

A Vegan Diet of Modest Protein Content, by Down-Regulating Akt-mTORC1 Activity in Lymphocytes, May Aid Induction of T Regulatory Cells

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Abstract

There is considerable evidence that many autoimmune disorders were comparatively rare in black sub-Saharan Africans and in East Asians during the middle years of the last century, when these people tended to be quite lean and to consume quasi-vegan diets of modest protein content. It is proposed that such a lifestyle, via its impact on the internal hormonal/nutrient milieu, tends to down-regulate PI3K-Akt-mTORC1 signaling in lymphocytes, resulting in increased induction of T regulatory lymphocytes that aid suppression of autoimmunity. Induction of Foxp3+ regulatory lymphocytes from naïve CD4+ cells requires transitory engagement of T cell receptors, but is blocked if PI3K-Akt-mTORC1 signaling is strong and sustained at this time. Prolonged Akt-mTORC1 signaling can inhibit Foxp3 transcription by modulating DNA and histone methylation in the Foxp3 promoter, and Akt per se suppresses this transcription by promoting nuclear exclusion of the foxo transcription factors Foxo1/Foxo3a. Plant-based diets tend to decrease circulating levels of free IGF-I, and promote leanness characterized by low leptin levels. Both IGF-I and leptin can stimulate PI3K-Akt-mTORC1 signaling in lymphocytes, and increased leptin has been linked to a decrease in Treg levels. Additionally, Tregs tend to promote induction of additional Tregs (“infectious tolerance”) by inducing in dendritic cells a number of enzymes which catabolize essential amino acids; the resulting microenvironmental depletion of essential amino acids inhibits mTORC1 activity in neighboring lymphocytes, encouraging their conversion to Tregs. This mechanism likely will be up-regulated in people whose baseline tissue level of essential amino acids is relatively low, as it presumably is in those consuming a plant-based diet of modest protein content. Hence, relatively low plasma levels of essential amino acids, free IGF-I, and leptin in long-term vegans might be expected to boost Treg induction and aid control of autoimmunity. This hypothesis appears consistent with clinical studies and anecdotal reports suggesting that vegan diets may be beneficial in the management of certain autoimmune disorders, but direct clinical assessment of the impact of such diets on Treg activity is needed.

Sub-Saharan Black Africans and East Asians Enjoyed Low Risk for Autoimmunity

It is well documented, as summarized in reviews by Trowell, that autoimmune disorders were quite uncommon in sub-Saharan black Africans during much of the twentieth century, increasing however among blacks who adopted Westernized urban lifestyles.¹⁻³ When rheumatoid arthritis did occur in this population, it tended to be of limited severity. No such protection has been observed in African-Americans – suggesting that genetic factors were unlikely to have been primarily responsible for the low risk for autoimmunity enjoyed by sub-Saharan blacks. There is also considerable evidence that rheumatoid arthritis, multiple sclerosis, ulcerative colitis, and type 1 diabetes were considerably less common in East Asian societies than in the West during the middle decades of the last century – and that these disorders are now increasing in frequency as these societies adopt diets richer in animal products and calories, and obesity becomes more common.⁴⁻²¹ It is notable that the East Asian and African societies at low risk for

autoimmunity during the last century were relatively lean and consumed diets that were primarily plant-based.

Lean vegans tend to be characterized by good insulin sensitivity associated with low diurnal insulin levels, decreased serum levels of total and free IGF-I, and low leptin levels. The decrease in serum IGF-I associated with vegan diets may reflect the down-regulatory impact of a modest degree of essential amino acid restriction on hepatic IGF-I secretion;²²⁻²⁹ the low diurnal insulin levels associated with insulin sensitivity tends to decrease the free fraction of circulating IGF-I by up-regulating hepatic secretion of IGFBP-1.^{30, 31} A low ratio of saturated to unsaturated fat typical of plant-based diets may contribute to the characteristic insulin sensitivity of vegans, and the associated reduction in diurnal insulin secretion may protect them from weight gain.³²

Other evidence points to the possibility that the hormonal and nutritional milieu associated with leanness and a plant-based diet may help to prevent or ameliorate the course of autoimmune disorders. Swank reported that a diet extremely low in saturated fat – perforce a quasi-vegan diet – appeared to have a very favorable impact on the clinical course of multiple sclerosis.^{33, 34} The utility of vegan diets in moderating the symptoms of rheumatoid arthritis has been demonstrated by Scandinavian and American researchers.³⁵⁻³⁷ And calorie restriction has been found useful for postponing the onset or mitigating the intensity of various autoimmune disorders in rodents.³⁸⁻⁴² Anecdotal reports that plant-based diets – sometimes preceded by a fast of several days - may sometimes aid control of autoimmunity have also appeared.⁴³⁻⁴⁵

The rarity of autoimmune disorders in many African and East Asian societies during the last century suggests that autoreactive T lymphocytes in these peoples were either eliminated more efficiently by thymic negative selection, or that they were better controlled by superior induction or activity of regulatory T lymphocytes (Tregs). The former possibility, addressed in a previous review, remains speculative.⁴⁶ More recent evidence appears consistent with the hypothesis that the relatively low circulating levels of essential amino acids, free IGF-I, insulin and leptin characteristic of these peoples were conducive to the induction of Foxp3+ Treg cells.

