retinoid X receptor (RXR), detecting a broad range of molecules (including inflammatory lipid mediators) and modulate the activity of genes involved in energy regulation and inflammatory processes, including wound healing, as well as reproduction [3-6]. They are also important in embryonic development, but only PPAR γ knockout is lethal – although placental rescue results in a phenotype with no body fat, which confirms its pivotal role in adipogenesis [2]. They therefore appear to be involved in many (apparently disparate) metabolic processes, which therefore raises a question, why did they evolve and what is their overall function?

We believe that PPARs may be an evolutionary solution to something we call the 'hypoxia-lipid' conundrum, where the ability to store and burn fat is essential for survival, but is a 'double-edged sword', as fats are potentially highly toxic. For instance, hypoxia results in the increased production of mitochondrial ROS, which can result in lipid peroxidation that is not only potentially damaging, but also a strong inflammatory signal, activating nuclear factor kappa-beta (NFkB) [7]. Thus, a group of transcription factors that integrate resistance to oxidative stress (inflammation, thus modulation of NFkB), with the ability to detect and orchestrate the storage and metabolism of lipids, while sparing glucose (which can be burnt anaerobically), was inevitable. Over time, this function engendered increasing functional longevity, and ultimately, as they evolved (they have been one of the fastest evolving group of nuclear receptors) [8], this may have enabled the evolution of longer lifespans for some species.

Key in this, we believe, may be their ability to modulate uncoupling proteins activity (UCPs), so reducing mitochondrial reactive oxygen species production (ROS), as well as their ability to induce insulin sensitisation – so optimising forkhead box class O factor (FOXO) activity by reducing insulin basal levels and therefore insulin 'drive': FOXO are a small subfamily of transcription factors key in stress resistance and calorie restriction-induced longevity, whose function is suppressed by high insulin/IGF-1 activity (reviewed by Morris BJ, 2005) [9]. Increased expression/activity of FOXO results in increased activity of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), which also plays a key role in longevity and the calorie restriction phenotype, in particular, it increases the expression of PPAR α [10]: 19% of the genes that are regulated during calorie restriction are modulated by PPAR α-including suppression of acute phase response (APR) genes [11]. These nuclear factors are also upregulated by exercise [12], which is known to improve median survival.

Overall, the ability of all the PPARs to reduce lipotoxicity and suppress inflammation would strongly suggest that they would all tend to reduce the need for basal insulin by encouraging insulin sensitivity. This indicates that as an ancient group of nuclear factors, which are essential for fat storage and metabolism, they are also key in suppressing oxidative stress: the ability to store fat and resist oxidative stress are both generally associated with improved survival and increased species lifespan [13,14]. We suggest that the phenotype associated with calorie restriction is thus the opposite of that seen with the metabolic syndrome and the balance between the two may be determined, to a large degree, by PPAR activity.

The transcriptional triad of survival: PPAR-FOXO-NFkB

Although each PPAR isoform is expressed in almost every tissue, they are expressed in a tissue- and time-specific manner in response to food, as well as to exercise and cold. PPAR α is very active during fasting and is predominantly found in the liver, while PPAR γ is active during feeding and is predominantly found in adipose tissue, where its main role appears to enable the deposition of fat: PPAR δ is ubiquitous, with its highest expression in the gut, but is now thought to be extremely important in exercise-induced switch to oxidative (type 1) myofibres, as well as in thermogenesis [13,15,16]. Overall, PPAR γ is thought to be essential for adipogenesis (and thus storage), whereas PPARs α/δ are more involved in fatty acid catabolism. Importantly, their expression and activity is intimately related to other transcription factors/co-factors, in particular, FOXO, PGC-1 and NFkB: figure 1 is simplified explanation of how these transcription factors might interact – the 'transcriptional triad'.

The calorie-restriction and longevity connection

FOXO is an important group of transcription factors that integrate energy metabolism with resistance to oxidative stress, as well as regulating cell cycle and DNA repair; for example they increase SOD (superoxide dismutase) and also modulate hunger [17]. PGC-1 was first discovered as a cold-inducible co-activator that regulates adaptive thermogenesis, and along with PPARs, induces mitochondrial uncoupling via the UCP-1, so generating warmth [18]. PGC-1 is also essential in controlling hepatic gluconeogenesis, which occurs in response to famine; it is thought to be a "master switch" that controls the change from carbohydrate- to fat-based metabolism, which includes a change from type II to type I muscle fibre use and increased mitochondrial biogenesis [19]. To be activated, PGC-1 requires interaction with FOXO1 [20]. Once activated, PGC-1 cooperates with PPAR α to activate genes encoding mitochondrial enzymes involved in fatty acid oxidation [21]: PPAR α is also of major importance in calorie restriction [11]. FOXO1 can inhibit PPAR γ activity in