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Micronutrients, immunology and inflammation
Effect of vitamin A deficiency on the immune response in obesity

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Obesity has been associated with low-grade systemic inflammation and with micronutrient deficiencies. Obese individuals have been found to have lower vitamin A levels and lower vitamin A intake compared with normal-weight individuals. Vitamin A plays a major role in the immune function, including innate immunity, cell-mediated immunity and humoral antibody immunity. It has also been recognised recently that vitamin A has important regulatory functions. Vitamin A status has an important effect on the chronic inflammatory response. Vitamin A deficiency increases a T-helper type 1 (Th1) response, elevates levels of pro-inflammatory cytokines, increases the expression of leptin, resistin and uncoupling proteins (UCP) and promotes adipogenesis. The effect of vitamin A deficiency on obesity might be increasing the risk of fat deposition and also the risk of chronic inflammation associated with obesity. Supplementation with vitamin A *in vitro* and in animal models has been found to reduce concentrations of adipocytokines, such as leptin and resistin. In conclusion, vitamin A deficiency increases a Th1 response in the presence of obesity and thus, increases the inflammatory process involved in chronic inflammation and fat deposition. The metabolism of leptin and other adipocytokines may play a critical role in the effect of vitamin A deficiency in the inflammatory response observed in obesity.

Vitamin A: Immunity: Obesity

Micronutrients are necessary to have an adequate immune response and inflammatory processes, including the production of cytokines[1,2]. Vitamin A and retinoids, vitamin A derivatives, are critical for the immune function, including innate immunity, cell-mediated immunity and humoral antibody immunity[3,4]. It has been recognised for some time that retinoids have important regulatory functions[5,6]. Of the existing retinoids, retinoic acid (RA) and retinaldehyde seem to have a major role in the immune response, but all-*trans*-RA is recognised to be the most active form of vitamin A[7,8].

The effect of micronutrient deficiencies, commonly present in protein-energy malnutrition, on the immune response has been widely documented and has been associated with higher risk of infectious diseases[9–11]. Vitamin A deficiency has been shown to increase the risk

to infections. Vitamin A supplementation has proven to be effective to reduce childhood mortality, and in some cases morbidity[1,12,13]. In addition, vitamin A deficiency also impairs the inflammatory response and may be contributing to increase the risk of low systemic inflammation.

Higher prevalence of micronutrient deficiencies have been observed in obese individuals compared with normal-weight individuals, and may be increasing the risk of fat deposition and chronic diseases[14]. Low concentrations of retinol have been found in overweight and obese individuals independent of age[15–19]. In Brazil, for example, a high prevalence of vitamin A deficiency was found among overweight children[19]; in adults with morbid obesity, vitamin A deficiency was significantly associated with insulin resistance ($P < 0.05$)[18]. A negative correlation was also found between serum retinol concentration and

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weight, BMI and hip circumference in overweight and obese Thai adults in a case–control study[19]. Also, low dietary intake of vitamin A has been associated with a high incidence of obesity in human populations[17].

Obesity is associated with low-grade systemic inflammation[20]. In obesity, vitamin A deficiency may be increasing the risk of chronic inflammation through the regulation of cytokines and leptin. This paper reviews the role of vitamin A in the immune system, including the adipose tissue, how vitamin A deficiency affects the immune response when obesity is present and how supplementation may reverse the effects of vitamin A deficiency in the immune response.

Vitamin A and the immune system

Vitamin A is a cofactor in the immune response and its effect is mediated by its action on the inflammatory cytokines. Vitamin A up-regulates the T-helper type 2 (Th2) response and down-regulates T-helper type 1 (Th1) response, while deficiency of this vitamin has the opposite effect[21–23]. The Th1 response is necessary for cellular immunity, production of immunomodulatory cytokines, promotion of cytotoxicity and activation of macrophages, while Th2 response promotes humoral immunity, antibody production, Ig maturation and deactivation of macrophages[24,25]. Th1 response is responsible for the protection against intracellular infections and Th2 response is responsible for protecting against non-invasive infections. To have an efficient immune response, the balance between Th1 and Th2-type responses is of the utmost importance[24]. Vitamin A supports Th2 response by development and differentiation between a Th1 and a Th2 response[21,22]. Specifically, vitamin A may be down-regulating the expression of inflammation markers and promoting a Th2 immune response by several mechanisms:

1. Inhibition of interferon-γ (IFN-γ).
2. Inhibition of TNFα.
3. Inhibition of NF-κB.
4. Inhibition of IL-12.
5. Modulator of transforming growth factor β.
6. Down-regulating leptin expression and other adipocytokines.

These pathways seem to be specific for RA[2,21,26–29]. Thus, vitamin A promotes an anti-inflammatory environment and adequate Th1:Th2 ratios.

Retinoids and cell differentiation

Cell differentiation is involved in the immune response through both innate and cell-mediated responses. Retinoids are responsible for cell differentiation through gene transcription and are mediated by the activation of the interaction of their nuclear retinoic acid receptor (RAR) and retinoid X receptor (RXR)[30–32]. These receptors belong to the nuclear hormone receptors superfamily, like PPARγ[32–34]. The RAR receptors respond to both all-trans-RA and 9-cis-RA, while RXR respond specifically to 9-cis-RA[33].