Prolonged Activation of Akt and mTORC1 Oppose Foxp3 Transcription

The transcription factor Foxp3 is a key mediator of the suppressor activity of Treg cells, and is crucial to prevention of autoimmunity.⁴⁷ Antigen-specific engagement of T cell receptors, associated with a transitory increase in PI3K-Akt-mTORC1 signaling, appears to be a necessary condition for expression of Foxp3 in naïve CD4+ lymphocytes. However, potent sustained activation of the PI3K-Akt-mTOR signaling module in these lymphocytes, whether triggered by prolonged engagement of T cell receptors or other factors, tends to block induction of Foxp3.⁴⁸ It is proposed that a vegan diet may work in various ways to oppose such sustained activation.

Several recent studies demonstrate that transcription of the Foxp3 gene is contingent on nuclear localization of either Foxo1 or Foxo3a, members of the foxo family of transcription factors.⁴⁸⁻⁵¹ It is well known that Akt activity phosphorylates these latter two factors, leading to their exclusion from the nucleus.^{52, 53} Hence, persistent activation of PI3K-Akt signaling in CD4+ lymphocytes has been shown to antagonize transcription of Foxp3, and to promote autoimmunity.^{48, 54} This helps to explain why transitory TCR/CD28 signaling – which sets in motion the activation of various transcription factors

required for Foxp3 expression, but then remits to allow the nuclear translocation of foxo factors – is more effective for Treg induction than prolonged signaling.⁵⁴

mTORC1 signaling – another downstream consequence of Akt activation - likewise can suppress induction of Foxp3 in lymphocytes.⁵⁵⁻⁵⁷ This appears to promote methylations of DNA and histones in the promoter of the Foxp3 gene that oppose its transcription. Conversely, inhibition of mTORC1 – as with rapamycin analogs such as everolimus – tends to reverse such methylations, enabling transcription of Foxp3. This presumably contributes to the efficacy of rapalogs for promoting transplantation tolerance.

Once Foxp3 induction has been achieved in formerly naïve CD4+ lymphocytes, transforming them to a regulatory phenotype, increased expression of PHLPP phosphatases that target Ser473 in Akt1 works to block Akt activation, such that hormonal signals stimulating PI3K activity are less likely to suppress Foxp3 expression; in this way, the Foxp3-mediated regulatory phenotype is “locked in”.⁵⁸ This constitutive suppression of Akt activity in Tregs has been shown to be essential to Treg suppressor activity.^{58, 59}

Impact of Hormonal and Nutritional Milieu on Induction of Foxp3+ Tregs

This model predicts that hormonal activities which stimulate the PI3K-Akt-mTORC1 pathway in naïve CD4+ lymphocytes undergoing T cell receptor engagement, will lessen the probability that these lymphocytes will be directed to a Foxp3+ regulatory lineage. Hence, it is of particular interest that both leptin and IGF-I, via activation of IRS-1/2, can stimulate PI3K-Akt-mTORC1 in lymphocytes.⁶⁰⁻⁶⁴ With respect to leptin, it is notable that ob/ob and db/db mice, which either lack the ability to produce leptin or fail to express leptin receptors, are resistant to the induction of autoimmune disorders, and show enhanced expression of Foxp3.⁶⁵ Resistance to autoimmunity in other strains of mice can be provoked by infusing monoclonal antibodies or receptor chimeras that inhibit leptin activity; increased numbers of Foxp3+ regulatory lymphocytes are also seen in these animals.⁶⁶ A 48-hour fast in mice increases Foxp3 expression in CD4+ lymphocytes; leptin levels decline notably during fasting, and leptin administration to fasting mice partially antagonizes the fasting-evoked increase in Foxp3 expression.⁶⁷ Free IGF-I levels also decline notably in fasting mice, and it would be of interest to determine whether IGF-I administration would likewise antagonize the impact of fasting on Foxp3 induction. Not surprisingly, Treg levels tend to be decreased in obese humans.⁶⁸ In a recent clinical study comparing multiple sclerosis patients with healthy controls of matched BMI, levels of leptin as well as of Tregs were found to be lower in the patients, and leptin correlated inversely with Treg level.⁶⁹

