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NI.1. ENDOPLASMIC RETICULUM STRESS INDUCES AN INFLAMMATORY RESPONSE: POTENTIAL REGULATION BY miRNAs

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Objectives: At decidualization, cells underwent endoplasmic reticular stress (ERS) and unfolded protein response (UPR), which will allow them to expand their endoplasmic reticulum with the corresponding machinery for protein folding. Here, we focus on the role of ERS/UPR during decidualization to induce a physiological sterile inflammatory response and whether it might be regulated by miRNAs.

Methods: We used an in vitro model of decidualization represented by human telomerase-immortalized endometrial stromal cell line St-T1b differentiated with 8-BrCAMP, and endometrial biopsies from patients with recurrent pregnancy loss (RPL) and recurrent in vitro fertilization failures (RIF).

Results: First, we evaluated the ERS by the expression of ATF6/PERK, and IRE1α. Decidualized cells increased the expression of the three sensors (p<0.05, t-test). This effect was also observed in the presence of Tg (ERS inducer). Then, we evaluated the expression of the UPR marker, CHOP, which also increased in decidualized cells (p<0.05, t-test). Then, we evaluated the modulation of TXNIP, a link between the ERS-pathway and inflammation. TXNIP increased in decidualized cells, and also the inflammasome NLRP3 and IL-1β expression (p<0.05, t-test). Using an in silico analysis using mirTarBase v8.0, we selected three miRNAs able to regulate these miRNAs signifying that ERS and UPR pathways: miR-193b-3p, miR-21-5p, and miR-17-5p. All these miRNAs significantly increased the expression in decidualized cells in the presence of Tg (p<0.05, t-test). Finally, we studied the expression and localization of miRNAs through an In Situ Hybridization (ISH) technique in endometrial samples. The three miRNAs were expressed in stromal and epithelial glandular cells in endometrial samples from RPL and RIF patients; endometrial samples from RPL patients displayed lower expression in comparison with those from RIF patients.

Conclusion: The present results suggest that decidualization in St-T1b cells is accompanied by an ERS and UPR associated with a sterile inflammatory response potentially regulated by miR-193b-3p, miR-21-5p, and miR-17-5p.

NI.2. CELLULAR SENESCENCE ASSOCIATION TO ENDOPLASMIC RETICULUM STRESS IN ENDOMETRIAL STROMAL CELLS

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Objectives: During the decidualization process, endometrial stromal cells (EnSCs) undergo endoplasmic reticulum stress (ERS). Recently, it was reported that a subpopulation of EnSCs also undergoes cellular senescence. Here, we hypothesize there is a link between both processes.

Methods: Human endometrial stromal cell line (HESC) was in vitro decidualized with MPA and db-cAMP for 8 days (Dec). To induce ERS, non-decidualized (nonDec) cells were stimulated with 1μg/ml thapsigargin (Tg), a strong pharmacological ERS inducer. Endometrial samples were obtained from fertile women and recurrent implantation failure (RIF) patients. Additionally, public data of genome-wide transcriptome analysis of primary EnSCs (GSE160702) was used to evaluate gene expression in primary cultures from human EnSCs. RT-qPCR was used to evaluate expression levels of senescence markers: Deiodinase 2 (DIO2) and Lumican (LUM); as well as mature Dec cells markers: Ferritin (FTL) and Forkhead box protein 01 (FOXO1). FOXO1 and β-galactosidase activity were tested by FACS. *p<0.05 was considered significant.

Results: β-galactosidase activity, a cellular senescence marker, was evaluated during the kinetics of HESC decidualization, displaying a peak during the first days of the process. Senescence markers DIO2 and FTL were respectively down and upregulated, while mature Dec cells markers LUM* and FOXO1* were upregulated (Dec vs nonDec). These results were in line with the in silico transcriptome analysis of primary ESC. Additionally, ER-stressed HESC cells (Tg treatment) showed a similar expression pattern. Finally, RIF biopsies showed downregulation of DIO2*and FOXO1* while FTL* was upregulated (vs fertile controls).

Conclusion: HESC cells in vitro decidualization model depicted a similar expression pattern of the evaluated genes compared to primary cultures. Additionally, pharmacological ERS induction showed a similar effect. Finally, RIF patients showed an altered senescence response which, in addition to the previously reported altered ERS response, might be related to endometrial receptivity failure.

