MSPR Plenary V - Pulmonary; Maternal Factors

Friday, October 9 9:30-11:00 AM CDT

Moderators
Jane Taylor – University of Pittsburgh Medical Center
Jae Kim – Cincinnati Children's Hospital Medical Center

CDT	Abstract	Title	Presenting Author
9:30 AM		Introduction & General Information	
9:35 AM	3470085	S-nitrosoglutathione reductase knockout mice are protected from neonatal hyperoxia alveolar and airway hyperreactivity changes	Thomas Raffay
9:45 AM	3476656	Pertussis immunization of murine infants exposed to antenatal inflammation alters protective immune response patterns	Dajana Sabic
9:55 AM	3476609	Decreased Insulin Sensitivity and Increased Allergic Inflammation in Offspring of Obese Mothers	Christopher Damron
10:05 AM	3475675	Maternal high-fat/high-sugar diet and postnatal lipopolysaccharide exposure alter hypothalamic appetite signaling in the developing male brain	Lauren Buckley
10:15 AM	3468558	Distinct placental responses to cytomegalovirus are elicited by maternal infection early versus late in pregnancy	Craig Bierle
10:25 AM	3476399	Extracellular superoxide dismutase may protect nitric oxide signaling but does not prevent pulmonary parenchymal or vascular remodeling during prolonged neonatal hyperoxia exposure in mice	Maxwell Mathias
10:35 AM	3476579	Impact of neonatal steroid therapy on long-term lung development in murine model of hyperoxic lung injury	Marta Perez
10:45 AM	3475697	Reg3g-mediated HSG polymerization as a drug-sensitive target of islet dysfunction in offspring of obese mice	Kok Lim Kua
10:55 AM		Wrap Up	

Note: Schedule subject to change based on presenter availability.

CONTROL ID: 3470085

TITLE: S-nitrosoglutathione reductase knockout mice are protected from neonatal hyperoxia alveolar and airway hyperreactivity changes

DIGITAL OBJECT IDENTIFIER (DOI):

ABSTRACT STATUS: Sessioned

PRESENTER: Thomas Michael Raffay

AUTHORS/INSTITUTIONS: R.B. Sopi, P.M. MacFarlane, R.J. Martin, T.M. Raffay, Pediatrics, UH Rainbow Babies and Children's Hospital Division of Pediatrics, Cleveland, Ohio, UNITED STATES|R.B. Sopi, P.M. MacFarlane, A. Jafri, R.J. Martin, T.M. Raffay, Case Western Reserve University, Cleveland, Ohio, UNITED STATES|B. Gaston, Pediatrics, Indiana University School of Medicine, Indianapolis, Indiana, UNITED STATES|

CURRENT CATEGORY: Basic Science

CURRENT SUBCATEGORY: None

ABSTRACT BODY:

Background: Bronchopulmonary dysplasia survivors display long-term obstructive lung disease with parenchymal simplification and airway hyperreactivity (AHR). We have shown in the murine lung that the endogenous bronchodilator and anti-inflammatory, S-nitrosoglutathione (GSNO), is degraded in neonatal hyperoxia by microRNA mediated upregulation of GSNO reductase (GSNOR). GSNOR knockout mice are protected from ova-induced asthmatic lung remodeling and AHR, but have not yet been studied in hyperoxia.

Objective: Test if GSNOR knockout mice have attenuated neonatal hyperoxia alveolar simplification and in vitro AHR.

Design/Methods: Newborn C57BL/6 wild type or GSNOR knockout mice were randomized on the first day of life and assigned to room air (21% O_2) or moderate hyperoxia (60% O_2) groups for three weeks to induce bronchopulmonary dysplasia. Animals were then recovered in room air until six weeks of age. Alveolar simplification was assessed by calculating the mean linear intercept (L_m) of inflation-fixed lungs. 5 non-overlapping masked images were analyzed and averaged per animal per condition. In different mice, AHR was assessed using precision-cut living lung slice preparations in response to increasing doses of bath-applied methacholine (MCh, 0.25-64 μM). AHR was calculated as percent change in airway lumen area from baseline. 2-3 airways of 100-230 μm diameter were imaged and averaged per animal per condition.

Results: Neonatal hyperoxia in wild type six week mice significantly increased L_m compared to the room air controls ($p<0.001$); hyperoxic GSNOR knockouts were protected ($p<0.001$; vs hyperoxic wild type) and did not differ from room air controls. All airways constricted in response to MCh. Neonatal hyperoxia in wild type six week mice significantly increased airway contractile responses to MCh compared to the room air controls ($p<0.001$); hyperoxia exposed GSNOR knockouts showed significantly attenuated AHR ($p<0.01$; vs hyperoxic wild type) and did not differ from room air controls.

Conclusion(s): These studies show that neonatal hyperoxia-exposed mice display longer-term alveolar simplification and in vitro AHR to MCh and that deletion of GSNOR protects against these hyperoxia changes. While the mechanisms conferring benefits need further investigation, we speculate that GSNOR may be a novel target for the prevention and treatment of bronchopulmonary dysplasia.

