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Plant-based Diets and Low-Insulin Lifestyles May Suppress Oxidative Stress by Disinhibiting FOXO3a

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ABSTRACT

FOXO transcription factors, notably FOXO3a, promote transcription of a wide range of mitochondrial antioxidant enzymes as well as catalase – an effect thought to contribute to the beneficial impact of caloric restriction on longevity in rodents. Activated Akt suppresses FOXO3a activity by promoting its exclusion from the nucleus. Hence, in the many tissues responsive to IGF-I and/or insulin – hormones which stimulate Akt activity – high circulating levels of free IGF-I or of insulin may have a pro-oxidant impact. Moreover, high insulin levels boost IGF-I bioactivity by inhibiting hepatic production of IGFBP-1, an IGF-I antagonist. Hence, the combination of a moderate-protein plant-based diet – which down-regulates hepatic IGF-I production via essential amino acid restriction – and a lifestyle that minimizes diurnal insulin levels, would appear likely to offer worthwhile antioxidant protection, possibly contributing to the markedly reduced risk for "Western" cancers and cardiovascular disease characteristic of quasi-vegan societies. The moderate methionine restriction associated with plant-based diets might also aid this effect by diminishing superoxide production via complex I of the mitochondrial respiratory chain, as observed in methionine-restricted rodents.

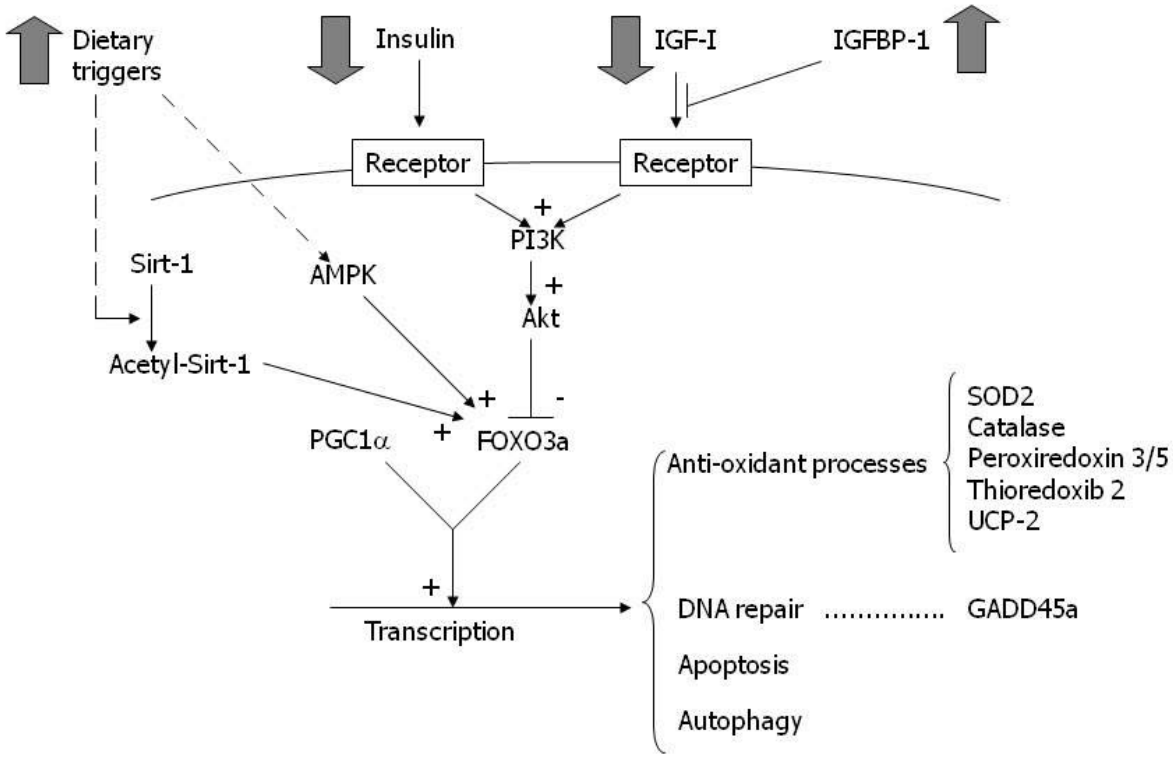
Growth Factor Suppression of FOXO3a Activity Promotes Oxidative Stress

