Dual, but opposing, roles for the double stranded RNA-dependent protein kinase in metabolic homeostasis

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Chronic inflammation is a hallmark of obesity and contributes to the development of numerous diseases, including insulin resistance, Type 2 diabetes, atherosclerosis and cancer. Metabolic and immune signalling pathways are intimately linked and understanding how nutrient excess promotes cellular inflammation is of considerable importance in understanding the pathogenesis of many chronic metabolic diseases. A recent study in *Cell* identified double stranded RNA-dependent protein kinase (PKR) as a core component of a "metabolic inflammasome" linking stress signalling to metabolic disease (Nakamura *et al.*, 2010). Using murine embryonic fibroblasts and macrophages from PKR-deficient mice on an inbred C57BL/6 background our results confirm that PKR is required for the induction of pro-inflammatory responses triggered by nutrient excess. However, and remarkably, PKR-deficient cells had 2 to 3-fold increases in the levels of numerous intracellular lipid types, including diacylglycerol and ceramide, lipid species linked to inflammation and insulin resistance, following treatment with fatty acids.

To examine the *in vivo* consequences of PKR deletion, we placed PKR-deficient and wild type (WT) mice on a high fat diet. PKR knockout (KO) mice had increased total body fat mass, higher leptin levels and increased lipid accumulation in skeletal muscle and liver. Furthermore, high fat fed PKR KO mice were hyperinsulinaemic, glucose intolerant and insulin resistant, compared to WT mice. Gene expression analysis of PKR-deficient and wild type macrophages, skeletal muscle and liver identified marked increases in the levels of the fatty acid transporter (FAT) CD36 and several fatty acid binding proteins (FABP). While we observed significantly greater recruitment of macrophages into the white adipose tissue of PKR KO mice, this was associated with similar levels of the pro-inflammatory genes Tnf and Il6 but higher levels of the anti-inflammatory gene Il10. We conclude that while PKR deletion may confer protection from nutrient excess-driven inflammation, it also promotes lipid accumulation, most likely *via* an increase in the expression of FAT/CD36 and specific FABP. Importantly, *in vivo* excess lipid accumulation appears to be the predominating effect of PKR deletion, leading to exacerbated glucose intolerance and insulin resistance.

Nakamura, T., Furuhashi, M., Li, P., Cao, H., Tuncman, G., Sonenberg, N., Gorgun, C.Z., and Hotamisligil, G.S. (2010). Double-stranded RNA-dependent protein kinase links pathogen sensing with stress and metabolic homeostasis. *Cell* **140:** 338-348.