Antenatal inflammation and postnatal respiratory disease

T.J.M. Moss, The Ritchie Centre, Monash Institute of Medical Research, PO Box 5418, Clayton, VIC 3268, Australia . (Introduced by Gavin Pinniger)

Respiratory disease is a major cause of morbidity and mortality in preterm newborns, and manifests in 2 principal forms: respiratory distress syndrome (RDS), which is due principally to surfactant deficiency arising from lung immaturity and results in early respiratory failure; and bronchopulmonary dysplasia (BPD), which is characterized by a long-term requirement for ventilatory support, often, but not always, following RDS.

Intrauterine inflammation or infection is the principle etiological factor in many, if not the majority, of preterm births. Clinical studies have shown that rates of RDS and BPD are altered by exposure to infection or inflammation before birth: the risk of RDS is decreased but the risk of BPD is increased. Our experimental studies are revealing the developmental mechanisms for these alterations in the risk of RDS and BPD.

Using sheep, we have induced intrauterine inflammation or infection using intra-amniotic injection of lipopolysaccharide (LPS) or live ureaplasmas (the microorganisms most often isolated from amniotic fluid of women who deliver preterm) and have shown consequent precocious production of pulmonary surfactant by the preterm lungs, consistent with a reduced risk of RDS. We are currently using transgenic mice to identify the underlying mechanism for increased surfactant production by the preterm lungs. Using glucocorticoid receptor knockout mice, we have shown that this conventional maturational pathway (the basis of the sole preventive treatment for RDS) is not necessary for inflammation-induced surfactant production. This observation raises the possibility of identifying a novel treatment for inducing precocious preterm lung maturation in pregnancies at risk of preterm birth. To this end, we have been investigating the role of prostaglandins in the fetal response to inflammation. These fundamental mediators of inflammation are known to be capable of stimulating surfactant production by the fetal lungs. We have observed increased expression of prostaglandin receptors and enzymes responsible for prostaglandin production in lung tissue of fetal sheep exposed to intrauterine inflammation. These observations suggest that the mechanism whereby inflammation leads to surfactant production may be *via* prostaglandin signalling.

Lung inflammation is now recognized as a characteristic feature of BPD and likely underlies the pathogenesis of this disease. Early clinical studies showed associations between inflammation or infection *in utero* and increased risk of BPD but recent studies suggest the relationship is not straightforward. It is now considered likely that intrauterine inflammation may be the first ‘hit’ in a series that ultimately results in the pulmonary pathology that underlies BPD. Consistent with this, we have shown that pulmonary inflammation induced by the initiation of ventilation is exacerbated by prior exposure to intrauterine inflammation. Further, intrauterine inflammation results in neonatal pulmonary hypertension, which is present in human cases of BPD with particularly poor outcomes.

Our initial studies in preterm sheep exposed to long term intrauterine inflammation showed lung structural changes (fewer, larger alveoli) and evidence of impaired surfactant secretion, consistent with observations of preterm infants with BPD. These structural changes are considered a hallmark of BPD and can be reproduced in a variety of animal models of the disease. We have recently been using sheep and mice to investigate the potential of a novel cell therapy for BPD. Human amnion epithelial cells (hAECs), derived from the embryonic epiblast, have the pluripotent capacity of embryonic stem cells, low immunogenicity, are relatively easy to harvest and do not form teratomas; these characteristics make them ideal candidates as a cell therapy. We have shown, using sheep, that administration of hAECs can attenuate the inflammatory response of the fetal lungs to intra-amniotic LPS injection and reduce consequent alterations in lung development. Using newborn mice exposed to hyperoxia, we have shown attenuation of BPD-like lung structural changes by hAECs. In both of these experiments, hAECs are not engrafting to repair lung injury. Rather, they appear to be altering the inflammatory response of the immature lung. Given that the developmental consequences of pulmonary inflammation appear fundamental to the pathogenesis of BPD, we believe that hAECs may have utility as a therapy for the prevention or treatment of BPD.

It is only recently that intrauterine inflammation has been revealed as a major contributor to preterm birth and its associated morbidities. Just as respiratory development is influenced by intrauterine inflammation, so to is development of (at least) the brain, kidneys, heart, gut and immune system; however the developmental mechanisms harnessed by the inflammatory response are largely unknown. Elucidation of the developmental effects of inflammation is likely to have significant benefit for our understanding, and ultimately the treatment and prevention, of neonatal respiratory (and other) disease.