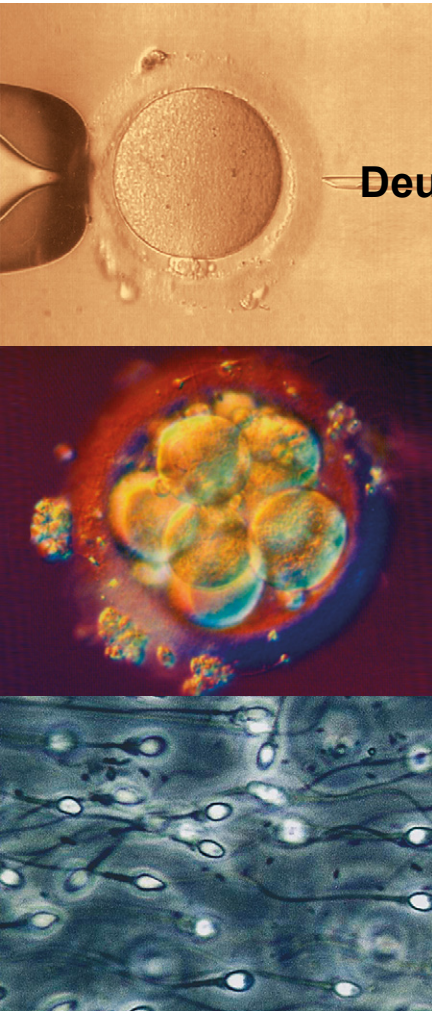


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**24. Treffen des Arbeitskreises Molekularbiologie der
Deutschen Gesellschaft für Reproduktionsmedizin 7. und
8. November 2025, Münster Abstracts**

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24. Treffen des Arbeitskreises Molekularbiologie der Deutschen Gesellschaft für Reproduktionsmedizin

7. und 8. November 2025, Münster

Ausgewählte Abstracts^{*)}

Immunohistochemical studies to analyze the implantation defect in the Cldn10 knockout mouse

I. Abaeva¹, S. Grund², D. Müller³, G. Wennemuth¹, R. Grümmel¹

¹Institut für Anatomie und ²Klinik für Endokrinologie, Diabetologie und Stoffwechsel, Universitätsklinikum Essen, Universität Duisburg-Essen, ³Klinik für Pädiatrie m. S. Nephrologie, Charité – Universitätsmedizin Berlin, Germany

Introduction Claudins are important components of tight junctions that regulate the selective barrier function of epithelial cells. We demonstrated before that Claudin- (Cldn) 10 expression is induced during the mesenchymal-epithelial remodeling in murine decidualization from day 4.5 post coitum (dpc) onwards. Moreover, an essential role of this Cldn10 induction for successful pregnancy has been proven since female mice revealing a conditional endometrium-specific Cldn10-knockout (KO) are infertile due to intrauterine embryonic loss around 8.5 dpc.

Material and methods In order to characterize the Cldn10 deficiency-mediated changes in the decidua leading to intrauterine fetal death, we here analyzed the size of the implantation chamber and of the decidualized area on HE-stained sections. Moreover, to decipher the defects in the Cldn10-KO decidua, immunohistochemical staining for CD31 was performed to analyze angiogenesis. Additionally, immune cell composition (anti-CD45, DBA-lectin) and extent of trophoblast growth (anti-cytokeratin-8) as well as the distribution of apoptotic cells (TUNEL assay) were analyzed.

Results In Cldn10-KO mice, implantation chambers were significantly smaller from 7.5 dpc onwards, with a markedly reduced decidualized area by 8.5 dpc compared to wildtype controls. CD31 staining revealed no major alterations in vascularization. However, Cldn10 deficiency was associated with a decrease in uterine NK cells and a pronounced increase in immune cell infiltration within the trophoblast area. Preliminary data further indicate elevated apoptosis in trophoblast cells of Cldn10-KO mice.

Conclusion Cldn10 is crucial for the maintenance of early pregnancy by supporting proper decidual development and embryo viability. While vascularization appears un-

affected, the loss of Cldn10 may disrupt immune cell regulation at the maternal-fetal interface. This dysregulation could lead to an aberrant increase in immune cell infiltration into the trophoblast region, potentially contributing to trophoblast apoptosis and impaired implantation. These findings suggest a dual role of Cldn10 in structural remodeling and immune homeostasis during decidualization.

Funktionelle Analyse von Syndecan-1 und -4 in der Endometriose: ein 3D-Modellansatz

J. Beckmann^{1,2}, P. Quasdorff^{1,2}, M. Götze¹, H. M. El-Shorafa¹

¹Universitätsklinikum Münster, Forschungslabor der Klinik für Frauenheilkunde und Geburtshilfe, ²Universität Münster, Deutschland

Einleitung Endometriose ist eine chronische, östrogenabhängige Erkrankung, bei der gewebeähnliche Strukturen der Gebärmutter-schleimhaut (Endometrium) außerhalb der Gebärmutter auftreten. Diese Läsionen reagieren zyklisch auf Hormone, genau wie das Endometrium selbst. Beeinträchtigungen der Fruchtbarkeit und Schmerzen sind hierbei die wichtigsten klinischen Symptome der Erkrankung.

