DBM FACTS

Periodisches Informationsblatt des Departementes Biomedizin
Universität Basel, Universitätsspital Basel und
Universitäts-Kinderspital beider Basel

Experimental Rheumatology Laboratory DBM | North Macedonia | DBM Summer Symposium

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Departement Biomedizin Basel

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Das DBM stellt sich vor

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Fotos
Pixabay/Shutterstock/Wikimedia Commons

Druck
buysite AG, Basel

Anschrift
Redaktion DBM Facts
Departement Biomedizin
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EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Herzlich willkommen zur ersten Ausgabe der DBM Facts im 2020. Schwierige Monate liegen hinter uns. Das Coronavirus hat auch das Departement Biomedizin in Atem gehalten. Nur ganz wenige Mitarbeitende wurden positiv getestet und die Infektionen verliefen bei allen Betroffenen ohne Komplikationen. Zu unserer Erleichterung erfolgte keine dieser Ansteckungen am Arbeitsplatz. An dieser Stelle möchte ich allen danken, die mit ihrem Einsatz und verantwortungsvollen Verhalten zum bisher guten Verlauf am DBM beigetragen haben. Aber wir dürfen jetzt nicht nachlässig werden. Die aufgestellten Regeln müssen weiter von allen befolgt werden.
Am DBM stehen bedeutende Wechsel an: Es freut mich sehr, dass Prof. Ivan Martin als designierter neuer Leiter des DBM gewählt wurde. Er wird die Leitung des DBM nächstes Jahr am 1. Juni 2021 übernehmen. Bis dahin wird er mir als gewählter Nachfolger zur Seite stehen und sich in die Übernahme der Leitungsaufgaben einarbeiten. Mit Ivan wird ein international renommierter Wissenschaftler, der als Forschungsgruppenleiter und Mitglied der Departementsleitung das DBM bereits sehr gut kennt, die Belange des DBM in Zukunft vertreten.
Leider wird uns Thos Geiger per Ende September 2020 verlassen und ins Management Office des Swiss Personalized Health Network (SPHN) Programms in Bern wechseln. Thos hat bei uns als Manager von "Personalized Health Basel" eine zentrale Rolle gespielt und seit bald einem Jahr hat er mich teilzeitlich auch als "Koordinator" für das DBM unterstützt. In beiden Funktionen wird er uns sehr fehlen. Wir wünschen ihm aber viel Erfolg an seiner neuen Stelle, die viel näher am Wohnort seiner Familie gelegen ist.
In der nun vorliegenden Ausgabe stellt Diego Kyburz die Forschung seiner Gruppe im Bereich der "Experimentellen Rheumatologie" vor (ab Seite 2), die aktuellsten Publikationen aus dem DBM finden Sie ab Seite 9. Aleksandra Maceski stellt uns ihre Heimat Nordmazedonien vor (ab Seite 29) und Hassan Melhem nimmt uns mit in den Libanon (ab Seite 34).
Eine interessante Lektüre und bleiben Sie gesund!

Radek Skoda

Dear Readers,

Welcome to the first 2020 edition of DBM Facts. Difficult months are behind us. The coronavirus has kept the Department of Biomedicine in suspense. Only a few employees tested positive and the infections passed without complications in all of those affected. To our relief, none of the infections originated in the workplace. At this point I would like to thank everyone who, through their commitment and responsible behaviour, has contributed to the good progress at DBM so far. But we must not be careless now. Everyone must continue to follow the established rules.
Significant changes are pending at the DBM: I am very pleased that Prof. Ivan Martin has been elected as the designated new head of the DBM. He will take over the management of the DBM next year on June 1, 2021. Until then, as the chosen successor, he will be at my side and will familiarize himself with taking on the management duties. As an internationally renowned scientist who, as a research group leader and member of the department management, already knows the DBM very well, Ivan will represent the interests of the DBM in the future.
Unfortunately, Thos Geiger will leave us at the end of September 2020 to join the management office of the Swiss Personalized Health Network (SPHN) program in Bern. Thos played a central role for us as the manager of "Personalized Health Basel" and for most of the past year he has also supported me part-time as a "coordinator" for the DBM. We will miss him very much in both functions. We wish him every success in his new position, which is much closer to where his family lives.
In the current issue, Diego Kyburz presents the research of his group in the field of "Experimental Rheumatology" (page 2), the latest publications from the DBM can be found on page 9. Aleksandra Maceski introduces us to her home country, North Macedonia (page 29), and Hassan Melhem takes us to Lebanon (page 34).
I wish you all an interesting read and stay healthy!

Radek Skoda

Experimental Rheumatology Laboratory DBM

The research of the Experimental Rheumatology (ER) group is focused on the pathogenetic mechanisms of inflammatory rheumatic diseases including chronic arthropathies such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA), connective tissue diseases such as systemic lupus erythematosus (SLE), Sjögren syndrome (SS) and systemic sclerosis (SSc), autoimmune vasculitis (AAV) as well as the crystal arthropathies gout and calcium pyrophosphate deposition disease.

In several research projects, including collaborations with academia and pharma/biotech industry, we investigate the immunopathogenesis of some of these disease with special focus on mechanisms of the innate immunity.

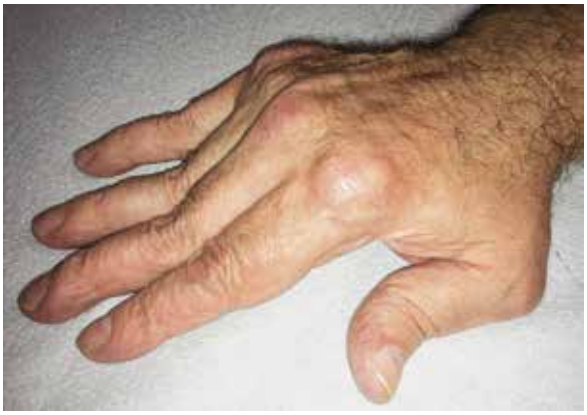


Figure 1:
Example of swollen and deformed joints of an RA patient's hand.

The research topics include:

- the regulation of inflammatory pathways during macrophage differentiation and polarization.
- immune-modulation by extracellular vesicles and the identification of their functional load in rheumatoid arthritis.
- the screening of novel inhibitors targeted against inflammatory pathways and autoimmune disease-relevant factors (e.g. inhibition of cathepsin S in Sjögren syndrome).
- the role of neutrophil extracellular traps and cell-free mitochondrial DNA in the pathogenesis of various rheumatic diseases.

The goal of our research is to gain insight into key mechanisms regulating inflammation. With this information, in a translational science approach, we aim at identifying biomarkers for prediction of disease prognosis or therapy response or possibly novel therapeutic targets.

Selected project summaries:

Regulation of monocyte differentiation/ macrophage polarization by microRNAs in inflammatory disease

Rheumatoid Arthritis (RA) is a systemic autoimmune disease affecting primarily the joints but also a variety of other organs. With a prevalence of around 1% of the global population RA is the most frequent inflammatory arthropathy. Over time the chronic inflammation of the joints leads to destructive changes of cartilage, bone and periarticular soft tissues which result in joint dysfunction, deformity and ultimately disability *(Figure1)*. Due to its frequency and the chronic progressive disease course the socio-economic impact of RA is substantial.

The pathogenesis of RA is divided into a preclinical and clinical phase. In the preclinical phase an activation of the adaptive immune system is occurring resulting in the production of autoantibodies against modified proteins, such as citrullinated proteins, but in the absence of clinically apparent disease. Triggered by factors which are not yet clearly delineated, inflammation in the joints starts after a latency phase which can last several years. Locally, the chronicity of RA is driven by the paracrine and autocrine activation of the cell population in the synovial membrane. Synovial macrophages and fibroblasts represent the main cellular components of this barrier. Both cell types express pattern recognition receptors such as Toll-like receptors (TLR) and TLR stimulation by damage-associated molecular patterns was shown to activate inflammatory pathways such as the NF-κB pathway leading to the expression of further inflammatory cytokines, chemokines and matrix metalloproteinases (MMP).

Chemokines produced by activated synovial macrophages and fibroblasts attract circulating immune cells including monocytes, neutrophils, B- and T-cells to the synovial tissue, which in turn are amplifying the inflammatory cascades ultimately causing an acute synovitis.

Monocytes and macrophages are important contributors to chronic inflammation. It has been shown that macrophages are the main source of TNFα and IL-6, a finding that has led to the successful development of anti-TNFα and anti-IL-6 therapy for RA and other inflammatory diseases. Immunohistology studies have shown that the number of macrophages in the joints is correlated with response to therapy. There is a considerable plasticity of macrophage functions and depending on the microenvironment, their origin and cellular interactions, macrophage function may switch between different inflammatory response phenotypes *(Ref 1)*. Based upon *in vitro* and animal studies macrophage subtypes were defined according to their phenotype and functions, with classical M1-macrophages displaying pro-inflammatory properties as opposed to alternative M2-macrophages which are segregated into several subtypes with either anti-inflammatory/resolving features or regenerative functions which support tissue homeostasis. There is evidence for a predominance of M1-like macrophages in the RA synovium which favor the exuberating pro-inflammatory environment. The factors driving polarization of macrophages towards a M1 phenotype are incompletely understood.

A key research topic of the Experimental Rheumatology group covers the regulation of inflammatory signaling pathways controlling macrophage differentiation, polarization and activity in disease. In a search for microRNA (miR) expressed by *in vitro* differentiated macrophages stimulated via TLR ligands we identified miR-221-3p from a number of differentially expressed miRs. We found that levels of miR-221-3p are increased in synovial fluid and tissue of patients with RA compared to patients with osteoarthritis (OA) as controls. Furthermore, differentiated M1 macrophages derived from circulating CD14+ monocytes express more miR-221-3p than M2, both in RA patients and healthy individuals. Importantly, we found that overexpression of miR-221-3p in M2-macrophages is repressing JAK3/STAT3 signaling that governs anti-inflammatory IL-10 secretion in these cells. We could demonstrate that miR-221-3p is directly targeting JAK3 protein and that increased levels of miR-221-3p are counteracting the TLR4-mediated JAK3/STAT3 activity necessary to mount an effective anti-inflammatory activity in M2-macrophages *(Figure 2)*. In addition, miR-221-3p overexpression or pharmacological inhibition of JAK3 not only suppressed IL-10 secretion but also imposed a pro-inflammatory cytokine profile in M2-macrophages, including an increased secretion of IL-12 and IL-6 *(Figure 3)*. The dysregulated miR expression in the RA joint therefore implicates an environment inhibiting the resolving anti-inflammatory M2-macrophages while favoring the pro-inflammatory activity of M1-macrophages. We hypothesize that this mechanism may contribute to chronic inflammation and destruction in RA *(Ref 2)*.

