Experimental Rheumatology

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The regulation of innate immune mechanisms by microRNA in the development of chronic arthritis

The laboratory of experimental rheumatology has been newly established in January 2015 at the Petersplatz location of DBM. Our general research interest is the role of the innate immune system in the pathogenesis of inflammatory rheumatic diseases, including chronic arthritis. Activation of receptors of the innate immune system, such as Toll-like receptors (TLR), has been shown to occur at an early stage of synovitis in patients with rheumatoid arthritis (RA)(Ospelt *et al.*, 2008). Increasing evidence indicates that inflammatory pathways are controlled by post-transcriptional mechanisms . Epigenetic control of gene expression by microRNA (miR) was demonstrated to be dysregulated in RA (Duroux-Richard *et al.*, 2011; Stanczyk *et al.*, 2008). In our work we have focused on miR regulation of TLR-dependent inflammatory pathways in synovial fibroblasts and monocytes/macrophages. *In vitro* TLR-ligand stimulated synovial cells and monocyte-derived macrophages showed differential expression of miRNA in low-density array analysis. Candidate miRs were confirmed by real-time PCR and possible target genes in the TLR-signaling pathway predicted in silico. A set of miR were identified that were found to be regulated by TLR-ligands. Expression of miR and their target genes are measured in blood or synovial fluid of patients with rheumatoid arthritis. To assess the functional effects of the candidate miRs, they are overexpressed in primary human synovial cells or monocyte-derived macrophages from the peripheral blood. Alternatively, miR antagonists are used to inhibit miR function in these cells. Subsequently, production of proinflammatory cytokines and chemokines as well as proliferation and apoptosis are measured.
We aim at a better understanding of the contribution of dysregulation of miR expression to the pathogenesis of chronic joint inflammation.

Duroux-Richard, I., Presumey, J., Courties, G., Gay, S., Gordeladze, J., Jorgensen, C., Kyburz, D., and Apparailly, F. (2011). MicroRNAs as new player in rheumatoid arthritis. Joint Bone Spine *78,* 17–22.
Ospelt, C., Brentano, F., Rengel, Y., Stanczyk, J., Kolling, C., Tak, P.P., Gay, R.E., Gay, S., and Kyburz, D. (2008). Overexpression of toll-like receptors 3 and 4 in synovial tissue from patients with early rheumatoid arthritis: toll-like receptor expression in early and longstanding arthritis. Arthritis Rheum *58,* 3684–3692.
Stanczyk, J., Pedrioli, D.M., Brentano, F., Sanchez-Pernaute, O., Kolling, C., Gay, R.E., Detmar, M., Gay, S., and Kyburz, D. (2008). Altered expression of MicroRNA in synovial fibroblasts and synovial tissue in rheumatoid arthritis. Arthritis Rheum *58,* 1001–1009.

Selected Publications

Hruska-Plochan M, Li B, Kyburz D, Krutzfeld J, Landmesser U, Aguzzi A, Polymenidou M. (2015) New and emerging roles of small RNAs in neurodegeneration, muscle, cardiovascular and in ammatory diseases. Swiss Med Wkly 145, w14192
Kyburz D, Karouzakis E, Ospelt C. (2014) Epigenetic changes: the missing link. Best Pract Res Clin Rheumatol 28, 577–587
Engler A, Niederer F, Klein K, Gay RE, Kyburz D, Camici GG, Gay S, Ospelt C. (2014) SIRT6 regulates the cigarette smoke-induced signalling in rheuma- toid arthritis synovial broblasts. Journal of molecular medicine 92, 757–767
Kyburz D, Finckh A. (2013) The importance of early treatment for the prognosis of rheumatoid arthritis. Swiss Med Wkly 143, w13865
Niederer F, Trenkmann M, Ospelt C, Karouzakis E, Neidhart M, Stanczyk J, Kolling C, Gay RE, Detmar M, Gay S, *et al.* (2012) Down-regulation of microRNA-34a* in rheumatoid arthritis synovial fibroblasts promotes apoptosis resistance. Arthritis Rheum 64, 1771–1779

Connection to Clinical Practice

Biomarker analysis for outcome prediction in early arthritis patients
We are conducting studies in patients with early stage rheumatoid arthritis to identify biomarkers that are related to disease progression and response to therapy. Biomarkers include cytokines, disease-associated autoantibodies and microRNA. Together with clinical and imaging characteristics we aim at improving prediction of disease outcome.