September 17th, 2021 15:00 - 17:00

PARALLEL SESSION 27 - LUNG 5

ID 287. THE ROLE OF TRANSFORMING GROWTH FACTOR BETA ISOFORMS IN THE DEVELOPMENT OF BRONCHOPULMONARY DYSPLASIA

Doctor Rebecca Calthorpe[1], Professor Alan Smyth[1], Dr Amanda Tatler[1]
[1]*University Of Nottingham, Nottingham, United Kingdom*

Background: Bronchopulmonary dysplasia (BPD) is the most common complication of prematurity. Mechanical ventilation is an essential treatment strategy in the care of extremely preterm infants, however it also contributes to BPD development. An important signalling pathway that is relevant lung development, remodelling and BPD development is the Transforming Growth Factor Beta (TGFβ) signalling pathway. TGFβ exists as 3 isoforms; TGFβ1, TGFβ2 and TGFβ3. Increased TGFβ1 results in increased matrix deposition and fibrosis, whilst caffeine inhibited TGFβ1 activation in epithelial cells and reduced fibrosis in ex-vivo precision cut lung slices in mice. The role of TGFβ2 and TGFβ3 in fibrosis, BPD development and the impact of caffeine and other medications commonly prescribed in the prevention or treatment of BPD on these isoforms are currently less well understood.

Methods: Immortalised human bronchial epithelial cells (iHBECs) were exposed to cyclical mechanical stretch (CMS) at 15% elongation, 1Hz vs control using the Flexcell system for up to 48 hours and results analysed by western blot and Elisa. Additionally, iHBECs were exposed to caffeine 50µM or dexamethasone 10µM (0-48 hours) and TGFβ isoform expression measured by real time qPCR.

Results: CMS increased TGFβ activation, demonstrated by increased pSmad2 at both 4 and 24 hours, compared with unstretched cells. Furthermore, caffeine and dexamethasone demonstrated TGFβ isoform specific effects. Caffeine citrate showed a >10 fold increase in TGFβ2 expression from 0 to 48 hours which was not seen with the other isoforms, whilst dexamethasone showed a trend towards increased TGFβ3 expression by 48 hours (p=0.07).

Conclusion: Based on these data, this suggests CMS used to mimic mechanical ventilation in a neonate increased TGFβ activation. This may be responsible for the increased fibrosis seen following mechanical ventilation, thus contributing to BPD development. Furthermore, caffeine and dexamethasone may have TGFβ isoform specific effects. A more detailed understanding of the role of TGFβ isoforms in fibrosis and BPD development is essential.

AS reports grants from Vertex and expenses from Teva and Vertex, outside the submitted work. RC is supported by a National Institute for Health Research (NIHR) Academic Clinical Fellowship.

ID 128. RISK FACTORS AND BRONCHOPULMONARY DYSPLASIA SEVERITY. DATA FROM THE SPANISH BRONCHOPULMONARY DYSPLASIA RESEARCH NETWORK

Doctor Cristina Ramos Navarro[1], Doctor Elena Maderuelo-Rodriguez[1], Doctor Ester Sanz-López[1], Doctor Ana Concheiro-Guisán[2], Doctor Santiago Pérez-Tarazona[3], Doctor Santiago Rueda-Esteban[4], Doctor Manuel Sánchez-Solís[5], Doctor Ana Sánchez-Torres[6], Professor Manuel Sánchez-Luna[1]

[1]Gregorio Marañon University Hospital, Madrid, Spain, [2]Álvaro Cunqueiro University Hospital, Vigo, Spain, [3]La Fe University Hospital, Valencia, Spain, [4]San Carlos University Hospital., Madrid, Spain, [5]Virgen Arrixaca University Hospital, Murcia, Spain, [6]La Paz University Hospital, Madrid, Spain