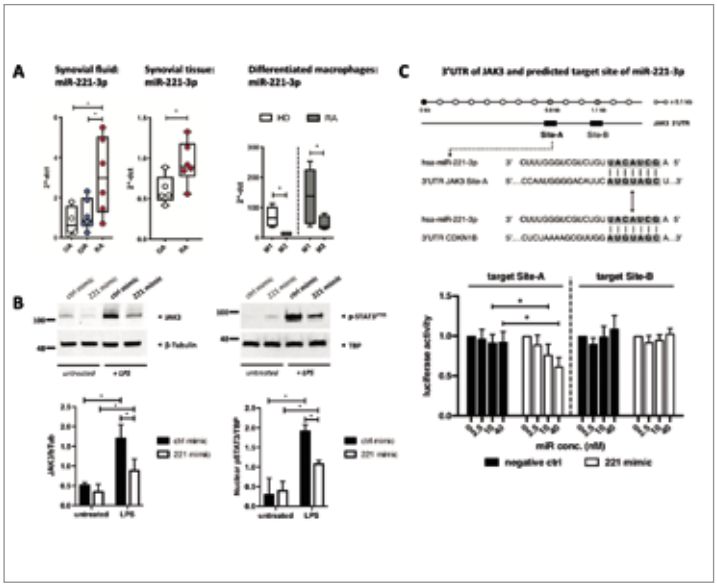


Figure 2:

(A) miR-221-3p expression is increased in synovial tissue of rheumatoid arthritis (RA) patients compared to other arthritides (OIA and OA), and is higher in M1- vs. M2-macrophages in healthy individuals and RA patients.

(B) miR-221-3p overexpression by miR mimics supresses JAK3/STAT3 signalling in TLR4-stimulated M2-macrophages by directly targeting JAK3 production.

(C) Location of two predicted miR-221-3p target sites (Site-A, Site-B) within the 3'UTR of the human JAK3 mRNA. Sequence of Site-A contains seed match region identical to already established miR-221-3p direct target on CDKN1B gene (gray shading). miR-221-3p is directly supressing JAK3 by targeting Site-A, but not Site-B, in the 3'UTR of JAK3 mRNA as shown by Luciferase reporter assay.

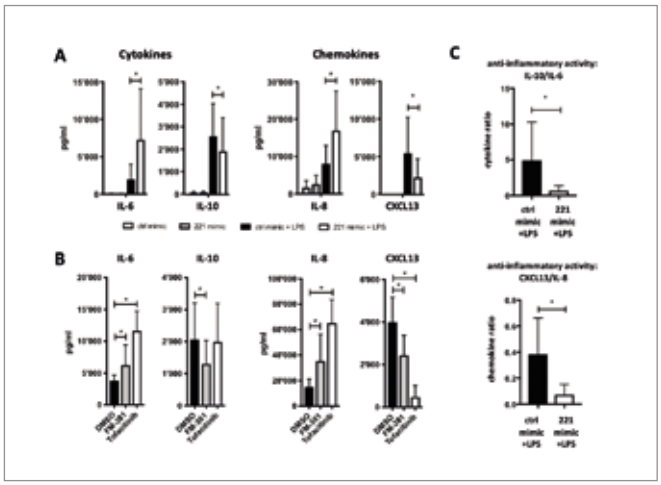


Figure 3:
(A) miR-221-3p overexpression in TLR4-stimulated M2-macrophages increases secretion of pro-inflammatory cytokines/chemokines (IL-6, IL-8) while supressing the release of anti-inflammatory mediators (IL-10, CXCL13).
(B) Inhibition of JAK3 activity in TLR4-stimulated M2-macrophages using two selective JAK inhibitors FM-381 and Tofacitinib displays similar effects as miR-221-3p overexpression.
(C) miR-221-3p overexpression decreases anti-inflammatory activity of TLR4-stimulated M2-macrophages as shown by the ratio of secreted cytokines IL-10 to IL-6 or chemokines CXCL13 to IL-8.

Notably, the detrimental cytokine production evoked by disproportionate macrophage activity is not only found in autoimmune diseases such as acute RA, but recent data suggest that it may also be driving severe pulmonary complications related to the emerging COVID-19 pandemic. Thus, elucidating the versatile function of macrophages in physiological and disease condition is highly relevant to understanding inflammation not just in inflammatory rheumatic diseases but inflammation in general.

Immune-modulation by extracellular vesicles and the identification of their functional load in rheumatoid arthritis

Extracellular vesicles (EVs) are small membrane bound particles that are generated and secreted into the extracellular microenvironment by both prokaryotic and eukaryotic cells upon stimulation, stress or activation. EVs can be broadly divided into three major types depending on their mode of biogenesis: 1) Exosomes (40 – 150 nm) are formed within the endosomal compartment as multivesicular bodies (MVB) and are subsequently released from the cell by the fusion of MVB with the plasma membrane; 2) Microvesicles (100 – 1000 nm) are formed by the budding/blebbing of plasma membrane and subsequent release from the cell; 3) Apoptotic bodies (1000 – 3000 nm) are much larger particles generated by cells undergoing apoptosis. The secretion of EVs was initially thought as a means of eliminating unneeded waste compounds from the cell. However, extensive research has shown that EVs are more than just garbage bins. EVs are known to carry cargo important for many biological processes; i.e. miRNA, mRNA, DNA and a variety of signaling proteins. EVs reflect their parent cells from where they originate, because their membrane orientation is the same as that of the donor cell. Thus, they can be considered to be miniature versions of a cell. This property of exosomes makes them attractive tools for the search of biomarkers.
One of our research projects focuses on small EVs (exosomes) in biofluids (synovial fluid and plasma) of patients with RA and OA. After isolating EVs from biofluids, we characterize them by Nanoparticle tracking analyzer (NTA), transmission electron microscopy and imaging flow cytometry (Imagestream) *(Figure 4)*. Collecting samples from cohorts of RA patient blood and synovial fluid we analyze differences in the cargo of the EVs with the goal of identifying biomarkers for disease outcome and response to therapy.

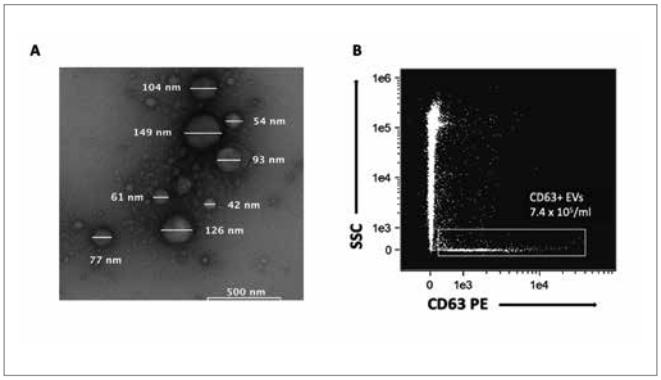


Figure 4:
(A) Transmission electron microscopy (TEM) of EVs isolated from synovial fluid (SF) of RA patient (L) and
(B) Imagestream data depicting EVs labelled with surface marker CD63PE antibody (marked area).

Inhibitors in rheumatic diseases – Differential effects of specific cathepsin S inhibition in biocompartments from patients with primary Sjögren syndrome

Sjögren syndrome is the second most common autoimmune disease in Western countries and has a prevalence of up to 2.7% in Europe. In primary Sjögren syndrome (pSS) one of the main features is dryness of mucosae with potentially other organs involvement. This autoimmune disorder targets first the exocrine glands leading to their failure and causing dryness of the associated mucosae (mainly eye and mouth dryness). Finally, pSS can also expand systemically leading to circulatory or kidney disorders. A lot is still to be understood in the pathology of pSS but it is well described now that lymphocytes T- and B-cells are infiltrating the epithelium of exocrine cells. One of the immune characteristics is the presence of anti-SSA (anti-Ribonucleoprotein) and anti-SSB (anti-Lupus La protein) antibodies. Both of these targets are expressed in the epithelium of exocrine glands. Cysteine protease cathepsin S (CatS) is an enzyme involved in processing of protein antigens to T-cell by presentation to the MHC class II. CatS is found to be increased in rheumatoid arthritis (RA), psoriasis (PsO) and pSS patients.

In collaboration with Roche Pharma AG, the ER group has recently published an article in Arthritis Research & Therapy where the potential role of CatS and its inhibition in the context of Sjögren syndrome was investigated *(Ref. 3)*. We have found that CatS represents a good marker of disease in particular in tears of pSS patients. In patients' samples, inhibition of antigen presentation using CatS inhibitor RO5459072 leads to inhibited cytokine response from T-cells and monocytes after auto-antigens stimulation. Future studies will need to evaluate if CatS inhibition could be a potential target to improve exocrine glands function and potentially prevent systemic syndrome.

Figure 6:
Schematic depiction of the interactions between neutrophils and engaged immune cells, such as platelets, macrophages (M) and dendritic cells (pDCs), leading to local damage of the endothelium, namely vasculitis, which underlies the exacerbated inflammatory response in SLE and AAV.

The role of neutrophil extracellular traps and cell-free mitochondrial DNA in the pathogenesis of various rheumatic diseases.

Activated neutrophils have been implicated in the pathogenesis of Systemic Lupus Erythematosus (SLE) and the ANCA-associated vasculitides (AAV) *(Ref. 4)*. Upon activation with various stimuli, neutrophils release DNA and chromatin material into the extracellular space, a process coined neutrophil extracellular trap (NET) formation *(Ref. 5) (Figure 5)*. TLR9 can recognize double stranded (ds) DNA and initiate the characteristic type I interferon (IFN) signature that has been implicated in the breakdown of peripheral tolerance and generation of autoreactive T- and B-cells *(Figure 6)*. Recent data suggests that subjects with SLE are characterized by impaired NET degradation, disseminating the availability of extracellular DNA as a pro-inflammatory stimulus to the innate immune system. NETs may also contain mitochondrial DNA (mtDNA), a dsDNA molecule which is phylogenetically evolved from

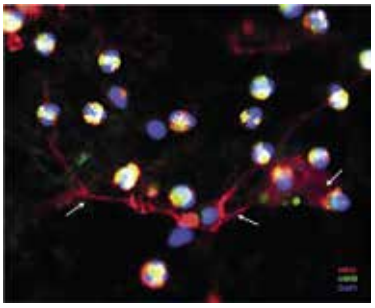
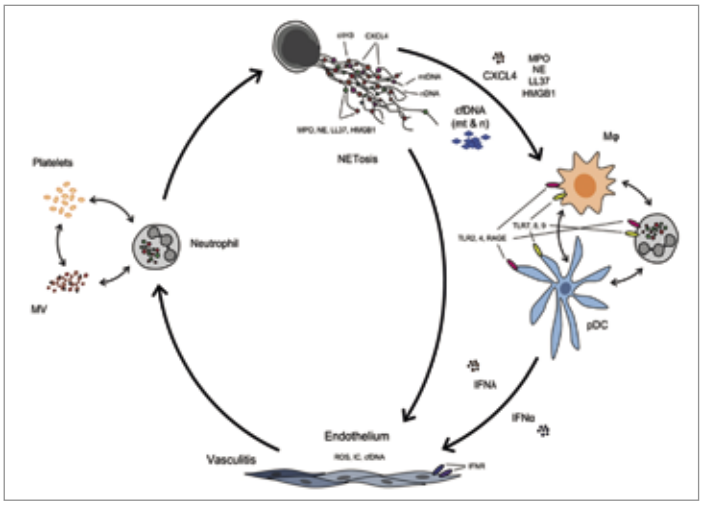


Figure 5:
Neutrophil extracellular trap (NET) formation in antineutrophil cytoplasmic autoantibody-associated vasculitis (AAV) patients (white arrows), induced with 10% plasma from AAV patients, stained with NET-specific antigens citrullinated histon3 (citH3, green) and myeloperoxidase (MPO, red). DNA was counterstained with 4',6-diamidino-2-phenylindole dihydrochloride (DAPI, blue).



bacteria and rich in hypomethylated CpG sequences, thus especially suited to trigger TLR9 signaling and disease flares.