NI.3. MATERNAL HYPOTHYROIDISM INCREASES THE IMMUNE RESPONSE OF THE OFFSPRING TO OVA-INDUCED FOOD ALLERGY

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Objectives: Food Allergy (FA) is a common allergic disease developed by 6% of children under 12-years and 3-4%. FA is characterized as an inflammatory response against a food protein where patients develop intestinal pain and inflammation, diarrhea, skin rash, and, in severe cases, anaphylactic shock. The most prevalent FA in the Chilean population is ovalbumin (OVA) or egg white protein (33%). Recent evidence suggests that alterations during fetal life can predispose individuals to postnatal diseases known as fetal programming. Thyroid hormones have important functions during gestational period, such as regulating cell proliferation and angiogenesis. A common endemic disorder during pregnancy is hypothyroxinemia (HTX). Evidence from our laboratory demonstrates that the offspring gestated under HTX present an exacerbated inflammatory immune response.

In this work, we analyze the role of gestational HTX as a risk factor for food allergy development, evaluating the impact of gestational hypothyroxinemia on the physio-pathological and immune response of HTX offspring to OVA-induced food allergy.

Methods: For this purpose, a murine model of C57BL/6 mice gestated or not under maternal HTX were subjected to an OVA peptide-induced food allergy. Allergic clinical score, rectal temperature, and feces water content were recorded. At the intestinal level, lymphoid and myeloid immune cells populations were analyzed by FACS.

Conclusion: Our results showed that HTX gestated offspring present a higher allergic clinical score, with a decrease in rectal temperature and an increase of the percentage of water content in feces during the food allergen sensitization period and during intragastric-OVA challenges. Immune cell analysis showed an increased percentage of mature dendritic cells at the intestine in the HTX offspring, suggesting an increased antigen presentation rate. This data supports the idea that gestation under HTX conditions could be considered a risk factor for developing FA.

NI.4. VERTICAL TRANSMISSION AND ANTIBODY RESPONSE OF WOMEN WITH ACTIVE SARS-COV2 INFECTION DURING PREGNANCY

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Objectives: Food allergies are a frequent cause of allergic disease. One of the most common food allergies is to OVA. The aim of this study was to determine the prevalence of OVA-specific IgG and IgA in women with active SARS-COV2 infection during pregnancy.

Methods: A cross-sectional study was conducted in women with active SARS-COV2 infection during pregnancy. Women were classified as active SARS-COV2 infection during pregnancy if they had a positive PCR test for SARS-COV2 within the last 2 weeks. Women were considered seropositive if they had a positive OVA-specific IgG and IgA test. The association between seropositivity and SARS-COV2 infection during pregnancy was assessed using the chi-square test.

Conclusion: The prevalence of OVA-specific IgG and IgA in women with active SARS-COV2 infection during pregnancy was 16%. The chi-square test showed a significant association between seropositivity and SARS-COV2 infection during pregnancy (p<0.05). These findings suggest that OVA-specific IgG and IgA are prevalent in women with active SARS-COV2 infection during pregnancy.
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Objective: To determine during pregnancy with active SARS-CoV2 infection, maternal antibody production and transmission to the baby, the presence of the virus in the placenta, and their association with the pregnancy outcomes.

Methods: Pregnant women with a confirmed diagnostic for Covid19 admitted to the Hospital Universitario del Valle for the delivery were invited to participate. Maternal and umbilical cord blood samples were collected for SARS-CoV-2 antibody IgM/IgG determination using COVID-19 IgG/IgM immunochromatography kits. Placentas were also collected and processed for SARS-CoV-2 viral detection according to the CDC 2019-nCoV Real-Time RT-PCR Diagnostic Panel. Data about the participants and their babies were obtained from medical reports.

Results: Twenty-nine participants were enrolled in the study, the average maternal age was 25.76±6.7 and gestational age was 36.2±3.3. The main symptoms at the time of diagnosis were cough 12(41.4%), fever 8(27.6%), fatigue 6(20.7%), shortness of breath 6(20.7%), and myalgias 5(17.2%). The antibody response against SARS-CoV-2 shows 2(5%) participants positive for IgM and 9(22.5%) for IgG. Umbilical cord blood samples were negative for IgM and 11(27.5%) were positive for IgG. Viral RNA was found in 2(5%) placentas. 9(31%) pregnant women had a critical COVID19 of which 5 required ICU attention associated with sepsis, one participant with a critical condition died (viral RNA in placenta). Most babies were healthy with a normal birth weight of 21 (72.4%), 6(20.7%) had low birth weight, and 2(6.9%) had very low birth weight. 6(20.7%) required neonatal care in ICU, 4 associated with sepsis. There were two stillbirths.

Conclusion: Pregnant women with active SARS-CoV2 infection show an antibody response against the virus and transmission of IgG antibodies to the babies. Evidence shows positive placentas for viral RNA, so placental transmission of the virus is possible.

