collagen type II [37-39], mediating cytokine-dependent susceptibility to oxidant injury [40] and inducing apoptosis [41]. Besides *ADORA2A*, the expression of *COX-2* as an important pharmacological target gene of inflammation was induced. The formation of prostaglandins by *COX-2* is a prominent inflammatory process; inhibition of *COX-2* has cartilage-protective properties, because specific *COX-2* inhibitors (such as celecoxib) have already facilitated distinct advances in RA therapy [42]. Expression of *PGES*, which is involved in the synthesis of prostaglandin E_2 downstream of *COX-2*, was induced in RASFsn-stimulated chondrocytes. *PGES* has already been reported to be induced in chondrocytes after proinflammatory stimuli and mechanical stress [43,44]. As shown here, this is consistent with the induction of *COX-2*, *PGES* and *MMP* genes in human chondrocytes cultured in alginate and stimulated with supernatants of RASF.

Furthermore, NF-κB-activating genes were induced in RASFsn-stimulated chondrocytes, including *RIPK2*, *TLR2*, the NF-κB-associated genes *NF-κB1* and *NF-κB2*, and *SMS*. Promoters of numerous genes involved in inflammation and MMP expression show NF-κB-binding sites [45-47]; NF-κB-dependent genes may therefore be prominent drug targets in RA therapy. RIPK2 has been shown to mediate TNF-α-induced NF-κB activation and induction of apoptosis [48,49].

The induction of numerous cytokines/chemokines fits into the scenario of molecular changes occurring in RA cartilage. Although mature articular cartilage shows little metabolic activity, chondrocytes have previously been described to secrete numerous cytokines/chemokines and chemokine receptors that induce the release of matrix-degrading enzymes and enhance cartilage catabolism [50-52]. RASFsn-stimulated chondrocytes showed an increased expression of *CXCL1–3* (*growth-related oncogene α-γ*; *Groα-γ*), *CXCL8* (*IL8*), *CCL20* (*macrophage inflammatory protein-β*; *MIP-1β*) and the chemokine receptor *CXCR4*. *CXCL1* has been described to initiate apoptosis in osteoarthritis chondrocytes and induces MMP-3 secretion acting through *CXCR2* [53]; *CXCL8* has powerful neutrophil chemotactic properties [54], and *CXCR4* and *CCL20* enhance the release of matrix-degrading enzymes [50,55,56]. Inflammatory cytokines that have already been established as markers for RA-related destruction of cartilage, such as IL-1β and IL-6, were differentially expressed in stimulated chondrocytes. Apart from the differential expression of numerous cytokines/chemokines, RASFsn-stimulated chondrocytes showed a decreased expression of genes protecting the cell from oxidative damage (*catalase* and *glutathione peroxidase 3*).

Furthermore, genes directly involved in ECM composition, such as *COMP*, *CSPG2*, numerous *collagens* and *THBS2*, are repressed in RASFsn-stimulated chondrocytes, that characterizes cartilage destruction in RA as a distinct suppression of chondrocyte ECM synthesis. Contributing to RA-related ECM turnover, the expression of *MMP10*, *MMP12* and *chemokine orphan receptor 1* (*CMKOR1*) was induced in RASFsn-stimulated chondrocytes. *MMP10* expression in chondrocytes after cytokine stimulus contributes significantly to collagen breakdown and thus to cartilage degradation [57], and overexpression of *MMP12* in transgenic rabbits has been shown to facilitate the development of inflammatory arthritis [58]. Treatment of human primary osteoarthritis chondrocytes with *CMKOR1* agonists has previously been reported to induce matrix degradation and MMP activity, suggesting an important role in the development of osteoarthritis [59]. In addition, *testican 1*, an inhibitor of MMP activation that has been described as having an important role in matrix turnover in osteoarthritis cartilage, was repressed in RASFsn-stimulated chondrocytes [60]. However, neither *CMKOR1* nor *testican-1* has yet been described for RA-cartilage turnover.