The working hypotheses underlying the SNF-funded project concerning NETosis and mtDNA in the pathogenesis, diagnosis and activity monitoring of SLE and AAV are:

1. that SLE and AAV patients have increased plasma concentrations of circulating extracellular mtDNA, possibly released by NET formation and

2. that elevated mtDNA concentrations are associated with disease flares in both conditions. NET formation on the one hand contributes to overt mtDNA release, and on the other is modulated by circulating mtDNA or nuclear DNA (nDNA), as well as by hormones and cytokines. The main goal of the particular study is to analyse the extent and nature of circulating extracellular DNA species (mtDNA vs. nDNA) in SLE and AAV and determine if mtDNA plasma concentrations can serve as a marker for diagnosis and disease activity. Using quantitative PCR, circulating DNA concentrations (mtDNA and nDNA) in centrifuged plasma samples from patients with SLE and AAV will be determined and compared with those of healthy controls and patients with RA. Uni- and multivariate statistics will correlate circulating DNA plasma concentrations with disease activity, using known disease activity markers as covariates. Furthermore, it is also planned to determine which factors promote, modulate and inhibit the NETotic release of mtDNA in comparison to nDNA. *In vitro* assessments will examine the possible triggers and inhibitors of NETosis in AID-derived neutrophils and plasma and analyse their presence in patients' plasma in comparison with that from healthy controls.

Manifest mtDNA release is likely to contribute to the pathology of SLE and AAV by feeding back to neutrophil activation and thereby to disease activity and systemic inflammation. An increased understanding of how this aberrancy is brought about will facilitate new targeted therapeutic approaches. An immediate benefit of this study is that it will indicate whether mtDNA quantification in patient plasma can serve as a novel test for disease screening and disease activity.

Diego Kyburz and Team

Diego Kyburz and his research group "Exp. Rheumatology". From left to right upper row: Diego Kyburz, André Tiaden, Edveena Hanser, Simone Häner Massimi, Douglas Daoudlarian. Bottom row: Ulrich Walker, Stavros Giaglis, Building Petersplatz.

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Auszeichnungen

Radek Skoda erhält EHA David Grimwade Award

Radek Skoda von der Forschungsgruppe "Experimental Hematology" (Departement Biomedizin Hebelstrasse) hat den David Grimwade Award der European Hematology Association für seine aussergewöhnlichen Beiträge im Bereich der Genetik und Pathogenese bei myeloproliferativer Neoplasie erhalten. Der Preis wurde im Juni 2020 verliehen.

Marten Trendelenburg Mitglied in SNF Kommission

Marten Trendelenburg von der Forschungsgruppe "Clinical Immunology" (Departement Biomedizin Hebelstrasse) ist seit Januar 2020 Mitglied der Evaluationskommission Postdoc Mobility Life Sciences Medicine des Schweizerischen Nationalfonds (SNF).

Karoliina Pelttari erhält ISCT Award

Karoliina Pelttari von der Forschungsgruppe "Tissue Engineering" (Departement Biomedizin Hebelstrasse) hat in der Kategorie "Musculoskeletal Repair & Regeneration" den Preis für den besten Abstract mit dem Titel "Engineered nasal cartilage for the repair of osteochondral knee cartilage defects" erhalten. Der Preis wurde ihr im Rahmen des Jahresmeetings der International Society Cell & Gene Therapy (ISCT) im Mai in Paris verliehen.

Simona Stivala erhält Young Investigator Award des Bereichs Medizin

Simona Stivala von der Forschungsgruppe "Myeloid Malignancies" (Departement Biomedizin Hebelstrasse) hat im Juni 2020 für die Publikation "Targeting compensatory MEK/ERK activation increases JAK inhibitor efficacy in myeloproliferative neoplasms" (JCI 2019 Mar 4;129(4):1596-1611) den Young Investigator Award des Bereichs Medizin (2. Platz) erhalten.

Hans Hirsch AST Fellow

Hans H. Hirsch von der Forschungsgruppe "Transplantation and Clinical Virology" (Departement Biomedizin Petersplatz) ist von der American Society of Transplantation (AST) anlässlich des diesjährigen American Transplant Congress im Juni 2020 zum "Fellow of the American Society of Transplantation" ernannt worden.

Herzliche Gratulation!

Dissertationen

Im August 2019 hat **Robert Brenig** von der Forschungsgruppe Translational Hepatology (Departement Biomedizin Hebelstrassse) seine Doktorarbeit im Rahmen des MD PhD Programms der Universität Basel erfolgreich beendet. Der Titel seiner Arbeit lautete: „Mer Receptor Tyrosine Kinase – key mediator of immune dysfunction and infection susceptibility in patients with cirrhosis?“

Im September 2019 stellte sich **Mohammedyaseen Syedbasha** von der Forschungsgruppe "Applied Microbiology Research" (Departement Biomedizin Hebelstrasse) erfolgreich den Fragen des Dissertationskomitees. Er beschäftigte sich in seiner Arbeit mit "The immune modulatory role of interferon lambda on human B-cell functions".

Seit Februar 2020 darf sich Claudia Donat von der Forschungsgruppe "Clinical Immunology" (Departement Biomedizin Hebelstrasse) Frau Dr. nennen. In ihrer PhD Thesis widmete sie sich dem Thema: "Immunological and functional consequences of von Willebrand factor binding to complement C1q".

Im März 2020 hat **Theresa Rohm** von der Forschungsgruppe "Translational Diabetes" (Departement Biomedizin Hebelstrasse) ihre Doktorandenzeit erfolgreich abgeschlossen. Der Schwerpunkt ihrer Dissertation lag auf dem Thema: "Targeting Colonic Macrophages as a Potential Therapeutic Option in Metabolic Disease."

Ebenfalls im März 2020 konnte **Alexandra Kosareva** von der Forschungsgruppe "Cardiovascular Molecular Imaging" (Departement Biomedizin Hebelstrasse) ihre Dissertation mit Erfolg beenden. Das Thema ihrer Doktorarbeit lautete: "Targeting of Vascular Cell Adhesion Molecule 1 with an Ultrasound Contrast Agent Bearing Designed Ankyrin Repeat Proteins as Targeting Ligands”

Im April 2020 stellte sich **Daria Monogiou Belik** von der Forschungsgruppe "Myocardial Research" (Departement Biomedizin Hebelstrasse) erfolgreich den Fragen des Dissertationskomitees. Der Titel ihrer Thesis lautete: "The role of the cancer kinome in the healthy and injured heart: focus on Flt3 and Plk2".

Im Juli 2020 endete auch die Doktorandenzeit für **Laura Power** und **Reihane Ziadlou**, beide von der Forschungsgruppe "Tissue Engineering" (Departement Biomedizin Hebelstrasse). Laura beschäftigte sich mit dem Thema “Novel quality controls for nasal chondrocyte-derived tissue engineered cartilage”, Reihanes These lautete: “Biological therapy and tissue engineering approaches for the treatment of osteoarthritis”.

CANCER DISCOVERY 2019;9:1736–53 IF 26.370

Ontogenic Changes in Hematopoietic Hierarchy Determine Pediatric Specificity and Disease Phenotype in Fusion Oncogene–Driven Myeloid Leukemia

Cécile K. Lopez[1,2,3,4], Esteve Noguera[1,2,4], Vaia Stavropoulou[5], Elie Robert[1,2,4], Zakia Aid[1,2,4], Paola Ballerini[6], Chrystèle Bilhou-Nabera[7], Hélène Lapillonne[8], Fabien Boudia[1,2,4,9], Cécile Thirant[1,2,4], Alexandre Fagnan[1,2,4,9], Marie-Laure Arcangeli[10], Sarah J. Kinston[11], M'Boyba Diop[2], Bastien Job[2], Yann Lecluse[2], Erika Brunet[12], Loélia Babin[12], Jean Luc Villeval[1,2], Eric Delabesse[13], Antoine H.F.M. Peters[14,15], William Vainchenker[1,2], Muriel Gaudry[1,2], Riccardo Masetti[16], Franco Locatelli[17,18], Sébastien Malinge[1,2,3,4], Claus Nerlov[19], Nathalie Droin[1], Camille Lobry[1], Isabelle Godin[1,2], Olivier A. Bernard[1,2,3,4], Berthold Göttgens[11], Arnaud Petit[6], Françoise Pflumio[10], Juerg Schwaller[5], and Thomas Mercher[1,2,4,9]

Abstract: Fusion oncogenes are prevalent in several pediatric cancers, yet little is known about the specific associations between age and phenotype. We observed that fusion oncogenes, such as *ETO2–GLIS2*, are associated with acute megakaryoblastic or other myeloid leukemia subtypes in an age-dependent manner. Analysis of a novel inducible transgenic mouse model showed that *ETO2–GLIS2* expression in fetal hematopoietic stem cells induced rapid megakaryoblastic leukemia whereas expression in adult bone marrow hematopoietic stem cells resulted in a shift toward myeloid transformation with a strikingly delayed in vivo leukemogenic potential. Chromatin accessibility and single-cell transcriptome analyses indicate ontogeny-dependent intrinsic and *ETO2–GLIS2*-induced differences in the activities of key transcription factors, including ERG, SPI1, GATA1, and CEBPA. Importantly, switching off the fusion oncogene restored terminal differentiation of the leukemic blasts. Together, these data show that aggressiveness and phenotypes in pediatric acute myeloid leukemia result from an ontogeny-related differential susceptibility to transformation by fusion oncogenes.

Significance: This work demonstrates that the clinical phenotype of pediatric acute myeloid leukemia is determined by ontogeny-dependent susceptibility for transformation by oncogenic fusion genes. The phenotype is maintained by potentially reversible alteration of key transcription factors, indicating that targeting of the fusions may overcome the differentiation blockage and revert the leukemic state.

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Nature Neuroscience Vol.22, 1834–1843(2019) IF 21.126

Adaptive disinhibitory gating by VIP interneurons permits associative learning

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Abstract

Learning drives behavioral adaptations necessary for survival. While plasticity of excitatory projection neurons during associative learning has been extensively studied, little is known about the contributions of local interneurons. Using fear conditioning as a model for associative learning, we found that behaviorally relevant, salient stimuli cause learning by tapping into a local microcircuit consisting of precisely connected subtypes of inhibitory interneurons. By employing deep-brain calcium imaging and optogenetics, we demonstrate that vasoactive intestinal peptide (VIP)-expressing interneurons in the basolateral amygdala are activated by aversive events and provide a mandatory disinhibitory signal for associative learning. Notably, VIP interneuron responses during learning are strongly modulated by expectations. Our findings indicate that VIP interneurons are a central component of a dynamic circuit motif that mediates adaptive disinhibitory gating to specifically learn about unexpected, salient events, thereby ensuring appropriate behavioral adaptations.

