iAR
Institute for Arthritis Research
Institut für Rheumaforschung
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SCIENTIFIC REPORT

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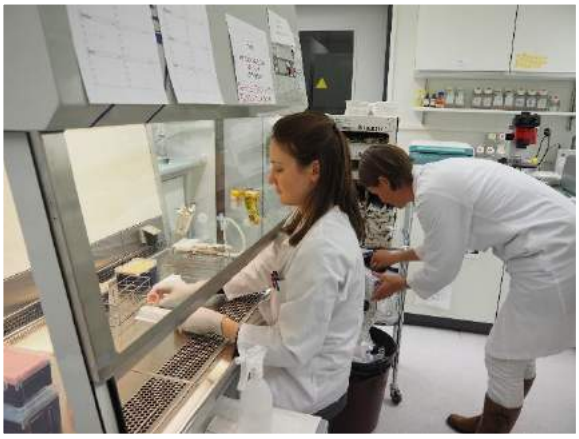

Turning research into better arthritis care

UNIVERSITY OF GENEVA

Research Group 1:

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Understanding the interleukin (IL)-1 family of cytokines

The aim of our current work is focused on better understanding the role of the interleukin (IL)-1 family of cytokines that comprises IL-1, IL-18, IL-33, Il-36, IL-37, and IL-38. We are using experimental models of arthritis and other experimental models of inflammatory diseases. In particular, we have generated several lines of transgenic mice to explore the role of interleukin-1 cytokines in vivo (see reference 2). More recently we have been working on the role of IL-36 and IL-38 on inflammatory responses (see references 3, 6, 7, 9, 10)

We are also working on IL-18 in inflammatory rheumatic diseases using both human samples from patients with inflammatory diseases (see references 5 and 8) and in experimental models in the mouse. The results led to an ongoing clinical trial using an IL-18 antagonist in adult onset-Still's disease, an inflammatory rheumatic condition. The results of this clinical trial will be published in February 2018 (figure below). We showed that among patients with refractory adult onset-Still's disease, 50% displayed a clinical and biological response to the administration of the recombinant IL-18 antagonist (tadekinig alfa). Twenty three patients were divided in two groups, ten and thirteen patients received 80 mg and 160 mg tadekinig alfa three times per week for 12 weeks. After 3 weeks 50% of the patients from each group achieved pre-defined response criteria. At 12 week the response was maintained with a good safety profile.

The results of a multicenter clinical trial led by our research group. Published by C. Gabay et al. Ann Rheum Dis 2018

	Week 3 (80 mg) (n=10)	Week 3 (160 mg) (n=12)	Week 12 (80 mg) (n=4)	Week 12 (160 mg) (n=12)	Week 12 (160 mg)* (n=18)
CRP reduction ≥50%	4 (40%)	5 (41.7%)	1 (25%)	6 (50%)	7 (38.9%)
CRP reduction ≥70%	2 (20%)	2 (16.7%)	1 (25%)	6 (50%)	7 (36.8%)
CRP normalisation (≤5 mg/L)	2 (20%)	3 (25%)	1 (25%)	4 (33.3%)	4 (22.2%)
Ferritin normalization (≤150 mg/L)	2 (20%)	6 (50%)	2 (50%)	6 (50%)	8 (38.9%)
SJC44† reduction ≥20%†	5 (83.3%)	5 (55.6%)	2 (100%)	8 (88.9%)	10 (76.9%)
TJC44† reduction ≥20%§	7 (87.5%)	4 (44.4%)	2 (100%)	5 (50%)	8 (50%)
Both joint counts reduction ≥20%	5 (83.3%)	3 (37.5%)	2 (100%)	5 (62.5%)	7 (58.3%)
Responders at week 3 (1 or 3 + no fever)	5 (50%)	6 (50%)	N/A	N/A	N/A
Responders at week 12 (2 or 3 or 4 and 7)	N/A	N/A	2 (50%)	7 (58.3%)	8 (44.4%)

We have also examined the role of signalling pathways involved in the modulation of inflammatory responses in macrophages and other myeloid cells (see reference 1 and 11). Our group is involved in various collaborations with laboratories in France, Spain, and USA.