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CONTROL ID: 3476656

TITLE: Pertussis immunization of murine infants exposed to antenatal inflammation alters protective immune response patterns

DIGITAL OBJECT IDENTIFIER (DOI):

ABSTRACT STATUS: Sessioned

PRESENTER: Dajana Sabic

AUTHORS/INSTITUTIONS: D. Sabic, J. McQuillan, J.M. Koenig, Pediatrics, Saint Louis University, St Louis, Missouri, UNITED STATES|

CURRENT CATEGORY: Basic Science

CURRENT SUBCATEGORY: None

ABSTRACT BODY:

Background: Histologic chorioamnionitis, a type of antenatal inflammation, can lead to increased infection risk through mechanisms that remain unclear. We previously observed that adult offspring exposed to antenatal lipopolysaccharide (LPS) had altered vaccine-induced protective immune responses, including a Th2 bias. Whether protective immunity is affected when LPS-exposed offspring are immunized in infancy, a situation particularly relevant to humans, has not been reported.

Objective: Our goal for this study was to determine how antenatal inflammation influences protective immune responses following pertussis immunization of LPS-exposed murine infants.

Design/Methods: Offspring of LPS-treated or control C57/Bl6 dams received a set of two IP TdaP (or saline, naïve mice) vaccinations beginning in infancy and repeated 4 weeks later. Inflammatory and cellular protective immune responses in the lungs or spleens of vaccinated (Vax) or naïve mice were determined by flow cytometry and compared under basal, uninfected conditions or following inoculation with intranasal Bordetella pertussis. Specific vaccine-induced cell-mediated responses were studied in splenocytes co-cultured with pertussis antigens.

Results: LPS-Vax mice had 30% lower splenic ($P<0.001$) and lung ($P<0.05$) CD4+IFNg+ (Th1) cell frequencies compared to vaccinated controls. Values did not differ between male and female mice under the same conditions. Higher pertussis-specific CD4+IL-17+ (Th17) cell frequencies were also observed in splenocytes of LPS-Vax mice ($P<0.05$ vs. Ctrl-Vax). In contrast, myeloid responses were similar in LPS-Vax and Ctrl-Vax mice.

Conclusion(s): Our studies suggest that antenatal inflammation uniquely alters Th1 and Th17 immune response patterns following immunization initiated in infancy. These findings contrast with the prominent Th2 responses we previously observed in exposed vaccinated adult offspring. Studies to better define age-dependent protective immunity in the context of antenatal inflammation are currently underway. This work was supported in part by a grant (to JMK) from the NIH (AI140206).

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CONTROL ID: 3476609

TITLE: Decreased Insulin Sensitivity and Increased Allergic Inflammation in Offspring of Obese Mothers

DIGITAL OBJECT IDENTIFIER (DOI):

ABSTRACT STATUS: Sessioned

PRESENTER: Christopher Damron

AUTHORS/INSTITUTIONS: C. Damron, J. Cohen, L. Schroeder-Carter, Indiana University School of Medicine, Indianapolis, Indiana, UNITED STATES|L. Haneline, K. Kua, Pediatric/Neonatal-Perinatal Medicine, Indiana University School of Medicine, Indianapolis, Indiana, UNITED STATES|J. Casasnovas, J. Cook-Mills, Pediatrics, Indiana University School of Medicine, Indianapolis, Indiana, UNITED STATES|

CURRENT CATEGORY: Basic Science

CURRENT SUBCATEGORY: None

ABSTRACT BODY:

Background: Maternal obesity and maternal allergy are major risk factors for asthma in human offspring. Recent studies implicated impaired lung insulin signaling as a mechanism promoting lung allergic inflammation. While decreased insulin signaling is common in many tissues of offspring born to obese mothers, the impact of maternal obesity on offspring lung insulin signaling is not known. Further, the combined effect of maternal obesity and maternal allergy has not been studied.

Objective: We hypothesize that maternal obesity decreases offspring lung insulin sensitivity and amplifies the effect of maternal allergy in promoting offspring lung inflammation.

Design/Methods: We fed female mice western diet from 7 weeks before pregnancy until weaning as a model of maternal obesity (MatOb). At postnatal day 21 (P21), ex-vivo insulin-stimulated Akt-phosphorylation was performed to evaluate offspring lung insulin sensitivity. To evaluate the combined effect of maternal allergy and maternal obesity, maternal allergy was induced using a standard sensitization protocol in dams prior to diet initiation. We also cross-fostered pups to dams from a different arm of the study to evaluate pre- and post-natal effect of maternal obesity. Allergic inflammation in offspring was evaluated by BAL, and assessed on postnatal day 21 (P21).