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Blood 2019;134(21):1832-1846 IF 16.601

JAK2-mutant hematopoietic cells display metabolic alterations that can be targeted to treat myeloproliferative neoplasms

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Increased energy requirement and metabolic reprogramming are hallmarks of cancer cells. We show that metabolic alterations in hematopoietic cells are fundamental to the pathogenesis of mutant JAK2–driven myeloproliferative neoplasms (MPNs). We found that expression of mutant JAK2 augmented and subverted metabolic activity of MPN cells, resulting in systemic metabolic changes in vivo, including hypoglycemia, adipose tissue atrophy, and early mortality. Hypoglycemia in MPN mouse models correlated with hyperactive erythropoiesis and was due to a combination of elevated glycolysis and increased oxidative phosphorylation. Modulating nutrient supply through high-fat diet improved survival, whereas high-glucose diet augmented the MPN phenotype. Transcriptomic and metabolomic analyses identified numerous metabolic nodes in JAK2-mutant hematopoietic stem and progenitor cells that were altered in comparison with wild-type controls. We studied the consequences of elevated levels of Pfkfb3, a key regulatory enzyme of glycolysis, and found that pharmacological inhibition of Pfkfb3 with the small molecule 3PO reversed hypoglycemia and reduced hematopoietic manifestations of MPNs. These effects were additive with the JAK1/2 inhibitor ruxolitinib in vivo and in vitro. Inhibition of glycolysis by 3PO altered the redox homeostasis, leading to accumulation of reactive oxygen species and augmented apoptosis rate. Our findings reveal the contribution of metabolic alterations to the pathogenesis of MPNs and suggest that metabolic dependencies of mutant cells represent vulnerabilities that can be targeted for treating MPNs.

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NATURE COMMUNICATIONS (2019) 10:5755 IF 11.878

LATS1 but not LATS2 represses autophagy by a kinase-independent scaffold function

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Abstract

Autophagy perturbation represents an emerging therapeutic strategy in cancer. Although LATS1 and LATS2 kinases, core components of the mammalian Hippo pathway, have been shown to exert tumor suppressive activities, here we report a pro-survival role of LATS1 but not LATS2 in hepatocellular carcinoma (HCC) cells. Specifically, LATS1 restricts lethal autophagy in HCC cells induced by sorafenib, the standard of care for advanced HCC patients. Notably, autophagy regulation by LATS1 is independent of its kinase activity. Instead, LATS1 stabilizes the autophagy core-machinery component Beclin-1 by promoting K27-linked ubiquitination at lysine residues K32 and K263 on Beclin-1. Consequently, ubiquitination of Beclin-1 negatively regulates autophagy by promoting inactive dimer formation of Beclin-1. Our study highlights a functional diversity between LATS1 and LATS2, and uncovers a scaffolding role of LATS1 in mediating a cross-talk between the Hippo signaling pathway and autophagy.

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NATURE COMMUNICATIONS (2020) 11:812 IF 11.878

Serum neurofilament light levels in normal aging and their association with morphologic brain changes

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Abstract

Neurofilament light (NfL) protein is a marker of neuro-axonal damage and can be measured not only in cerebrospinal fluid but also in serum, which allows for repeated assessments. There is still limited knowledge regarding the association of serum NfL (sNfL) with age and subclinical morphologic brain changes and their dynamics in the normal population. We measured sNfL by a single molecule array (Simoa) assay in 335 individuals participating in a population-based cohort study and after a mean follow-up time of 5.9 years (n = 103). Detailed clinical examination, cognitive testing and 3T brain MRI were performed to assess subclinical brain damage. We show that rising and more variable sNfL in individuals >60 years indicate an acceleration of neuronal injury at higher age, which may be driven by subclinical comorbid pathologies. This is supported by a close association of sNfL with brain volume changes in a cross-sectional and especially longitudinal manner.

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Biomaterials 223 (2019) 119468 IF 10.273

Magnetic nanocomposite hydrogels and static magnetic field stimulate the osteoblastic and vasculogenic profile of adipose-derived cell

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Abstract

Exposure of cells to externally applied magnetic fields or to scaffolding materials with intrinsic magnetic properties (*magnetic actuation*) can regulate several biological responses. Here, we generated novel magnetized nanocomposite hydrogels by incorporation of magnetic nanoparticles (MNPs) into polyethylene glycol (PEG)-based hydrogels containing cells from the stromal vascular fraction (SVF) of human adipose tissue. We then investigated the effects of an external Static Magnetic Field (SMF) on the stimulation of osteoblastic and vasculogenic properties of the constructs, with MNPs or SMF alone used as controls. MNPs migrated freely through and out of the material following the magnetic gradient. Magnetically actuated cells displayed increased metabolic activity. After 1 week, the enzymatic activity of Alkaline Phosphatase (ALP), the expression of osteogenic markers (Runx2, Collagen I, Osterix), and the mineralized matrix deposition were all augmented as compared to controls. With magnetic actuation, strong activation of endothelial, pericytic and perivascular genes paralleled increased levels of VEGF and an enrichment in the $CD31^+$ cells population. The stimulation of signaling pathways involved in the mechanotransduction, like MAPK8 or Erk, at gene and protein levels suggested an effect mediated through the mechanical stimulation. Upon subcutaneous implantation in mice, magnetically actuated constructs exhibited denser, more mineralized and faster vascularized tissues, as revealed by histological and micro-computed tomographic analyses. The present study suggests that magnetic actuation can stimulate both the osteoblastic and vasculogenic potentials of engineered bone tissue grafts, likely at least partially by mechanically stimulating the function of progenitor cells.

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PNAS January 7, 2020 117 (1) 541-551 IF 9.580

Optimized antiangiogenic reprogramming of the tumor microenvironment potentiates CD40 immunotherapy

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Abstract

Cancer immunotherapies are increasingly combined with targeted therapies to improve therapeutic outcomes. We show that combination of agonistic anti-CD40 with antiangiogenic antibodies targeting 2 proangiogenic factors, vascular endothelial growth factor A (VEGFA) and angiopoietin 2 (Ang2/ANGPT2), induces pleiotropic immune mechanisms that facilitate tumor rejection in several tumor models. On the one hand, VEGFA/Ang2 blockade induced regression of the tumor microvasculature while decreasing the proportion of nonperfused vessels and reducing leakiness of the remaining vessels. On the other hand, both anti-VEGFA/Ang2 and anti-CD40 independently promoted proinflammatory macrophage skewing and increased dendritic cell activation in the tumor microenvironment, which were further amplified upon combination of the 2 treatments. Finally, combined therapy provoked brisk infiltration and intratumoral redistribution of cytotoxic $CD8^+$ T cells in the tumors, which was mainly driven by Ang2 blockade. Overall, these nonredundant synergistic mechanisms endowed T cells with improved effector functions that were conducive to more efficient tumor control, underscoring the therapeutic potential of antiangiogenic immunotherapy in cancer.

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Cell Reports 30, 1013–1026, January 28, 2020 IF 7.815

Chronic Viral Infection Promotes Efficient Germinal Center B Cell Responses

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Summary

Persistent viral infections subvert key elements of adaptive immunity. To compare germinal center (GC) B cell responses in chronic and acute lymphocytic choriomeningitis virus infection, we exploit activation-induced deaminase (AID) fate-reporter mice and perform adoptive B cell transfer experiments. Chronic infection yields GC B cell responses of higher cellularity than acute infections do, higher memory B cell and antibody secreting cell output for longer periods of time, a better representation of the late B cell repertoire in serum immunoglobulin, and higher titers of protective neutralizing antibodies. GC B cells of chronically infected mice are similarly hypermutated as those emerging from acute infection. They efficiently adapt to viral escape variants and even in hypermutation-impaired AID mutant mice, chronic infection selects for GC B cells with hypermutated B cell receptors (BCRs) and neutralizing antibody formation. These findings demonstrate that, unlike for $CD8^+$ T cells, chronic viral infection drives a functional, productive, and protective GC B cell response.

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Cell Reports 29, 2041–2053, November 12, 2019 IF 7.815

White Noise Background Improves Tone Discrimination by Suppressing Cortical Tuning Curves

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SUMMARY

The brain faces the difficult task of maintaining a stable representation of key features of the outside world in noisy sensory surroundings. How does the sensory representation change with noise, and how does the brain make sense of it? We investigated the effect of background white noise (WN) on tuning properties of neurons in mouse A1 and its impact on discrimination performance in a go/no-go task. We find that WN suppresses the activity of A1 neurons, which surprisingly increases the discriminability of tones spectrally close to each other. To confirm the involvement of A1, we optogenetically excited parvalbumin- positive (PV^{+}) neurons in A1, which have similar effects as WN on both tuning properties and frequency discrimination. A population model suggests that the suppression of A1 tuning curves increases frequency selectivity and thereby improves discrimination. Our findings demonstrate that the cortical representation of pure tones adapts during noise to improve sensory acuity.

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Neurol Neuroimmunol Neuroinflamm 2020;7:e656 IF 7.353

Increased HLA-DR expression and cortical demyelination in MS links with HLA-DR15

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Abstract

Objective To investigate molecular changes in multiple sclerosis (MS) normal-appearing cortical gray matter (NAGM).

Methods We performed a whole-genome gene expression microarray analysis of human brain autopsy tissues from 64 MS NAGM samples and 42 control gray matter samples. We further examined our cases by HLA genotyping and performed immunohistochemical and immunofluorescent analysis of all human brain tissues.

Results HLA-DRB1 is the transcript with highest expression in MS NAGM with a bimodal distribution among the examined cases. Genotyping revealed that every case with the MS-associated *HLA-DR15* haplotype also shows high HLA-DRB1 expression and also of the tightly linked *HLA-DRB5* allele. Quantitative immunohistochemical analysis confirmed the higher expression of HLA-DRB1 in *HLA-DRB1*15:01* cases at the protein level. Analysis of gray matter lesion size revealed a significant increase of cortical lesion size in cases with high HLA-DRB1 expression.

Conclusions Our data indicate that increased HLA-DRB1 and -DRB5 expression in the brain of patients with MS may be an important factor in how the *HLA-DR15* haplotype contributes to MS pathomechanisms in the target organ.

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Neurol Neuroimmunol Neuroinflamm 2020;7:e675 IF 7.353

Growth differentiation factor 15 is increased in stable MS

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Abstract

Objective To assess whether serum concentrations of the anti-inflammatory cytokine growth differentiation factor 15 (GDF-15) differ in patients with highly active multiple sclerosis (MS) vs patients with stable MS and healthy controls (HCs).

Methods GDF-15 concentrations were measured by ELISA in serum and CSF in a cross-sectional cohort of patients with MS, patients with other inflammatory neurologic diseases (OIND), patients with noninflammatory neurologic diseases (NIND), and healthy controls (HC). Serum GDF-15 concentrations were measured in a longitudinally sampled cohort of clinically and radiologically well-characterized patients with MS and corresponding controls.

Results Cross-sectionally measured median serum GDF-15 concentrations were significantly higher in patients with OIND (n = 42) (600 pg/mL, interquartile range [IQR] = 320–907 pg/mL) compared with HCs (n = 29) (325 pg/mL, IQR = 275–419 pg/mL; $p = 0.0007$), patients with NIND (n = 46) (304 pg/mL, IQR = 245–493 pg/mL; $p = 0.0002$), or relapsing MS (n = 42) (356 pg/mL, IQR = 246–460 pg/mL; $p = 0.0002$). CSF and serum concentrations of GDF-15 were correlated (r = 0.41, 95% CI = 0.25–0.56, $p < 0.0001$). In a longitudinally sampled cohort of patients with MS (n = 48), deeply phenotyped with quantitative clinical and MRI assessments, mean GDF-15 concentrations were significantly higher in patients with a stable disease course (405 pg/mL, SD = 202) than in patients with intermittent MRI activity (333 pg/mL, SD = 116; $p = 0.02$).

Conclusions Serum GDF-15 concentrations are increased in patients with MS with a stable disease course. These data suggest that GDF-15 may serve as a biomarker for disease stability in MS.

