Special Article

NUTRITION REVIEWS

Mechanistic perspective on the relationship between pyridoxal 5'-phosphate and inflammation

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A variety of inflammatory disease conditions have been found to be associated with low levels of plasma pyridoxal 5'-phosphate (PLP), the active form of vitamin B_6, without any indication of a lower dietary intake of vitamin B_6, excessive catabolism of the vitamin, or congenital defects in its metabolism. The present review was conducted to examine the existing literature in this regard. Current evidence suggests that the inverse association between plasma PLP and inflammation may be the result of mobilization of this coenzyme to the site of inflammation, for use by the PLP-dependent enzymes of the kynurenine pathway of tryptophan degradation, metabolism of the immunomodulatory sphingolipids, ceramide and sphingosine 1-phosphate, and for serine hydroxymethylase for immune cell proliferation.

INTRODUCTION

Pyridoxal 5'-phosphate (PLP), the active form of vitamin B_6, functions as a cofactor for a wide variety of enzymes involved in the metabolism of proteins, lipids and carbohydrates, and in processes essential for the synthesis or metabolism of hemoglobin, neurotransmitters, nucleic acids, one-carbon units, immunomodulatory metabolites, etc.[1–5] Vitamin B_6 availability also plays a critical role in both the innate and adaptive immune responses.[6] A variety of disease conditions have repeatedly been found to be associated with low levels of plasma PLP, including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), cardiovascular disease, deep vein thrombosis, diabetes, and cancer.[7–14] An inverse relationship has been found between the inflammatory marker C-reactive protein (CRP) and plasma PLP status among participants of the Framingham Heart Study and the National Health and Nutrition Examination Survey (NHANES),[15,16] as well as in case-control and cross-sectional studies on inflammatory conditions such as RA, IBD, or coronary disease.[7,8,17–19] In addition, plasma concentration of PLP is negatively associated with the acute-phase protein alpha1-acid glycoprotein, tumor necrosis factor-α, and the proinflammatory cytokine interleukin-6 in RA and IBD.[7,8,20]

The inverse association between low plasma PLP status and inflammatory diseases has been interpreted to mean that low dietary intake of vitamin B_6 confers an increased risk of disease. While this may be true in some instances,[21,22] in most studies of inflammatory conditions, including RA, IBD, diabetes, and cancer, there is a lack of correlation between vitamin B_6 intake and plasma PLP concentration and no indication of low dietary intake of vitamin B_6.[7,11,23–25] Despite the lower plasma PLP concentrations, RA patients exhibit normal measures of other indicators of long-term vitamin B_6 status, including erythrocyte aspartate transaminase (EAST) activity coefficient and erythrocyte PLP concentration.[7,23,26] Urinary excretion of 4-pyridoxic acid, which is a measure of vitamin B_6 metabolism, was not correlated with plasma PLP in RA patients, suggesting that low plasma PLP in this condition is not due to increased metabolism of vitamin B_6.[23] In a rat model of RA, there was also no difference in urinary 4-pyridoxic acid excretion between control animals and those with experimental RA.[27] The

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temporal relationships between PLP and inflammation are best demonstrated in studies of RA and IBD, both of which are characterized by an overactive immune response accompanied by periods of intense inflammation, that are followed by periods of remission. Plasma PLP concentration of IBD patients with active disease is lower than that of patients in remission.[8] In RA, plasma PLP concentration is inversely correlated with severity of the disease.[26] Thus, it appears that the lower plasma PLP concentration that is observed in inflammatory diseases is not linked to a dietary inadequacy or to vitamin B_6 deficiency in most cases, but rather is due to a metabolic phenomenon inherent to inflammation. Among the participants of the NHANES, the prevalence of low (<20 nmol/L) plasma PLP is about 2.5-fold higher in individuals with higher (>10 mg/L) CRP concentrations than in those with lower (≤3 mg/L) CRP concentrations.[16] These data suggest there is a higher need for plasma PLP by the immune system during active inflammation.

