5 MONOCYTES TRANSCRIPTOM FROM SLE AND RA PATIENTS REVELAED THE DISEASE-SPECIFIC IMPRINT OF TNFα, IFNα AND IFNγ

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Background and objectives Many cytokines are involved in the pathogenesis of chronic rheumatic diseases like systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). To estimate the role of cytokines in these diseases is intriguing considering the fact that they act together within complex cytokine networks. Although various cell types produce cytokines, monocytes are considered as their principal source. Nevertheless, how functions of monocytes are altered in the course of different rheumatic diseases and how cytokines influence these alterations remained largely unknown.

Materials and methods The global gene-expression profiling has been utilised for development and analyses of SLE and RA profiles (Affymetrix HG-arrays). To decipher the alterations in SLE and RA in more details, cytokine-specific signatures were developed following monocytes stimulation in vitro by tumour necrosis factor α (TNFα), IFNα2a and interferon γ (IFNγ). Ingenuity pathway analysis were utilised for identifying the molecular pathways and cytokine networks within SLE and RA profiles. Whole-genome rVISTA was applied for the promoter analyses of these profiles.

Results Monocytes from SLE and RA patients revealed diseases-specific gene-expression profiles. Ingenuity pathway analysis of SLE and RA profiles identified cytokines as essential players in shaping profiles from diseases and the alterations

within IFNα/IFNγ (IFNs) and TNFα signalling pathways. To decipher the SLE and RA profiles in more details, TNFα–, IFNα2a– and IFNγ–reference signatures were generated in vitro. Comparisons between disease-specific and the in vitro-generated reference signatures showed that the SLE profile was predominantly driven by IFNs, while the RA profile was primarily influenced by TNFα. The IFN-imprints in SLE was characterised by an activation of the transcription factor STAT1. Interestingly, the activation of STAT1 was found to be silenced by TNFα in patients with RA. However, the IFN-imprints were also identified in RA and the TNFα-imprint was evident in SLE. It was obvious that the responses to the same cytokines in SLE and RA were qualitatively and quantitatively different.

Conclusions Altogether, this study has demonstrated that monocytes from RA and SLE patients exhibit disease-dependent gene-expression profiles, which can be molecularly dissected when compared to in vitro-generated cytokine-signatures. The IFNs- and TNFα-imprints were identified to be disease-dependent and principally they reflected the interplay of cytokines within various inflammatory milieus. The results from this study suggest that estimating the imprints of cytokines in rheumatic diseases would be indispensible for an improvement of diagnosis, proper selection of particular cytokine target(s) for therapeutic intervention and for following up and predicting the response to anticytokine drug(s).