Syndecane sind Transmembran-Proteoglykane, deren extrazellulären Domäne Heparansulfat- oder Chondroitinsulfatkette trägt. Über diese Glykosaminoglykanketten binden Syndecane Wachstumsfaktoren, Zytokine und extrazelluläre Matrixkomponenten. Als Co-Rezeptoren vermitteln sie somit die Kommunikation zwischen der Zelle und ihrer Umgebung und können die Zelladhäsion, Migration und intrazelluläre Signalübertragung beeinflussen. Syndecan-1 (SDC1) und -4 (SDC4) weisen in endometriotischem Gewebe eine veränderte Expression auf. Um ihre potenziell funktionelle Rolle in Endometriose zu untersuchen, wurde in einem 3D-Modell des Endometriums ein Knock-down (KD) der Genexpression durchgeführt.

Material und Methoden Zur funktionellen Analyse von SDC1 und SDC4 in der Endometriose wurde ein 3D-Modell des Endometriums nachgebaut. Hierfür wurden zwei Zelllinien verwendet: die Stromazelllinie St-T1b und die Epithelzelllinie Ishikawa. In beiden Zelllinien wurden die Expression von SDC1 bzw. SDC4 mittels transgener siRNA Transfektion herunterreguliert.

Das 3D-Modell wurde aus folgenden Schichten zusammengebaut: Die transfizierten St-T1b-Zellen wurden in eine mit Kollagen 1 beschichtete 96-Well-Platte ausgesät. Dar-

auf wurde eine Matrigelschicht gegeben, auf welche dann wiederum die Ishikawa-Zellen ausgesät wurden. Die beiden KD-Modelle (siSDC1 und siSDC4) wurden in folgenden funktionellen Assays mit einem Kontroll-Modell verglichen.

Mithilfe des Modells wurde die Zellviabilität, sowie die Trophoblasten-Adhäsion untersucht. In einem Live-Cell-Imaging des Modells wurde die Trophoblast-Eindringtiefe ermittelt. Es erfolgte außerdem eine RNA-Sequenzierung mit anschließenden Differentialgenanalysen und Funktionsanalysen. Die Ergebnisse der Sequenzierung wurden mittels RT qPCR bestätigt.

Ergebnisse Im siSDC1-Modell liegt im Vergleich zum Kontroll-Modell eine signifikant niedrigere Zellviabilität vor. Für das siSDC4-Modell konnte kein signifikanter Unterschied festgestellt werden.

Für die Untersuchung der Trophoblasten-Adhäsion konnten für beide KD-Modelle keine signifikanten Unterschiede ermittelt werden.

In der RNA-Sequenzierung konnten mehrere Gene mit veränderter Expression festgestellt werden: IL-1Ra (Interleukin 1 Rezeptor Antagonist) weist im siSDC1-Modell, sowie in den Ishikawa-Zellen im 2D-Modell eine signifikant niedrigere Expression auf. IL-1Ra codiert für das Protein IL-1Ra, welches an den IL-1-Rezeptor bindet, jedoch keine Signalweiterleitung auslöst. Es blockiert somit die Bindung von IL-1 β an den Rezeptor, welche die Aktivierung von NF- κ B auslösen würde. IL-1Ra kann somit eine entzündungshemmende Wirkung zugesprochen werden.

FTH1P3 (Ferritin Heavy Chain 1 Pseudogene 3) liegt im siSDC1 Modell, sowie in beiden Zelllinien im 2D-Modell signifikant niedriger exprimiert vor. FTH1P3 wird in Verbindung mit der Induktion von EMT gebracht. Für das siSDC4-Modell konnte eine erhöhte Expression von CCR4 (CC Motif Chemokine Receptor 4) ermittelt werden, welches eine Rolle in der Immunantwort spielt und die gezielte Migration von Immunzellen vermittelt. Im siSDC4-Modell, sowie in den St-T1b-Zellen liegt INHBB (Inhibin Subunit Beta B) signifikant niedriger exprimiert vor. INHBB wird im Zusammenhang mit rezidivierendem Implantationsversagen untersucht.

Schlussfolgerung Die Ergebnisse zeigen, dass SDC1 die Zellviabilität beeinflusst und in Verbindung mit entzündlichen Signalwegen steht. SDC4 könnte indirekt Immunreaktionen beeinflussen. Sowohl SDC1 als auch SDC4 scheinen potenziell relevante Funktionen in der Endometriose zu übernehmen.

^{*)} Begutachtet und zusammengestellt vom wissenschaftlichen Komitee. Ein alphabetisches Verzeichnis der präsentierenden Autoren finden Sie auf Seite 221.