PROPOSED ROLE OF PLP IN INFLAMMATION

Current evidence points to the possibility that the inverse association between plasma PLP and inflammation is the result of mobilization of plasma PLP to sites of active inflammation for use by PLP-dependent enzymes that play a role in the inflammatory response.[19,27] Approximately 80% of the body store of PLP is in muscle, bound to glycogen phosphorylase.[28] The PLP in muscle is not readily released; thus, when there is an increase in demand for PLP during inflammation or when intake of vitamin B_6 is low, PLP is supplied by liver and plasma stores.[27,29] Hence, plasma PLP concentration would be highly susceptible to a sudden increase in PLP demand during an immune response. Mobilization of PLP for inflammatory processes was implied in a study of an animal model of RA, which found that, during active disease, a decrease in PLP was seen in plasma and liver, two readily accessible compartments, but not in other tissues.[27] It is proposed here that the lower plasma PLP observed during inflammation is due to the mobilization of this coenzyme to the site of inflammation for degradation of tryptophan via the kynurenine pathway, metabolism of immunomodulatory sphingolipids, and the proliferation of immune cells.

PLP and indoleamine 2,3-dioxygenase-dependent degradation of tryptophan

Degradation of tryptophan through the indoleamine 2,3-dioxygenase (IDO) pathway is a hallmark of inflammation (Figure 1). IDO is ubiquitous in nonhepatic tissues and is present in an inducible form in myeloid tissues, such as macrophages, dendritic cells, and monocytes.[30] In the liver, tryptophan degradation is initiated by tryptophan 2,3-dioxygenase (TDO), which catalyzes the same reaction as IDO, but is not involved in inflammation.[31] IDO is induced by a number of proinflammatory molecules, including interferon gamma, lipopolysaccharide, and CD40 ligands.[30,32–35]

The involvement of IDO-dependent degradation of tryptophan in immune response and immune tolerance has been demonstrated in multiple studies. A role for the IDO pathway in immune tolerance was demonstrated by showing that the activity of IDO is required to prevent T-cell-mediated rejection of allogeneic fetuses in pregnant mice.[36] Induction of IDO-dependent tryptophan degradation in macrophages and dendritic cells allows them to block unwanted T-cell responses by suppressing their activation, thus resulting in immune tolerance.[37] In a mouse model, IDO activity suppresses the development of RA[38] and prevents tumor cells from being rejected by mice that have been immunized against the tumor.[39] Inflammation response and mortality increase in colitis upon inhibition of IDO expression.[40]

An important aspect of IDO-dependent degradation of tryptophan is that PLP functions as a cofactor for many of the enzymes of this pathway (Figure 1). These include enzymes that carry out the conversion of kynurenine to kynurenic acid or anthranilic acid, as well as the conversion of 3-hydroxy kynurenine to 3-hydroxyanthralinic acid or xanthurenic acid. It has been proposed that the IDO-dependent effect is linked to depletion of tryptophan, which will result in cellular starvation for this amino acid.[41] However, there are a number of studies that show that the downstream products of tryptophan degradation, many of which are formed through the action of PLP-dependent enzymes, mimic the actions of the IDO-dependent immune modulation as described below. Activity of the flavin-dependent enzyme kynurenine monooxygenase is necessary for development of immune tolerance in vivo, suggesting a role for the downstream products of kynurenine.[42] It has been shown that even in the absence of a functional IDO, addition of the tryptophan degradation product kynurenine can modulate immune response in vitro.[42] 3-hydroxyanthranilic acid (HAA), a product of a PLP-dependent reaction (Figure 1), induces apoptosis of human T helper-1 (TH1) cells that are responsible for autoimmune response, but not that of T helper-2 (TH2) cells responsible for immunity to extracellular pathogens.[43] Multiple tryptophan metabolites, HAA, 3-hydroxykynurenine, and N-3,4, dimethoxycinnamoyl) anthranilic acid (3,4-DAA), which is a synthetic derivative of anthranilic acid, inhibit production of the TH1 proinflammatory cytokines interleukin-2, interferon gamma, and tumor necrosis factor-α, thereby skewing the T-cell profile from TH1 to TH2.[44] HAA also induces the death of T-cells activated by

