or miR-140 expression level correlates with the disease progression of knee OA (Zhang et al.; Chao et al.). Under certain circumstances, miRNAs can be released into the body fluids and easily be detected in the blood samples. Therefore, miRNAs are hot candidates as biomarkers for early diagnosis or structural progression of OA.

Objectives: The aim of this study was to evaluate circulating miRNAs in patients with hand osteoarthritis (HOA) and healthy individuals. Simultaneously, we studied specific miRNAs in order to differentiate between erosive and non-erosive subsets of the disease.

Methods: Eight patients with HOA (erosive: n=4, 3 females, mean age=63.7±7 yrs; non-erosive: n=4, 3 females, mean age= 62.4±6 yrs) and 4 healthy controls (3 females, mean age=63.5±7 yrs) were included in this study. Firstly, Advance TaqMan low-density assay (TLDA) was performed for the purpose of miRNA high-throughput screening. Differently expressed miRNAs were further verified by real-time qPCR on the validation cohort in 31 patients with hand OA (19 females, mean age=66.2±7 yrs, erosive: n=9, non-erosive: n=10, healthy controls: n=12).

Results: TLDA profiling displayed 346 circulating miRNAs in plasma of patients with HOA and healthy controls. We demonstrated 40 differently expressed circulating miRNAs in patients with HOA compared with healthy controls. Using a real-time qPCR, we verified increased expression levels of 10 circulating miRNAs in patients with HOA compared with healthy controls, e.g. miR-191-5p (3.4 fold), miR-151a-3p (3.4 fold) or miR-222-3p (2.4 fold). We did not find any specific miRNA, which could distinct erosive from a non-erosive subset of the disease.

Conclusion: Extensive profiling of circulating miRNAs revealed several miRNAs that can be associated with HOA and can help to better understand OA pathogenesis.

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AB0039 AGRIN REPAIRS BONE AND CARTILAGE IN VIVO

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Background: Cartilage defects in the joints are reported in 61% of all arthroscopies^{1&2}. The size of the cartilage repair market is estimated to be \$2.195 million by 2025³. Cartilage defects can evolve into osteoarthritis, in which abnormal load results in cartilage breakdown, joint pain and reduced mobility. Osteoarthritis is the leading cause of permanent disability and absenteeism and affects up to 1/3 of the people over 60yrs. In western countries osteoarthritis costs 1.5-2% of the GDP⁴. Joint replacement with a prosthesis restores some degree of independence but in up to 20% of patients it does not meet expectations⁵ and has a limited life span. There is no pharmacological intervention that arrests or reverts the course of osteoarthritis, despite the desperate need.

We previously published that agrin plays an important role in cartilage homeostasis⁶. The addition of agrin to chondrocytes *in vivo* resulted in enhanced cartilage formation, suggesting a potential role for agrin in cartilage repair.

Objectives: Investigate the potential of agrin for use in cartilage repair.

Methods: Critical size osteochondral defects were generated in mice and sheep and injected intraarticularly with type I collagen gel containing agrin or vehicle. Animals were monitored for 8 weeks or 6 months respectively. MicroCT, histological analysis, qPCR, lineage tracking, reporter assays, chondrogenesis assay, immunohistochemistry were performed.

Results: A single intraarticular administration of agrin induced regeneration of critical-size osteochondral defects in mice, restoring the tissue architecture and bone-cartilage interface. Agrin stem cells to the site of injury and, through simultaneous activation of CREB and suppression of canonical WNT signalling, induced GDF5 expression and differentiation into stable articular chondrocytes, forming stable articular cartilage. In sheep, agrin treatment resulted in regeneration of bone and cartilage, which promoted increased ambulatory activity.

Conclusion: Agrin orchestrates repair morphogenesis at the joint surface by modulating multiple signalling pathways, supporting the therapeutic use of agrin for joint surface regeneration.

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AB0040 PYRUVATE DEHYDROGENASE KINASES AS A POTENTIAL TARGET IN THE TREATMENT OF OSTEOARTHRITIS TO UNLEASH THE METABOLIC FLOW?

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Background: While osteoarthritis (OA) is the most common joint disease worldwide, rheumatoid arthritis (RA) represents the most common type of autoimmune arthritis. In both diseases, fibroblast-like synoviocytes (FLS), which maintain the structural and dynamic integrity of the joint, have been identified as key drivers of cartilage degradation. FLS can be divided into two major populations. The destructive phenotype which is restricted to the THY1- FLS of the synovial lining promotes bone erosion, while THY1+ FLS of the sublining layer drives synovitis. The FLS phenotype is shaped by glucose metabolism, which promotes disease progression in patients with synovitis. However, profound knowledge about the contribution of FLS to pathogenic mechanisms in cartilage degradation is limited.

