Asthma and metabolic syndrome in search of the incipient interfaces

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Body: The emerging interface of asthma and metabolic syndrome merits attention. Markers of metabolic syndrome such as insulin resistance (IR) have been associated with reduced lung function and asthma. Direct impact of hyperinsulinemia and IR on lung function, and inflammation is not fully understood. Studying the effect of hyperinsulinemia on lung cellular physiology is a useful step towards understanding the link between metabolic syndrome and asthma. Methods: Endogenous diet induced and exogenous insulin intranasal models of hyperinsulinemia were developed in mice. Consequences of hyperinsulinemia on lung morphology, airway hyperresponsiveness, and cell stress parameters were measured and confirmed in cultured human lung cells. Results: Hyperinsulinemia or intranasal exposure to insulin, led to airway hyperresponsiveness, bronchial apoptosis, peribronchial collagen deposit and inflammation. Increased levels of Wnt/β-catenin signaling were found to be involved in insulin as well as in IL-13-induced changes in lung epithelium, suggesting a common point of integration between allergic and metabolic mechanisms of asthma pathogenesis. Mitochondrial dysfunction, that has previously been causally implicated in asthma pathogenesis, was induced by insulin in lung epithelial cells. We also observed that insulin potentiates the intracellular calcium response to histamine and acetylcholine in primary human airways smooth muscle cells, and promotes proliferation. Conclusion: Our work provides initial understanding of how systemic and cellular metabolic changes are critical to asthma pathogenesis and this is a multifaceted process driven not only by inflammatory mechanisms, but also processes independent of inflammatory cells.