Energizing the Lung Vasculature in the Premature Infant to Promote Alveolar Formation

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Background/Objective: Chronic lung disease of prematurity, bronchopulmonary dysplasia (BPD) occurs when infants born with underdeveloped immature lungs are forced to navigate the expansion of future air spaces, with irregular vascular formation proceeding development of BPD. Lung development has distinct and dynamic metabolic requirements. We recently identified by mass spectrometry that nicotinamide adenine dinucleotide (NAD⁺), generated from vitamin B₃ ‘Nicotinamide’ (NAM), was significantly reduced in a hyperoxia murine model of BPD. As NAM/NAD⁺ are dynamic regulators of tissue regenerating neovascularization in other disease processes, we hypothesized that NAM/NAD⁺ metabolic deficiencies contribute to compromised angiogenesis formation and alveolar formation.

Methods: Impact of NAM supplementation on circulating human neonatal endothelial colony-forming cells (ECFCs) were assessed for differential capillary formation properties of angiogenesis (Matrigel), migration (wound healing), proliferation (WST1 and crystal violet staining), and mitochondrial function in normoxia and hyperoxia (85% oxygen) conditions.

Results: Hyperoxia suppresses ECFC angiogenesis, while NAM supplementation in hyperoxia significantly rescued vascular networks, branched nodes, and branch points (p<0.001). Wound healing assays suggest that NAM promotes cell migration in normoxia and hyperoxia (p<0.0001). Although NAM increased WST1 activity in hyperoxia, crystal violet analysis determined that NAM had no impact on ECFC proliferation. Lastly, NAM significantly reduced hyperoxia induced mitochondrial oxidative stress in a dose dependent manner (p<0.05).

Conclusion and Clinical Implications: Lung development has specific metabolic needs during different stages of development that are disrupted by premature birth. Replenishment of NAM promotes angiogenesis and migration in hyperoxia while reducing mitochondrial activity. Future studies are necessary to explore the role of NAM/NAD⁺ axis in the developing lung.