Lung Biology Research & Trainee Day
June 7, 2021

Category: Staff/Tech/Other
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Title: Neonatal Hyperoxia Suppresses Fatty Acid Synthesis and Proliferation in Atrial Cardiomyocytes by Disrupting Mitochondrial Function and Activating AMPK
Abstract: Preterm birth increases the risk of diastolic heart failure later in life through poorly understood mechanisms. Exposing mice to hyperoxia from birth to postnatal day 4 inhibits the proliferation and survival of atrial cardiomyocytes by suppressing fatty acid synthesis genes, resulting in adult diastolic heart failure like that of former preterm infants. Pathway analysis and western blotting to compare the atria of hyperoxia-exposed mice to age-matched controls showed hyperoxia permanently activated AMP kinase. AMP kinase is activated by high ADP levels to promote mitochondrial biogenesis and other ATP generating processes while inhibiting ATP consuming ones like fatty acid synthesis. Hyperoxia reduced the ATP linked respiration of HL-1 atrial cardiomyocytes and may thus activate AMP kinase by disrupting mitochondrial function and increasing the ADP to ATP ratio. The AMP kinase dependent repression of fatty acid synthesis genes may become maladaptive since it inhibits atrial cardiomyocyte proliferation and survival. Since fatty acid synthesis was previously shown to suppress AMP kinase in the hearts of adult mice, disrupting fatty acid synthesis may also create a positive feedback loop that maintains AMP kinase activity and the repression of fatty acid synthesis genes after oxygen exposure. While fatty acid synthase over expression partially restores cardiomyocyte proliferation and survival in hyperoxia, it does not reduce mitochondrial reactive oxygen species in HL-1 cells and DNA damage response genes were unaffected by hyperoxia in our prior study. The effects of hyperoxia on atrial cardiomyocyte proliferation may thus result from metabolic dysfunction, energetic failure and the reduced production of phospholipids needed for new membrane synthesis and not the reactive oxygen species induced DNA damage implicated in the growth arrest of pulmonary epithelial cells. These data and future studies will add to our understanding of how hyperoxia inhibits atrial cardiomyocyte proliferation and may one day lead to novel treatments to prevent diastolic heart failure in former preterm infants.