Results: Compared to offspring of chow-fed (con) non-allergic mothers, pups of MatOb non-allergic mothers demonstrated significantly lower insulin-induced Akt-phosphorylation in lung explant ($p<0.01$, 57±6% decrease in phospho-Akt/Akt; n=4/group), indicating a decrease in lung parenchymal insulin sensitivity. Among offspring of non-allergic dams, exposure to maternal obesity resulted in significantly higher lung eosinophils (Con 149±28, MatOb 1228±258; n=7-16, $p<0.01$). Interestingly, offspring exposed to both maternal obesity and allergy had the highest lung eosinophilia compared to offspring of non-obese, allergic mothers ($p<0.01$, Con-allergic 2310±635, MatOb-allergic 9235±2221; n=8-12). In the cross-fostering experiment, we found that pups exposed to pre- and post-natal maternal obesity had the highest BAL eosinophil count.

Conclusion(s): Our data demonstrate that mice offspring born to obese mothers have decreased lung insulin sensitivity and have increased allergic inflammation in the lungs, which is enhanced further in conjunction with maternal allergy. Interestingly, our data demonstrates that there is both a pregnancy and post-pregnancy aspect of eosinophilic inflammation in offspring.

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CONTROL ID: 3475675

TITLE: Maternal high-fat/high-sugar diet and postnatal lipopolysaccharide exposure alter hypothalamic appetite signaling in the developing male brain

DIGITAL OBJECT IDENTIFIER (DOI):

ABSTRACT STATUS: Sessioned

PRESENTER: Lauren Buckley

AUTHORS/INSTITUTIONS: L. Buckley, D. Kulhanek, G. Singh, T. Gisslen, M. Paulsen, Pediatrics, University of Minnesota, Minneapolis, Minnesota, UNITED STATES|

CURRENT CATEGORY: Basic Science

CURRENT SUBCATEGORY: None

ABSTRACT BODY:

Background: Perinatal inflammation, as seen in maternal overnutrition and neonatal sepsis, is associated with obesity in offspring. The compounding effect of multiple inflammatory stressors on the developing hypothalamus is not well understood. We hypothesize that exposure to two inflammatory stressors during critical periods of hypothalamic development alters appetite signaling, further increasing risk of obesity in offspring.

Objective: Determine the effect of maternal overnutrition (high-fat/high-sugar diet, HFHS) and neonatal sepsis (postnatal lipopolysaccharide exposure, LPS) on hypothalamic appetite signaling in the developing male mouse brain.

Design/Methods: Female C57BL/6J mice (n = 6) were fed HFHS or control (CON) diet through lactation. On postnatal day (PN) 7, male pups (n = 17) received an intraperitoneal injection of LPS (1 μg/g) or saline (SAL). Necropsy was performed on PN9. Hypothalamic mRNA expression of markers for inflammation (IL-1β, IL-6, TLR4, TNFα, Ikkα) and appetite signaling (Pomc, Npy, Nr3c1, Crh, InsR, LepR) was determined by RT-qPCR. Group differences were determined by unpaired t-test, two-way ANOVA and Tukey's MCT. Pearson correlation coefficient was used to measure linear correlation. An alpha level of < 0.05 was considered statistically significant.

Results: HFHS males were 26% heavier than controls on PN7 ($p = 0.01$). Maternal caloric intake, but not weight, was correlated with PN7 weight ($r = +0.71$, $p = 0.001$). HFHS diet was associated with lower hypothalamic satiety neuropeptide, Pomc ($p = 0.02$), leptin receptor, LepR ($p = 0.02$), glucocorticoid receptor, Nr3c1 ($p = 0.03$), IL-6 ($p = 0.02$) and TNFα ($p = 0.02$). TLR4 and Ikkα did not differ between groups. HFHS/LPS males had 67% lower LepR compared to CON/SAL males ($p = 0.04$). CON/LPS males trended towards increased IL-1β ($p = 0.06$) compared to CON/SAL males. In contrast, IL-1β did not differ in HFHS/LPS males compared to all other groups. IL-6 was strongly correlated with hypothalamic hunger neuropeptide, Npy ($r = +0.84$, $p < 0.001$), HPA-axis mediator, Crh ($r = +0.79$, $p = 0.001$), and Nr3c1 ($r = +0.80$, $p < 0.001$).

Conclusion(s): Maternal HFHS diet and postnatal LPS exposure alter hypothalamic appetite signaling in the developing male brain. HFHS/LPS males may have an abnormal stress response compared to CON/LPS and HFHS/SAL males. We speculate that males exposed to multiple perinatal inflammatory stressors are programmed for obesity through permanent alterations in hypothalamic appetite signaling.