Human sFLT1-induced preeclampsia and a high-caloric diet increase the risk of a metabolic syndrome only in male mouse offspring

A. Edinger¹, E. M. Elfroth¹, L. Hübner¹, M. Seibel¹, R. Steffen², M. Serdar², R. Kimmig¹, I. Bendix², A. Gellhaus¹

¹Department of Gynecology and Obstetrics, and ²Department of Paediatrics I, Neonatology and Experimental perinatal Neurosciences, University Hospital Essen, Germany

Introduction Preeclampsia (PE), a placental disease affecting 3–7% of pregnant women, is characterized by elevated levels of anti-angiogenic soluble fms-like tyrosine kinase-1 (sFLT1), often leading to fetal growth restriction (FGR). According to the developmental origins of health and disease (DOHaD) theory, adverse intrauterine conditions can lead to chronic disease in later life. Therefore, fetal adaptations to adverse intrauterine environment during PE may negatively pre-program the metabolism of the fetus/offspring, resulting in long-term metabolic changes. Additional external stressors like a high-caloric diet can further aggravate these effects and could contribute to excessive weight gain until adolescence. To analyze the potential risk factors, we challenged the offspring from a preeclampsia mouse model with a high caloric western style diet and investigated the risk for the offspring to develop a metabolic syndrome.

Material and Methods We used a human sFLT1 (hsFLT1) PE/FGR mouse model and examined the offspring metabolic response to a high-caloric Western-style diet (WD) versus standard diet (SD). Insulin (ITT) and glucose tolerance tests (GTT) were performed throughout the postnatal development and metabolically relevant tissues (liver, pancreas, gonadal fat, hypothalamic brain region) were collected on postnatal days P28 (juvenile) and P90 (young adult) to assess morphological changes and altered mRNA and protein levels due to PE pregnancy and/or dietary intervention. Liver tissue samples were analyzed histologically regarding the amount of stored glycogen levels (PAS staining) and fat accumulation (Red oil). Further, leptin and insulin signaling pathways were evaluated via Western Blotting in the liver and hypothalamus. Pancreatic alterations were investigated via immunohistochemical staining of pancreatic islets (glucagon and insulin expression).

Results We found evidence of obesity and pre-diabetes exclusively in male offspring resulting from an hsFLT1-induced PE pregnancy. Body and organ weights are increased only in PE males with WD. Blood glucose level responses during GTT were impaired in PE males fed a WD compared to controls, implying a pre-diabetic status of these animals. Liver and hypothalamic insulin- and leptin receptor signaling were altered. In PE males, the PI3K/AKT signaling as well as MEK/ERK signaling pathway are affected by hsFLT1 exposure in utero and additional postnatal western style. PE females with WD exhibited increased insulin sensitivity measured via ITT. Pancreatic insufficiency was detected in the PE offspring, independent of sex or dietary change.

Conclusion The results suggest that hsFLT1-induced PE/FGR in mice may increase the risk of developing a metabolic syndrome and (pre-) diabetes only in male offspring. These effects are aggravated after feeding a high-caloric diet, while PE-females seemed to be protected from harmful effects of this high-caloric diet. Subsequent analysis of the mechanism for the sex-specific responses towards the in utero exposure to hsFLT1 and postnatal diet change are in progress.

Complement proteins, Annexin V, and angiogenic markers in placental tissue of autoimmune disease patients

P. Fuentes-Zacarias^{1*}, A. S. Castellanos-Gutiérrez^{1,2*}, F. Figueras³, G. Espinosa³, T. Groten⁴, D. M. Morales-Prieto¹, N. Baños³, U. Markert¹

¹Placenta Lab, Department of Obstetrics, Jena University Hospital, Jena, Germany; ²Department of Maternal-Fetal Medicine, Institute Clinic of Gynecology, Obstetrics and Neonatology (ICGON), Hospital Clinic-IDIBAPS, University of Barcelona and Centre for Biomedical Research on Rare Diseases (CIBER-ER), Barcelona, Spain; ³Department of Autoimmune Diseases, Hospital Clinic, Barcelona, Catalonia, Spain; ⁴Klinik und Poliklinik für Geburtsmedizin, Köln University Hospital, Köln, Germany

*These two authors contributed equally to this work.

Introduction Autoimmune diseases (AID) such as systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS) or non-criteria-obstetric antiphospholipid syndrome (NC-OAPS) increase the risk of adverse perinatal outcomes (APO). During pregnancy the deregulation of the complement system and the angiogenic factors cause damage to the placenta, resulting in the development of APO. The aim is to evaluate the placental expression of complement proteins, Annexin V (ANNV) and angiogenic factors in patients diagnosed with AID and compare it with healthy controls and fetal growth restricted (FGR) cases.

Materials and Methods Placental samples were classified into: AID with (13) and without (9) APO, FGR without AID (13), and healthy control group (13). Tissue sections were stained using antibodies against human complement proteins and ANNV. Results were expressed as mean-of-fluorescence-intensity (MFI) values. Total RNA was extracted from paraffin sections and mRNA expression of the angiogenesis-related factors was evaluated by qPCR and normalized using the 2- Δ Ct method relative to GAPDH.

Results Lower expression of ANNV in AID+APO ($p = 0.028$), and AID ($p = 0.034$) compared to the control. Higher levels of C5b-9 ($p = 0.0005$ AID+APO and $p < 0.0001$ AID), C3b ($p < 0.0001$ both AID groups) and C4d ($p < 0.0001$ both AID groups and $p = 0.0006$ in FGR) were found compared to the control group. PlGF expression showed significant increase in the AID group without APO compared to the control group.

Conclusion Excessive complement activation and placental deposition while reduced ANNV is present in SLE, APS and NC-OAPS patients. Elevated PlGF placental expression

is a feature of patients with AID without adverse perinatal outcomes.