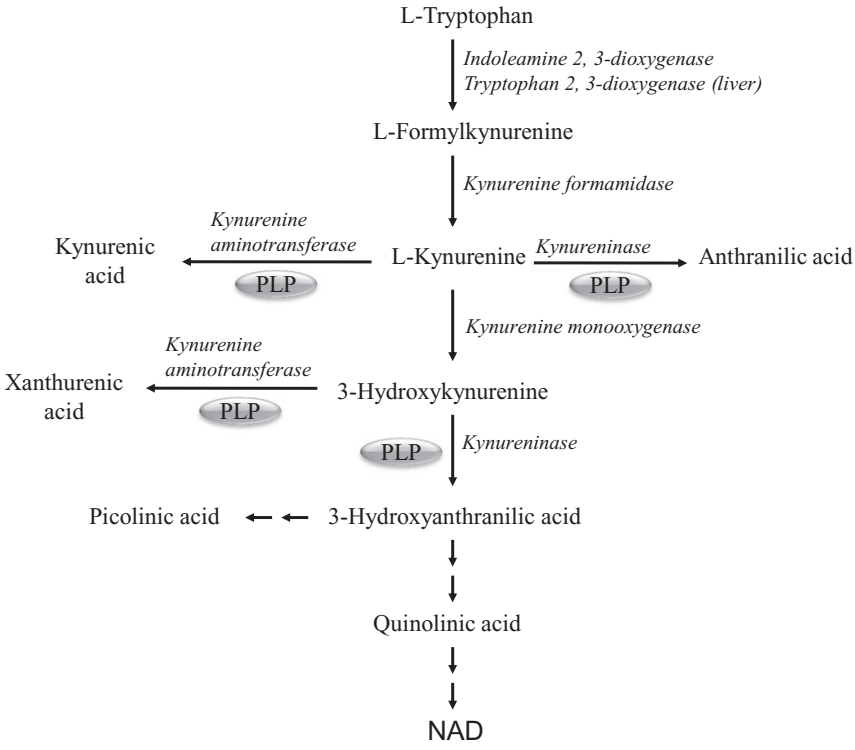

Figure 1 **Indoleamine 2,3-dioxygenase-dependent degradation of tryptophan. Many of the reactions of this pathway are PLP-dependent. The initial step in tryptophan degradation can also be brought about by the hepatic enzyme tryptophan deoxygenase.**
Abbreviation: NAD, nicotinamide adenine dinucleotide.

CD3[45] and inhibits T-cell proliferation by cytokines.[43] 3,4-DAA administration can reverse the paralysis of mice with experimental autoimmune encephalomyelitis, which is a model for multiple sclerosis.[44] Rejection of an implanted heart in a rat model was shown to be delayed by administration of HAA in combination with donor's bone marrow cells prior to the implant, potentially by eradicating the T-cell response to the graft.[46] In mice, kynurenine and 3-hydroxykynurenine and xanthurenic acid, which is a product of a PLP-dependent reaction, contribute to development of immunotolerence in airway inflammation in allergic asthma.[47] Additional evidence for involvement of PLP-dependent reactions of the kynurenine pathway in immune response comes from the accumulation of quinolate (Figure 1) at micromolar concentrations or greater in lymphoid tissues and macrophages during immune response.[48] Thus, it appears that tryptophan degradation via PLP-dependent reactions is involved in developing immune tolerance, suppression of inflammation, and reducing tissue damage due to immune response.

Recent studies demonstrate the potential mechanisms by which kynurenine metabolites regulates immune response. Kynurenine and two of its metabolites, kynurenic acid and xanthurenic acid, have been shown to be endogenous ligands for the arylhydrocarbon receptor.[49,50] Transcriptional response mediated by aryl hydrocarbon receptor activated by these compounds can lead to induction of interleukin-6, which is a protumorigenic cytokine and generation of immunosuppressive regulatory T-cells.[50,51] These are processes that may reduce immune surveillance of malignant cells and promote tumor progression. Kynurenic acid is also a ligand of the G protein-coupled receptor, GPR35, which is primarily expressed in immune cells and gastrointestinal tissues.[52] Kynurenic acid has been shown to suppress the lipopolysaccharide-induced tumor necrosis factor-α secretion in mice[53] and cultured immune cells that express GPR35.[52]