Objectives: Here, we present the phenotypic features of FLS obtained from patients with OA (OA-FLS) compared to bone marrow-derived mesenchymal stromal cells (MSC) on transcriptomic, proteomic and metabolic levels with the aims (i) to identify novel targets for the development of disease-modifying osteoarthritis drugs and (ii) to distinguish both cell types.

Methods: To this end, we comprehensively compared human bone marrow-derived MSC with OA-FLS isolated from human knee joint sections. MSC and OA-FLS were characterized in detail according to their multipotency, surface marker pattern, cell viability, proliferation rate, morphology and expression of fibroblast- and metabolic-related markers using flow cytometry, immunofluorescence and Seahorse™. More in-depth, selected gene and protein expression patterns were analyzed using qPCR and mass spectrometry.

Results: We observed a similar phenotype of OA-FLS and MSC with regard to the minimal criteria that define a MSC phenotype. In-depth comparison of

OA-FLS and MSC on proteome level revealed 598 differentially expressed proteins. We observed no differences in the expression of classical fibroblast markers such as vimentin, tenascin C and decorin as confirmed on RNA level. Remarkably, fibronectin, which is mainly produced by fibroblasts, is significantly lower expressed at both protein and RNA levels in OA-FLS together with collagen type 1 and CD106. Conversely, CD9, CD54 and fibroblast-specific protein-1 were expressed significantly higher in FLS at both levels, while hyaluronan synthase 1-3 remained unchanged. Of note, in terms of mitochondrial function, human OA-FLS show a significantly lower basal respiration and ATP production than MSC, but a comparable spare respiratory capacity and cellular mitochondrial dehydrogenase activity (NADH amount) per cell. Additionally, we identified the pyruvate dehydrogenase kinase (PDK) 3 to be highly expressed in OA-FLS, while the expression of mitochondrial ATP synthase subunits, electron transport chain complexes and glycolytic enzymes was comparable with MSC. Finally, inhibition of PDK by using DCA resulted in a significant increase in oxygen consumption rate and ATP production in OA-FLS. Thus, our data newly suggest, that PDKs may play a crucial role in the pathogenesis of OA and possibly RA.

Conclusion: Our data provide evidence that, although the classical fibroblast markers do not discriminate between MSC and FLS, the latter demonstrate a significantly higher expression of PDKs, known to inhibit the pyruvate entry into the TCA cycle which finally limits the mitochondrial ATP production. Therefore, shifting the metabolism of FLS from glycolysis to mitochondrial respiration via inhibition of PDKs might be a novel approach in OA for the development of disease-modifying osteoarthritis drugs in order to unleash the metabolic flow.

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AB0041

TO ESTIMATE THE PREVALENCE OF ACETABULAR OSSIFICATIONS IN THE ADULT POPULATION WITH ASYMPTOMATIC, MORPHOLOGICALLY NORMAL HIPS AT CT AND TO DETERMINE WHETHER THE PRESENCE OF LABRAL OSSIFICATIONS IS ASSOCIATED WITH PATIENT-RELATED OR HIP-RELATED PARAMETERS

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Background: In clinical practice, ossifications adjoining the acetabular rim are frequently seen in healthy-appearing hip joints, at all ages. The origin of these acetabular rim ossifications (ARO) is unclear. While ARO have been described by some authors as variants that may mimic marginal acetabular osteophytes, others have hypothesized that ARO may be the cause or the consequence of femoroacetabular impingement. Overall, the literature on ARO is limited, in particular in the healthy population, and their characteristics and origin not fully understood.

Objectives: To estimate the prevalence of acetabular rim ossifications in the adult population with asymptomatic, morphologically normal hips at CT and to determine whether the presence of these ossifications is associated with patient-, or hip-related parameters.

Methods: We prospectively included all patients undergoing thoracoabdominal CT over a 3-month period. After exclusion of patients with a clinical history of hip pathology and/or with signs of osteoarthritis on CT, we included a total of 150 hips from 75 patients. We analyzed the presence and the size of ossifications around the acetabular rim. The relationships between the size of acetabular rim ossifications and patient-related (sex, age, BMI), or hip-related parameters (joint space width, and cam- and pincer-type femoroacetabular impingement morphology) were tested using multiple regression analysis.