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Neuropsychopharmacology (2020) 45:462–471 IF 7.160

Distinct acute effects of LSD, MDMA, and D-amphetamine in healthy subjects

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Abstract

Lysergic acid diethylamide (LSD) is a classic psychedelic, 3,4-methylenedioxymethamphetamine (MDMA) is an empathogen, and D-amphetamine is a classic stimulant. All three substances are used recreationally. LSD and MDMA are being investigated as medications to assist psychotherapy, and D-amphetamine is used for the treatment of attention-deficit/hyperactivity disorder. All three substances induce distinct acute subjective effects. However, differences in acute responses to these prototypical psychoactive substances have not been characterized in a controlled study. We investigated the acute autonomic, subjective, and endocrine effects of single doses of LSD (0.1 mg), MDMA (125 mg), D-amphetamine (40 mg), and placebo in a randomized, double-blind, cross-over study in 28 healthy subjects. All of the substances produced comparable increases in hemodynamic effects, body temperature, and pupil size, indicating equivalent autonomic responses at the doses used. LSD and MDMA increased heart rate more than D-amphetamine, and D-amphetamine increased blood pressure more than LSD and MDMA. LSD induced significantly higher ratings on the 5 Dimensions of Altered States of Consciousness scale and Mystical Experience Questionnaire than MDMA and D-amphetamine. LSD also produced greater subjective drug effects, ego dissolution, introversion, emotional excitation, anxiety, and inactivity than MDMA and D-amphetamine. LSD also induced greater impairments in subjective ratings of concentration, sense of time, and speed of thinking compared with MDMA and D-amphetamine. MDMA produced greater ratings of good drug effects, liking, high, and ego dissolution compared with D-amphetamine. D-Amphetamine increased ratings of activity and concentration compared with LSD. MDMA but not LSD or D-amphetamine increased plasma concentrations of oxytocin. None of the substances altered plasma concentrations of brain-derived neurotrophic factor. These results indicate clearly distinct acute effects of LSD, MDMA, and D-amphetamine and may assist the dose-finding in substance-assisted psychotherapy research.

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Nanoscale 2019, 11, 22559–22574 IF 6.970

Metronidazole-functionalized iron oxide nanoparticles for molecular detection of hypoxic tissues†

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Abstract

Being crucial under several pathological conditions, tumors, and tissue engineering, the MRI tracing of hypoxia within cells and tissues would be improved by the use of nanosystems allowing for direct recognition of low oxygenation and further treatment-oriented development. In the present study, we functionalized dendron-coated iron oxide nanoparticles (dendronized IONPs) with a bioreductive compound, a metronidazole-based ligand, to specifically detect the hypoxic tissues. Spherical IONPs with an average size of 10 nm were obtained and then decorated with the new metronidazole-conjugated dendron. The resulting nanoparticles (metro-NPs) displayed negligible effects on cell viability, proliferation, and metabolism, in both monolayer and 3D cell culture models, and a good colloidal stability in bio-mimicking media, as shown by DLS. Overtime quantitative monitoring of the IONP cell content revealed an enhanced intracellular retention of metro-NPs under anoxic conditions, confirmed by the *in vitro* MRI of cell pellets where a stronger negative contrast generation was observed in hypoxic primary stem cells and tumor cells after labeling with metro-NPs. Overall, these results suggest desirable properties in terms of interactions with the biological environment and capability of selective accumulation into the hypoxic tissue, and indicate that metro-NPs have considerable potential for the development of new nano-platforms especially in the field of anoxia-related diseases and tissue engineered models.

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Cell Mol Gastroenterol Hepatol 2020;9:195–218 IF 6.850

Unique T-Cell Populations Define Immune-Inflamed Hepatocellular Carcinoma

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Background & Aims The characterization of T cells infiltrating hepatocellular carcinoma (HCC) provides information on cancer immunity and also on selection of patients with precise indication of immunotherapy. The aim of the study was to characterize T-cell populations within tumor tissue and compare them with non-neoplastic liver tissue as well as circulating cells of the same patients.

Methods The presence of unique cell populations was investigated in 36 HCC patients by multidimensional flow cytometry followed by t-distributed stochastic neighbor embedding analysis. Functional activity of tumor-infiltrating T cells was determined after activation by phorbol 12-myristate 13-acetate and ionomycin.

Results Within the tumor there were more cells expressing CD137 and ICOS than in non-neoplastic liver tissue, possibly after recent antigenic activation. These cells contained several populations, including the following: (1) functionally impaired, proliferating $CD4^+$ cells co-expressing Inducible T-cell costimulator (ICOS) and T cell immunoreceptor with Ig and ITIM domains (TIGIT); (2) functionally active $CD8^+$ cells co-expressing CD38 and Programmed cell-death protein 1 (PD1); and (3) CD4-CD8 double-negative T-cell receptor αβ and γδ cells (both non–major histocompatibility complex–restricted T cells). When the identified clusters were compared with histologic classification performed on the same samples, an accumulation of activated T cells was observed in immune-inflamed HCC. The same analyses performed in 7 patients receiving nivolumab treatment showed a remarkable reduction in the functionally impaired $CD4^+$ cells, which returned to almost normal activity over time.

Conclusions Unique populations of activated T cells are present in HCC tissue, whose antigen specificity remains to be investigated. Some of these cell populations are functionally impaired and nivolumab treatment restores their responsiveness. The finding of ongoing immune response within the tumor shows which lymphocyte populations are impaired within the HCC and identifies the patients who might take benefit from immunotherapy.

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Acta Biomaterialia 102 (2020) 458–467 IF 6.638

Dispersion of ceramic granules within human fractionated adipose tissue to enhance endochondral bone formation

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Abstract

Engineering of materials consisting of hypertrophic cartilage, as physiological template for *de novo* bone formation through endochondral ossification (ECO), holds promise as a new class of biological bone substitutes. Here, we assessed the efficiency and reproducibility of bone formation induced by the combination of ceramic granules with fractionated human adipose tissue ("nanofat"), followed by *in vitro* priming to hypertrophic cartilage. Human nanofat was mixed with different volumetric ratios of ceramic granules (0.2-1 mm) and cultured to sequentially induce proliferation (3 weeks), chondrogenesis (4 weeks), and hypertrophy (2 weeks). The resulting engineered constructs were implanted ectopically in nude mouse. The presence of ceramic granules regulated tissue formation, both in vitro and in vivo. In particular, their dispersion in nanofat at a ratio of 1:16 led to significantly increased cell number and glycosaminoglycan accumulation *in vitro*, as well as amount and inter-donor reproducibility of bone formation *in vivo*. Our findings outline a strategy for efficient utilization of nanofat for bone regeneration in an autologous setting, which should now be tested at an orthotopic site.

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Oncogene (2020) 39:1498–1513 IF 6.634

Histone deacetylases, Mbd3/NuRD, and Tet2 hydroxylase are crucial regulators of epithelial–mesenchymal plasticity and tumor metastasis

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Abstract

An epithelial–mesenchymal transition (EMT) represents a basic morphogenetic process of high cell plasticity underlying embryogenesis, wound healing, cancer metastasis and drug resistance. It involves a profound transcriptional and epigenetic reprogramming of cells. A critical role of epigenetic modifiers and their specific chromatin modifications has been demonstrated during EMT. However, it has remained elusive whether epigenetic control differs between the dynamic cell state transitions of reversible EMT and the fixed differentiation status of irreversible EMT. We have employed varying EMT models of murine breast cancer cells to identify the key players establishing epithelial–mesenchymal cell plasticity during reversible and irreversible EMT. We demonstrate that the Mbd3/NuRD complex and the activities of histone deacetylases (HDACs), and Tet2 hydroxylase play a critical role in keeping cancer cells in a highly metastatic mesenchymal state. Combinatorial interference with their functions leads to mesenchymal–epithelial transition (MET) and efficiently represses metastasis formation by invasive murine and human breast cancer cells in vivo.

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Br J Pharmacol 2020;177:2696–2711 IF 6.583

Anti-αLβ2 antibodies reveal novel endocytotic cross-modulatory functionality

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Abstract

Background and Purpose Antibodies targeting cell surface receptors are considered to enable highly selective therapeutic interventions for immune disorders and cancer. Their biological profiles are found, generally, to represent the net effects of antibody–target interactions. The former therapeutic anti-integrin αLβ2 antibody efalizumab seems to defeat this paradigm by eliciting, via mechanisms currently unknown, much broader effects than would be predicted based on its target specificity.

Experimental Approach To elucidate the mechanisms behind these broad effects, we investigated in primary human lymphocytes in vitro the effects of anti-αLβ2 antibodies on the expression of αLβ2 as well as unrelated α4 integrins, in comparison to Fab fragments and small-molecule inhibitors.

Key Results We demonstrate that anti-αLβ2 mAbs directly induce the internalization of α4 integrins. The endocytotic phenomenon is a direct consequence of their antibody nature. It is inhibited when monovalent Fab fragments or small-molecule inhibitors are used. It is independent of crosslinking via anti-Fc mAbs and of αLβ2 activation. The cross-modulatory effect is unidirectional and not observed in a similar fashion with the α4 integrin antibody natalizumab.

Conclusion and Implications The present study identifies endocytotic cross-modulation as a hitherto unknown non-canonical functionality of anti-αLβ2 antibodies. This cross-modulation has the potential to fundamentally alter an antibody's benefit risk profile, as evident with efalizumab. The newly described phenomenon may be of relevance to other therapeutic antibodies targeting cluster-forming receptors. Thus, pharmacologists should be cognizant of this action when investigating such antibodies.

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Cell Death and Disease (2019) 10:110 IF 5.959

Pasireotide protects mammalian cochlear hair cells from gentamicin ototoxicity by activating the PI3K–Akt pathway

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Abstract

Gentamicin is a widely used antibiotic for the treatment of gram-negative bacterial infections; however, its use often results in significant and permanent hearing loss. Hearing loss resulting from hair cell (HC) degeneration affects millions of people worldwide, and one major cause is the loss of sensory HCs in the inner ear due to aminoglycoside exposure. Strategies to overcome the apparently irreversible loss of HCs in mammals are crucial for hearing protection. Here, we report that the somatostatin analog pasireotide protects mouse cochlear HCs from gentamicin damage using a well-established in vitro gentamicin-induced HC loss model and that the otoprotective effects of pasireotide are due to Akt up-regulation via the PI3K–Akt signal pathway activation. We demonstrate active caspase signal in organ of Corti (OC) explants exposed to gentamicin and show that pasireotide treatment activates survival genes, reduces caspase signal, and increases HC survival. The neuropeptide somatostatin and its selective analogs have provided neuroprotection by activating five somatostatin receptor (SSTR1–SSTR5) subtypes. Pasireotide has a high affinity for SSTR2 and SSTR5, and the addition of SSTR2- and SSTR5-specific antagonists leads to a loss of protection. The otoprotective effects of pasireotide were also observed in a gentamicin-injured animal model. In vivo studies have shown that 13 days of subcutaneous pasireotide application prevents gentamicin-induced HC death and permanent hearing loss in mice. Auditory brainstem response analysis confirmed the protective effect of pasireotide, and we found a significant threshold shift at all measured frequencies (4, 8, 16, 24, and 32 kHz). Together, these findings indicate that pasireotide is a novel otoprotective peptide acting via the PI3K–Akt pathway and may be of therapeutic value for HC protection from ototoxic insults.