Modellansätze zur Untersuchung plazentarer Fibrose im Kontext diabetischer Schwangerschaften

B. Grimm¹, L. Hausdorf¹, S. Große¹, T. Groten^{1,2,3}

¹Plazentalabor/Klinik für Geburtsmedizin, Jena Universitätsklinikum, ²Klinik und Poliklinik für Geburtsmedizin, Köln Universitätsklinikum, ³Zentrum für Frühschwangerschaft und reproduktive Gesundheit (CEPRE; www.uniklinikum-jena.de/cepre), finanziert durch das Bundesministerium für Bildung und Forschung (BMBF; Förderreferenz: 01GR2305A), Deutschland

Einleitung Die molekularbiologischen Grundlagen des Plazentaversagens bei Typ-1-Diabetes mellitus (T1DM) sind weitestgehend unklar, äußern sich aber in schlechterer Funktion der Plazenta, gemessen an der Oxygenierung des Nabelschnurblutes und der erhöhten perinatalen Mortalität dieser Schwangerschaften. Bei Vorliegen eines T1DM wurden in anderen Organsystemen, wie der Leber und der Niere, eine Fibrosierung und ein konsekutiver Funktionsverlust beobachtet. Diese Fibrosierung kann durch die glukose-induzierte epithelial-mesenchymale Transition (EMT) ausgelöst werden. Vorausgehende Untersuchungen konnten bereits immunhistochemisch eine signifikante Fibrose in diabetischen Plazenten nachweisen, die auch mit klinischen Endpunkten, wie die Verlegung auf die NICU oder Schwangerschaften, die im intrauterinen Fruchttod enden, positiv korrelierten. Außerdem wurde durch Zellkulturversuche herausgefunden, dass die Expression von profibrotischen Proteinen wie β -Catenin, TGF- β 1 und Snail nach Kultivierung in hyperglykämischen Bedingungen erhöht war. Unser Ziel war es daher, diese fibrotischen Befunde anhand von drei verschiedenen Versuchsmodellen genauer zu untersuchen.

Methoden Zur Untersuchung von EMT- und Fibrose-Markern in diabetischen Plazenten wurde deren Expression in Chorionzotten von 13 T1DM-Schwangerschaften und 13 Kontrollen mittels qRT-PCR analysiert. Zusätzlich wurde die Transkription von EMT- und Fibrose-Markern in AC-1M32-Trophoblastzellen nach 72-stündiger bzw. 7-tägiger Glukosebehandlung untersucht. Analysiert wurden Marker für profibrotische Signalwege (TGF- β 1, Snail), mesenchymale Zellen (Kollagen 1A1, Vimentin) und epitheliale Zellen (N-Cadherin, E-Cadherin, β -Catenin). Plazentäre Explantate wurden ebenfalls mit Glukose behandelt und mittels qRT-PCR, Western Blot und TGF- β 1-ELISA auf EMT- und Fibrose-Marker untersucht. In den Explantat-Überständen wurden zudem Hormone (Estradiol, Progesteron), Metabolite (Laktat, Glukose) und der pH-Wert gemessen.

Ergebnisse Die Vorergebnisse konnten mit den gewählten Modellen nicht bestätigt werden. Weder in Plazenten von T1DM-Patientinnen noch in Zellkulturversuchen oder plazentären Explantaten ließ sich eine erhöhte Kollagen-1A1-Genexpression nachweisen. Ebenso konnte die vermutete Hochregulation profibrotischer Signalmoleküle wie β -Catenin, TGF- β 1 und Snail auf Gene-

bene nicht bestätigt werden. Darüber hinaus zeigten sich ebenfalls keine signifikanten Veränderungen in den plazentären Explantaten unter hyperglykämischen Bedingungen im Vergleich zu der Kontrollgruppe.

Schlussfolgerung Um einen möglichen Signalweg zu untersuchen, der dem Plazenta-versagen in diabetischen Plazenten zugrunde liegt, sollten die Modellansätze nochmal überdacht werden und Anpassungen vorgenommen werden. Eine große Rolle spielt dabei unter anderem die Wahl der Analysezeitpunkte oder auch das Gestationsalter der Plazenten (Termingeburt vs. 1. Trimester). Außerdem könnte die Wahl eines anderen Zellmodells wie zum Beispiel frisch isolierte Trophoblastzellen aus der Plazenta oder Stammzellen mehr Erfolge liefern.

Variants in TOPAZ1 are associated with human male infertility

L. Herrmann¹, J. Steingröver^{1,2}, S. Koser^{1,2}, M. Anfosso³, C. Krallmann³, S. Kliesch³, F. Tüttelmann^{1,2}, B. Stallmeyer¹, C. Friedrich¹

¹Institute of Reproductive Genetics (IRG), Centre of Medical Genetics (CMG), University of Münster; ²Department of Medical Genetics, Centre of Medical Genetics (CMG), and ³Department of Andrology, Centre of Reproductive Medicine and Andrology (CeRA), University Hospital Münster, Germany

Impaired spermatogenesis resulting in severely reduced sperm counts (oligo-, crypto-, or azoospermia) and male infertility is often caused by pathogenic variants in genes encoding testis-specific proteins. TOPAZ1 (testis- and ovary-specific PAZ domain-containing protein 1) is a candidate gene for human male infertility as it is specifically expressed in germ cells and male knockout mice are infertile. Here, we describe three men with infertility caused by varying degrees of spermatogenic failure who carry homozygous variants predicted to impair TOPAZ1 function.