Results: The prevalence of acetabular rim ossifications in this population of asymptomatic, non-osteoarthritic hips was 96% (95%CI=[80.1;100.0]). The presence of ossifications and their size were correlated between right and left hips (Spearman coefficient=0.64 (95%CI=[0.46;0.79]), $p<0.05$). The size of acetabular rim ossifications was significantly associated with age ($p<0.0001$) but not with BMI ($p=0.35$), gender ($p=0.05$), joint space width ($p\geq 0.53$ for all locations) or any of the qualitative or quantitative parameters associated with femoroacetabular morphology ($p\geq 0.34$).

Conclusion: Acetabular rim ossifications are highly prevalent in asymptomatic, non-osteoarthritic adult hips at all ages. Their size is not correlated with any patient-, or hip-related parameters except for the age. These findings suggest that ossifications at the acetabular rim, when present in isolation, should not be considered as signs of osteoarthritis or femoroacetabular impingement morphology.

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Table 1. Association between the average severity size of ossifications and patient-related, and hip-related parameters

		Regression coefficient	p-value
Patient-related parameters	BMI	0.02	0.35
	Age	0.04	<0.001
	Gender	-0.43	0.05
Joint space width	Apical	0.17	0.53
	Supero-medial	0.17	0.65
	Supero-lateral	0.06	0.82
Cam morphotype parameters	Angle alpha 45	0.00	0.81
	Offset	0.09	0.34
Pincer morphotype parameters	Acetabular version angle	-0.01	0.83
	Lateral center-edge angle	0.02	0.56
	Acetabular index	0.03	0.53
	Crossover sign	0.26	0.41
	Posterior wall sign	-0.25	0.47

Figure 1. Coronal reformats of CT examinations showing different sizes of labral ossifications in the posterosuperior quadrant (arrows). (a) No labral ossification, (b-c-d-e) Increasingly large labral ossification from left to right. Two lines are visible at the location of the ossification, formed by the contour of the acetabular rim and of the ossification (double line-sign).

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Rheumatoid arthritis - aetiology, pathogenesis and animal models

AB0042

THREE HEMATOLOGIC/IMMUNE SYSTEM-SPECIFIC EXPRESSED GENES ARE CONSIDERED AS THE POTENTIAL BIOMARKERS FOR THE DIAGNOSIS OF EARLY RHEUMATOID ARTHRITIS THROUGH BIOINFORMATICS ANALYSIS

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Background: Rheumatoid arthritis (RA) is a common chronic autoimmune connective tissue disease that mainly involves the joints. The incidence of RA is 5 to 10 per 1000 people[1]. Early diagnosis and treatment of RA can effectively prevent disease progression, joint damage, and other complications in 90% of patients[2]. At present, serum biomarkers used in the diagnosis of established RA are rheumatoid factor and anti-cyclic citrullinated peptide antibody[3]. However, early RA especially serum RF and anti-CCP antibody-negative is difficult to diagnose due to the lack of effective biomarkers. Therefore, it is vital to identify new and effective biomarkers for the early diagnosis and treatment of RA.

Objectives: This study aimed to identify new biomarkers and mechanisms for RA disease progression at the transcriptome level through a combination of microarray and bioinformatics analyses.

Methods: Microarray datasets for synovial tissue in RA or osteoarthritis (OA) were downloaded from the Gene Expression Omnibus (GEO) database, and differentially expressed genes (DEGs) were identified by R software. Tissue/organ-specific genes were recognized by BioGPS. Enrichment analyses were performed and protein-protein interaction (PPI) networks were constructed to understand the functions and enriched pathways of DEGs and to identify hub genes. Cytoscape was used to construct the co-expressed network and competitive endogenous RNA (ceRNA) networks. Biomarkers with high diagnostic value for the early diagnosis of RA were validated by GEO datasets. The ggpubr package was used to perform statistical analyses with Student's t-test.

Results: A total of 275 DEGs were identified between 16 RA samples and 10 OA samples from the datasets GSE77298 and GSE82107. Among these DEGs, 71 tissue/organ-specific expressed genes were recognized. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis indicated that DEGs are mostly enriched in immune response, immune-related biological process, immune system, and cytokine signal pathways. Fifteen hub genes and gene cluster modules were identified by Cytoscape. Eight hematologic/immune system-specific expressed hub genes were verified by GEO datasets. GZMA, PRC1, and TTK may be biomarkers for diagnosis of early RA through combined the analysis of the verification results and the receiver operating characteristic (ROC) curve. NEAT1-miR-212-3p/miR-132-3p/miR-129-5p-TTK, XIST-miR-25-3p/miR-129-5p-GZMA,