PB and SF cells were collected from each RA patient, whereas only PB cells were collected from HSSs. The expression of CD14 and CD16 surface markers allowed to identify the monocyte population and the monocyte subsets: “classical” (CD14+CD16−), “intermediate” (CD14+CD16+), and “non-classical” (CD14−CD16+). The M1 phenotype (M1 monocyes) was identified by the evaluation of CD80, CD86, TLR2 and TLR4, whereas the M2 phenotype (M2 monocytes) was identified evaluating CD204, CD163 and CD206 surface markers. Results were expressed as percentage of positive cells over total leukocytes from PB and SF. Statistical analysis was carried out by Mann-Whitney non-parametric test.

Results: In RA patients, the percentage of CD14+CD16+ monocytes was significantly higher in PB compared to that in HS (p<0.001), and it was higher in SF compared to PB (p<0.05). The percentage of CD14+CD16− monocytes was significantly increased in RA-PB compared to HS-PB and RA-SF (p<0.01; p<0.05). RA patients were characterized by an increased percentage of M1 monocyte (CD80+CD86+TLR2+TLR4+CD204+CD163+CD206+cells) in PB compared to HSs and compared to RA-SF. The percentage of M2 monocytes (CD204+CD163+CD206+CD80−CD68−TLR2−TLR4−cells) was also increased in RA-PB compared to HS-PB and to RA-SF, but this increase was lower and not significant than that observed for M1 monocytes. Moreover, the M1-M2 monoocyte ratio was 8:1 in RA-PB. Therefore, in RA patients, circulating M1 monocytes belonged to the “non-classical” subset, whereas M2 monocytes belonged to the “classical” subset. The percentage of circulating mixed M1/M2 monocytes (CD80+CD86−TLR2−TLR4−CD204+CD163−CD206−cells) was higher in RA patients compared to HSs. Moreover, in RA patients, the percentage of these cells was higher in SF than in PB and they primarily belonged to the “intermediate” monocyte subset. Interestingly, the highest percentage of M2 and mixed M1/M2 monocytes was observed in PB and SF of RA patients receiving a higher daily (25mg) and cumulative glucocorticoid dosages.

In conclusion, this study is the first to systematically analyze the changes in immune cell infiltration between younger and older RA patients and to obtain hub age-related genes, which may provide the basis for illuminating the pathogenesis of RA and informing treatment strategies.

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AB0083

CD14+CD90+ CELLS IN PERIVASCULAR AREAS OF RHEUMATOID ARTHRITIS SYNOVIAL TISSUES HAVE POTENTIAL TO DIFFERENTIATE INTO DENDRITIC CELLS

Keywords: Rheumatoid arthritis, Synovium

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Background: We have previously reported that CD14+ dendritic-shaped cells show a dendritic morphology under the electron microscopy and engage in a pseudoperipolysis phenomenon with lymphocytes. CD14+ dendritic-shaped cells express CD90 in the perivascular areas of RA synovial tissues.

Objectives: To examine the differentiation potential of CD14+CD90+ cells into dendritic cells and their relationship to chronic inflammation in RA.

Methods: RA synovial tissues harvested at the time of joint surgeries were used after obtaining informed consent. The harvested tissues were cultured in vitro, and CD14+CD90+ cells were sorted using flow cytometry. Subsequently, the cells were divided into CD14+CD90+ and non-CD14+CD90+ cell groups and cultured in dendritic cell differentiation medium. The populations of cells expressing CD83 and HLA-DR were examined by flow cytometry to determine their differentiation potential into dendritic cells.

Results: At day 7 after dendritic cell differentiation culture, the group of CD14+CD90+ cells had a higher percentage of cells expressing CD83 and HLA-DR than the group of non-CD14+CD90+ cells.

Conclusion: CD14+ dendritic-shaped cells detected in RA synovial tissues are considered to be derived from CD14+CD90+ cells in the perivascular areas, which may be involved in RA inflammation as dendritic cells.

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AB0084

EVALUATING THE IMPACT OF METFORMIN TARGETS ON THE RISK OF RHEUMATOID ARTHRITIS: A MENDELIAN RANDOMIZATION STUDY

Keywords: Rheumatoid arthritis

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Background: Metformin is a first-line therapeutic agent for the treatment of type 2 diabetes, and despite its widespread long-term use in type 2 diabetes, the A variety of specific mechanisms of action of metformin are still being elucidated. Metformin is able to regulate cellular metabolism, proliferation, growth and autophagy, so it may have disease-modifying effects under a variety of other conditions. Metformin has been reported to improve a number of autoimmune diseases. Metformin has anti-inflammatory effects through a variety of mechanisms, including inhibition of tumour necrosis α (TNF-α) induced synovial cell inflammation and angiogenesis[1]. Previously, observational studies have demonstrated the ability of metformin to ameliorate the pathogenesis of rheumatoid arthritis (RA). However, the causality from metformin related targets on the risk of RA remains unknown.

Objectives: The aim of this study was to assess the causal effect of metformin related targets (AMPK, MCI, MG3, GDF15 and GLP1/GCG) on the risk of RA using a two-sample Mendelian randomization (MR) study.

Methods: Genetic proxies for the effects of metformin drug targets were identified as variants in the gene for the corresponding target that associated with HbA1c level. Genetic proxies for the effects of metformin drug targets were identified as variants in the gene for the corresponding target that associated with HbA1c level. The selected genetic variants were associated with HbA1c at a nominal level of statistical significance (p < 0.05) in the Meta-Analyses of Glucosel and Insulin-related traits Consortium (MAGIC), restricted to people of European ancestry to minimise population stratification (n = 88355). Data on RA have been obtained from the NHGRI-EBI Catalog of human genome-wide association studies (14361 cases and 42923 healthy controls)[2]. Two-sample Mendelian randomization (MR) study was conducted to examine the association of metformin related targets and the risk of RA, including the inverse-variance weighted (IVW) method, MR-Egger, and Weighted median (WM). We followed by sensitivity analyses. In addition, we also performed Cochran's Q test, MR pleiotropy residual sum and outlier (MR-PRESSO), leave-one-out sensitivity test to test for heterogeneity, horizontal multiplicity and stability of results.

Results: Genetically predicted 5 targets were not associated with RA with odds ratio (AMPK [OR=1.21, 95% CI=0.61, 2.39, p = 0.58], MCI [OR=1.16, 95% CI=0.92,1.48, p = 0.20], MG3[OR=1.76, 95% CI=0.49, 6.31, p = 0.14], GDF15 [OR=0.63, 95% CI=0.19, 2.05, p = 0.31], GLP1/GCG [OR=0.97, 95% CI=0.80, 1.16, p = 0.78]) (Figure1). In addition, no apparent heterogeneity and no horizontal pleiotropy were observed in the sensitivity analysis.

Conclusion: Our study using MR herein indicated that the metformin related targets is not causally associated with the risk of RA. Future studies shall further systematically explore other potential pathways that metformin may affect to explore the association.

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