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Journal of Neuroinflammation (2020) 17:26 IF 5.700

Neonatal hypoxia-ischemia in rat elicits a region-specific neurotrophic response in SVZ microglia

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Abstract

Background Recent findings describe microglia as modulators of neurogenesis in the subventricular zone (SVZ). SVZ microglia in the adult rat are thought to adopt a neurotrophic phenotype after ischemic stroke. Early postnatal microglia are endogenously activated and may therefore exhibit an increased sensitivity to neonatal hypoxia-ischemia (HI). The goal of this study was to investigate the impact of cortico-striatal HI on the microglial phenotype, function, and gene expression in the early postnatal SVZ.

Methods Postnatal day (P)7 rats underwent sham or right-hemispheric HI surgery. Microglia in the SVZ, the uninjured cortex, and corpus callosum were immunohistochemically analyzed at P10, P20, and P40. The transcriptome of microdissected SVZ and cortical microglia was analyzed at P10 and P20, and the effect of P10 SVZ microglia on neurosphere generation in vitro was studied.

Results The microglial response to HI was region-specific. In the SVZ, a microglial accumulation, prolonged activation and phagocytosis was noted that was not observed in the cortex and corpus callosum. The transcriptome of SVZ microglia and cortical microglia were distinct, and after HI, SVZ microglia concurrently upregulated pro- and anti-inflammatory as well as neurotrophic genes. In vitro, microglia isolated from the SVZ supported neurosphere generation in a concentration-dependent manner.

Conclusions Microglia are an inherent cellular component of the early postnatal SVZ and undergo developmental changes that are affected on many aspects by neonatal HI injury. Our results demonstrate that early postnatal SVZ microglia are sensitive to HI injury and display a long-lasting region-specific response including neurotrophic features.

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Cells 2019, 8, 1422 IF 5.656

Combinatory Multifactor Treatment Effects on Primary Nanofiber Oligodendrocyte Cultures

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Abstract

Multiple sclerosis (MS) is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system. Neurological deficits are attributed to inflammatory demyelination, which compromises axonal function and survival. These are mitigated in experimental models by rapid and often complete remyelination of affected axons, but in MS this endogenous repair mechanism frequently fails, leaving axons increasingly vulnerable to the detrimental effects of inflammatory and metabolic stress. Understanding the molecular basis of remyelination and remyelination failure is essential to develop improved therapies for this devastating disease. However, recent studies suggest that this is not due to a single dominant mechanism, but rather represents the biological outcome of multiple changes in the lesion microenvironment that combine to disrupt oligodendrocyte differentiation. This identifies a pressing need to develop technical platforms to investigate combinatory and/or synergistic effects of factors differentially expressed in MS lesions on oligodendrocyte proliferation and differentiation. Here we describe protocols using primary oligodendrocyte cultures from Bl6 mice on 384-well nanofiber plates to model changes affecting oligodendrogenesis and differentiation in the complex signaling environment associated with multiple sclerosis lesions. Using platelet-derived growth factor (PDGF–AA), fibroblast growth factor 2 (FGF2), bone morphogenetic protein 2 (BMP2) and bone morphogenetic protein 4 (BMP4) as representative targets, we demonstrate that we can assess their combinatory effects across a wide range of concentrations in a single experiment. This in vitro model is ideal for assessing the combinatory effects of changes in availability of multiple factors, thus more closely modelling the situation in vivo and furthering high-throughput screening possibilities.

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Cerebral Cortex 2019;00: 1–14 IF 5.437

A Late Critical Period for Frequency Modulated Sweeps in the Mouse Auditory System

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Abstract

Neuronal circuits are shaped by experience during time windows of increased plasticity in postnatal development. In the auditory system, the critical period for the simplest sounds – pure frequency tones – is well defined. Critical periods for more complex sounds remain to be elucidated. We used in vivo electrophysiological recordings in the mouse auditory cortex to demonstrate that passive exposure to frequency modulated sweeps (FMS) from postnatal day 31 to 38 leads to long-term changes in the temporal representation of sweep directions. Immunohistochemical analysis revealed a decreased percentage of layer 4 parvalbumin-positive (PV^+) cells during this critical period, paralleled with a transient increase in responses to FMS, but not to pure tones. Preventing the PV+ cell decrease with continuous white noise exposure delayed the critical period onset, suggesting a reduction in inhibition as a mechanism for this plasticity. Our findings shed new light on the dependence of plastic windows on stimulus complexity that persistently sculpt the functional organization of the auditory cortex.

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Journal of Neurochemistry 019;00:e14921 IF 4.870

Combination of antioxidants and NFAT (nuclear factor of activated T cells) inhibitor protects auditory hair cells from ototoxic insult

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Abstract

Hair cell (HC) degeneration causes hearing loss in millions of people worldwide. Aminoglycoside exposure is one major cause of sensory HC damage. Aminoglycosides generate free radicals within the inner ear, permanently damaging sensory cells, and thus causing hearing loss. Hearing protection requires strategies to overcome the apparently irreversible loss of HCs in mammals. The nuclear factor of activated T cells (NFAT) inhibitor 11R-VIVIT reportedly protects HCs from gentamicin toxicity. Here we investigated whether the combination of 11R-VIVIT with the antioxidant L-carnitine or N-acetylcysteine could protect mouse cochlear HCs from gentamicin damage. Compared to single-component treatment, combined treatment with 11R-VIVIT plus L-carnitine yielded significant protection from gentamicin, and 11R-VIVIT plus N-acetylcysteine provided almost complete protection of HCs from gentamicin. Caspase activity in organ of Corti was significantly reduced by combined treatment with 11R-VIVIT + N-acetylcysteine + gentamicin, compared to 11R-VIVIT + gentamicin or gentamicin alone. Analysis of relative gene expression by qPCR revealed down-regulation of the pro-apoptotic genes Fasl and *Casp9* , and up-regulation of the antioxidant genes *Hmox1* and *Nrf2* after treatment with 11R-VIVIT + N-acetylcysteine + gentamicin, compared to single-compound treatment or gentamicin alone in cultures. Selective NFAT inhibition by 11R-VIVIT may be a good strategy for preventing gentamicin-induced HC damage. L-carnitine and N-acetylcysteine, with their ROS-reducing properties, contribute to the synergistic effectiveness with 11R-VIVIT by decreasing ROS-induced NFAT translocation. Our data suggest that a combined approach of NFAT inhibition together with an antioxidant, like N-acetylcysteine, could be useful for hearing loss treatment and/or prevention.

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Transplantation Nov. 2019, Vol. 103, Issue 11, p e384-e385 IF 4.743

Can HLA-B51 Protect Against BKPyV-DNAemia?

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We read with great interest the report by Wunderink et al on the reduced risk of plasma BK polyomavirus (BKPyV)-DNAemia in HLA-B51-positive kidney transplant recipients (KTRs).[1] In their cohort of 407 living-donor KTRs, 111 developed BKPyV-DNAemia, but only 2 (2%) were HLA-B51-positive compared with 34 (11%) among the 296 nonviremic recipients ($P = 0.002$). In several multivariate modeling approaches, the statistical pitfalls of which have been critically reviewed in the accompanying commentary,[2] HLA-B51-positive recipients remained associated with a reduced risk of BKPyV-DNAemia, whereas high BKPyV-Vp1-capsid antibody levels in the respective donors increased the risk of BKPyV-DNAemia. Given the lack of experimental or functional data, Wunderink et al used bioinformatic prediction algorithms and identified four potential epitopes predicted to be presented by HLA-B51 including the BKPyV T-antigen-derived 9mer LPLMRKAYL. By giving explicit reference to our recent work on identifying immunodominant BKPyV 9mer epitopes in healthy donors and KTRs,[3,4] the authors suggested that HLA-B51-positive KTRs might be less susceptible to BKPyV-DNAemia because of BKPyV-specific CD8+ cytotoxic T-cell responses to the BKPyV T antigen–derived 9mer LPLMRKAYL presented by HLA-B51.

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The authors declare that funding provided as a nested project O56 of the Swiss Transplant Cohort Study and that there is no conflict of interest.
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J Immunol January 1, 2020, 204 (1) 180-191 IF 4.718

Activation of TCR Vδ1$^+$ and Vδ1$^-$Vδ2$^-$ γδ T Cells upon Controlled Infection with *Plasmodium falciparum* in Tanzanian Volunteers

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Abstract

Our understanding of the human immune response to malaria remains incomplete. Clinical trials using whole-sporozoite-based vaccination approaches such as the Sanaria PfSPZ Vaccine, followed by controlled human malaria infection (CHMI) to assess vaccine efficacy offer a unique opportunity to study the immune response during *Plasmodium falciparum* infection. Diverse populations of T cells that are not restricted to classical HLA (unconventional T cells) participate in the host response during *Plasmodium* infection. Although several populations of unconventional T cells exist, the majority of studies focused on TCR Vγ9Vδ2 cells, the most abundant TCR γδ cell population in peripheral blood. In this study, we dissected the response of three TCR γδ cell subsets and mucosal-associated invariant T cells in healthy volunteers immunized with PfSPZ Vaccine and challenged by CHMI using Sanaria PfSPZ Challenge. Using a flow cytometry-based unbiased analysis followed by T cell cloning, several findings were made. Whereas major ex vivo alterations were not detectable after immunization with PfSPZ Vaccine, TCR Vδ2, and mucosal-associated invariant T cells expanded after asexual blood-stage parasitemia induced by CHMI. CHMI, but not vaccination, also induced the activation of TCR Vδ1 and Vδ1$^-$Vδ2$^-$ γδ T cells. The activated TCR Vδ1 cells were oligoclonal, suggesting clonal expansion, and upon repeated CHMI, showed diminished response, indicating long-term alterations induced by blood-stage parasitemia. Some TCR Vδ1 clones recognized target cells in the absence of parasite-derived Ags, thus suggesting recognition of self-molecules. These findings reveal the articulate participation of different populations of unconventional T cells to *P. falciparum* infection.

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Frontiers in Immunology April 2020 | Volume 11 | Article 751 IF 4.716

MR1-Restricted T Cells Are Unprecedented Cancer Fighters

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Non-polymorphic MHC class I-related molecule MR1 presents antigenic bacterial metabolites to mucosal-associated invariant T (MAIT) cells and self-antigens to MR1-restricted T (MR1T) cells. Both MR1-restricted T cell populations are readily identified in healthy individuals, with MAIT cells accounting for 1–10% of circulating T cells, while MR1T cells have frequencies comparable to peptide-specific T cells (<0.1%). Self-reactive MR1T cells display a heterogeneous phenotype, and are capable of releasing both T_{H1} and T_{H2} cytokines, supporting not only activation of inflammation but also contributing to its regulation. Importantly, MR1T cells recognize and kill a diverse range of MR1-expressing tumor cells. On the other hand, evidence suggests MAIT cells augment cancer growth and metastases. This review addresses the potential role of MR1-restricted T cells in controlling tumor cells, facilitating their elimination and regulating cancer immunity. We also discuss therapeutic opportunities surrounding MR1-restricted T cells in cancer.