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CONTROL ID: 3468558

TITLE: Distinct placental responses to cytomegalovirus are elicited by maternal infection early versus late in pregnancy

DIGITAL OBJECT IDENTIFIER (DOI):

ABSTRACT STATUS: Sessioned

PRESENTER: Craig John Bierle

AUTHORS/INSTITUTIONS: Z.W. Berkebile, D.S. Putri, C.J. Bierle, Pediatrics, University of Minnesota, Minneapolis, Minnesota, UNITED STATES|J.E. Abrahante, Informatics Institute, University of Minnesota, Minneapolis, Minnesota, UNITED STATES|D.M. Seelig, Veterinary Clinical Sciences, University of Minnesota, Minneapolis, Minnesota, UNITED STATES|

CURRENT CATEGORY: Basic Science

CURRENT SUBCATEGORY: None

ABSTRACT BODY:

Background: Placental infections caused by human cytomegalovirus (HCMV) are likely both sufficient to cause fetal injury or demise and a prerequisite for congenital infection. The timing of maternal HCMV infection during pregnancy is a determinant of fetal outcomes, but the molecular basis for HCMV-associated placental injury and how placental development affects pregnancy outcomes post-infection remain unclear.

Objective: Using a guinea pig model, we sought to test whether the development of the placenta affects the organ's susceptibility to cytomegalovirus infection and/or infection-associated injury.

Design/Methods: Time-mated guinea pigs were infected with guinea pig cytomegalovirus (GPCMV) at either 21 or 35 days gestation (dGA). At 21 days post-infection, droplet digital PCR was used to quantify GPCMV viral loads in tissue. The transcriptomes of placentas from GPCMV-infected and control dams were profiled by RNA sequencing. Placental pathology was evaluated after tissue was stained with either hematoxylin and eosin or a GPCMV-specific RNAscope assay.

Results: No significant difference in viral loads was noted in placentas after maternal infection early or late in pregnancy. Gene expression in placentas from dams infected at 21 dGA was nearly indistinguishable from control tissue while nearly 200 transcripts were dysregulated after maternal infection at 35 dGA. Notably, multiple transcripts associated with immune activation (e.g. Cxcl10, Ido1, Tgtp, and Tlr8) were upregulated in the placenta of dams infected late in pregnancy. Histopathologic assessment revealed distinct patterns of infection-associated lesions. No pathologic findings could differentiate the GPCMV-infected and control placentas from dams infected at 21 dGA. In contrast, there was a significant loss of the subplacenta and basal layer, presumably caused by necrosis of the tissue, and regional areas of hemorrhage and congestion in the labyrinth when guinea pigs had been infected with GPCMV at 35 dGA. Large areas of GPCMV-infected cells were also only noted in placentas after maternal infection late in gestation.

Conclusion(s): GPCMV infection late in pregnancy has long been known to cause high rates of stillborn pups. Our results implicate the placental immune response to GPCMV infection as the cause of placental insufficiency and fetal demise. Future studies will assess whether immunomodulatory therapies can improve pup outcomes after maternal viral infection late in pregnancy.

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CONTROL ID: 3476399

TITLE: Extracellular superoxide dismutase may protect nitric oxide signaling but does not prevent pulmonary parenchymal or vascular remodeling during prolonged neonatal hyperoxia exposure in mice

DIGITAL OBJECT IDENTIFIER (DOI):

ABSTRACT STATUS: Sessioned

PRESENTER: Maxwell Mathias

AUTHORS/INSTITUTIONS: M. Mathias, J. Taylor, M. Perez, Neonatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, UNITED STATES|M. Mathias, M. Perez, Neonatology, Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, Illinois, UNITED STATES|E. Mendralla, Touro College of Osteopathic Medicine, Middletown, New York, UNITED STATES|

CURRENT CATEGORY: Basic Science

CURRENT SUBCATEGORY: None

ABSTRACT BODY:

Background: Prolonged neonatal hyperoxia exposure is associated with remodeling of the lung parenchyma (alveolar simplification) and pulmonary vasculature. However, the mechanism of these effects is not yet known. The extracellular superoxide dismutase (ecSOD) is an antioxidant enzyme localized to the intercellular space between pulmonary vascular endothelium and smooth muscle. We utilized mice deficient in ecSOD to evaluate its role in hyperoxic pulmonary remodeling.

Objective: Evaluate the role of ecSOD in neonatal hyperoxic pulmonary remodeling.

Design/Methods: Wild-type age-matched neonatal C57Bl/6 (WT) and ecSOD -/- (KO) mice were placed in normoxia (21% O_2) or hyperoxia (75% O_2) within 24 hours of birth for 14 days continuously, then euthanized. Lungs were inflation-fixed at 25 cm H_2O and paraffin-embedded. Alveolar area, alveolar counts, and pulmonary vessel density were measured. Additional lungs were harvested for Western blot analysis of antioxidant enzymes and nitrotyrosine (a marker of reactive nitrogen species), normalized to β-actin. Groups were compared using one-way ANOVA with multiple comparisons.

Results: Alveolar area was increased in KO animals by 77 ± 23% vs WT littermates in normoxia but had similar levels of alveolar simplification in hyperoxia. Alveolar counts and vessel density were decreased in KO animals by 41 ± 9% and 37 ± 13%, respectively, vs WT littermates in normoxia but not hyperoxia. No differences in antioxidant enzyme expression pattern were noted between genotypes. There was a trend towards increased nitrotyrosine levels in KO mice compared to WT.