The Male Reproductive Genomics (MERGE) study cohort, which comprises sequencing data of ~3,000 infertile men, was screened for homozygous high-impact variants (rare [minor allele frequency < 0.01] missense variants with a CADD score > 25 or rare loss-of-function variants [stop gain, frameshift, splice site]) in TOPAZ1. Pedigree information of the affected men's families was obtained and genetic variants were validated by Sanger sequencing. Available testicular biopsies were examined by periodic acid-Schiff staining.

Individual M1466 carried missense variant c.2155G>A p.(Asp719Asn) (CADD: 26) and presented with azoospermia due to severely reduced spermatogenesis and highly fibrotic seminiferous tubules in his testicular biopsy. M1446 had the frameshift variant c.127_128insC p.(Cys43SerfsTer5) and presented with severe oligozoospermia. M4182 showed azoospermia due to meiotic arrest and carried the stop gain variant c.2868del p.(Leu957Ter).

With one man with infertility affected by putatively pathogenic variants in TOPAZ1 published before [Oud et al., Nat Commun, 2022] and the three men described here, the gene-disease relationship of TOPAZ1 and

male infertility was validated. Thus, TOPAZ1 should be included to gene panels to increase the diagnostic yield.

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Recognition of mtDNA released in extracellular vesicles from stressed trophoblasts

A. M. Hernández-Bustos¹, D. M. Morales-Prieto¹, F. Steiniger², U. R. Markert¹, J. M. Murrieta-Coxca¹

¹Placenta Lab, Obstetrics Department and ²Electron Microscopy Center, Jena University Hospital, Jena, Germany

Introduction Placental oxidative stress and mitochondria dysfunction is linked to several serious pregnancy complications. Stress signals and defective mitochondrial function generate increased production of reactive oxygen species (ROS), which in turn causes further mitochondrial deterioration and global cellular damage. However, dysfunctional mitochondria can contribute to cell aging independently of ROS. This could happen for example by releasing mitochondrial DNA (mtDNA) to the extracellular milieu encapsulated in extracellular vesicles (EV). In this study, we report the stress-induced release of mtDNA-containing EV by trophoblasts cells and the mtDNA-induced inflammation.

Materials and methods BeWo cells were cultured in F12K complete media in presence or absence of forskolin (50 nM) and 5 nM H₂O₂. Cytotrophoblast cells (CTBs) from term placenta were isolated and cultivated in DMEM supplemented with 20% FBS exosome-depleted. THP-1 cells were cultivated in RPMI complete medium. THP-1 monocytes were differentiated with 100 ng/mL phorbol 12-myristate 13-acetate. Supernatants were collected and EV were isolated by ultracentrifugation. The size and concentration distribution of EV was measured by nanotracking analysis and visualized by transmission electron microscopy. Total DNA was isolated from EVs and the presence of mtDNA genes was assessed by qPCR. Cytokine release profile was measured by Legenplex assay.

Results Oxidative stress induced by H₂O₂ increased the amount of EV released by BeWo cells and CTBs. Stress-derived EVs contained higher amounts of total DNA. mtDNA genes including CO₂, ND2, ND4, CYB, ATP8, RND2 were detected in EVs isolated from BeWo cells and CTBs. We found higher levels of ATP8 and RND2 in stress-derived EVs but no difference in EV release and mtDNA content from BeWo cells treated with forskolin. Elevated cytokine release and expression of genes related to TLR-9 and cGAS pathways were observed in macrophages stimulated with mtDNA fragments.

Conclusion Stressed trophoblasts (CTBs but not syncytialized cells) release large quantities of EV enriched in mtDNA. Immune cells can internalize EV and the mtDNA can be recognized by TLR-9 and cGAS inducing release of pro-inflammatory cytokines. Stress-derived mtDNA might serve as a signal of mitochondrial damage propagating stress

to healthy cells and contributing with the induction of senescence-associated secretory phenotype within the placenta.

Transepithelial trophoblast invasion in a human in-vitro implantation model

L. Izmaylova, I. Classen-Linke, R. E. Leube
Institute of Molecular and Cellular Anatomy (MOCA), Uniklinik RWTH Aachen, Germany

Embryo implantation into the uterine endometrium is a distinct and highly species-specific process. It starts with the attachment of the trophoblast to the apical surface of the endometrial epithelium and is followed by the transepithelial invasion of the embryo which is essential for successful implantation. This phase of implantation is not well documented in humans until now. To get some insights, it is important to define the exact cellular events and forces underlying this process.

To investigate the role of cell-cell junctions and their associated cytoskeletal elements in this process, we developed an invasion model consisting of human trophoblast-derived spheroids (AC-1M88 cells) attaching to and invading through a monolayer of human endometrial epithelial cells (adenocarcinoma-derived Ishikawa cells or primary human cells). Endometrial epithelial cells were grown on soft polyacrylamide hydrogels with a defined stiffness of 4 kPa to mimic the stiffness of healthy, non-pregnant endometrium.

