Bronchopulmonary Dysplasia

SUMMARY

Bronchopulmonary dysplasia (BPD) is a form of chronic lung disease, peculiar to the extremely preterm infant, born at the early stages of lung development. Up to 40% of the infants below 29 weeks' gestation are diagnosed with BPD, while the composite outcome death and/or BPD occurs in 65% of the infants below 29 weeks' gestation. Despite the continuous advances of perinatal care, BPD remains a significant burden of extreme prematurity, because it lacks a safe and effective treatment and/ or prevention strategies.

In the past few years, increasing insight into stem cell biology has generated excitement about the potential of stem cells to regenerate damaged organs. Among stem cells, mesenchymal stromal (stem) cells (MSCs) have attracted much attention because of their ease of isolation, multilineage potential, and immunomodulatory properties. Perivascular cells (PCs) from diverse human tissues give rise to adherent multilineage progenitor cells that exhibit all the features of MSCs and may embody the precursors of MSCs. MSCs and PCs may represent a novel therapeutical option for so far untreatable diseases, including BPD.

While the definitive prevention of BPD could only be obtained by avoiding preterm birth, prenatal and postnatal preventive efforts are also directed at the reduction of the other stressors that may worsen the injury to the developing lung.

The present thesis is a collection of studies aimed at investigating the potential use of MSCs and PCs in the treatment of BPD and evaluating the possible role of probiotic supplementation and mother's own milk (MOM) diet in the prevention of BPD.

In chapter I, we summarize and discuss the current state of knowledge on BPD pathophysiology
and the potential therapeutic targets, with special emphasis on the role of MSCs and PCs.

In chapter II we tested the potential of MSCs and their precursors (PCs) in preventing and treating the oxygen-induced lung injury in a murine model of BPD. We showed that MSCs and PCs are able to prevent and restore features of BPD in the hyperoxia-induced lung injury in rats with long term safety and efficacy. We investigated the homing of the cells, showing that it is minimal. As a consequence we proved that the media where cells are cultured, called conditioned medium (CdM) has similar effects as the whole cell therapy in preventing and treating the oxygen-induced lung injury.

In Chapter III we performed a Cochrane meta-analysis to analyze the studies that have tested the possible role of MSCs in the treatment of BPD. We did not find any RCT or quasi-RCT that fulfilled the inclusion criteria. However, several trials are underway.

In Chapter IV we performed a systematic review and meta-analysis to test the potential of probiotics in preventing BPD. Fifteen randomized controlled trials (4782 infants; probiotics: 2406) were included. None of the included studies assessed BPD as the primary outcome. Meta-analysis confirmed a significant reduction of necrotizing

enterocolitis (NEC) and an almost significant reduction of late-onset sepsis (LOS). In contrast, meta-analysis could not demonstrate a significant effect of probiotics on BPD, defined either as oxygen dependency at 28 days of life (relative risk (RR) 1.01, 95% CI 0.91 to 1.11, p = 0.900, 6 studies) or at 36 weeks of postmenstrual age (RR 1.07, 95% CI 0.96 to 1.20, p = 0.203, 12 studies). Meta-regression did not show any significant association between the RR for NEC or LOS and the RR for BPD.

In Chapter V we performed a systematic review and meta-analysis to test the potential of MOM in preventing BPD. Fifteen studies met the inclusion criteria (4,984 infants, 1,416 BPD cases). The use of exclusive MOM feedings was associated with a significant reduction in the risk of BPD (RR 0.74, 95% CI 0.57–0.96, 5 studies). In contrast, meta-analysis could not demonstrate a significant effect on BPD risk when infants were fed with a mixed diet of MOM and formula milk.

Finally, in chapter VII, we discuss and put into perspective the findings of this thesis. We also present two future studies. In the first one we aim to explore the MSC potency, function, stemness, aging, differentiation capacity and extracellular vesicles production under different perinatal conditions (i.e. chorioamnionitis, pregnancy induced hypertension, diabetes, IUGR) as compared to healthy pregnancy at different gestational ages.
The other one is a systematic review to advance the understanding of the antecedents of BPD, in particular the vascular disorders of the placenta.