Mammals have at least five UCP homologues: UCPs are also found in plants and fungi, and belong to an ancient superfamily of mitochondrial metabolite carriers [65]. It was originally thought that one of their prime functions was to uncouple the mitochondrial deltapsi gradient (so reducing ROS production), and certainly for UCP-1 (which was the first to be discovered) this is true – as it plays a critical role in thermogenesis [18]. However, a precise role for the other UCPs is still being defined, as it is now thought that their primary function maybe as anionic transporters – although a secondary protonophore function may still be very important. For instance, UCP-3 is thought to transport fatty acids out of the mitochondrial matrix (in exchange for a proton equivalent) and is predominantly found in muscle and adipose tissue and is induced by fasting (when lipid levels rise), and thus may play a role in preventing lipotoxicity; this would certainly be supported by the observation that it is decreased in the muscles of T2D patients, and its levels can be restored by PPAR γ activation [66].

Hence, fatty acids may potentially reduce ROS production by directly stimulating UCPs, and the potency of unsaturated fats may reflect their susceptibility to oxidation. Importantly, these same fatty acids would also activate PPARs and increase the expression of UCP (s). Thus, we hypothesize that PPARs may have a vital role to play in reducing hypoxia-related lipid damage through their induction of UCPs and, in so doing, improve functional longevity by suppressing ROS production (and reducing the potential for lipotoxicity); this would be enhanced by their well-described ability to increase the activity of other antioxidant enzymes, such as superoxide dismutaste (SOD) or catalase [67-69].

Shifting the phenotype; reducing the need for insulin

The ability of PPAR γ to improve glucose dispersal is well described, and is now being described for PPAR δ [70] and PPAR α (although there have been some conflicting results) [71,72]. One of the main ways they do this is to channel fatty acids to where they are needed; this prevents the build up of excessive intramyocellular lipid, which is thought to be one of the major causes of insulin resistance in obesity [73]. In addition, it is also becoming clear that an increase in ROS can also cause insulin resistance [74]. This would support the observation that increasing free fatty acid (FFA) concentrations can induce NFkB activity (and ROS) [75], and in the liver, this may partly explain hepatic insulin resistance [76]. However, it has been long known that ROS is involved in insulin (and that of other growth factors) signalling, possibly through NADPH oxidase (Nox) production of H_2O_2 (reviewed by Goldstein, Mahadev 2005) [77]. This would imply that not only is control of intracellular redox vital, but that excessive insulin signalling, (apart from suppressing FOXO), may also contribute to increased cellular oxidative stress.

It has been proposed for some time that 'thrifty' genes would have given our ancestors a survival edge in harder times by enabling rapid storage of fat, but in times of plenty, may have resulted in increased levels of diabetes [78]; key to this insulin resistance may be the role of lipids. In contrast, in times of plenty selective pressure may have resulted in 'unthrifty' genes, which would be associated with insulin sensitivity. For instance, the PPAR γ ala allele, which is diabetes protective and probably arose between 32,000 to 58,000 years ago [79]. Thus, both insulin resistance and sensitivity can be potential survival traits – so what is the role of the PPARs in determining this balance?

Keeping FOXO active: PPARs modulate insulin 'drive'

The facility of a rapid food-induced insulin response and the ability to store food efficiently after starvation, while retaining a degree of insulin resistance post-prandially, may be example of a "thrifty adaptation" to spare glucose for the CNS and provide energy for muscle during times of hardship – both for movement and thermogenesis [80]. Certainly, muscle insulin resistance combined with adipose insulin sensitivity may comprise a 'fat catch-up' paradigm by ensuring fatty acid channelling to adipose tissue and decreased muscle thermogenesis [81]. In addition, the recent discovery of a hormone associated with longevity called 'klotho' that can induce insulin resistance and upregulate FOXO [82] is therefore significant, as is supports the observation that the right degree of insulin resistance may aid long-term survival. For instance, if normal human subjects are starved for 48 hours, they become insulin resistance, which is thought to be a natural response to maintain glucose levels and is related to decreased glucose dispersal by down-regulation of muscle PDC [83]. This insulin resistance is probably related to increased intramyocellular fat, as during starvation, FFA levels rise [84]. Similarly, 60 hour starvation of patients with T2D or obesity can result in increased insulin resistance, but only in those who were relatively insulin sensitive to begin with; in some highly insulin resistant patients, starvation improved sensitivity [85]. Indeed, it has been observed for many years that crash dieting can actually induce severe insulin resistance and T2D is some obese patients [86].

FOXO, which is one of the most important transcription factors in improving functional longevity during fasting, is negatively regulated by insulin [9]. We suggest that a critical function of the PPARs is to reduce insulin "drive" (via appropriate tissue insulin sensitisation) and thereby increase functional longevity by preventing the insulin-mediated downregulation of FOXO. This process is also