extended directly to insulin production, as PPARs are involved in controlling glucose-stimulated insulin release, a process that is modulated by fatty acids and may involve UCPs: increased PPAR α activity is associated with down regulation of insulin production during fasting, while PPAR γ islet over-expression can also suppress insulin release [87,88]. Interestingly, saturated fat is far more insulinotropic than unsaturated fat [89], which might suggest that PPARs are more effective at reducing insulin production in response to unsaturated fats. This is in keeping with the susceptibility of unsaturated fats to oxidative damage. In contrast, saturated fat is less effective than unsaturated fat at stimulating the incretin, glucagon-like peptide-1 (GLP-1), from the gut [90]. The biological activities of GLP-1 include stimulation of glucose-dependent insulin secretion and insulin biosynthesis, inhibition of glucagon secretion and gastric emptying, and inhibition of food intake. This may suggest an evolved bias towards unsaturated dietary fat intake from the gut, but an internal system to react to nascent saturated fat produced from glucose (or fructose): i.e. we are far more able to tolerate ingestion of unsaturated fat, compared to saturated fat – but the system is designed to recognise and deal with *de novo* saturated fat generated from carbohydrate. Human data suggest that rosiglitazone can activate desaturases, so reducing levels of saturated fat in the system [91], which would further indicate that reduction of excess saturated fat is a biological imperative.

We propose that at it simplest, muscle insulin sensitivity may result in increased thermogenesis through futile cycling and thus, would be associated with an 'unthrifty' genotype. Key in either the thrifty, or unthrifty genotypes (as indicated by the PPAR ala/pro mutation), would be the role of the PPARs: increased adipose PPAR γ activity would result in better fat storage (adipose insulin sensitivity), whereas an improved ability to burn fat in muscle (PPAR α/δ) might be associated with better muscle insulin sensitivity and less efficient feed efficiency (but a better tolerance to cold). Hence, by modulating tissue-specific fatty acid metabolism and storage, PPARs are able to maximise FOXO activity and thus optimise resistance to oxidative stress by reducing the need for insulin. One obvious exception to this is the mutually suppressive effects of PPAR γ and FOXO in adipose tissue [22]; increased PPAR γ activity would act to store fatty acids, while still maintaining an anti-inflammatory effect (reduce oxidative stress) by suppression of NFkB. Certainly, basal NFκB activity increases during adipocyte differentiation [92]. This would suggest a possible adipose-inflammatory paradigm, whereby increased NFkB activity could conceivably suppress both FOXO and PPAR γ, resulting in 'inflammatory' lipolysis. During starvation, FOXO would be expected to suppress both NFkB and PPAR γ and result in 'starvation' lipolysis. However, in obesity, this natural suppression of inflammation is lost due to the high adipose-related inflammatory signal, which suppresses both PPAR γ and FOXO: this could lead to the metabolic syndrome.

The metabolic syndrome; PPARs keep the acute phase response in check

It has been suggested that in addition to the 'thrifty' genotype, another adaptation may also be needed to develop the metabolic syndrome, and that is a 'high cytokine responder' genotype, with an improved ability to resist injury (i.e. a stronger inflammatory response) [93]. It has been known for many years that injury can result in profound insulin resistance and is associated with the APR, which is a systemic inflammatory injury response to protect the host (being both haemostatic and anti-microbial) characterised by the hepatic production of acute phase proteins (e.g. c-reactive peptide, CRP) and glucose, increased cytokine production and turnover of protein, glycerol free and fatty acids, and has been called the 'hypermetabolic response' [94,95]. This 'hypermetabolic' (catabolic) state can be mimicked by injection of the stress hormones cortisol, glucagon and ephedrine in human volunteers [96]. However, this 'hypermetabolic' state is usually associated with increased thermogenesis (pyrexia) and is anorexic, and probably involves inflammatory-mediated modulation of appetite systems, such as the melanocortin pathway [97]; this is clearly not the case in the metabolic syndrome. Interestingly, leptin is known to mediate the effects of lipopolysaccharide (LPS) induced anorexia and fever [98], but central leptin (and insulin) resistance is a common finding in obesity and could be related to leptin itself via effects on phosphatidylinositol 3-kinase (PI3K) and phosphodiesterase 3B (PDE3B) activities and reduction in cyclic AMP (cAMP) [99] and/or the pro-inflammatory effects of a high fat diet [100]. This might also represent a another thrifty adaptation to ensure a high state of 'inflammatory readiness', but conservation of energy stores.

It was suggested by Pickup and colleagues in 1997 that 'syndrome X' (now called the metabolic syndrome) was in fact a disease caused by the chronic activation of the innate immune system and contributed to the hypertriglyceridaemia, low HDL cholesterol, hypertension, glucose intolerance, insulin resistance and accelerated atherosclerosis of NIDDM [101]. This hypothesis for the development of T2D (and the metabolic syndrome) was further supported by data from the Atherscleroses Risk in Communities study (ARIC) [102]. Importantly, the APR and inflammation can result in increased insulin output, which can in turn suppress the APR – so providing a possible negative feedback mechanism [103]. Interestingly, IL-6, a potent inflammatory cytokine-inducer of the APR produced by adipose tissue, is significantly associated