NL5. ASSOCIATION BETWEEN IL-6 AND SERUM FERRITIN IN THIRD TRIMESTER PREGNANT WOMEN LIVING IN THE NORTH COAST OF COLOMBIA

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Objective: In a previous study, we found an inverse relationship between adverse perinatal outcomes and iron status in third-trimester pregnant women recruited in a maternal hospital in Cartagena, Colombia. Since serum ferritin (SF) levels may be a surrogate marker of a pro-inflammatory status, we sought to determine the relationship between pro-inflammatory cytokines and serum ferritin (SF) in this population.

Method: From a prospective cohort of pregnant women (n=1218), 100 subjects at the extremes of the distribution (≤ 25th and ≥ 75th percentiles) of SF were randomly selected. We included 49 patients from SF quartile 1 (Q1: ≤12 ng/mL) and 51 patients from quartile 4 (Q4: 24.9 - 350 ng/mL). Serum cytokine levels (IL-1β, IL-6, IL-8, IL-10, TNF-α, and IL-12p70) were quantified by flow cytometry using the Human Inflammatory Cytokine Cytometric Bead Array kit. In a generalized linear model, cytokine levels were compared between the two groups. Age and hypertension presentation were included as covariates.

Results: IL-1 β and IL-12p70 levels were undetectable in all participants, while TNF-α was detected in 5 mothers. Mean IL-6 levels [Q1: 7.7 pg/mL (SD ± 14.4) vs Q4: 18.25 pg/mL (SD ± 33.3)], but not IL-8 [C1: 216.92 pg/mL (SD ± 502.23) vs C4: 430.62 pg/mL(SD ± 1580.90)] were higher in Q4 compared to Q1 group. IL-6 levels were significantly associated with SF quartiles (β = 10.9 – 20.9 to –0.82, p = 0.034), but not with participant age or the presentation of hypertension during pregnancy. No association was found between IL-8 and SF, neither between any of the two cytokines and hemoglobin (analyzed either a continuous variable or categorized by anemic status).

Conclusion: Serum IL-6 levels in late pregnancy are directly associated with a high of serum ferritin level.

NL6. CHRONIC INFLAMMATION OF THE MALE GENITAL TRACT IMPAIRS MALE FERTILITY

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Objective: Urogenital inflammation is a putative cause of male infertility. Indeed, epidemiological studies have revealed that male urogenital inflammation underlies at least 15% of male infertility cases. However, available supporting evidence from animal models is very scarce. As our laboratory has pioneered the development of Experimental Autoimmune Prostatitis rodent models, which have reflected most human disease features, we herein analyze its development and impact on male fertility potential.

Methods: C57BL/6 male mice were immunized with prostate antigens (PA) or saline (C) plus adjuvant on days 0 and 15. Pelvic pain induction was assayed as tactile allodynia using Von Frey filaments. On day 24, mating experiments with BALB/c female mice were performed and different fertility parameters were analyzed. Animals were euthanized on day 26 and the specific immune response, prostate histopathology, and infiltrating leukocytes were analyzed.

Results: Chronic pelvic pain development was evidenced by increased allodynia responses in the pelvic region of PA-immunized mice. Furthermore, these animals showed significantly increased PA-specific lymphoproliferative responses with IFNγ and IL17 secretion together with marked prostate periglandular infiltration and inflammatory tissue changes. Infiltrates were mainly composed of CD4+ T cells and macrophages. Also, PA-immunized mice showed significantly elevated serum levels of PA-specific IgG autoantibodies. On the contrary, none of these changes were observed in control mice. Interestingly, mating experiments revealed a significant decrease in the fertility index and augmented percentages of pre- and post-implantation embryo loss in BALB/c female mice mated with PA-immunized C57BL/6 mice with respect to females mated with controls.

Conclusion: Our results indicate that Th1/Th17 associated immune responses develop and induce chronic pelvic pain and prostate inflammation after PA immunization of C57BL/6 mice. In turn, prostate inflammation significantly impairs male fertility potential by reducing the fertilizing ability of sperm and increasing the rate of embryo loss.

NL7. TOXOPLASMA GONDII INFECTION OF HUMAN PLACENTAL EXPLANTS IS MEDIATED BY MIR-190B EXPRESSION

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Objective: Toxoplasmosis is caused by the parasitic protozoa Toxoplasma gondii (T. gondii) and constitutes a significant public health problem worldwide. T. gondii can be transmitted congenitally, causing severe illnesses or even death. Although host-pathogen interactions determine the success or failure of congenital infection, modulation of the host’s gene expression by small non-coding RNAs, particularly micro-RNAs (miRNAs), has been associated with resistance or susceptibility to infections. T. gondii infection induces specific miRNAs profiles in infected hosts, and we previously reported that T. gondii infection of human placental explants (HPE) deregulates miR-190b expression. However, the