE Instruments and Settings

UPE was measured using a 600 series CCD camera system (Spectral Instruments, Inc., Tucson, AZ) equipped with a closed-cycle mechanical cryogenic unit (held at −120 °C) as the cooling system. Prior to the UPE measurement, mice were maintained in controlled dark conditions. The detailed settings of the CCD system including figures about the measured location on mice is described in Van Wijk et al. [20]. In brief, the CCD camera with 2048 × 2048 pixel resolution and 13.5 × 13.5 mm pixel size was mounted on the top of a dark chamber, and the animal was immobilized using isoflurane anesthesia. A specially designed lens system with 0.5 numerical aperture (on the detector side) and 7 pieces of the restricted number of lenses was used for the UPE measurement, leading 47 photon/s/cm^2 as a minimum detectable number of photons on each pixel. Using this equipment, UPE can be described by intensity (counts/15 min/pixel) at five independent regions on each paw, and was used for further correlation analysis. The regions were named according to the paw measured, and numbers were added (ranging from 1 to 5, indicating the location closest to the tip of the paw through the location farthest from the tip of the paw) as follows: LFP (left front paw) 1 through LFP5; LHP (left hind paw) 1 through LHP5; RFP (right front paw) 1 through RFP5; and RHP (right hind paw) 1 through RHP5.

2.2.2. Extraction of Plasma Metabolites and Metabolomics Analysis

Plasma samples were aliquoted and extracted via different methods in order to obtain separate classes of compounds, including oxylipins, amine metabolites, and oxidative stress–related metabolites. Oxylipins (bioactive lipid mediators derived from polyunsaturated fatty acids) were extracted using solid phase extraction and analyzed using an Agilent 1290 HPLC coupled to an Agilent 6490 triple quadrupole mass spectrometer with electrospray ionization as described previously [14, 39]. Amine metabolites (including free amino acids and their biogenic metabolites) were extracted using AccQ-TagAQC derivatization and analyzed using a Waters ACQUITY UPLC coupled to a Waters Xevo mass spectrometer with electrospray ionization source as described by Noga et al. [40]. Oxidative stress–mediated metabolites—primarily PGs/IsoPGs, NO_2-FAs, lysophosphatidic acids, and sphingosine/sphingosine-related sphingolipids—were extracted using liquid–liquid extraction and analyzed using a validated method with an Agilent 1290 HPLC coupled to an Agilent 6490 triple quadrupole mass spectrometer with electrospray ionization. The peak area of each target compound was corrected using the appropriate internal standard (ISTD), leading to a ratio (target compound/ISTD) that was used for further analysis in the correlation study.

2.3. Data Preprocessing and Statistical Analysis

The metabolomics and UPE data collected from both the CIA and Ctrl groups were included in the correlation analysis. Univariate correlations were performed using the Spearman's rank correlation method using RStudio software (version 3.0.3). Absolute values of the Spearman's rank correlation coefficient ($|r|$) > 0.7 were considered to reflect a strong correlation between parameters, and this threshold was used to create highly correlated graphical networks using Cytoscape software (version 3.3.0, http://www.cytoscape.org) with the MetScape plug-in for extracting and integrating information and for visualizing the correlation networks [41,42]. Positive and negative correlations were indicated by positive and negative values of *r*, respectively.

3. Results and Discussion

3.1. Collagen-induced Arthritis Alters the Local Distribution of UPE

Differences in UPE between CIA and Ctrl mice have been reported previously [20]. A schematic figure was displayed, in order to show the CCD setup of UPE instrument as well as the locations for UPE measurements on mouse front and hind paws (Fig. 1). Here, we used correlation networks to visualize the relationship between individual UPE

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