Background: GEIDIS is a national based research-net registry of patients with bronchopulmonary dysplasia (BPD) from public and private Spanish hospitals. It was created to provide data on the clinical characterization and follow up of infants with BPD until adulthood. The purpose of this observational study was to analyze the characteristics and the impact of perinatal risk factors on BPD severity.
Methods: The study involves the analysis of the data collected prospectively in the GEIDIS registry between January 2016 and August 2020.
Results: 1,780 patients diagnosed with BPD were included. Of the total sample, 98.6% were premature (less than 37 weeks) and 89,4% less than 30 weeks of gestation. The median gestational age was 27.1 weeks (25.8–28.5) and median birth weight 890 g (740–1,090 g). 52.3% (n=931) were classified as mild (type 1), 25.1% (n=447) were moderate (type 2), and 22.6% (n=402) severe BPD (type 3). Independent prenatal risk factors associated for type 2/3 BPD were male gender (OR 1.394; 95% CI 1.142-1.727), oligohydramnios (OR 1.568; 95% CI 1.142-2.152), and intrauterine growth restriction (OR 1.611; 95% CI 1.216-2.134). Postnatal risk factors included the need for FiO2 of > 0.30 in the delivery room (OR 1.303; 95% CI 1.02-1.33), two or more doses of surfactant administration (OR 1.313; 95% CI 1.003-1.717), nosocomial pneumonia (OR 1.055; 95% CI 1.043-1.063), and the length of exposure to mechanical ventilation (MV; days) (OR 1.062; 95% CI 1.052-1.073). In the group of patients with type 3 BPD, those who required an FiO2 > .30 at 36 weeks' PMA had a higher morbidity, both during hospitalization and at discharge, compared to the group of patients with nasal positive pressure but at a FiO2 < .30 (Table 1.)
Conclusions: In this national based research-net registry of BPD patients the length of MV is the most important risk factor associated with type 2/3 BPD. Among type 3 BPD patients, those who required an FiO2 > .30 at 36 weeks' postmenstrual age had a higher morbidity, during hospitalization and at discharge, compared to those with nasal positive pressure but FiO2 < .30.

	Type 3a BPD with FiO_2 >. 30 (N=135)	*Type 3b BPD with positive pressure (nCPAP) or nasal cannula > 2 L/min and FiO_2 < .30 (n=267)*	*Type 2 BPD with nasal cannula < 2 L/min and FiO_2 < .30 (n=447)*	*P value*
Gestational age (weeks)	26.5 (24.8-28.1)	26.7 (25.1-28.8)	26.8 (25.6-28.4)	0.089
Weight (g)	770 (650-980)	832 (650-1050)	850 (728-1000)	0.054
Prenatal corticosteroids	91% (121/133)	88.7% (236/266)	88.2% (389/441)	0.830
Sex (male)	59.3% (80/135)	63% (167/265)	57% (254/446)	0.139
Clinical chorioamnionitis	15.6% (21/135)	12.7% (34/267)	13.6% (61/447)	0.902
Histological chorioamnionitis	12.6% (17/135)	10.9 (29/267)	14.5% (65/447)	0.408
Intrauterine growth restriction	26.8% (34/127)	24.2% (60/248)	20.7% (88/426)	0.240