In humans, IDO-dependent degradation of tryptophan has been implicated as an important modulator of activity in a variety of diseases, including immune deficiency syndromes, amyotrophic lateral sclerosis, RA, coronary artery disease, and various types of cancers,[54] many of which have also been associated with low plasma PLP status. Most human cancers express IDO and TDO constitutively[49,55] and it has been reported that women with early-stage breast cancer have higher tryptophan degradation than controls,[56] suggesting a means by which some neoplasms might evade the immune system. Occur-

rence of increased tryptophan degradation in these diseases is manifested by higher plasma kynurenine: tryptophan concentration ratios.[54] Participation of PLP-dependent enzymes during enhanced tryptophan degradation of these diseases is suggested from the imbalance of metabolites from PLP-dependent reactions in cases compared to healthy controls.[54] A high kynurenine: tryptophan ratio has been reported to predict major coronary events,[57] and there is an inverse relationship between plasma PLP concentration and 3-hydroxykyneurenine, one of the degradation products of tryptophan, in coronary heart disease patients with one or more inflammation markers in the upper tertile.[19]

PLP-dependent metabolism of sphingolipids

Reduced availability of PLP is associated with reduction in several components of the immune response, including significant decreases in lymphocyte numbers, especially T-helper cells and IL-2 production in humans.[6] Lymphocytes isolated from vitamin B_6-deficient subjects also show reduction of lymphoproliferative responses to mitogens that activate both T and B cells when grown in a culture medium containing adequate concentration of PLP.[6] This has been attributed to the lower numbers of T-helper cells in the lymphocyte population from vitamin B_6-deficient subjects. Maturation and egress of lymphocytes, especially T-cells, from thymus and lymph nodes relies on the gradient of sphingosine-1-phosphate (S1P). PLP-dependent enzymes play a major role in the synthesis and breakdown of S1P, which is a potent metabolite that regulates inflammation and immune response processes such as cell growth, survival, differentiation, lymphocyte trafficking, vascular integrity, and cytokine and chemokine production.[58,59] PLP is required for the activity of serine palmitoyl transferase that catalyzes the condensation of serine and palmitoyl CoA into 3-keto-dihydrosphingosine, which is then converted to S1P in a series of reactions.[58–60] PLP is also a cofactor for sphingosine-1-phosphate lyase, which irreversibly cleaves S1P to regulate its concentration.[58,59,61] A gradient of S1P is required for lymphocyte egress from thymus and peripheral lymphoid organs, which is maintained by S1P lyase.[62] Administration of vitamin B_6 antagonist 4' deoxypyridoxine interferes with the S1P gradient, results in accumulation of mature lymphocytes in the thymus, and depletes B- and T-lymphocytes from lymph causing lymphopenia.[62] These conditions can be reversed by providing excess vitamin B_6 in the diet.[62] During inflammation, S1P concentration increases in the inflamed peripheral tissues,[63] which functions as a chemoattractant for the inflammatory cells.

One of the intermediate products during the synthesis of S1P from 3-keto-dihydrosphingosine is ceramide, which plays an important role in inflammatory processes. Ceramide functions as a second messenger mediating the effects of tumor necrosis factor-α and interferon-γ on programmed cell death and regulating senescence.[64,65] An increase in cellular ceramide concentration is observed in cystic fibrosis, experimental autoimmune encephalomyelitis, and diet-induced insulin resistance, all of which are marked by chronic inflammation.[66–68] The importance of ceramide in these diseases is demonstrated by the fact that manipulation of ceramide concentration via inhibition of serine palmitoyl transferase or mutation of sphingomyelinase, reverses the pathology of the disease.[66–68] Ceramide-1-phosphate, which is derived from ceramide, activates mast cells that mediate inflammation.[69]

Thus, it is possible that is a higher demand exists for PLP during inflammation due to the role of PLP in the synthesis of S1P and ceramide, and maintenance of S1P gradient.