Conclusion(s): Neonatal ecSOD KO mice demonstrate baseline alveolar simplification and decreased pulmonary vessel density, but these findings are not exacerbated by hyperoxia exposure. In addition, antioxidant expression pattern does not appear to be affected by ecSOD KO. In contrast, nitrotyrosine levels appear increased in ecSOD KO mice regardless of oxygen exposure. This supports the hypothesis that ecSOD protects nitric oxide signaling from free radical disruption under both normoxia and hyperoxia, and that hyperoxic pulmonary remodeling occurs via an ecSOD-independent pathway.

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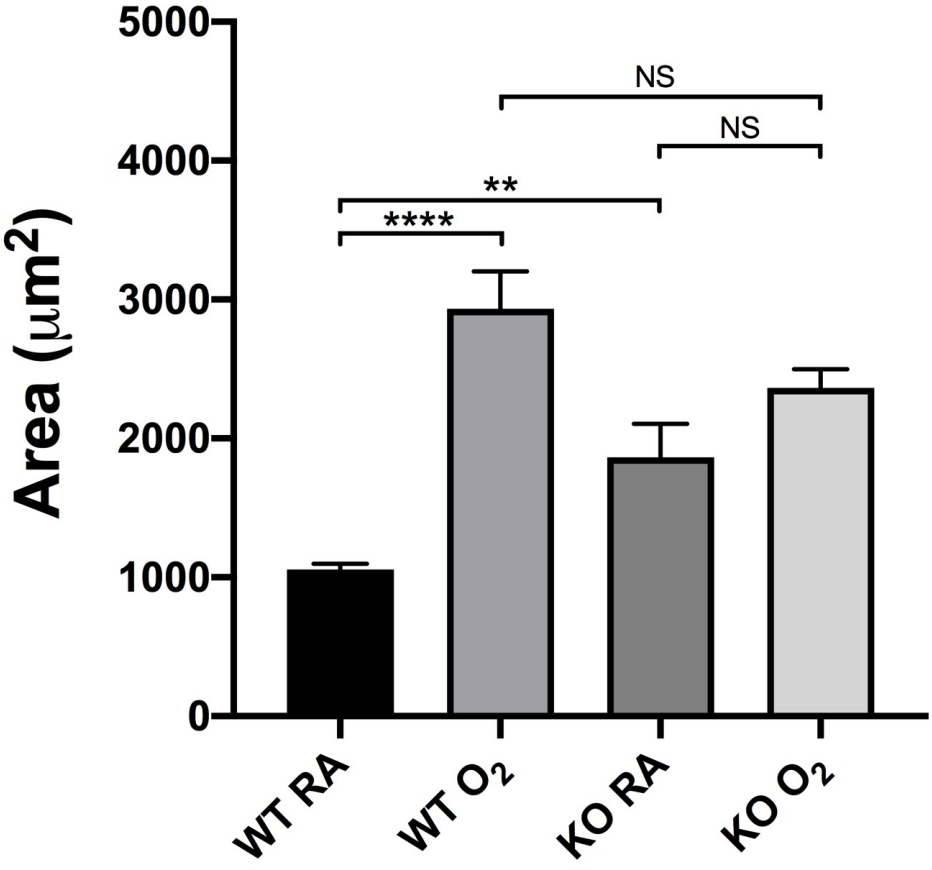
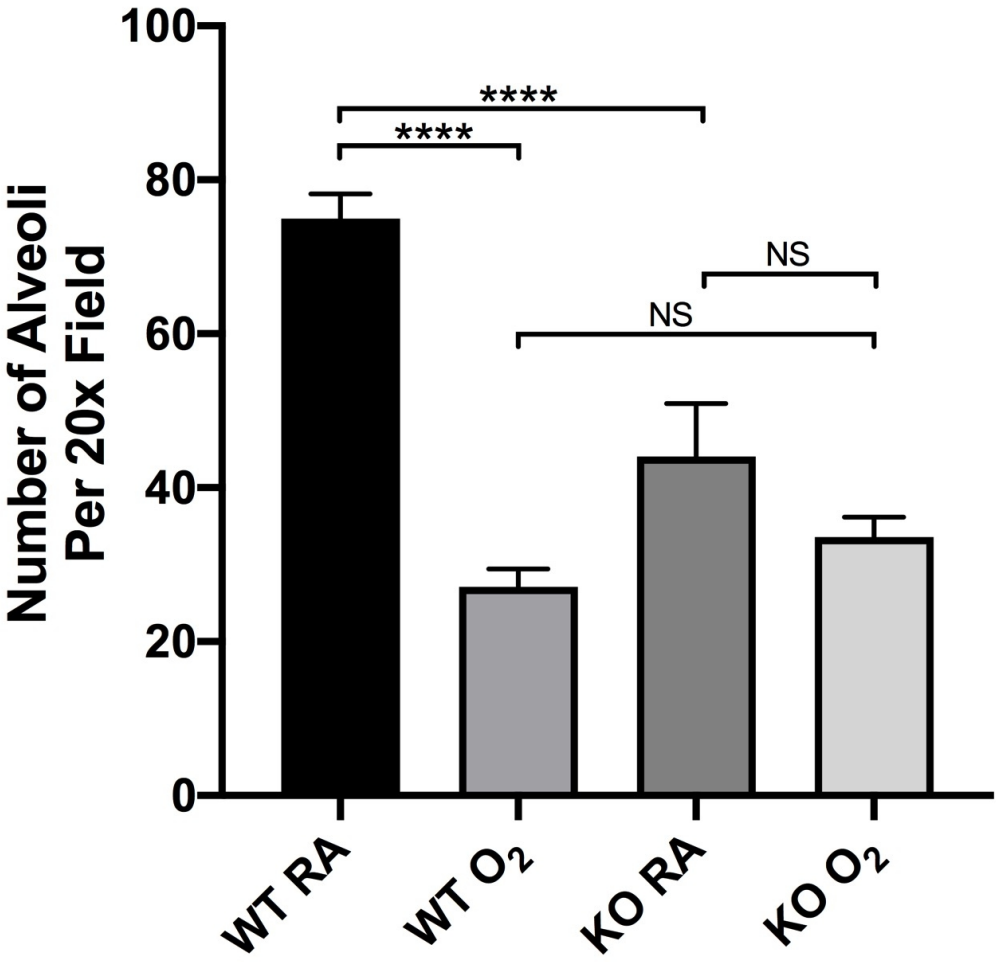
IMAGE CAPTION:

Alveolar Area



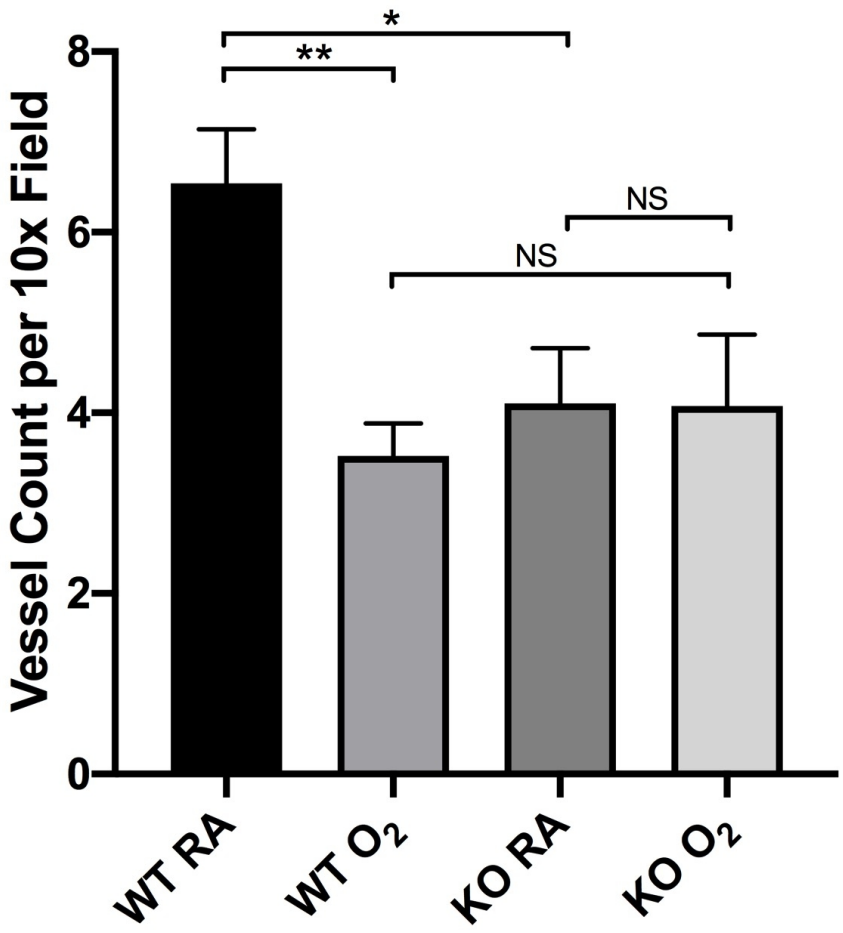
Data presented as mean plus standard error. **p<0.01; ****p<0.0001.

