GRAPPA 2019 Research Recipient Awards Report

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ABSTRACT

A summary of the research conducted by the recipients of the 2019 GRAPPA Research Awards is presented. Dr Alla Ischenko's project was "Role of Metabolomics in Diagnosis, Disease Severity and Progression in Psoriasis and Psoriatic Arthritis: a 2 year prospective pilot study" and Dr Zhenrui Shi's project was "Preclinical analysis of CCR6 and CCL20 in mouse and human joints, respectively, as targets of therapeutic intervention in psoriatic arthritis".

At the GRAPPA 2020 annual meeting, we were pleased to include a session highlighting progress made by recipients of the 2019 GRAPPA Research Awards. The recipients were Dr Alla Ischenko, whose project was "Role of Metabolomics in Diagnosis, Disease Severity and Progression in Psoriasis and Psoriatic Arthritis: a 2-year prospective pilot study" and Dr Zhenrui Shi, whose project was "Preclinical analysis of CCR6 and CCL20 in mouse and human joints, respectively, as targets of therapeutic intervention in psoriatic arthritis". The presentations were outstanding and well received. GRAPPA is proud to highlight the progress made by these promising investigators, and we wish them well as they advance in their careers. Below is a summary of their reports.

Role of Metabolomics in Diagnosis, Disease severity and extent of damage in patients with psoriatic arthritis: a 2-year prospective study by Alla Ishchenko, RJ. Lories, K. de Vlam. The concept of psoriatic disease includes psoriasis (Pso) and psoriatic arthritis (PsA), viewed as an entity, with shared genetic background and overlapping pathophysiology. Both are frequently associated with metabolic disturbances, cardiovascular morbidity and mortality. There is growing evidence that these comorbidities and psoriatic disease share changes in common pathways. Hence, we have formulated the hypothesis of bi-directional effect between metabolic problems and Pso and PsA suggesting not only psoriatic disease predisposes to cardiovascular and metabolic morbidity, but through shared pathways, metabolic comorbidities also directly influence the severity and progression of psoriatic disease.

The objectives of the study are to determine specific metabolic profile in treatment naïve patients with PsA and Pso, to identify “clusters” within patients with PsA based on their metabolic signature, to determine the change in metabolic profile of Pso and PsA patients during the follow up period and to understand the impact of the metabolic signature of the disease with metabolic disturbances associated with PsA and Pso.

This is a pilot longitudinal 2-year prospective observational study with aim to recruit 30 consecutive adult patients with newly diagnosed and treatment naïve PsA, fulfilling CASPAR classification criteria, and 30 patients with Pso, naïve to systemic treatment. Besides demographic, clinical, laboratory data, collected at baseline, at 1 and 2 years of follow up, blood samples will be used for metabolomics analysis of serum and plasma. Nuclear magnetic resonance spectroscopy (NMRS) will be used to perform metabolomic analysis. We will use an untargeted approach and analyze a wide range of metabolites in order to determine alterations in metabolic pathways to identify patterns specific for PsA and Pso. Exploratory analysis including dimensionality reduction based on Multidimensional scaling and Principal component analysis (PCA) will be performed. The collected data will be correlated with clinical and radiographic information.

Preclinical analysis of CCR6 and CCL20 in mouse and human joints, respectively, as targets of therapeutic intervention in psoriatic arthritis, by Zhenrui Shi with Siba P. Raychaudhuri and Sam T. Hwang. Psoriasis arthritis (PsA) develops in about 30%

of psoriasis patients (1). Despite many recent advances, there is still a need for new therapeutic approaches that target the immunopathology of psoriasis and PsA.

Chemokines and their receptors are critical for governing cell movement and interaction. The chemokine receptor CCR6 marks a subset of T cells expressing IL-17 and has a key role in the recruitment of these cells into inflammatory sites (2). The chemokine/chemokine receptor pair CCL20/CCR6 is thought to be highly involved in psoriatic skin disease (3), but its role in PsA is still vague.

We previously engineered a novel CCL20 variant, a CCL20 locked dimer (CCL20LD) that blocks CCR6-dependent cell migration and prevents the development of psoriasiform dermatitis (PsD) in an IL-23 intradermal injection mice model (4). Hydrodynamic delivery (HD) of minicircle DNA(MC) vectors devoid of bacterial DNA resulted in rapid and persistent, systemic high-level transgene expression *in vivo*. In using an IL-23 minicircle (MC)-based murine model, which develops both features of PsD and PsA (5,6), we were able to show that CCL20LD not only ameliorates skin inflammation, but joint inflammation as well (under review). These preliminary data suggest that CCR6-CCL20 could be a key player in the pathogenesis of both psoriatic skin and joint inflammation and that CCL20LD could be therapeutically effective in human psoriasis and PsA.

To further investigate CCR6-CCL20 as a therapeutic target for PsA, we first determined whether CCL20 is expressed or upregulated in PsA joint fluid aspirates. To this end, we chose an antibody array that detects multiple kinds of cytokines and chemokines simultaneously (AAH-CYT-5-2, Raybiotech) and then screened the

presence of chemokines and cytokines in synovial fluid (SF) from a small cohort of patients with PsA or osteoarthritis (OA). As expected, levels of most chemokines were higher in SF from patients with PsA as compared to OA patients. It was striking, however, that the fold change of CCL20 in PsA compared to OA patient samples was the highest among all 17 measured chemokines (CCL2, CCL4, CCL5, CCL7, CCL8, CCL11, CCL17, CCL20, CCL22, CXCL1, CXCL5, CXCL6, CXCL8, CXCL9, CXCL10, CXCL12, CXCL13). Moreover, the intensity of CCL20 was positively correlated with IL-6 intensity in PsA patients, but not in OA patients.

We next investigated if CCR6 expression was increased in the IL-23 MC mouse model that recapitulates some clinical and immunological features of both PsO and PsA. IL-23 MC given to the mice led to enhanced accumulation of CCR6-positive $\gamma\delta$ T cells into the ear skin, cervical skin draining lymph nodes, ankle joints and popliteal lymph nodes. Moreover, we also observed an increased infiltration of CCR6-positive $\gamma\delta$ T cells in the Achilles tendon from IL-23 MC mice. To summarize, we showed that CCL20 was highly upregulated in PsA SF.

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