One-Carbon Metabolism, a Nutrient Dependent Mediator of Angiogenesis and Alveolar Formation in the Developing Lung.

Noah Nisen[1], Dushani Ranasinghe[2], Andrew Kim[2], Margaret Schwarz[123]
[1]Indiana University School of Medicine; [2]Department of Chemistry & Biochemistry, University of Notre Dame; [3]Department of Pediatrics, Indiana University School of Medicine

Background/Objective: Lung maturation has discrete dynamic shifts in metabolic derivatives that give rise to stage specific metabolite signatures. Components of one-carbon metabolism (OCM) are significantly increased in the late saccular and alveolar stage while hyperoxia disrupts OCM metabolism during these lung developmental stages. We hypothesize that disrupted OCM metabolites in the immature lung disrupts vessel dependent alveolar formation thus contributing to alveolar dysplasia. Our studies explore the impact that restoration of OCM has on angiogenesis and alveolar formation.
Methods: Isolated human neonatal circulating Endothelial Colony Forming Cells (ECFCs) were examined for proliferation (WST-1), migration (scratch assay), and angiogenesis (matrigel) in response to supplementation of OCM derivatives, essential amino acid methionine and nicotinamide. OCM enzyme levels were assessed via Western blotting, NNMT, NAMPT, DNMT. Lastly, alveolar formation in a hyperoxia murine model of prematurity (HMMP) with dietary supplement of methionine vs control was assessed, MLI, H&E, and vessel formation (endomucin).
Results: Methionine and nicotinamide increased ECFC proliferation ($p<0.05$) and OCM enzymes. Nicotinamide increased ECFC angiogenesis ($p<0.05$). ECFC migration was not impacted by methionine or nicotinamide supplementation (p NS). Methionine dietary supplementation in a HMMP model improved distal alveolar formation.
Conclusion and Clinical Implications: Lung maturation is dependent on shifting metabolic needs during development. Replenishment of disrupted key OCM metabolites in HMMP promotes vessel and alveolar formation. Future studies are necessary to explore the role of precision nutritive supplementation in alveolar development of premature infants.