Other PLP-dependent reactions necessary for immune cell proliferation

There is increased turnover of immune cells in inflammation. Proliferation of immune cells requires N5, N10-methylene tetrahydrofolate (a key folate intermediate and the source of carbons 2 and 8 of purine), as well as the methyl group for the synthesis of thymidylate and methionine synthesized in a PLP-dependent reaction via serine hydroxyl methyltransferase (SHMT).[70] Studies on vitamin B_6-deficient mice have shown that DNA synthesis, as determined by the incorporation of labeled precursors of nucleic acid into DNA, depends on the availability of vitamin B_6.[70] Adequate vitamin B_6 nutrition is required for the activity of SHMT and for protein turnover.[71] The addition of vitamin B_6 antagonist 4' deoxypyridoxine inhibits induction of SHMT in activated lymphocytes.[72] SHMT activity is 5- to 20-fold higher under conditions where there is high cell division, as in leukemia, and in activated lymphocytes.[72–74] Hence, during inflammation, the increased proliferation of immune cells may result in an increased requirement for PLP.

CONCLUSION

A variety of inflammatory disease conditions, including RA, IBD, and diabetes, have been found to be associated with low concentrations of plasma PLP, the active form of vitamin B_6, without any indication of a lower dietary intake of vitamin B_6, excessive catabolism of the vitamin, or congenital defects in its metabolism. Current evidence suggests the inverse association between plasma PLP and inflammation may be the result of mobilization of this coenzyme into inflammatory sites for PLP-dependent reactions of tryptophan degradation via the kynurenine

pathway for developing immune tolerance, generation of the immunomodulatory sphingolipids S1P and ceramide, maintenance of the gradient of S1P, and for the proliferation of immune cells. The majority of the body store of PLP is in muscle[28] and is not readily released when there is an increase in demand for PLP during inflammation[27] or when intake of vitamin B_6 is low[29]; instead, PLP is supplied by liver and plasma.[27,29] This makes plasma PLP highly susceptible to the higher demand for this coenzyme during inflammation. The possibility that PLP is mobilized for these important aspects of the immune response, however, needs to be verified by targeted studies using both animal and cell culture models.