The FOXO transcription factors are homologs of transcription factors found in lower organisms such as worms and flies whose activity is inhibited by signaling pathways homologous to the insulin/IGF-I pathway in vertebrates. Calorie restriction activates these factors in worms and flies, and fails to increase lifespan if these factors are genetically ablated.[1-3] Hence, the FOXO transcription factors are suspected to contribute to lifespan increase in calorically restricted vertebrates. Seemingly consistent with this view are studies demonstrating that certain alleles of the polymorphic FOXO3a gene are significantly enriched in aged humans, presumably because they confer a survival advantage.[4-7]

Control of oxidative stress is clearly necessary, though not likely sufficient, for lifespan extension. Recent research demonstrates that, in human vascular endothelial cells, FOXO3a, acting in conjunction with the transcriptional coactivator PGC-1alpha, boosts transcription and expression of genes coding for a range of antioxidant enzymes, including the mitochondrial (manganese-dependent) superoxide dismutase, catalase, peroxiredoxin 3, peroxiredoxin 5, thioredoxin 2, thioredoxin reductase 2, as well as for UCP-2 and PGC-1alpha.[8-13] Working in collaboration, these proteins can be expected to suppress mitochondrial release of hydrogen peroxide and peroxynitrite, and to lessen the functional impact of oxidative stress on mitochondrial structure and function; moreover, catalase could also aid control of oxidative stress of cytoplasmic origin. Other key targets of FOXO transcriptional activity include genes that promote efficient DNA repair (GADD45a), apoptosis, autophagy, cell cycle arrest, immune regulation, and muscle atrophy.[14, 15]

Growth factor signaling inhibits the transcriptional activity of the FOXO transcription factors.[14, 16] (See Figure 1.) This comes about because the kinase Akt – activated via PI3K – phosphorylates these factors, thereby promoting their exclusion from the nucleus. (This effect is seen with FOXO1, FOXO3a, and FOXO4, whereas Akt-mediated phosphorylation of FOXO6, expressed primarily in the brain, inhibits

Figure 1



its transcriptional activity without regulating its subcellular location.[17]) In the many tissues that are responsive to IGF-I and/or insulin, elevated blood levels of insulin and/or free IGF-I can therefore be expected to impede antioxidant defenses by inhibiting the transcriptional activity of FOXO3a and other FOXO factors. This effect presumably would be somewhat less functionally meaningful in tissues in which autocrine growth factor activity makes an important contribution to Akt activation.

Antioxidant Potential of Plant-based Diets and Low-Insulin Lifestyles

Vegan diets of moderate protein content are associated with reduced circulating levels of IGF-I, likely because a modest degree of essential amino acid restriction suppresses hepatic IGF-I synthesis and secretion.[18-26] Moreover, certain lifestyle strategies are characterized by relatively low diurnal insulin levels, and thus would be likely to lessen Akt activation both in insulin-sensitive tissues, and – owing to an expected increase in hepatic production of the IGF-I antagonist IGFBP-1[27, 28] – in IGF-I responsive tissues as well. Feasible measures for lessening diurnal insulin secretion include exercise training, leanness, diets with low saturate-unsaturate ratios, reliance on lower-glycemic-index carbohydrates, avoidance of insulinotropic milk protein, calorie restriction, meal-skipping, and carbohydrate-concentrated diets.[29-36] Addition of almonds, soluble fiber, and vinegar to the diet may also diminish diurnal insulin secretion.[37-39] Vegan and Mediterranean diets appear to be inherently useful in this regard, owing to their low saturate-unsaturate ratios and tendencies to promote relative leanness.[29]

It is therefore reasonable to propose that vegan diets of moderate protein content, as well as low-insulin lifestyles, can boost antioxidant protection in many tissues by increasing FOXO activity and consequently the expression of a number of key antioxidant enzymes and proteins. While it has generally been assumed that plant-based diets rich in

antioxidant phytochemicals would promote antioxidant defense, both by the direct scavenging activity of these phytochemicals and their propensity to trigger phase 2 induction,[40-45] the mechanism proposed here is independent of, and presumably complementary to, the protective impact of phytochemical induction.