Using this model, 3D visualization of the invasion process could be obtained. We monitored tight and adherens junctions as well as desmosomes by immunohistochemistry using confocal microscopy and transmission electron microscopy at invasion sites. We were able to detect the formation of heterologous junctions between endometrial and trophoblast cells. Functional tests by blocking junction proteins were performed in order to elucidate the role of heterologous desmosomes for transepithelial invasion.

In summary, our findings strongly indicate that the identified heterologous junctions between embryonal and maternal epithelia play a crucial role in the early stages of human embryo implantation.

MicroRNA-mediated regulation of senescence and SASP pathways in the aging endometrium

L. Materazzi¹, A. Schafir¹, L. Castagnola¹, E. Grasso¹, E. Soczewski², M. Irigoyen³, A. Cattaneo³, M. Soledad Gori¹, C. Pérez Leirós¹, U. R. Markert², R. Ramhorst¹

¹Laboratorio de Inmunofarmacología, Instituto de Química Biológica de la Facultad de Ciencias Exactas y Naturales (QUIBICEN-CONICET), Universidad de Buenos Aires, Argentina; ²Placenta Lab, Department of Obstetrics, Jena University Hospital, Jena, Germany; ³Fertilis Medicina Reproductiva, Buenos Aires, Argentina

Introduction The progressive delay of motherhood has become a global phenomenon associated with increased infertility and pregnancy complications. While ovarian aging has been extensively studied, the molecular mechanisms underlying endometrial aging and its impact on receptivity remain

poorly understood. The endometrium undergoes cyclic regeneration, in which decidualization of stromal cells generates mature and senescent subpopulations. Physiological senescence supports implantation through the senescence-associated secretory phenotype (SASP), which shapes the immune microenvironment. However, with advancing age, chronic low-grade inflammation (inflammaging) may disturb this balance, compromising tissue function. This study aims to identify microRNAs (miRNAs) associated with endometrial aging, explore their regulatory roles in SASP and senescence pathways, and assess their potential as biomarkers of uterine aging.

Material and Methods An in-silico analysis was performed using the publicly available GEO transcriptomic dataset GSE234354, which includes secretory-phase endometrial samples from women of different ages. Gene Set Enrichment Analysis (GSEA) was applied to identify age-associated activation of senescence and SASP pathways. To validate these findings, RT-qPCR analyses were conducted on endometrial biopsies from fertile patients to evaluate the expression of senescence- and inflammation-related genes. Candidate miRNAs were predicted using the miRDB database. Ongoing work includes in situ hybridization (ISH) to localize miRNA expression in endometrial tissue sections and extracellular vesicle (EV) isolation from stromal cells to investigate whether these miRNAs are secreted and could serve as non-invasive biomarkers of endometrial aging.

Results The in silico analysis revealed up-regulation of senescence- and SASP-related pathways in women of advanced reproductive age, along with increased expression of inflammatory in endometrial biopsies from older versus younger patients. These findings indicate a progressive activation of stress and inflammatory responses associated with age. Based on pathway enrichment and target prediction, hsa-miR-519d-3p, hsa-miR-29b-3p, and hsa-miR-17-5p emerged as strong candidates potentially regulating genes involved in senescence and inflammaging.

Conclusion Our findings suggest that endometrial aging is accompanied by the progressive activation of senescence and SASP pathways, which are potentially modulated by microRNA-dependent mechanisms. The integration of transcriptomic data, gene expression validation, and forthcoming analyses of miRNA localization and EV cargo will provide a comprehensive view of endometrial inflammaging and may uncover novel non-invasive biomarkers of uterine aging. Moreover, the study of miRNA-containing extracellular vesicles opens the possibility of exploring bidirectional communication between the aging endometrium and the aged ovary, offering new insight into the coordinated decline of reproductive tissues and its impact on fertility.

Wirken pränklampische Stimuli vor allem auf vorgealterten Endothelzellen oder lassen sie Endothelzellen altern?

E. Pusch¹, L. Lode¹, S. Große¹, T. Groten^{1,2,3}

¹Placenta-Labor Uniklinik Jena, ²Klinik für Geburtsmedizin, Universitätsklinikum Köln, ³Zentrum für Frühschwangerschaft und Reproduktive Gesundheit (CEPRE; www.uniklinikum-jena.de/cepre), gefördert vom Bundesministerium für Bildung und Forschung (BMBF; Förderkennzeichen: 01GR2305A), Deutschland

Einleitung Präeklampsie (PE) ist durch eine generalisierte endotheliale Dysfunktion gekennzeichnet. Das danach bestehende lebenslang erhöhte Risiko für kardiovaskuläre Erkrankungen wird auf Gefäßalterung zurückgeführt. Bislang ist unklar, ob PE das Gefäßsystem altern lässt oder ob pränklampische Stimuli stärker auf prämaturn gealterte Endothelzellen wirken. Dies soll in diesem Projekt untersucht werden.