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J Cell Mol Med. 2019;00:1–11 IF 4.658

Arginine- but not alanine-rich carboxy-termini trigger nuclear translocation of mutant keratin 10 in ichthyosis with confetti

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Abstract

Ichthyosis with confetti (IWC) is a genodermatosis associated with dominant-negative variants in keratin 10 (*KRT10*) or keratin 1 (*KRT1*). These frameshift variants result in extended aberrant proteins, localized to the nucleus rather than the cytoplasm. This mislocalization is thought to occur as a result of the altered carboxy (C)-terminus, from poly-glycine to either a poly-arginine or -alanine tail. Previous studies on the type of C-terminus and subcellular localization of the respective mutant protein are divergent. In order to fully elucidate the pathomechanism of IWC, a greater understanding is critical. This study aimed to establish the consequences for localization and intermediate filament formation of altered keratin 10 (K10) C-termini. To achieve this, plasmids expressing distinct *KRT10* variants were generated. Sequences encoded all possible reading frames of the K10 C-terminus as well as a nonsense variant. A keratinocyte line was transfected with these plasmids. Additionally, gene editing was utilized to introduce frameshift variants in exon 6 and exon 7 at the endogenous *KRT10* locus. Cellular localization of aberrant K10 was observed via immunofluorescence using various antibodies. In each setting, immunofluorescence analysis demonstrated aberrant nuclear localization of K10 featuring an arginine-rich C-terminus. However, this was not observed with K10 featuring an alanine-rich C-terminus. Instead, the protein displayed cytoplasmic localization, consistent with wild-type and truncated forms of K10. This study demonstrates that, of the various 3' frameshift variants of *KRT10*, exclusively arginine-rich C-termini lead to nuclear localization of K10.

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SCIENTIFIC REPORTS (2020) 10:3035 IF 4.011

Inhibition of IL-1beta improves Glycaemia in a Mouse Model for Gestational Diabetes

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Abstract

Gestational diabetes mellitus (GDM) is one of the most common diseases associated with pregnancy, however, the underlying mechanisms remain unclear. Based on the well documented role of inflammation in type 2 diabetes, the aim was to investigate the role of inflammation in GDM. We established a mouse model for GDM on the basis of its two major risk factors, obesity and aging. In these GDM mice, we observed increased Interleukin-1β (IL-1β) expression in the uterus and the placenta along with elevated circulating IL-1β concentrations compared to normoglycemic pregnant mice. Treatment with an anti-IL-1β antibody improved glucose-tolerance of GDM mice without apparent deleterious effects for the fetus. Finally, IL-1β antagonism showed a tendency for reduced plasma corticosterone concentrations, possibly explaining the metabolic improvement. We conclude that IL-1β is a causal driver of impaired glucose tolerance in GDM.

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Life Science Alliance vol 3 | no 1 | e201900465

Expression of AXL receptor tyrosine kinase relates to monocyte dysfunction and severity of cirrhosis

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Abstract

Infectious complications in patients with cirrhosis frequently initiate episodes of decompensation and substantially contribute to the high mortality. Mechanisms of the underlying immuneparesis remain underexplored. TAM receptors (TYRO3/AXL/MERTK) are important inhibitors of innate immune responses. To understand the pathophysiology of immuneparesis in cirrhosis, we detailed TAM receptor expression in relation to monocyte function and disease severity prior to the onset of acute decompensation. TNF-α/IL-6 responses to lipopolysaccharide were attenuated in monocytes from patients with cirrhosis (n = 96) compared with controls (n = 27) and decreased in parallel with disease severity. Concurrently, an AXL-expressing (AXL^+) monocyte population expanded. AXL^+ cells ($CD14^+CD16^{high}HLA\text{-}DR^{high}$) were characterised by attenuated TNF-α/IL-6 responses and T cell activation but enhanced efferocytosis and preserved phagocytosis of *Escherichia coli*. Their expansion correlated with disease severity, complications, infection, and 1-yr mortality. AXL^+ monocytes were generated in response to microbial products and efferocytosis in vitro. AXL kinase inhibition and down-regulation reversed attenuated monocyte inflammatory responses in cirrhosis ex vivo. AXL may thus serve as prognostic marker and deserves evaluation as immunotherapeutic target in cirrhosis.

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REVIEWS

Nature Reviews Immunology 19, pages734–746(2019) IF 44.019

Targeting innate immune mediators in type 1 and type 2 diabetes

Marc Y. Donath[1,2*], Charles A. Dinarello[3] and Thomas Mandrup-Poulsen[4]

Abstract

Type 1 and type 2 diabetes are characterized by chronic inflammation; both diseases involve pancreatic islet inflammation, while systemic low-grade inflammation is a feature of obesity and type 2 diabetes. Long-term activation of the innate immune system impairs insulin secretion and action, and inflammation also contributes to macrovascular and microvascular complications of diabetes. However, despite strong preclinical evidence and proof-of-principle clinical trials demonstrating that targeting inflammatory pathways can prevent cardiovascular disease and other complications in patients with diabetes, there are still no approved treatments for diabetes that target innate immune mediators. Here, we review recent advances in our understanding of the inflammatory pathogenesis of type 1 and type 2 diabetes from a translational angle and point out the critical gaps in knowledge that need to be addressed to guide drug development.

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Clinical Microbiology Reviews October 2019 Vol. 32 Issue 4 e00042-19 IF 17.750

Community-Acquired Respiratory Viruses in Transplant Patients: Diversity, Impact, Unmet Clinical Needs

Michael G. Ison[a], Hans H. Hirsch[b,c,d]

SUMMARY

Patients undergoing solid-organ transplantation (SOT) or allogeneic hematopoietic cell transplantation (HCT) are at increased risk for infectious complications. Community-acquired respiratory viruses (CARVs) pose a particular challenge due to the frequent exposure pre-, peri-, and post-transplantation. Although influenza A and B viruses have a top priority regarding prevention and treatment, recent molecular diagnostic tests detecting an array of other CARVs in real time have dramatically expanded our knowledge about the epidemiology, diversity, and impact of CARV infections in the general population and in allogeneic HCT and SOT patients. These data have demonstrated that non-influenza CARVs independently contribute to morbidity and mortality of transplant patients. However, effective vaccination and antiviral treatment is only emerging for non-influenza CARVs, placing emphasis on infection control and supportive measures. Here, we review the current knowledge about CARVs in SOT and allogeneic HCT patients to better define the magnitude of this unmet clinical need and to discuss some of the lessons learned from human influenza virus, respiratory syncytial virus, parainfluenzavirus, rhinovirus, coronavirus, adenovirus, and bocavirus regarding diagnosis, prevention, and treatment.

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Above you can find the abstracts of recent articles published by members of the DBM. The abstracts are grouped according to the impact factor of the journal where the work appeared. To be included, the papers must meet the following criteria:

1. The first author, last author or corresponding author (at least one of them) is a member of the DBM.
2. Department of Biomedicine and University of Basel affiliation must be mentioned in authors list as published by the journal.
3. The final version of the article must be available (online pre-publications will be included when the correct volume, page numbers etc. becomes available).

We are focussing on original publications. Due to page constraints, abstracts of publications that appeared in lower ranked journals may not be able to be included. Review articles are generally not considered, unless they appeared in the very top journals (e.g. Cell, Science, Nature, NEJM, etc.). The final decision concerning inclusion of an abstract will be made by the chair of the Department of Biomedicine.

If you wish that your article will appear in the next issue of DBM Facts please submit a pdf file to the Departmental Assistant, Manuela Bernasconi: manuela.bernasconi@unibas.ch

Deadline for the next issue is November 30, 2020.

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Congratulations

Sofia Gili Sole
Geboren am 11. Juli 2020

Luuk Diepenbruck
Geboren am 14. August 2020

Herzlich willkommen, allerseits!

Summer 2020

North Macedonia

Maybe you wonder what is Macedonia? A fruit salad? A part of Greece? Indeed, it is the name of a mixed fruit salad as well as a northern region of Greece, but it is also the name of my homeland country. The Republic of Macedonia, renamed to the Republic of North Macedonia in 2019, is a small landlocked country in the center of the Balkan Peninsula in Southeast Europe.

Macedonia is a small country, half the size of Switzerland but larger than the likes of San Marino, Andorra or Lichtenstein. However, you need to zoom in to visualize it on Google Maps. With an area of 25 000 km^2 the country has a population of about 2.1 million consisting mainly of Macedonians and minorities such as Albanians, Turks, Romani, Serbs and others. The capital city is Skopje, and a third of the entire population lives there. Divided into two parts by the river Vardar, the city is a combination of ancient history and advanced modernity.

Macedonia has its own language called Macedonian, a South Slavic language with a Cyrillic alphabet and no similarities whatsoever with the Greek language. The Albanian language is the largest minority language and has some official status. There are also other minority languages such as Turkish, Serbian and Romani.

Like the salad, Macedonia's diversity of culture, traditions and nature are attractive for visitors. Recently, Macedonia's popularity as a tourist destination has increased significantly. Some of the highlights that this small piece of land includes are the oldest lake in Europe, the deepest underwater cave in the world, a Bronze Age megalithic observatory, great food and a warm welcome. It is a pleasure for me to write this article and give you, the DBM readers of DBM Facts, a short trip to my homeland.

Lake Ohrid, Macedonia's Unesco World Heritage site, St Kaneo

National park Mavrovo, photo by Maja Najdovska

The History

Once a part of Yugoslavia, the Republic of Macedonia gained its independence in 1991, but following that the name remained a subject of a dispute with bordering Greece. The dispute was finally resolved in February 2019 with the "Prespa Agreement" and the official name of the country became the Republic of North Macedonia.

The modern North Macedonia most closely relates to the ancient kingdom of Paeonia from the 4th century BC. With the fall of Paeonian Kingdom it became a Roman province, with its capital Stobi. Via Egnatia is one of the main Roman roads that ran through present day Albania, North Macedonia, Greece and Turkey and passed through Heraclea Lynkestis – a strategic city during the rule of the Byzantine Empire. The first university in Europe was founded in 886 A.D. by St. Clement of Ohrid with the purpose of studying Cyrillic scripts and Slavic literature more than 100 years before foundation of the universities at Bologna and Oxford.

Conquered by the Ottoman Empire, the state remained under its rule for five centuries with the capital in Manastir (present day – Bitola). A big historical event during the Ottoman rule happened on August 2nd 1903 (St. Elijah's Day – Ilinden) when an uprising against the Ottoman rule led to the forming of "Republic of Krushevo" which is a precursor to the modern Macedonian state. This day became an inspiration for the national anthem and is celebrated each year as the Day of the Republic – A National Holiday. Following the fall of the Ottoman Empire, Macedonia became member of Yugoslavia and later on, in 1991, gained its independence. Present day North Macedonia has a full NATO membership and is an aspiring member of European Union.

Geography and Biodiversity

Bordered by Albania, Kosovo, Serbia, Bulgaria and Greece this small landlocked country has a mainly continental climate. It is surrounded by mountain ranges with a central valley formed by the Vardar river. There are more than 50 lakes and 34 mountains with peaks over 2,000 meters high. It is the fifth highest country in Europe (741m), be-

Lake Ohrid view from Trpajca, photo by Daniela Pelivanovska

Mountain Jablanica, photo by Darko Kostevski

hind Andorra (highest), Switzerland, Austria and Turkey. Macedonia boasts three national parks: Pelister, Galichica and Mavrovo. Moreover, Mavrovo is the largest and at the same time contains the highest mountain peaks in the country. Impressive forests contain more than 100 rare species of trees and wild herbs as well as endemic animal species such as bears, wolves, lynx and Ohrid trout.

The major lakes are Lake Ohrid, Lake Prespa and Lake Dojran, colouring the Macedonian landscape and postcard portfolio. Ohrid lake is the oldest and the deepest lake in Europe. The lake is host to "Ohridska pastrmka" (Ohrid Trout), an endemic species of trout. Numerous rivers and sources enrich the country, among which largest are Vardar, Black River and Black Drim. Altogether, the breath-taking landscapes and flora and fauna biodiversity makes this country authentic and unexplored for the curious lovers of the untouched nature.