Less attention has been devoted to the possible impact of IGF-I/insulin activity on Treg induction. A significant proportion of activated CD4+ lymphocytes express IGF-I and/or insulin receptors, which are functionally active.⁷⁰⁻⁷³ As noted, IGF-I can provoke PI3K-Akt activation in lymphocytes, and insulin is reported to promote IRS-1 phosphorylation in PHA-stimulated lymphocytes.⁷¹ (Recall that insulin may also contribute indirectly to Akt activation in CD4+ lymphocytes by suppressing hepatic secretion of IGFBP-1 and thereby increasing plasma levels of *free* IGF-I.) Treg expression is markedly increased in insulin-deficient, streptozotocin-treated rats.⁷⁴ Intriguingly, the expression of IGF-I receptors by CD4+ lymphocytes has been shown to be elevated in patients with rheumatoid arthritis, and the fraction of CD4+ lymphocytes expressing such receptors is elevated in patients with Graves disease.^{72, 73} Nonetheless, the association of free IGF-I levels with Treg expression in humans does not appear to have been assessed to date.

While a relatively low dietary intake of essential amino acids might influence Treg induction by its down-regulatory impact on hepatic IGF-I secretion, it may also influence lymphocyte function by a more direct impact on lymphocyte mTORC1 activity. Tregs can promote induction of other Tregs through a phenomenon known as “infectious tolerance”.⁷⁵ When Tregs interact with dendritic cells, they induce increased expression in these cells not only of indoleamine 2,3-dioxygenase, an enzyme which catabolizes tryptophan, but of a range of other enzymes that degrade essential amino acids. This results in a microenvironment which is locally depleted of certain essential amino acids. When other T lymphocytes subsequently engage with these dendritic cells, mTORC1 activity in these lymphocytes is suppressed by a local deficiency of essential amino acids, with the result that these interactions are more likely to provoke induction of Foxp3 in the lymphocytes, converting them to Tregs.^{57,75} It is reasonable to suspect that, in vegans whose circulating levels of certain essential amino acids are relatively low at baseline, this phenomenon of infectious tolerance will be up-regulated, as a lesser degree of amino acid catabolism will be needed to suppress lymphocyte mTORC1 activity.

Toward a Lifestyle Strategy for Prevention and Control of Autoimmunity

In aggregate, these findings appear consistent with the hypothesis that induction of Foxp3+ Treg cells will be encouraged when serum levels of essential amino acids, free IGF-I, insulin, and leptin are relatively low – and that this phenomenon was at least partially responsible for the paucity of autoimmunity among sub-Saharan black Africans and East Asians when these peoples consumed quasi-vegan diets and were quite lean. If this hypothesis is correct, it further suggests that lifestyle measures which promote leanness and minimize serum levels of essential amino acids, leptin, insulin, and free IGF-I may be of some value in the long-term management of autoimmune disorders. In particular, whole-food plant-based diets of modest but adequate protein content and moderate glycemic index, complemented by exercise training that optimizes muscle insulin sensitivity while promoting fat catabolism, could be recommended for this purpose. (Maintaining good vitamin D status through regular exposure to *uv*-rich sunlight and/or supplementation may also be helpful in this regard.⁷⁶) It will be of interest to determine whether long-term adoption of such regimens does indeed tend to boost Foxp3+ Treg levels while providing clinical benefit in patients afflicted with autoimmunity.

Nonetheless, increased induction of Tregs seems unlikely to be the only explanation for the low risk for autoimmunity enjoyed by quasi-vegan societies. It should be noted that the low saturated fat content of most vegan diets may favorably impact inflammation and autoimmunity. Long-chain saturated fats – most notably palmitic acid, a ceramide precursor – can promote a pro-inflammatory phenotype in macrophages and microglia by boosting TLR4 signaling.⁷⁷⁻⁸¹ Conceivably, this phenomenon may help to explain the beneficial impact of the low-saturated-fat diet employed by Swank in multiple sclerosis, and the lower risk for Alzheimer’s and Parkinson’s disease associated with “Mediterranean” or plant-based diets.⁸²⁻⁸⁴ Whole-food plant-based diets have a modulatory impact on gut microflora, and it has been suggested that this might play a role in their impact on rheumatoid arthritis and other autoimmune disorders.⁸⁵ There is also a school of thought that the low risk for autoimmunity that formerly characterized sub-Saharan Africans reflected a high frequency of chronic parasitic disease in this population.^{86,87} Whether or not the specific proposals offered in this essay prove to have validity, further efforts to explain the low risk for autoimmunity enjoyed by sub-Saharan Africans and East Asians in the last century are clearly warranted, and if successful may provide us with valuable resources for the prevention and treatment of autoimmune disorders.

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