Oligohydramnios	22.7% (30/132)	12.3% (32/261)	15% (66/439)	0.067
Intubation at birth	60.7% (82/135)	53.9% (144/267)	50.3% (225/447)	0.100
FiO_2 > .30 at birth	85.7% (114/133)	78.2% (205/262)	77.4% (340/439)	0.128
FiO_2 > .60 at birth	32.3% (43/133)	30.2% (79/262	24.6% (108/439)	0.126
Intubation in first hour of life	67.4% (91/135)	58.4% (156/267)	58.2% (260/447)	0.139
Surfactant	80% (108/135)	76.2% (198/260)	80% (351/439)	0.551
Two or more surfactant doses	55.2% (58/105)	42.4% (81/191)	38.6% (128/332)*	0.013
MV during hospitalization	95.6% (129/135)	85.7% (227/265)*	82.6% (366/443)*	0.001
Nitric oxide therapy	41.7% (55/132)	21.2% (56/264)*	14.4% (63/437)*	<0.001
Ectopic air	19.5% (26/133)	10.6% (28/263)*	8.4% (37/443)*	0.007
MV, days	32 (15-60)	24.5 (9-36)*	12 (5-25)* #	<0.001
Positive pressure, days	48 (32.7-74.2)	44 (29.2-64)	33 (18-48) *#	<0.001
High-flow oxygen, days	24.5 (14.2-37)	25 (11-40)	13 (3-24)* #	<0.001
Oxygen, days	104 (83-130)	65.5 (43.7-90)*	67 (50-82)*	<0.001
Postnatal corticosteroids (BPD)	71.9% (97/135)	43.8% (117/267)*	30.4% (136/447)*#	<0.001
Nosocomial sepsis	80.9%(106/131)	71.4% (182/255)	60.8% (265/436)* #	<0.001
Nosocomial pneumonia	53% (70/132)	27.6% (71/257)*	18.7% (82/438)* #	<0.001
Patent ductus arteriosus	62.7% (79/126)	65.8% (171/260)	55.8% (244/437) #	0.038
PDA surgical closure	25.2% (34/135)	20.6% (55/267)	14.8% (66/447)*	0.016
Diagnosis of PH	32.2% (43/133)	15.1% (39/259)*	12.1% (53/438)*	<0.001
Treatment with sildenafil	20% (27/135)	6% (16/267)*	2.2% (10/447)* #	<0.001
Leukomalacia (> grade 1)	13% (16/123)	8.3% (21/253)	4.4% (19/428)*	0.006
IVH (grade 3 or higher)	13% (16/123)	9.1% (23/254)	7.7% (33/427)	0.235
Periventricular infarction	16.8% (19/113)	18.8% (43/228)	16.8% (61/363)	0.574
Ventricular Shunt	6.9% (7/101)	1.9% (4/212)	2.6% (7/273)	0.084
Retinopathy greater than 2	51.9% (41/79)	35.8% (37/103)	27.8% (52/187)*	0.001
Respiratory support at discharge	66.9% (81/121)	38.2% (96/251)*	29.1% (127/436)* #	<0.001
Feeding by NGT/gastrostomy at discharge	20% (27/135)	12.3% (31/252)*	6.3% (28/447)*#	<0.001
Bronchodilators at discharge	23% (31/135)	6.4% (17/267)*	3.6% (16/447)*	<0.001
Inhaled corticosteroids at discharge	34.1% (46/135)	11.6% (31/267)*	16.3% (73/447)*	<0.001
Diuretics at discharge	23.7% (32/135)	17.6% (47/267)	8.1%(36/447)*	<0.01
Antireflux treatment	20% (27/135)	18.4% (49/267)	8.7% (39/447)*#	<0.001
Mortality	8.7% (11/126)	2.4% (6/251)*	0.7% (3/428)*	<0.001

Comparison of the perinatal variables and morbidity at discharge. Data expressed in percentage (n) or median (interquartile range) * Difference with type 3a BPD; # difference with type 3b BPD.

None declared

ID 223. INCIDENCE, PREDICTORS AND OUTCOMES OF PULMONARY HYPERTENSION IN EXTREMELY PREMATURE BABIES WITH MODERATE TO SEVERE BRONCHO PULMONARY DYSPLASIA: TEN YEARS' EXPERIENCE FROM A TERTIARY SURGICAL NEONATAL CENTRE IN UNITED KINGDOM

Doctor Irina Branescu[1], Doctor Simona Vladareanu[2], Doctor Sandeep Shetty[3], Doctor Justin Richards[3], Doctor Anay Kulkarni[3]

[1]'Carol Davila' University of Medicine and Pharmacy, St. George's University Hospital, London, United Kingdom, [2]'Carol Davila' University of Medicine and Pharmacy , Bucharest, Romania, [3]St. George's University, St. George's University Hospital, London, United Kingdom

Incidence, predictors and outcomes of pulmonary hypertension in extremely premature babies with moderate to severe Broncho Pulmonary Dysplasia: ten years' experience from a tertiary surgical neonatal centre in United Kingdom

Irina Branescu [1], Simona Vladareanu [2], Sandeep Shetty [1], Anay Kulkarni [1]

Background: As extreme prematurity survival rates increase, bronchopulmonary dysplasia (BPD) remains the most common morbidity. Pulmonary hypertension (PHT) is independently associated with poor outcomes in babies with BPD. The incidence of PHT in BPD patients have been reported to be between 17-24% and carry high mortality up to 50% within 2 years of diagnosis.

Methods: Single centre retrospective cohort study with prospective objective review by a single observer of all echocardiography assessments done for screening for PHT in extremely premature babies with moderate to severe BPD. All infants ≤ 32 weeks' gestation, admitted to St George's Hospital between March 2010 and July 2020 with moderate to severe BPD at 36 weeks' corrected gestation, were included. Infants with complex congenital anomalies, genetic syndromes and surgical conditions were excluded.