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REFERENCES

1. Smolin LA, Benevenga NJ. Accumulation of homocyst(e)ine in vitamin B-6 deficiency: a model for the study of cystathionine β-synthase deficiency. J Nutr. 1982;112:1264–1272.
2. Schulman MP, Richert DA. Heme synthesis in vitamin B_6 and pantothenic acid deficiencies. J Biol Chem. 1957;226:181–189.
3. Percudani R, Peracchi A. A genomic overview of pyridoxal-phosphate-dependent enzymes. EMBO Rep. 2003;4:850–854.
4. Robert AJ. Pyridoxal phosphate-dependent enzymes. Biochim Biophys Acta. 1995;1248:81–96.
5. Christen P, Mehta PK. From cofactor to enzymes. The molecular evolution of pyridoxal-5′-phosphate-dependent enzymes. Chem Rec. 2001;1:436–447.
6. Meydani SN, Ribaya-Mercado JD, Russell RM, et al. Vitamin B-6 deficiency impairs interleukin 2 production and lymphocyte proliferation in elderly adults. Am J Clin Nutr. 1991;53:1275–1280.
7. Roubenoff R, Roubenoff RA, Selhub J, et al. Abnormal vitamin B_6 status in rheumatoid cachexia. Association with spontaneous tumor necrosis factor alpha production and markers of inflammation. Arthritis Rheum. 1995;38:105–109.
8. Saibeni S, Cattaneo M, Vecchi M, et al. Low vitamin B_6 plasma levels, a risk factor for thrombosis in inflammatory bowel disease: role of inflammation and correlation with acute phase reactants low vitamin B_6 levels and IBD. Am J Gastroenterol. 2003;98:112–117.
9. Dalery K, Lussier-Cacan S, Selhub J, et al. Homocysteine and coronary artery disease in French Canadian subjects: relation with vitamins B_{12}, B_6, pyridoxal phosphate, and folate. Am J Cardiol. 1995;75:1107–1111.
10. Cattaneo M, Lombardi R, Lecchi A, et al. Low plasma levels of vitamin B_6 are independently associated with a heightened risk of deep-vein thrombosis. Circulation. 2001;104:2442–2446.
11. Wilson RG, Davis RE. Serum pyridoxal concentrations in children with diabetes mellitus. Pathology. 1977;9:95–98.
12. Sanderson CR, Davis RE. Serum pyridoxal in patients with gastric pathology. Gut. 1976;17:371–374.
13. Le Marchand L, White KK, Nomura AM, et al. Plasma levels of B vitamins and colorectal cancer risk: the multiethnic cohort study. Cancer Epidemiol Biomarkers Prev. 2009;18:2195–2201.
14. Wei EK, Giovannucci E, Selhub J, et al. Plasma vitamin B_6 and the risk of colorectal cancer and adenoma in women. J Natl Cancer Inst. 2005;97:684–692.
15. Friso S, Jacques PF, Wilson PW, et al. Low circulating vitamin B_6 is associated with elevation of the inflammation marker C-reactive protein independently of plasma homocysteine levels. Circulation. 2001;103:2788–2791.
16. Morris MS, Sakakeeny L, Jacques PF, et al. Vitamin B-6 intake is inversely related to, and the requirement is affected by, inflammation status. J Nutr. 2010;140:103–110.
17. Friso S, Girelli D, Martinelli N, et al. Low plasma vitamin B-6 concentrations and modulation of coronary artery disease risk. Am J Clin Nutr. 2004;79:992–998.
18. Friedman AN, Hunsicker LG, Selhub J, et al. Clinical and nutritional correlates of C-reactive protein in type 2 diabetic nephropathy. Atherosclerosis. 2004;172:121–125.
19. Midttun O, Ulvik A, Ringdal Pedersen E, et al. Low plasma vitamin B-6 status affects metabolism through the kynurenine pathway in cardiovascular patients with systemic inflammation. J Nutr. 2011;141:611–617.
20. Huang SC, Wei JC, Wu DJ, et al. Vitamin B_6 supplementation improves pro-inflammatory responses in patients with rheumatoid arthritis. Eur J Clin Nutr. 2010;64:1007–1013.
21. Verhoef P, Stampfer MJ, Buring JE, et al. Homocysteine metabolism and risk of myocardial infarction: relation with vitamins B_6, B_{12}, and folate. Am J Epidemiol. 1996;143:845–859.