Vegan diets which are relatively restricted in methionine may also have the potential to decrease mitochondrial oxidant production by an additional mechanism. Significant dietary methionine restriction can increase maximal lifespan in rodents, even with ad libitum calorie consumption; the magnitude of this effect is about half that of optimal calorie restriction.[46-48] Studies by Barja and colleagues have shown that methionine restriction somehow suppresses superoxide production by complex I of the mitochondrial respiratory chain.[49-51] Theoretically, since vegan diets of modest protein content tend to be rather low in methionine, this phenomenon might contribute to antioxidant protection in vegans.[49, 52] It should be noted however, that the diets used to implement methionine restriction in rodent studies have been synthetic diets devoid of cysteine; hence, these diets are sulfur deficient, not just methionine deficient. Whether concurrent ingestion of cysteine might blunt the impact of methioinine-restricted diets on longevity and mitochondrial oxidant production needs to be assessed. (To the contrary, it might be argued that cysteine ingestion would amplify the antioxidant merits of such diets by boosting glutathione production.)

In individuals with metabolic syndrome, adoption of diets low in saturated fat (such as vegan or Mediterranean diets typically are) may lessen activation of NADPH oxidase in various tissues by decreasing the stimulation of protein kinase C via newly synthesized diacylglycerol.[29, 53] And the lower circulating concentration of LDL particles associated with such diets could be expected to decrease NADPH oxidase-mediated endothelial oxidative stress.[54] Hence, plant-based diets, especially those that are phytochemical rich, may work in several complementary ways to minimize oxidative stress, globally or in specific tissues.

A recent clinical study shows that serum markers of oxidative stress improve in volunteers consuming a low-glycemic-index vegan diet for 21 days.[55] While this finding is consistent with the hypothesis presented here, it is conceivable that increased phytochemical intakes are largely responsible for this finding. Hence, this hypothesis might best be tested by measuring activities of mitochondrial antioxidant enzymes in accessible tissues, such as peripheral blood leukocytes, during such a diet.

These considerations suggest that some of the beneficial health impacts of vegan diets and low insulin lifestyles may be mediated by improved control of oxidant stress. Conceivably, this phenomenon could contribute to the considerably reduced risks for "Western" cancers and cardiovascular disease typically observed in Third World cultures whose members consume quasi-vegan diets and tend to be lean. Conversely, the elevated risks for these disorders in obese individuals may be attributable in part to increased oxidative stress. Vegan diets and low-insulin lifestyles may have utility as adjuvant strategies when nutraceutical or pharmaceutical antioxidants are employed to prevent or treat disorders driven to some degree by oxidative stress.

The transcriptional activity of FOXO factors, while inhibited bv Akt, is boosted by phosphorylations mediated by AMPK, and by de-acetylation via Sirt1.[56-60] Hence, measures which activate AMPK and/or Sirt1 may be useful for amplifying the impact of vegan diets or low insulin lifestyles on antioxidant defenses. Metformin presumably would be a two-edged sword in this regard, as it is thought to somehow activate AMPK by *increasing* complex I superoxide production.[61, 62] But other strategies for activating AMPK – such as vinegar, short-chain fatty acids, lipoic acid[63-70] – might be more beneficial in this regard, and effective Sirt1 activators (perhaps resveratrol or quercetin, for example[71-73]) might likewise promote FOXO-mediated antioxidant defenses.

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