In summary, our microarray data determined key regulatory molecules of RA-related destruction of cartilage that are consistent with already established marker molecules or that have not yet been determined. As we have established an *in vitro* model that abstracts *in vivo* tissue features, some regulations expected for cartilage destruction, such as a decreased expression of collagen type II or an increased expression of collagenases, were not observed. However, we consider our data to be convincing because the induction of major mediators of inflammation (*COX-2*, *PGES*, *ADORA2A*, *IL-1β*, *IL-6*, *CXCL8* and *CXCR4*) and cartilage destruction (*MMP10* and *MMP12*) and the repression of key ECM components (*COMP* and *CSPG2*) are most probably important reasons for chondrocyte dysfunction in RA-related destruction of cartilage.

Because direct cell attachment of SF to chondrocytes was not provided, soluble mediators secreted from RASF regulated the expression of chondrocyte genes and thus disturbed the catabolic–anabolic homeostasis of mature cartilage function. Although the attachment of RASF to cartilage is a significant feature of RA-related destruction of cartilage in comparison with other non-destructive forms of arthritis, direct cell contact between chondrocytes and RASF seems not to be necessarily required for the destructive modulation of chondrocyte function.

Conclusion

The present study provides a comprehensive insight into the RA-related destruction of cartilage on the basis of chondrocyte gene expression pattern involving marker genes of inflammation and cartilage destruction. We identified molecules already known to be involved in RA-related destruction of cartilage; remarkably, we detected the expression of genes not previously associated with RA chondrocyte dysfunction. Thus, the established *in vitro* model emerged to determine the specific role of distinct genes in the pathogenesis of cartilage

destruction in RA and may disclose potent pharmacological targets for cartilage regeneration and repair.

Therefore, this *in vitro* model may help in understanding the molecular effects of anti-rheumatic pharmaceuticals on cartilage regeneration and may facilitate the identification of putative pro-cartilage substances. Because SF treated with frequently used anti-rheumatic drugs showed a reversion of the gene expression of typical RA-related genes [23], a hypothesized drug-related change in the synthesis of disease mediators in RASF may affect the expression in chondrocytes of RA-related target genes of cartilage destruction, demonstrating the molecular effects of anti-rheumatic pharmaceuticals and putative pro-cartilage substances on cartilage regeneration and repair.

Competing interests

CK is an employee of TransTissueTechnologies GmbH (TTT). MS, TH and JR work as consultants for TTT. TTT develops autologous tissue transplants for the regeneration of cartilage and bone. The other authors declare that they have no competing interests.

Authors' contributions

KA and CL performed the gene expression data processing, participated in the design and coordination of the study and drafted the manuscript. KA, LM and TD conducted the cell culture experiments and performed the protein membrane arrays and the PCR validation studies. TH and JR participated in gene expression data processing and in study design and coordination. CK and MS conceived the study and participated in its design and coordination. All authors read and approved the final manuscript.

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3.4 Verwendung von Referenzsignaturen zur Untersuchung der krankheitsspezifischen Expressionsänderung im Blut

In den vorangegangenen Studien wurden vornehmlich die ortständigen Gewebezellen, die Synovialfibroblasten untersucht. Wesentliche Entzündungsvermittler sind aber auch die infiltrierenden Immunzellen. Sie werden von den Gewebezellen bei Entzündungen angelockt und steuern spezifische Immunprozesse bzw. phagozytieren und beseitigen Zielstrukturen der Immunantwort. Als ständig patrouillierende Zellen sind sie im Blut vertreten und damit über die Entnahme von Blut relativ leicht zugänglich. Allerdings werden die vollen Aktivierungszustände dieser Zellen erst im Gewebe erreicht. Dennoch kann zunächst die Untersuchung der Immunzellen aus dem Blut wertvolle molekulare Merkmale sowohl über die Zelltypen als auch über die im Krankheitsfall vorliegende Aktivierung liefern.