Alveolar Counts

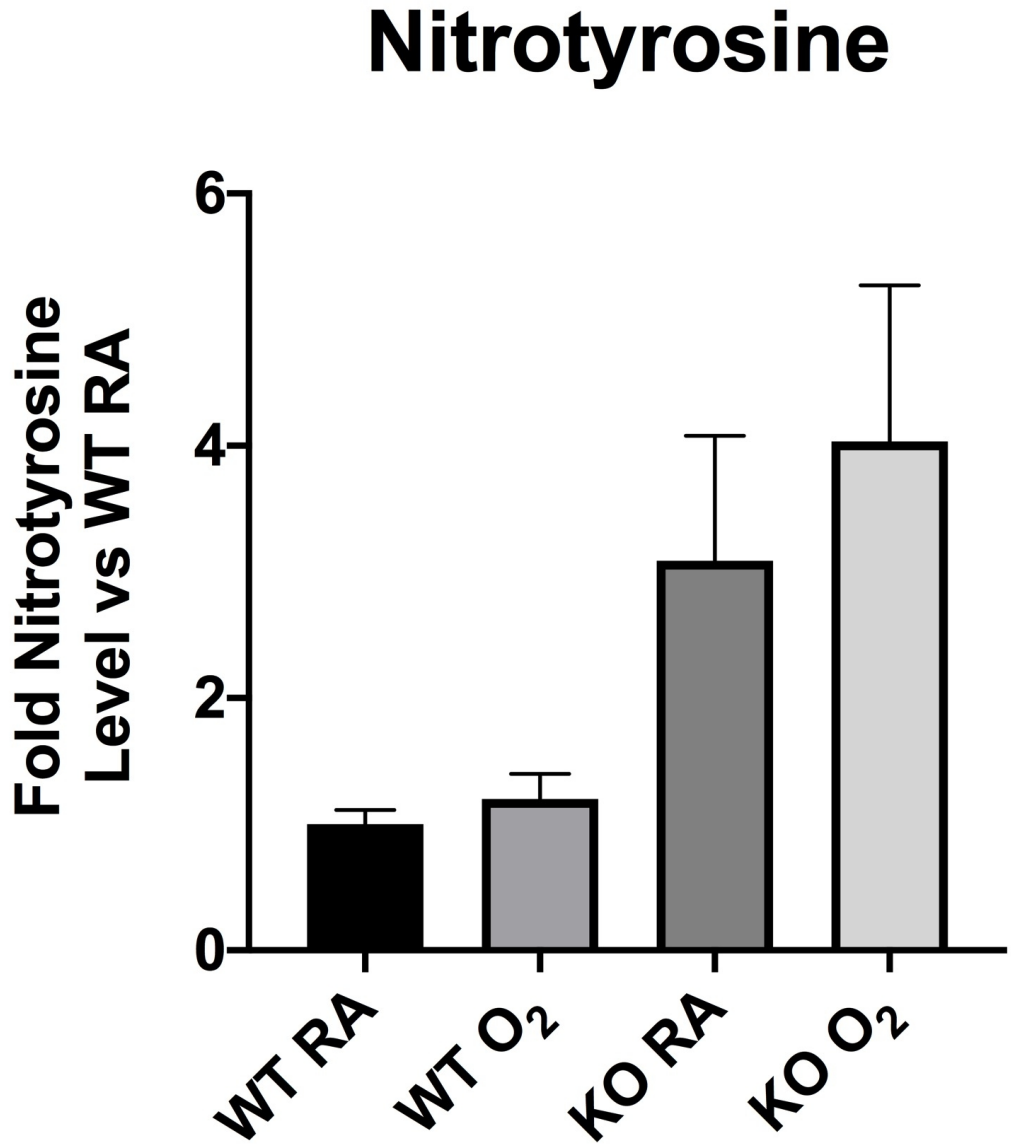


Data presented as mean plus standard error. ****p<0.0001.

Vascular Density



Data presented as mean plus standard error. *p<0.05; **p<0.01.



Nitrotyrosine level, normalized to β-actin. Data presented as mean plus standard error. There was a trend towards increased nitrotyrosine levels in ecSOD KO mice.

CONTROL ID: 3476579

TITLE: Impact of neonatal steroid therapy on long-term lung development in murine model of hyperoxic lung injury

DIGITAL OBJECT IDENTIFIER (DOI):

ABSTRACT STATUS: Sessioned

PRESENTER: Marta Perez

AUTHORS/INSTITUTIONS: M. Perez, M.E. Robbins, R.J. Moskal, J. Taylor, A. Hamvas, Ann and Robert H Lurie Children's Hospital of Chicago, Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, IL, US, hospital/children, Chicago, Illinois, UNITED STATES|M. Perez, M.E. Robbins, J. Taylor, A. Hamvas, Northwestern University Feinberg School of Medicine, Chicago, Illinois, UNITED STATES|

CURRENT CATEGORY: Basic Science

CURRENT SUBCATEGORY: None

ABSTRACT BODY:

Background: Systemic corticosteroids can improve short-term lung function in infants with bronchopulmonary dysplasia. Their effects on long-term lung growth are less clear. We have previously reported that of hydrocortisone (HC), one of the most commonly utilized steroids in the NICU, impairs alveolar formation in a dose-dependent manner in a murine model of neonatal hyperoxic lung injury, including alveolar simplification even in room air.

Objective: We sought to determine the impact of HC on long-term lung development in a neonatal mouse model of hyperoxic lung injury.