22. Rimm EB, Willett WC, Hu FB, et al. Folate and vitamin B_6 from diet and supplements in relation to risk of coronary heart disease among women. JAMA. 1998;279:359–364.
23. Chiang EP, Bagley PJ, Roubenoff R, et al. Plasma pyridoxal 5′-phosphate concentration is correlated with functional vitamin B-6 indices in patients with rheumatoid arthritis and marginal vitamin B-6 status. J Nutr. 2003;133:1056–1059.
24. Eussen SJ, Vollset SE, Hustad S, et al. Vitamins B2 and B6 and genetic polymorphisms related to one-carbon metabolism as risk factors for gastric adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition. Cancer Epidemiol Biomarkers Prev. 2010;19:28–38.
25. Ahn HJ, Min KW, Cho YO. Assessment of vitamin B_6 status in Korean patients with newly diagnosed type 2 diabetes. Nutr Res Pract. 2011;5:34–39.
26. Chiang EP, Bagley PJ, Selhub J, et al. Abnormal vitamin B_6 status is associated with severity of symptoms in patients with rheumatoid arthritis. Am J Med. 2003;114:283–287.
27. Chiang EP, Smith DE, Selhub J, et al. Inflammation causes tissue-specific depletion of vitamin B_6. Arthritis Res Ther. 2005;7:R1254–R1262.
28. Coburn SP, Mahuren JD, Kennedy MS, et al. B_6 vitamer content of rat tissues measured by isotope tracer and chromatographic methods. Biofactors. 1988;1:307–312.
29. Coburn SP, Ziegler PJ, Costill DL, et al. Response of vitamin B-6 content of muscle to changes in vitamin B-6 intake in men. Am J Clin Nutr. 1991;53:1436–1442.
30. Opitz CA, Wick W, Steinman L, et al. Tryptophan degradation in autoimmune diseases. Cell Mol Life Sci. 2007;64:2542–2563.
31. Knox WE, Mehler AH. The adaptive increase of the tryptophan peroxidase-oxidase system of liver. Science. 1951;113:237–238.
32. Pfefferkorn ER, Rebhun S, Eckel M. Characterization of an indoleamine 2,3-dioxygenase induced by gamma-interferon in cultured human fibroblasts. J Interferon Res. 1986;6:267–279.
33. Taylor MW, Feng GS. Relationship between interferon-gamma, indoleamine 2,3-dioxygenase, and tryptophan catabolism. FASEB J. 1991;5:2516–2522.
34. Yoshida R, Oku T, Imanishi J, et al. Interferon: a mediator of indoleamine 2,3-dioxygenase induction by lipopolysaccharide, poly(I) X poly(C), and pokeweed mitogen in mouse lung. Arch Biochem Biophys. 1986;249:596–604.
35. Mellor AL, Munn DH. IDO expression by dendritic cells: tolerance and tryptophan catabolism. Nat Rev Immunol. 2004;4:762–774.
36. Munn DH, Zhou M, Attwood JT, et al. Prevention of allogeneic fetal rejection by tryptophan catabolism. Science. 1998;281:1191–1193.
37. Munn DH, Shafizadeh E, Attwood JT, et al. Inhibition of T cell proliferation by macrophage tryptophan catabolism. J Exp Med. 1999;189:1363–1372.
38. Seo SK, Choi JH, Kim YH, et al. 4-1BB-mediated immunotherapy of rheumatoid arthritis. Nat Med. 2004;10:1088–1094.
39. Uyttenhove C, Pilotte L, Theate I, et al. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. Nat Med. 2003;9:1269–1274.
40. Gurtner GJ, Newberry RD, Schloemann SR, et al. Inhibition of indoleamine 2,3-dioxygenase augments trinitrobenzene sulfonic acid colitis in mice. Gastroenterology. 2003;125:1762–1773.
41. Munn DH, Sharma MD, Baban B, et al. GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase. Immunity. 2005;22:633–642.
42. Belladonna ML, Grohmann U, Guidetti P, et al. Kynurenine pathway enzymes in dendritic cells initiate tolerogenesis in the absence of functional IDO. J Immunol. 2006;177:130–137.
43. Weber WP, Feder-Mengus C, Chiarugi A, et al. Differential effects of the tryptophan metabolite 3-hydroxyanthranilic acid on the proliferation of human CD8+ T cells induced by TCR triggering or homeostatic cytokines. Eur J Immunol. 2006;36:296–304.