Dies wurde am Beispiel der rheumatoiden Arthritis während und nach der Schwangerschaft mit der Analyse von mononukleären Zellen des peripheren Blutes (PBMC) untersucht. Bei den meisten Patientinnen mit rheumatoider Arthritis kommt es während der Schwangerschaft zur Remission der Erkrankung. Leider erfahren jedoch 70-80% dieser Frauen nach der Schwangerschaft einen Schub der Arthritis. In der nachfolgenden Arbeit wurden erstmalig Referenzsignaturen eingesetzt, um eine Änderung der zellulären Zusammensetzung von Proben zu detektieren und zu quantifizieren. Es wurde anhand von Vergleichen zwischen Signaturen von hochaufgereinigten Granulozyten, Monozyten, B-Zellen, T-Zellen und NK-Zellen Markergene für die jeweilige Zellpopulation etabliert. In einem Mischexperiment konnte über die Expressionsstärke dieser Markergene die Änderung der zellulären Zusammensetzung nachvollzogen werden. Diese Analysetechnik wurde auf die Expressionsprofile der PBMC von rheumatoide Arthritis Patientinnen und Kontrollen während und nach der Schwangerschaft angewandt. Es zeigten sich bei gesunden Frauen Unterschiede in der zellulären Zusammensetzung mit einer Dominanz von monozytären Genexpressionskomponenten während der Schwangerschaft und einer Dominanz von lymphozytären Genexpressionskomponenten nach der Schwangerschaft. Bei Patientinnen mit rheumatoider Arthritis waren während der Schwangerschaft kaum Unterschiede zu gesunden Schwangeren festzustellen. Nach der Schwangerschaft jedoch blieb die Dominanz der monozytären Profilkomponente bestehen. Es wurde im Mittel aber auch eine postpartale Zunahme der lymphozytären Profilkomponente beobachtet. Eine funktionelle Bewertung nach Zugehörigkeit zu KEGG Signalwegen ergab eine Aktivierung von Genen, die vornehmliche zu Prozessen der Zelladhäsion und -migration, der Pathogenabwehr und verschiedenen Signaltransduktionsprozessen (NOTCH, Phosphatidyinositol, mTOR, Wnt, MAPK) gehören. Diese Aktivierungen waren deutlich größer als die durch die Verschiebung der zellulären Zusammensetzung zu erwartenden Änderungen.

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Reactivation of Rheumatoid Arthritis After Pregnancy

Increased Phagocyte and Recurring Lymphocyte Gene Activity

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Objective. **Pregnancy is associated with reduced disease activity in rheumatoid arthritis (RA) and frequently with disease exacerbation after delivery. This study was undertaken to generate a systematic overview of the molecular mechanisms related to disease remission and postpartum reactivation.**

Methods. **Transcriptomes of peripheral blood mononuclear cells (PBMCs) were generated from RA patients and healthy women by transcription profiling during the third trimester and 24 weeks after delivery. For functional interpretation, signatures of highly purified immune cells as well as Kyoto Encyclopedia of Genes and Genomes pathway annotations were used as a reference.**

Results. **Only minor differences in gene expression in PBMCs during pregnancy were found between RA patients and controls. In contrast, RA postpartum profiles presented the most dominant changes. Systematic comparison with expression signatures of monocytes, T cells, and B cells in healthy donors revealed reduced lymphocyte and elevated monocyte gene activity during pregnancy in patients with RA and in controls. Monocyte activity decreased after delivery in controls but persisted in RA patients. Furthermore, analysis of 32 immunologically relevant cellular pathways demonstrated a significant additional activation of genes related to adhesion, migration, defense of pathogens, and cell activation, including Notch, phosphatidylinositol, mTOR, Wnt, and MAPK signaling, in RA patients postpartum.**

Conclusion. **Our findings indicate that innate immune functions play an important role in postpartum reactivation of arthritis. However, this may depend not only on the monocyte itself, but also on the recurrence of lymphocyte functions postpartum and thus on a critical interaction between both arms of the immune system.**

For details see:
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