FRI0014

A PUTATIVE ROLE OF IGF-1R ON THE PATHOGENESIS OF GOUT THROUGH BINDING TO TRANSCRIPTION FACTORS

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Background: Recent studies showed that SNPs on IGF-1/IGF-1R were highly associated with hyperuricemia and gout [1,2]. It was shown that the IGF-1/IGF-1R signaling pathway played a role in regulating the serum urate level. By modulating the uric acid transporters, IGF-1/IGF-1R influenced the resorption and secretion of uric acid. However, we demonstrated that the increased activation of IGF1R could activate the mTOR pathway, leading to a higher inflammatory response upon pathogen stimulation [3]. This finding indicates that IGF-1/IGF-1R has a role in inflammation, which could result in gout. The IGF-1/IGF-1R pathway may have an overall influence on both urate transporters and inflammatory pathways. It was shown that IGF-1R was not only expressed on the cell surface, but could also internalize into the nucleus and recruit RNA polymerase, regulating the expression of other transcription factors[4]. These transcription factors have been shown to regulate inflammation and have been predicted to bind promoter regions of urate transporters [5]

Objectives: To unveil how the IGF-1/IGF1-R associates with hyperuricemia and gout by studying the IGF-1R SNP rs6598541.

Methods: To assess the influence of the SNP to IGF1-R, the protein expression of IGF-1R on the cell surface was identified by flow cytometry in different genotypes. Additionally, we measured the in vitro immune response of PBMCs with different genotypes upon exposure to MSU and/or LPS. To estimate the overall influence of the SNP on the immune response, we analyzed the SNP's function on transcription factors.

Results: We observed an enhanced inflammatory response in the homozygous genotype with the risk alleles upon LPS and/or MSU stimulation, indicative of a higher risk for gout. However, the IGF-1R surface expression level was comparable between different genotypes. Furthermore, in epigenetic analysis, we found that rs6598541 located in an enhancer region, which is bound by c-FOS, c-JUN and other transcription factors. In recent years, c-FOS and c-JUN have been shown to regulate inflammatory responses.

Conclusion: The risk allele of rs6598541 is associated with a higher inflammatory response, which might be the key factor for gout. Because of the location of the SNP, it might explain the function of IGF-1R in gout, and the pathogenesis might be modulated through transcription factors. According to the recent study, intracellular IGF-1R could act as a transcription factor regulating other transcription factors expression, like c-JUN. Additionally, c-JUN has been shown to regulate inflammatory responses. It is tempting to speculate that IGF-1R regulates transcription factors expression and leads to an overall immune responses, which influence the risk of gout.

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FRI0015

PHENOTYPE AND FUNCTION OF THE PERIPHERAL BLOOD DENDRITIC CELLS OF PSORIASIS PATIENTS WITH AND WITHOUT ARTHRITIS

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Background: Psoriasis is a frequent skin disease that can appear with an arthritic manifestation in approximately 30% of the cases [1]. The underlying excessive immune reaction caused by pro-inflammatory cytokines can be triggered by several risk factors [2]. Various subgroups of Dendritic cells (DCs) in the skin play a crucial role in the induction of the dermal inflammatory response [3].

Objectives: As the role of peripheral blood DCs remains unknown and the cause of an arthritic manifestation is still not completely understood [4], this project aimed to detect differences in phenotype or function of peripheral blood DCs in psoriatic patients with or without arthritis.

Methods: We analyzed peripheral blood cells of 60 psoriasis patients with and without arthritis. Different DC subpopulations were detected by flow cytometry. Monocyte-derived DCs were cultured with or without Lipopolysaccharides to gain immature (iDC) and mature (mDC) cells. The DC phenotype was determined by staining with CD80, CD83, CD86, CD206, CCR7, CD1a, HLA-DR, CD40, GPN-MB, DC209 and CD14. Their T-cell stimulatory capability was analyzed by co-incubation with Carboxyfluorescein succinimidyl ester stained lymphocytes and the quantification of CD4+ T-lymphocytes afterwards. To measure the migration capacity DCs were seeded into transwell chambers with a semipermeable membrane and partly supplemented with Macrophage Inflammatory Protein 3 Beta (Mip3b). Migrated cells were detected by flow cytometry. Measured cell counts were normalized to cell counts without Mip3b stimulation.

Results: Comparing the factor of increase of migrated mDC counts due to mip3b stimulation, we detected a significant lower rate in samples of patients with arthritis (PsA) compared to those of patients without (Ps). Assays of mDCs without mip3b stimulation showed a significant higher count of migrated cells in the samples of the arthritic group [Figure 1]. Cell counts with Mip3b stimulation did vary slightly in the groups. The DC subpopulations and the expression of analyzed cell surface proteins did not show significant differences. The amounts of stimulated T-Lymphocytes did not differ significantly.

Figure 1. Migration assay showing mDCs following Mip3b (+mip3b) as multiples of mDCs without stimulation (-mip3b). The factor of increase is significantly lower in patients with arthritis (PsA) compared to patients without (Ps). Absolute counts of migrated mDCs without Mip3b are significantly higher in the arthritic group. Cell counts with stimulation do not differ significantly (data not shown). N=24, p<0.05

Conclusion: CCL19 (Mip3b) is a potent ligand to the CCR7 receptor inducing migration of DCs towards the lymphatic node [5]. The CCR7 amounts on the DC surface did not differ significantly in the groups. The mDCs without CCL19 stimulation migrated in higher amounts in samples of arthritic patients. Cell counts of stimulated DCs showed only slight differences. These results could be generated by a different appearance of the DCs of arthritic patients that might facilitate migration. Further experiments focusing on this aspect should be performed. A possible effect of disruptive factors (age, sex, medication...) needs to be clarified.

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