Material und Methodik HUVEC (human umbilical vein endothelial cells) werden mit den PE-Markern lösliche Fms-like Tyrosine Kinase-1 (sFlt-1) und lösliche Endoglin (sEng) über 8 Tage stimuliert und Seneszenz wird mithilfe Seneszenz-assoziiierter β -Galaktosidase (SA β -Gal-) Färbung, PI-Färbung zur Zellzyklus-Analyse und Western Blot-Analyse von Seneszenzmarkern untersucht. In jungen und per Wasserstoffperoxid vorgealterten HUVEC wird die mittels 24-stündiger sFlt-1- und sEng-Stimulation-induzierte Dysfunktion anhand erhöhter ROS-Produktion (reaktive oxygen species), Expression von Adhäsionsmolekülen und Zytokinen, sowie per Permeabilitätsmessung untersucht.

Ergebnisse Eine Behandlung von HUVEC mit 50 oder 250 ng/ml sFlt-1 und sEng für 24 h löst weder in jungen noch in vorgealterten Endothelzellen eine Barrierestörung, erhöhte ROS Produktion, Expression von Adhäsionsmolekülen oder proinflammatorischen Zytokinen aus. Eine Stimulation über 8 Tage führt zur Expression von SA- β -Gal, sowie p16.

Schlussfolgerung Unsere Ergebnisse zeigen, dass vorgealterte Endothelzellen nach 24 h nicht verstärkt auf pränklampische Stimuli reagieren. Über einen längeren Zeitraum hinweg lösen PE-simulierende Stimuli jedoch Endothelzellalterung aus. Dies weist darauf hin, dass Gefäßalterung eine Folge von PE ist.

Teratogenic effects and transplacental transfer of *Tityus serrulatus* venom: insights from zebrafish and human placental models

I. C. dos Santos¹, M. W. Gualque^{1,2}, A. M. Fusco Almeida^{1,2}, J. M. Murrieta-Coxca^{3,4}, U. R. Markert^{3,4}, M. Berto Pucca^{1,2}

¹Graduate Program in Bioscience and Biotechnology Applied to Pharmacy and ²Department of Clinical Analysis, School of Pharmaceutical Sciences, São Paulo State University, Brazil; ³Placenta Lab. Department of Obstetrics, Jena University Hospital, Jena, Germany; ⁴Center for Early Pregnancy and Reproductive Health (CEPRE; www.uniklinikum-jena.de/cepre) (funded by the German Federal Ministry of Research, Technology and Space, BMFT; funding reference: 01GR2305A), Germany

Introduction Scorpionism is a significant public health concern in Brazil, with *Tityus serrulatus* being the most dangerous and widely distributed species. Its venom contains neurotoxins that act on sodium and potassium channels, leading to excessive neurotransmitter release and triggering a pro-inflammatory “cytokine storm”. Studies indicate that scorpion venom can induce neurological and immunological responses associated with embryonic and fetal malformations or even fetal death in severe cases. Despite advances in understanding envenomation mechanisms, there is still no consensus on the ability of the toxins to cross the placental barrier. Given the gap in the literature regarding the effects of *T. serrulatus* venom on pregnant women and their fetuses, this study aims to investigate its teratogenic potential and its ability to cross the transplacental barrier, affecting the fetuses of pregnant women exposed to scorpionism.

Materials and Methods: We used the zebrafish (*Danio rerio*) model and human placental cell lines BeWo and JEG-3, exposed to different venom concentrations. In the zebrafish model, embryos were exposed to five venom concentrations and evaluated for 72 hours post-fertilization (hpf), with teratogenic effects analyzed according to OECD 236. In human placental cells, ATP production was measured using an ATP luminescence assay (CellTiter-Glo®), assessing changes in cellular metabolic activity in response to venom exposure. Additionally, a placenta-on-a-chip (PoC) model is being investigated to simulate the maternal-fetal interface and study venom transfer across the placental barrier. Ex-vivo assays using unilateral and bilateral human placental perfusion models are also being investigated to assess whether the venom can cross the barrier and affect the fetus, considering both maternal and fetal circulation.

Results In zebrafish assays, malformations were observed at different venom concentrations and exposure times, confirming the teratogenic potential of *T. serrulatus* venom. At the highest concentration (100 μ g/mL), survival was approximately 30% at 72 hpf. Cellular assays revealed significant metabolic changes, evidenced by increased ATP levels, suggesting possible interference with placental physiology.

Conclusion In conclusion, *T. serrulatus* venom demonstrated teratogenic potential under the experimental conditions evalu-

ated, affecting embryonic development and highlighting the need to investigate its effects in the gestational context. The novelty of this study lies in its integrative approach, combining alternative models from in-vitro assays to human placental studies, providing new perspectives for reproductive toxicology research, particularly with advanced placental models.

Microplastic accumulation in placentas and umbilical cords from pregnancies in Brazil

C. Wanderley Lopes de Oliveira¹, S. Ospina-Prieto¹, L. C. Emídio de Barros², C. J. da Silva², L. F. Azevedo de Magalhães Oliveira³, E. J. da Silva Fonseca³, A. U. Borbely¹
¹Cell Biology Laboratory, Institute of Biological and Health Sciences, ²Group of Nano-Photonics and Imaging, Physics Institute, ³Group of Optics and Nanoscopic, Physics Institute, Federal University of Alagoas, Brazil

Introduction Microplastics (MPs) are plastic particles typically ranging in size from $\leq 1 \mu\text{m}$ up to 5 mm, originating from the degradation of larger plastics or manufactured at micro-scale. MPs can be excreted via urine and stool, but not all MPs are eliminated, some bioaccumulate in various organs and fluids of the human body. Several countries associate MPs with geographical factors, size, and polymer type; however, no evidence is available for Brazil or Latin America. This study aimed to investigate the presence of microplastics (MPs) in the placentas and umbilical cords of pregnant women from the state of Alagoas, Brazil, providing the first evidence of MP accumulation during pregnancy in a Latin American population.