Design/Methods: Neonatal C57BL/6 mice were placed in 21% O2 or 75% O2 within 24h of birth and received HC (10 mg/kg subcutaneously every other day) or equivalent volume of vehicle. At 14d, lungs were inflation-fixed or harvested. Whole lung RNA was used for high-throughput, sequencing-based transcriptome analysis (RNA-Seq). Protein expression of HopX, an alveolar Type I cell (AEC1) marker, and SPC (AEC2 marker), was measured by Western blot, normalized to ß-actin. Proliferation was assessed via Ki67 IHC staining. Additional animals were allowed to recover in room air until 12 weeks of age when their lungs were inflation-fixed for evaluation of lung morphometry.

Results: Compared to room air or hyperoxia exposure alone, HC treatment was associated with significant upregulation of multiple pathways related to the cell cycle. Ki67 staining did not reveal any differences in proliferation in HC-treated mice. Expression of HopX was increased by HC 1.5-fold in room air with a trend towards increased expression in hyperoxia. SPC, a marker of AEC2, was increased 5-fold by hyperoxia exposure but did not increase further with HC treatment. Following neonatal HC treatment, lungs of adult animals demonstrated resolution of alveolar simplification in room air mice with continued simplification in hyperoxia-exposed animals.

Conclusion(s): High dose HC results in reversible alveolar simplification in mice exposed to neonatal normoxia but not hyperoxia. While the precise mechanisms underlying these changes remain to be determined, we speculate that they may be linked to increased expression of AEC1 population in animals treated with high dose steroids without the additional insult of hyperoxia. Combined steroid and hyperoxia exposure results in persistent alveolar simplification.

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CONTROL ID: 3475697

TITLE: Reg3g-mediated HSG polymerization as a drug-sensitive target of islet dysfunction in offspring of obese mice

DIGITAL OBJECT IDENTIFIER (DOI):

ABSTRACT STATUS: Sessioned

PRESENTER: Kok Lim Kua

AUTHORS/INSTITUTIONS: S. Archer-Hartmann, P. Azadi, University of Georgia Complex Carbohydrate Research Center, Athens, Georgia, UNITED STATES|J. Casasnovas, J. Jarrell, C. Damron, K. Kua, Pediatrics/Neonatal-Perinatal Medicine, Indiana University School of Medicine, Indianapolis, Indiana, UNITED STATES|

CURRENT CATEGORY: Basic Science

CURRENT SUBCATEGORY: None

ABSTRACT BODY:

Background: Human offspring born to obese mothers suffer higher risk of developing type 2 diabetes due to insufficient islet insulin secretion. Animal studies demonstrated the sex-differences in offspring islet function, but the mechanistic targets underlying islet dysfunction in offspring of obese mothers is unknown. We found that the increase in islet Reg3g (Regenerating Islet Derived Protein 3-Gamma) in female offspring of obese dams is associated with the maintenance of islet insulin secretion. Reg3g binds to EXTL3 glycosyltransferase that initiates heparan sulfate glycosaminoglycan (HSG) formation. To date, the role of Reg3g mediated HSG polymerization in modulating islet β-cell health in offspring of obese mice is unclear.

Objective: We hypothesize that the upregulation of Reg3g mediated HSG polymerization protects offspring of obese mice from glucose intolerance and islet dysfunction.

Design/Methods: Female mice were fed regular chow as controls (Con) or western diet to induce maternal obesity (MatOB). Offspring pups were evaluated on postnatal day 21 (P21) for glucose tolerance, glucose-stimulated insulin secretion (GSIS), and islet Reg3g gene/protein expression. Pancreatic HSG was measured with immunohistochemistry and validated with SAX-HPLC. To determine the causality of Reg3g, heterozygous Reg3g mutant (Reg3g+/-) females receiving chow or western diet were mated with WT males to generate WT and Reg3g +/- offspring in each diet group. Lastly, we tested the therapeutic effect of Reg3g and HSG by injecting male MatOb pups intraperitoneally with saline, recombinant Reg3g (rReg), or heparan sulfate analogue (HS) every other day from P14-20. Results with * have $p<0.05$.

Results: Compared to same-sex controls, P21 female MatOb pups had higher islet Reg3g gene/protein expression* (n=3-6), higher islet HSG* (n=3/3), and unchanged GSIS. Male MatOb pups had unchanged Reg3g or HSG staining. SAX-HPLC studies showed that total pancreatic HSG was lower in male MatOb pups* (n=3/3), indicating a shorter HSG length. Additionally, male MatOb pups had decreased glucose intolerance* (n=9-19) and 30% decrease in GSIS* (n=5/5). This sex-difference in glucose tolerance was ablated in Reg3g+/- mice (n=2-5), where female MatOb Reg3g+/- pups exhibited significantly impaired GTT. Lastly, male MatOb pups that received rReg3g or HS had improved glucose tolerance (n=2-3) and in-vivo GSIS* (n=3-4).

Conclusion(s): Our findings supported the role of Reg3g as a drug-sensitive target mediating islet dysfunction in MatOb offspring

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