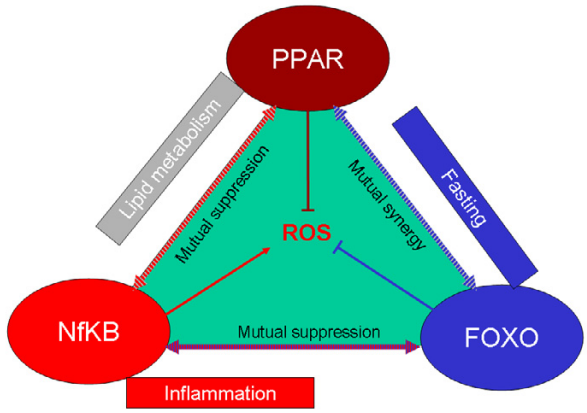

Figure 1
Transcriptional triad of survival. PPARs promote mitochondrial proton gradient uncoupling, reduce ROS and increase heat generation, while ensuring safe lipid storage and burning (reducing lipotoxicity), safe carbohydrate storage and reducing need for insulin. They also suppress inflammation. NFkB promotes resistance to infections and aids healing, but suppresses incentive salience and increases thermogenesis – it can be said to have general anorexic actions. Also promotes ROS production, both as a signal and as a defence. Response amplified by increasing fat stores. Promotes inflammation. FOXO promotes resistance to oxidative stress, enhances DNA repair, suppresses proliferation, and encourages incentive salience and survival in low food situations – it is thought to be generally orexigenic. Can oppose inflammation.

adipose cells and vice versa [22], but it can enhance PPAR α activation of lipoprotein lipase in muscle [23]. This would support the flow of fatty acids from adipose tissue during fasting to energy requiring tissues (and thus shrinkage of the adipose store), but the flow of fats into adipose tissue during feeding.

PPAR activity decreases with age, a process that can be slowed by calorie restriction [24], while aging is associated with increased constitutive activity of NFkB [25]. Indeed, it has been suggested that PPARs may play a role in modulating the 'molecular inflammatory process of ageing' [26], and may be important in suppressing the ageing-associated increase in NFκB activity [27]. Certainly, calorie restriction has been shown to result in a generalised increase in PPAR activity, which is associated with increased adiponectin [28]; adiponectin can also suppress NFkB activity [29]. This would be supported by the well described observation that pharmaceutical activation of PPARs α & γ is broadly beneficial, reversing many aspects of the metabolic syndrome; the same is now thought to be true for PPAR δ [30]. At the transcriptional level, NFκB and FOXO do appear to have mutually exclusive activity, as IkB (inhibitor of NFkB) kinase (IKK), can result in the activation of NFkB by inhibiting IkB, but the direct inhibition of FOXO, which maybe be important in cancer [31]. In addition, NFkB and PPARs can also transrepress each others activity [32-35]. Hence, there is both anecdotal and transcriptional evidence that PPAR activity is associated with a longer-lived phenotype.

Why adipose tissue is inflammatory, and why PPARs are anti-inflammatory

One of the more interesting aspects of the PPARs is that they seem to integrate inflammation and energy metabolism. It is now becoming apparent that adipose tissue is metabolically very active and increasing adipose mass is associated with increasing inflammatory tone. It is now thought that this may be an evolutionarily technique to enhance survival in relation to famine and immunity/inflammation, which are both highly energy dependent: one key signal for this may be leptin [36]. This would explain why excessive obesity is generally associated with sub-clinical inflammation, and why there is generally an evolutionarily-driven imbalance between orexigenic (stronger) and anorexic (weaker) signals, leading to high feed-efficiency and a propensity to store fat [37-39]. However, it would also be an evolutionary trade-off, as a food-rich environment, with little need for physical activity, might continually increase fat mass and lead to increasing oxidative stress (and thus, production of ROS) and a shortened lifespan (figure 2) – this could be an example of antagonistic pleiotropy. Certainly, obese adipose tissue can attract macrophages, resulting in a heightened inflammatory response – which can be reversed by weight loss [40]. Thus the finding that PPAR γ activation can induce apoptosis of macrophages found in adipose tissue [41], might suggest that not only does PPAR γ ensure fat storage, but that it might also suppress the adipose-related inflammation signal.

This therefore supports the 'transcriptional triad of survival' paradigm (figure 1). FOXO, which is mainly active during fasting/famine, maintains resistance to oxidative stress and improves long-term survival: NFkB, which is highly important in resistance to injury/infection, engenders oxidative stress as a survival strategy. However, PPARs, are essential to ensure that energy-related oxidative stress is kept to a minimum, either during storage, or during metabolism (such as exercise, fasting or infection).

The hypoxia-lipid conundrum

The main problem with lipids is that they require oxygen to be burnt as fuel. However, the only way to do this is via mitochondria, which are also one of the prime cellular sources of ROS; ROS production is increased when levels of the ultimate electron acceptor, oxygen, is decreased. Thus, there is the potential for lipid peroxidation and