Economy

Following the breakup of Yugoslavia the transition from the old communist ideology to a new democratic multiparty system took a toll on the country's economy. Previously government owned industry interconnected within the old Yugoslavia collapsed and the country struggled to stabilize the economy. However, the government's determination is to follow the path of the western democratic countries and bring the country closer the European Union and one day become its full member.

During these years, small and medium size private companies started to emerge. Free economic zones have been built, taxes have been lowered, transport infrastructure has been improved and all this to entice both domestic and foreign investors. In terms of foreign trade, the major sectors contributing to the country's export are metal compounds (ferro-nickel, iron and steel products), clothes, petroleum products and tobacco. Macedonia's main export partners are Germany, Italy, Greece, Bulgaria and Serbia. Tourism and wine producing are both still under development and have the potential to take the economic spotlight. Nowadays, North Mace-

Skopje central square fountain Warrior on Horse, North Macedonia

donia is an upper-middle-income country that has made great progress in reforming its economy over the past decade and is one of the less expensive countries in Europe to live in. Nevertheless, the COVID 19 outbreak has had highly negative impact on Macedonian's as well as worldwide economies.

Let's have a trip to Macedonia

Macedonia is perfect for those who love breath-taking nature, authentic architecture, good food and a bit of history. With lots of mountains, rivers and lakes it offers different activities from hiking, trekking and biking to tandem paragliding and diving in Lake Ohrid.

Being once part of the Byzantian and Ottoman Empires, there are a number of remarkable orthodox churches and multi-coloured mosques. Nowadays tourists can explore fascinating mosaics and the ancient Roman theatre of Stobi and Heraclea or navigate through The Bay of Bones (an ancient pile dwelling village on the banks Lake Ohrid). Skopje's Ottoman bazaar known as Čaršija, with its authentic shops, restaurants and cafes leads to the recently reconstructed central square and its monumental statue named "Warrior on a Horse". Not far from Skopje, the Matka Canyon is famous for rock climbing and kayaking has an iconic view of Skopje and several medieval monasteries. The canyon is a host to the world's deepest underwater cave, Cave Vrelo and being such an unique site just adds to its popularity and it is regularly overcrowded with tourists. Kokino, to the north of the country, is one of the world's oldest observatories, as recognized by NASA, and dates back to the 19th century BC. It is inscribed in a UNESCO "tentative" list of protection.

Do not miss the majestic Lake Ohrid town that shares its name – Macedonia's postcard symbol. The tectonic lake is among the oldest (estimated to be 4 million years old) and deepest (300 m) lakes in Europe. This landscape is crowded with ancient monasteries and churches (once having 365 churches – one for each day of the year) and is also known as the Jerusalem of the Balkans. Listed as an UNESCO site for both its natural and cultural significance, the region is a rare, fragile mixture of traditions, architecture and natural wonders complemented with chic beach bars, superb fish restaurants and cultural activities (festivals, swimming marathon and concerts). One must not miss a tour to Bitola (the Consulat's town) or

Berovo and its wonderful surrounding forests, lake and thermal baths.

When it comes to food, no one can resist the delicious salads and vegetables from the local producers, the organic wild blackberries and raspberries. Macedonia's national dishes are Tetovsko tavce gravce (bean dish with paprika and few spices), Ajvar (paprika based that a friend of mine called "paprika caviar"), Pastrmalija (pie with sliced meat cubes on top of it), Turli Tava (vegetables and meat based dish) or freshly backed Maznik or Burek (cheese or meat pie). Macedoni's Grilled Ohriska pastrmka (Ohrid trout with makalo) or breaded carp can be found on the menu of the Ohrid lake restaurants, do not hesitate – they are amazing!

Ohrid trut and Temjanika with wine, Radozda, Struga

Macedonian national dishes Tetovsko tavche gravch, shopska salad and Rakija

Macedonian lunch or dinner always starts with the so-called 'meze' the traditional appetizers: fresh salad (shopska, mixte or cabbage salad), ajvar, makalo (garlic paste) accompanied with a glass of the traditional drink called Rakija.

Untreated wine and homemade brandies (called Rakija and Mastika) are the traditional drinks. Why is it difficult to find Macedonian wine on the European market? The running joke is that one of the reasons why there isn't more Macedonian wine outside our country is because it's been drunk before it reaches the border.

Macedonia puts a novel spotlight on its diverse metropolis capital, historic and protected lakes, hiking trails, national parks and ancient, old-world culture. Nonetheless, the best way to know much more about Macedonia is to visit and personally explore the beauty of my homeland. I would be glad to provide more information, do not hesitate to ask me if you need any additional information or tips.

Aleksandra Maceski

Facts and tips

Official country name:	North Macedonia (mainstream name: Macedonia)
Size:	Tiny and shiny spread on an area of 25,000km2
Population:	estimated 2.1 million
Economy status:	many improvements in recent years and increase of the GDP
Macedonian lunch or dinner:	starts always with "meze", don't miss having one
Visiting local:	Table full of food and at least 2 shots of Rakija, Turkish coffee for goodbye

Today: Hassan Melhem, Gastroenterology

Lebanon

Hey! My name is Hassan Melhem. I'm 34 years old. I'm born in Tripoli, the largest city in northern Lebanon. I studied at the "Mar Elias School of Carmelite Fathers." What you see in the picture is my different classes through the years, where I always chose my place near the window. After finishing my school education, I moved to France, where I did my bachelor's and PhD studies. After my PhD, I had post-doc positions in Zurich, Bern, and Basel, where I had lots of pleasant memories.

However, the most important period for every one of us is when we were little kids. I think, of all my childhood memories, the most memorable are from when I was in school. The best memories at school were when the teacher was absent, and we enjoyed playing on the school grounds instead. This was a really wonderful feeling. One of the best moments for me at school was when the teacher called me to clean the board!! Yes, the current smart board generation will never know what it means to "clap erasers" or "clean the board" for the teacher. I felt like I was the VIP of the class. At school, I had four best friends, the five of us did everything together, good and bad things. The best, and you could also say the worst at the time, was when I was caught stealing food from the school canteen.

Mar Elias School of Carmelite Fathers

Another unforgettable memory during my childhood is playing with the marbles "gilleh". This is the game that would certainly not get out of my mind. I could actually play this for years. I never wanted to stop playing, but my mum would always say that I had to be home at a certain time.

During summer, I used to go to my grandfather's bee farm out in the country. We'd travel out there on a bike with an extra seat, pedalling really quick. Grandma would feed us on a gallon of milk and home-made bread. When we arrived, we put milk in jars in the mountain river, so it would stay cool and wouldn't go off. We ate freshly harvested honey with bread and drank milk. It was unforgettable. At home, I spent most of my time watching cartoons. My favourite was Tom and Jerry, and I still watch that with my daughter. I remember it like it was yesterday.

Lebanon

Lebanon used to be called "Switzerland of the Middle East". It has a heritage almost as old as the earliest evidence of mankind. Its geographic position as a crossroads linking the Mediterranean Basin with the great Asian hinterland has conferred on it a cosmopolitan character and a multicultural legacy. Lebanon has an Arab culture coloured by Western influences. Its proximity to the sea has ensured that throughout its history Lebanon has held an important position as a trading center. This tradition of commerce began with the Phoenicians and continued through many centuries, remaining almost unaffected by foreign rule and the worst periods of internal strife.

Basic expressions in Lebanese	
Marhaba	Hi
Shoukran	Thank you
Kifak	How are you
Shou esmak	What is your name
Iza betrid	Please
Enta jamil	You are beautiful

...Best places to visit

Raouche Rocks

Raouche Rocks are rock formations surrounded by the sea and have a majestic look. It is a must-see site in Lebanon!

Location

Located in Rouche, in Beirut, in the middle of the Mediterranean Sea.

Activities

› Enjoy the amazing view

Qadisha Valley

It is an historic site that holds some of the most important monasteries in the world which date back to the time when Christianity was still spreading. However, its historic value is not the only interesting thing about it, as it also has a fantastic natural view, as it contains the Forest of the Cedars of God which is a site in the list of UNESCO World Heritage Sites, which will be discussed in detail next.

Location

Located in Basharri North Governorate, north of Mount Lebanon.

Activities

› Take a hike at the foot of the valley

› Visit the historical monasteries

Cedars of God

The cedar tree is the Lebanese logo, and it is one of the most amazing, unique sights in Lebanon. You do not want to miss the breath-taking sight, or the exciting stories behind the trees, whether epic legends, or stories from holy texts.

Location

Located in Basharri North Governorate, at Qadisha Valley.

Activities

› Hike through the forest
› Learn the stories about the cedar trees
› Enjoy the amazing scenery

Byblos Castle

Byblos castle was built by the Crusaders in the 12th century. It is now one of the most iconic historical places in Lebanon, and it houses the Byblos Site Museum that displays remains found by archaeologists in Byblos. It is definitely one of the best places to visit in Lebanon.

Location

Located in Byblos, in Ancient Byblos, and close to the L shaped Temple.

Activities

› Learn about Lebanon's history
› Visit the Byblos Site Museum and watch the marvellous remains
› Enjoy the view of the castle

…Best Lebanese hummus recipe

Ingredients

› 100 grams (3.5 ounces) dried chickpeas
› 1 teaspoon baking soda
› 1½ tablespoon tahini
› the juice of half lemon
› 1½ tablespoon extra virgin olive oil + 1 tablespoon to drizzle on top (optional)
› ½ clove garlic crashed
› ½ teaspoon salt
› ¼ teaspoon cumin
› 1 tablespoon cooking water
› tablespoon to garnish (optional): paprika and/or whole chickpeas, 1 extra virgin olive oil

Instructions

1. Soak the chickpeas overnight in cold water and 1 teaspoon of baking soda. Baking soda helps softening them quicker.
2. The next day, rinse with fresh water, bring it to a boil on high heat, then let it simmer on low heat until soft (more or less 1 hour).
3. As soon as the water starts boiling a white foam will appear on top, try to scrape out as much of it as possible.
4. Drain the chickpeas then place them in the bowl of a food processor and blend for 1 minute.
5. Add the tahini, extra virgin olive oil, lemon juice and keep mixing until it becomes creamy. Stop to scrape down the sides once or twice.
6. Add the garlic, salt and cumin and blend for 3 – 4 minutes until thoroughly mixed and smooth.

7. Taste and adjust the seasonings, adding more salt or lemon if needed.
8. Place in a shallow bowl, drizzle 1 tablespoon of olive oil, garnish with a few chickpeas and sprinkle with paprika.

Tips for making the best hummus

1. Soak chickpeas in baking soda.
2. Peel the chickpeas.
3. Add ice cubes to the blender.
4. Use a strong blender.
5. Enjoy it.

Departement Biomedizin Basel

Wednesday, September 2, 2020

DBM Summer Symposium

9:00 – 15:00
Kleiner Hörsaal ZLF
Hebelstrasse 20, 4031 Basel

Presentations by DBM postdocs, DBM PhD students and DBM project leaders

DBM 20 Anniversary Party

postponed to 2021

18:00 – 23:00
University Hospital Basel, Centro

For DBM members only

UKBB Universitäts-Kinderspital beider Basel
Universität Basel
Universitätsspital Basel

« Es ist leicht,
einen leeren Kopf
hochzutragen. »

Aus dem Libanon