A073 Therapeutic Knockdown of RIPK1 Pathway Halts the Progression of Diet-induced Obesity and Improves Insulin Resistance

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Introduction: Obesity is a major public health issue in Australia – 67% of adults are overweight or obese. It accelerates other life-threatening conditions such as diabetes, heart disease and cancer. Despite decades of public health and lifestyle interventions, obesity remains a growing problem. Key characteristics of obesity are altered metabolism and chronic inflammation – a response mediated by the immune system. Recently, we identified a novel inflammatory gene, RIPK1, that regulates fat tissue inflammation and obesity in both humans and mice. RIPK1 is a key regulator of inflammation, and along with its downstream, target, MLKL, drives inflammatory cell death (necroptosis). Here, we investigate whether knocking down RIPK1 or MLKL in established obesity halts disease progression. **Methods:** After 12 weeks of high-fat diet to induce obesity, C57Bl/6 male mice were administered weekly injections of 50mg/kg control or RIPK1 or MLKL antisense oligonucleotides (ASOs) for another 12-18 weeks. Metrics of obesity and insulin sensitivity were measured. *In vitro*, bone-marrow derived macrophages (BMDMs) and 3T3L1 adipocytes were utilised to characterise inflammation and cell death pathways. **Results:** After 8-weeks of either RIPK1 or MLKL ASO therapy, mice had marked weight reduction compared to control ($p<0.01$). Interestingly, both ASO-treated mice also had reduced fat mass, however, only RIPK1 ASO-treated mice had increased lean mass, suggesting differential gene regulation in different tissue depots. Importantly, both ASO therapies improved insulin resistance (insulin tolerance test; $p<0.0001$). Preliminary studies indicate that the saturated fatty acid, palmitic acid, promotes inflammatory gene expression (e.g. NF-kB) in BMDMs, and role of RIPK1 and/or MLKL in these pathways are currently being investigated. **Conclusion:** Intervention with either RIPK1 or MLKL ASO therapy markedly reduced body weight and improved insulin sensitivity in obese mice, paving the path to develop novel therapeutics to treat obesity and associated co-morbidities.