Publications

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Autophagy in the deregulation of the immune response in autoimmune and inflammatory disorders

Macroautophagy is a major catabolic pathway in the cells, which constantly delivers cytoplasmic constituents and organelles to the lysosomal compartment for degradation. The pathway is an important contributor of cellular homeostasis, and therefore is active and up-regulated in various conditions of cellular stress and inflammation. In this context macrautophagy has been implicated in shaping the innate and adaptive immune responses by acting at multiple and diverse levels such as cytokine secretion, and antigen presentation. Therefore, it is not surprising that macroautophagy has recently been linked to the initiation and onset of autoimmune diseases. Interestingly in rheumatoid arthritis (RA) the SNP rs548234, located 133kb from the ATG5 region was shown to be associated to the risk of developing RA.

The focus of our laboratory is the contribution of autophagy to the pathogenesis of rheumatoid arthritis and ankylosing spondylitis.

In order to address the contribution of macroautophagy to the adaptive immune response during arthritis, we used two mice models of arthritis, the collagen induced arthritis model (CIA), and the antigen induced arthritis (AIA) model in mice deficient for autophagy in their dendritic cells or in their macrophages. In the AIA model, we found that mice lacking autophagy in their dendritic cells (DC/ATG5-/-) showed enhanced cartilage destruction and bone erosion compare to their littermate controls. In the CIA model, clinical scores were more severe in (DC/ATG5-/-) mice. Interestingly, the Th17 response in DC/ATG5-/- mice was significantly increased in both models of arthritis. We have shown that the mechanism behind this phenotype is related to the instability of regulatory T cells (Tregs) in context of inflammation, in DC/ATG5-/- mice. This work identifies autophagy as a negative regulator of the immune response in an arthritis mouse model. We are now investigating the precise mechanism of how autophagy in antigen presenting cells impact the function and stability of the regulatory T cell compartment upon inflammation.

During the course of RA, our data indicate that autophagy is up regulated in synovial biopsies of patients, in different cellular subsets. We have therefore analysed the role of autophagy in the degradation of different auto-antigens relevant to RA. We found that autophagy regulates the degradation of both the vimentin and the alpha-enolase in different cell types including dendritic cells, and synovial fibroblasts. We are now investigating the contribution of the pathway to antigen presentation and citrullination of selected DR4 epitopes from these autoantigens.

Finally we have defined a new role for macroautophagy in controlling both the internalization and degradation of MHC class I molecules, in mouse antigen presenting cells. The precise molecular mechanism involves the adaptor-associated kinase 1 (AAK1), which binds LC3 and MHC class 1 molecules and targets them to autophagosomes. We have translated this finding in human cells. We have shown an involvement of autophagy in human HLA class 1 surface expression and degradation. Interestingly, the allele HLA-B*27:05, associated with ankylosing spondylitis (AS), seems not to be affected by gain and loss of functions experiments. We are currently adressing the molecular mechanism behind this phenotype, in order to understand why B27 escape autophagic degradation.

We hope to unravel with our projects some new aspects of macroautophagy regulation of the adaptive immune response during autoimmune and inflammatory disorders. Using both mouse models and human samples and cells, our projects are addressing how autophagy can play a role in different inflammatory context and autoimmune set up, with a focus on rheumatoid arthritis and ankylosing spondylitis.

Publications

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Macroautophagy proteins control MHC class I levels on dendritic cells and shape anti-viral CD8+ T cell responses Loi M, Lippmann A, Steinbach K, Barreira da Silva R, Nowag H, Albrecht R, Garcia-Sastre A , Merkler D, Münz C* and Gannagé M* (co-last authors) Cell Report. 2016 May 3;15(5):1076-87. Impact Factor: 8.28