Methods A total of 20 pregnant women were randomly selected for inclusion in the study. Following delivery, each placenta was placed in a glass container and transported to the laboratory. Socio-demographic and clinical data were collected. All samples were handled using a plastic-free protocol. They were washed with glass-filtered solutions, initially with Milli-Q water, and subsequently incubated in a 10% potassium hydroxide solution (1:9, w/v) in glass containers at room temperature for one week to promote tissue digestion. The digested material was then

filtered using glass filters and stored in metal containers for analysis by optical microscopy and Raman spectroscopy. Data analysis was conducted using KnowItAll (Wiley) software and the SLOPP/SLOPPE microplastic libraries.

Results Microplastics were detected in all 20 participants, with a total of 384 particles identified: 247 in placental tissues and 137 in umbilical cords. No statistically significant correlations were found between microplastic presence and maternal or neonatal variables, likely due to the limited sample size and resulting reduced statistical power. The most frequently identified polymers in both placenta and umbilical cord samples were: Polyethylene (PE), Polyethylene Vinyl Acetate (PVA), Polyethylene-co-Polypropylene (PE-co-PP), Polyurethane (PU), and Polyamide (PA). Various chemical additives were also detected in association with MPs, though their composition varied considerably across samples.

Conclusion This study provides the first documented evidence of microplastic contamination in pregnant women from a Latin American population, with all analyzed placentas and umbilical cords showing the presence of MPs. The detection of MPs in umbilical cords highlights fetal exposure to plastic polymers and associated chemicals during intrauterine development. These findings emphasize the urgent need for stronger environmental regulations regarding plastic pollution and call for further research into the potential long-term health impacts of prenatal MP exposure.

ZP2 induces CatSper signaling in mammalian spermatozoa

C. Wiesehöfer, L. Sunjic, L. Suetin, M. Wiesehöfer, M. Lyndin, G. Wennemuth
 Department of Anatomy, Medical Faculty University Duisburg-Essen, Essen, Germany

Introduction Fertilization can only happen after a successful journey of the sperm cell to and its fusion with the oocyte. During their way along the oviduct sperm undergo an early activation by bicarbonate and a late

activation, which leads to changes in the sperm membrane and the activation of ion-channels, like CatSper. Mammalian oocytes are surrounded by an extracellular matrix called zona pellucida (ZP) which mediates the initial binding of sperm to oocytes and consists in mouse of three functional glycoproteins (ZP1–ZP3). In our previous study, we showed that the N-terminal ZP2 protein leads to a significant sperm motility increase and changes in sperm movement pattern, probably essential for reaching the oocyte. However, the underlining signaling cascade behind the ZP2-induced changes is still unknown.

Material and Methods The study was performed with murine and human sperm. The induction of the acrosome reaction by ZP2 was assessed using two independent approaches: FITC-PSA staining, and spermatozoa from a transgenic SU9/Acr3 mouse line with GFP-tagged acrosin and RFP labelled mitochondria. To evaluate calcium influx upon ZP2 stimulation on single and multi-cell levels, the fluorescent indicator Fluo-4 AM was used. Protein–protein interactions between ZP2 and the sperm-specific Ca^{2+} channel (CatSper) were analyzed by immunoprecipitation.

Results Contact to N-terminal ZP2 leads in capacitated murine and human sperm to a significant $[\text{Ca}^{2+}]_i$ increase. By using CatSper1-deficient mouse sperm and a CatSper1-specific inhibitor, it was shown that the ZP2-induced Ca^{2+} influx is CatSper-dependent in both mice and humans. The induction of acrosomal exocytosis, a Ca^{2+} dependent process, was confirmed after ZP2 contact in mice. First biochemical assay results reveal that ZP2 directly binds to CatSper, suggesting a dual role as both ligand and channel activator.

Conclusion Our findings demonstrate that ZP2 serves as a potent physiological trigger of the acrosome reaction in capacitated murine sperm via CatSper-mediated Ca^{2+} influx. The identification of a direct interaction between ZP2 and CatSper provides novel mechanistic insights into sperm activation and highlights a crucial step in mammalian fertilization.

Autorenindex (nur Erstautoren)

A	E	I
Abaeva I. 217	Edinger A. 218	Izmaylova L. 219
B	F	M
Beckmann J. 217	Fuentes-Zacarias P. 218	Materazzi L. 219
C	G	P
Castellanos-Gutiérrez A. S. 218	Grimm B. 218	Pusch E. 220
D	H	W
dos Santos I. C. 220	Hernández-Bustos A. M. 219	Wanderley Lopes de Oliveira C. 221
	Herrmann L. 219	Wiesehöfer C. 221

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