44. Platten M, Ho PP, Youssef S, et al. Treatment of autoimmune neuroinflammation with a synthetic tryptophan metabolite. Science. 2005;310:850–855.
45. Terness P, Bauer TM, Rose L, et al. Inhibition of allogeneic T cell proliferation by indoleamine 2,3-dioxygenase-expressing dendritic cells: mediation of suppression by tryptophan metabolites. J Exp Med. 2002;196:447–457.
46. Dai X, Zhu BT. Suppression of T-cell response and prolongation of allograft survival in a rat model by tryptophan catabolites. Eur J Pharmacol. 2009;606:225–232.
47. Taher YA, Piavaux BJ, Gras R, et al. Indoleamine 2,3-dioxygenase-dependent tryptophan metabolites contribute to tolerance induction during allergen immunotherapy in a mouse model. J Allergy Clin Immunol. 2008;121:983–991 e982.
48. Moffett JR, Blinder KL, Venkateshan CN, et al. Differential effects of kynurenine and tryptophan treatment on quinolinate immunoreactivity in rat lymphoid and non-lymphoid organs. Cell Tissue Res. 1998;293:525–534.
49. Opitz CA, Litzenburger UM, Sahm F, et al. An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. Nature. 2011;478:197–203.
50. DiNatale BC, Murray IA, Schroeder JC, et al. Kynurenic acid is a potent endogenous aryl hydrocarbon receptor ligand that synergistically induces interleukin-6 in the presence of inflammatory signaling. Toxicol Sci. 2010;115:89–97.
51. Mezrich JD, Fechner JH, Zhang X, et al. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. J Immunol. 2010;185:3190–3198.
52. Wang J, Simonavicius N, Wu X, et al. Kynurenic acid as a ligand for orphan G protein-coupled receptor GPR35. J Biol Chem. 2006;281:22021–22028.
53. Moroni F, Cozzi A, Sili M, et al. Kynurenic acid: a metabolite with multiple actions and multiple targets in brain and periphery. J Neural Transm. 2012;119:133–139.
54. Chen Y, Guillemin GJ. Kynurenin pathway metabolites in humans: disease and healthy states. Int J Tryptophan Res. 2009;2:1–19.
55. Schroecksnadel K, Fiegl M, Prassl K, et al. Diminished quality of life in patients with cancer correlates with tryptophan degradation. J Cancer Res Clin Oncol. 2007;133:477–485.
56. Lyon DE, Walter JM, Starkweather AR, et al. Tryptophan degradation in women with breast cancer: a pilot study. BMC Res Notes. 2011;4:156–163.
57. Pedersen ER, Midttun O, Ueland PM, et al. Systemic markers of interferon-gamma-mediated immune activation and long-term prognosis in patients with stable coronary artery disease. Arterioscler Thromb Vasc Biol. 2010;31:698–704.
58. Bourquin F, Capitani G, Grutter MG. PLP-dependent enzymes as entry and exit gates of sphingolipid metabolism. Protein Sci. 2011;20:1492–1508.
59. Spiegel S, Milstien S. The outs and the ins of sphingosine-1-phosphate in immunity. Nat Rev Immunol. 2011;11:403–415.
60. Merrill AH Jr, Wang E, Mullins RE. Kinetics of long-chain (sphingoid) base biosynthesis in intact LM cells: effects of varying the extracellular concentrations of serine and fatty acid precursors of this pathway. Biochemistry. 1988;27:340–345.
61. Van Veldhoven PP, Mannaerts GP. Subcellular localization and membrane topology of sphingosine-1-phosphate lyase in rat liver. J Biol Chem. 1991;266:12502–12507.
62. Schwab SR, Pereira JP, Matloubian M, et al. Lymphocyte sequestration through S1P lyase inhibition and disruption of S1P gradients. Science. 2005;309:1735–1739.
63. Ledgerwood LG, Lal G, Zhang N, et al. The sphingosine 1-phosphate receptor 1 causes tissue retention by inhibiting the entry of peripheral tissue T lymphocytes into afferent lymphatics. Nat Immunol. 2008;9:42–53.
64. Obeid LM, Linardic CM, Karolak LA, et al. Programmed cell death induced by ceramide. Science. 1993;259:1769–1771.
65. Venable ME, Lee JY, Smyth MJ, et al. Role of ceramide in cellular senescence. J Biol Chem. 1995;270:30701–30708.
66. Teichgraber V, Ulrich M, Endlich N, et al. Ceramide accumulation mediates inflammation, cell death and infection susceptibility in cystic fibrosis. Nat Med. 2008;14:382–391.
67. Ussher JR, Koves TR, Cadete VJJ, et al. Inhibition of de novo ceramide synthesis reverses diet-induced insulin resistance and enhances whole-body oxygen consumption. Diabetes. 2010;59:2453–2464.
68. Schiffmann S, Ferreiros N, Birod K, et al. Ceramide synthase 6 plays a critical role in the development of experimental autoimmune encephalomyelitis. J Immunol. 2012;188:5723–5733.
69. Mitsutake S, Kim T-J, Inagaki Y, et al. Ceramide kinase is a mediator of calcium-dependent degranulation in mast cells. J Biol Chem. 2004;279:17570–17577.
70. Axelrod AE, Trakatellis AC. Relationship of pyridoxine to immunological phenomena. Vitam Horm. 1964;22:591–607.
71. Martinez M, Cuskelly GJ, Williamson J, et al. Vitamin B-6 deficiency in rats reduces hepatic serine hydroxymethyltransferase and cystathionine beta-synthase activities and rates of in vivo protein turnover, homocysteine remethylation and transsulfuration. J Nutr. 2000;130:1115–1123.
72. Trakatellis A, Dimitriadou A, Exindari M, et al. Effect of pyridoxine deficiency on immunological phenomena. Postgrad Med J. 1992;68(Suppl 1):S70–S77.
73. Thorndike J, Pelliniemi TT, Beck WS. Serine hydroxymethyltransferase activity and serine incorporation in leukocytes. Cancer Res. 1979;39:3435–3440.
74. Eichler HG, Hubbard R, Snell K. The role of serine hydroxymethyltransferase in cell proliferation: DNA synthesis from serine following mitogenic stimulation of lymphocytes. Biosci Rep. 1981;1:101–106.