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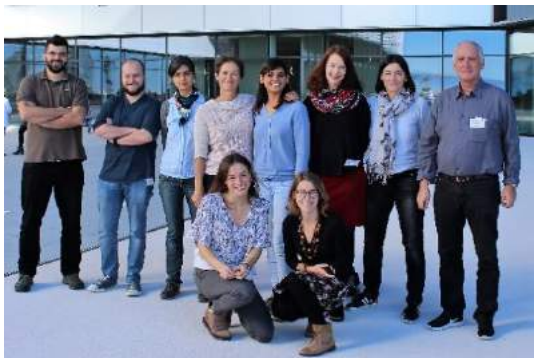

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Immune response in human inflammatory pathologies

In the last years, a growing amount of evidence supports the involvement of viral infections in the pathology of rheumatoid arthritis (RA). Toll-like receptors (TLRs) expressed by macrophages or RA synovial fibroblasts could play a major role in initiating a potent, type 1 interferon driven, pro-inflammatory response. Indeed, several viruses, including alphaviruses, HCV, HIV and parvovirus B19 have been found in the synovial tissue and have been implicated in the development of RA. TLRs play a fundamental role in the initiation and self-perpetuation of RA, inducing the production of pro-inflammatory cytokines, which lead to the recruitment of inflammatory cells and consequent tissue damage, resulting in cell death and release of more TLR ligands, creating a vicious cycle.
To guide treatment strategies, to better predict, avoid, and manage the complications of such hyper-inflammatory processes, we reported macrophage survival assays using different TLRs and set-up drug screens using high content microscopy. This in turn could have an impact on potential synergistic therapeutic effects for inflammatory diseases with, or without, a viral component.
In paralell, we focused on the importance of TLR3 and searched for signaling pathways implicated in the survival of macrophages and we reported the essential role of IFN-β in driving the production of IL-6 and TNF-α. We furthermore examined the relevance of IL-17 in the inflammatory response and in the spreading of inflammation to secondary sites

in immuno-compromised situations. We additionally demonstrated that inflammation can be reactivated by subsequent infection and determined the importance of TLR3, IFN-β and its activation in the poor responsiveness to specific drugs. In clinically related investigations, we demonstrated that co-infection could be predictive of clinical complications such as first-line treatment failure, increased and reactivated inflammation, and symptomatic relapses, which are relevant in RA.

Publications

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Epigenetic changes in Rheumatoid Arthritis (RA)

Synovial fibroblasts are the major stromal cells in the joint synovium and play a crucial part in inflammation and joint destruction in RA. With funding from the iAR we were able to create a comprehensive epigenetic profile of human synovial fibroblasts isolated from different joints, disease conditions and under basal or stimulatory (TNF) conditions. We can use this information to decipher how these cells are activated in RA, how they contribute to disease and how they can be therapeutically targeted. This work was presented at the EULAR 2017 congress, June 2017, Madrid, Spain, as oral presentation and at the Annual iAR (IRR-IRF) Meeting, December 2017, Lausanne, Switzerland. We have further shown that the epigenetic configuration at gene promoters of synovial fibroblasts and macrophages regulates cell type-specific LPS-induced responses. This primes synovial fibroblasts to sustain their inflammatory response in chronic arthritis and enhances their inflammatory and destructive response during repeated activation of Toll-like receptor 4.

Epigenetic changes are long-lasting changes in gene expression and can be transmitted from parents to offspring. We analyse epigenetic changes in sperm of patients with rheumatic diseases and in the blood of pregnant patients with rheumatoid arthritis and systemic lupus erythematodes to clarify the influence of transgenerational epigenetic inheritance in the development of rheumatic diseases.

Apoptosis resistance contributes to the massive accumulation of synoviocytes in the affected joints of patients with RA. Of particular interest, the Fas receptor (FasR) - Fas ligand (FasL) apoptotic pathway appears altered in RA synovial fibroblasts (RASF) resulting in increased amounts of soluble FasR (sFasR) which prevents FasL-induced cell death. Our data revealed a mechanism, which may underlie apoptosis-resistance in RASF. We could show that in a pro-inflammatory cytokine milieu upregulated FAS-AS1 lowers the responsiveness of cells to death signals. Thus, targeting lncRNA FAS-AS1 might prevent apoptosis resistance and synovial hyperplasia in RA.

Publications

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IMPRESSUM

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