Results: Out of total 563 preterm infants ≤ 32 weeks' gestation, 275 babies with moderate to severe BPD were included in the study. Echocardiography screening for PHT was done for 229 babies. Thirty-four babies (12%) were observed to have PHT with 13 babies (4%) having severe / supra-systemic PHT. Need for invasive or non-invasive respiratory support at 36 weeks corrected gestation was associated with PHT (OR: 5.7, 95% CI: 2.64- 12.3). None of the babies who didn't need non-invasive/invasive respiratory support at 36 weeks corrected gestation developed severe PHT. Ten babies (30%) with PHT associated to severe BPD died before discharge from neonatal unit. PHT was associated with death before discharge from the neonatal unit (OR: 9.7, 95% CI: 3.5-27).

Conclusion: Incidence of PHT in babies with moderate to severe BPD was lower than reported literature. Extremely premature babies with severe BPD, who need invasive/non-invasive respiratory support at 36 weeks' corrected gestation, are more likely to develop PHT. Babies with severe BPD and PHT are more likely to die before discharge from the neonatal unit than babies without PHT.

None

ID 258. The translational potential of the preterm rabbit as a BPD animal model

Mr Matteo Storti[1], Mss Francesca Ricci[2], Mss Costanza Casiraghi[2], Mss Chiara Catozzi[2], Mr Giorgio Aquila[2], Mss Ilaria Minato[1], Mss Maria Chiara Iannitello[1], Mr Danilo Tatoni[1], Prof Francesca Ravanetti[3], Prof Luisa Ragionieri[3], Mss Roberta Ciccimarra[3], Mr Matteo Zoboli[3], Mr Gino Villetti[2], Mr Fabrizio Salomone[2], Prof Barbara Montanini[1], Prof Simone Ottonello[1]

1University of Parma, Department of Chemical & Life Sciences and Environmental Sustainability, Parma, Italy, 2Chiesi Farmaceutici, Parma, Italy, 3University of Parma, Department of Veterinary Sciences, Parma, Italy

Background: Bronchopulmonary dysplasia (BPD) is the most common complication of premature babies born with underdeveloped lungs. Animal models are pivotal to study its pathophysiology. Given the low maintenance cost and the short gestation period, BPD mouse models are commonly used in pre-clinical practice. However, unlike babies who are born at term in the alveolar phase, mice are naturally delivered with structurally immature (although functional) lungs in the saccular phase (gestational age, GA 21th). Rabbits share some of the mice practical advantages, but they are born at term (GA 31th) in the alveolar phase of lung development, as it occurs in humans and can be delivered prematurely (GA 28th). To date, a comparative transcriptomic analysis is lacking. The aim of the study was to compare the relevant gene expression (GE) profiles of both species to evaluate the rabbit translational potential as a BPD model.
Methods: GE analysis was performed on lung samples from term (GA 31th) and preterm (GA 28th) rabbits and compared with the mouse lung GE dataset (GA 18.5th and GA 21th) generated by Beauchemin K.J. et al (GSE74243). Pathways enrichment analysis was performed based on differentially expressed genes identified in each species (GA 18.5th vs GA 21th and GA 28th vs GA 31th). Common pathways involved in lung development of preterm rabbits and term mice were evaluated.
Results: Lung development-related pathways such as cell cycle and mitosis-related processes were significantly enriched in both GA 18.5th mice and preterm-delivered (GA 28th) rabbits lungs, compared to their term counterparts. Common pathways, including angiogenesis, vasculature development, humoral immune system, and leukocyte migration, were found to be enriched in both species delivered at term, despite their different lung developmental phases. In contrast, no enriched common pathways emerged from the comparison between preterm rabbits and term mice.
Conclusion: Our analysis revealed that common enriched pathways are present in mice and rabbits born both preterm and term, despite their different lung development phases. Since preterm delivery is not feasible in mice, this study suggests a potential higher translational of the preterm rabbit model for studying the dysregulation of lung development-related pathways, leading to BPD in humans.

Ricci F., Casiraghi C., Catozzi C., Aquila G., Salomone F. and Villetti G. are Chiesi employees. Other authors have no conflict of interest