Both RAR and RXR regulate the expression of hundreds of genes such as skin keratins, retinol-binding protein, leptin and IFN-γ[35–39]. The regulation of gene expression by retinoids has been recently reviewed by Amann et al.[5]. Transcription regulation by the retinoid receptors can be through two different pathways. The first direct pathway involves binding of RAR:RXR or RXR:RXR to specific response elements located in the promoter or enhancer region of a specific target gene[32–34,40]. Also, the transcription of genes can be regulated indirectly by interfering with other transcription factors[5,33].

Retinoic acid and immunity

The role of RA on inflammation and immunity has been reviewed recently[41]. Briefly, RA production is induced in tissue cells through retinol metabolism when an inflammation process begins. RA induces and regulates the expression of immune cells such as neutrophils, macrophages, dendritic cells and lymphoid cells, which include T-cells, T-regulatory cells and B-cells[41]. B-cells are part of the immune regulatory response and are responsible for the production of antibodies. RA is necessary for the development and maturity of B-cells, B-cell proliferation, B-cell differentiation and antibody-secreting plasma cells[41–43]. The effect that RA has on cell differentiation involves the RAR and RXR pathways. RA induces cell differentiation by binding to RAR, and thus induces gene transcription of transcription factors, signalling proteins, and interacts with RXR to activate the transcription of primary target genes[44,45]. The RXR pathway seems to be the one involved in maintaining a Th2-type response[45,46].

RA has been shown to inhibit NF-κB activity in human cell lines and also repress the transcription of NF-κB genes such as IL-6, monocyte chemoattractant protein-1 and cyclooxygenase-2, all involved in inflammation processes[47–51]. Also, it is now recognised that RA is responsible for the down-regulation of the gene expression of IFN-γ and TNFα, contributing to the Th2 anti-inflammatory response[20,51,21,29,52].

RA is also produced at high concentrations in the intestine and is a key factor in mucosal immunity[41,53]. It has been shown that RA promotes epithelial integrity to produce mucosal secretions, and induces immunity to protect the intestine after immunisation in animal models[53–54]. In addition, RA is known to modulate transforming growth factor β in the epithelial intestine cells and this contributes to an anti-inflammatory response in the gut[28,55].

Vitamin A and the adipose tissue

Vitamin A actively participates in the adipocyte metabolism. It is estimated that 15–20% of total retinoids are located in the adipose tissue[56]. The role of vitamin A in adipose tissue development and metabolism has been previously reviewed[57–59].

During obesity, the adipose tissue undergoes an important expansion and cell differentiation as well as adipocyte maturation. PPARγ is the major regulator of adipogenesis and its expression is mediated through several pathways, one of which involves retinoids. Vitamin A, retinaldehyde

and RA are all present in the adipocyte and are actively involved in cell differentiation, as well as transcription of PPARγ[59,60]. Also, vitamin A is involved in the production of anti-inflammatory cytokines in the adipocyte promoting a Th2-type response[27,29].

White adipose tissue (WAT) and brown adipose tissue (BAT) regulate retinoid metabolism, and differentiation between WAT and BAT is associated with the amount of intracellular retinoids[57,61]. Both RAR and RXR are expressed differently in WAT and BAT, and thus, there are different gene expressions depending on the type of adipose tissue[62]. In BAT, for example, RA induces transcription of the uncoupling protein (UCP)-1 gene mediated through RAR and RXR and the response element located at the enhancer; UCP-1 is the protein responsible for the thermogenic function attributed to BAT[63–67]. *In vitro*, RA increased 1·6 times UCP-1 mRNA expression in the BAT and slightly decreased its expression in WAT adipocytes[68].

In addition to the UCP-1 gene transcription, RA has been found *in vitro* to decrease preadipocyte survival time and to inhibit or promote adipose cell differentiation depending on the dose, probably regulated by RA intracellular lipid-binding protein-II[59,69–72].

In addition to RA, retinaldehyde can also play an important role in gene expression through nuclear receptors, similar to RA[8]. Both *in vivo* and *in vitro* adipogenesis have been shown to regulate retinaldehyde metabolism. In addition, Ziouzenkova *et al.*[8] demonstrated in rodents that retinaldehyde inhibits adipogenesis and suppresses PPAR and RXR response.

Retinoids and leptin

Leptin is an important adipocytokine that actively participates in the regulation of energy homoeostasis and its importance in body weight control has been demonstrated in human subjects and animals[73–75]. High leptin concentrations are associated with an increase in adipose tissue observed in obesity[73–75]. Also, leptin is induced as part of the acute phase response in response to inflammation, but it is also part of the chronic inflammation response associated with obesity[76,77]. It is now recognised that leptin regulates both the innate and adaptive immune response; low leptin concentration is associated with a higher risk of infections and high leptin concentration is responsible for increasing pro-inflammatory cytokine levels[77,78]. Thus, leptin is a key modulator of inflammation and obesity.

Leptin is involved in the activation and infiltration of macrophages into WAT, the activation and development of natural killer cells, induces chemotaxis of neutrophils, suppresses the proliferation of T-regulatory cells and regulates the Th1 and Th2 response[75,79–83]. Leptin has been shown to induce a Th1 response with an increased production of IFN-γ and TNFα[82,84]. In *ob/ob* mice, decreased secretion of pro-inflammatory cytokines, such as TNFα, IL-6, IFN-γ and IL-1β, was observed, which is reversed when leptin is administered[85]. The interactions between leptin and other pro-inflammatory cytokines is complex, and leptin can help modulate the inflammation

response[86]. Therefore, leptin plays an important role in the pathways leading to chronic inflammation.

Of the different active metabolites of vitamin A, RA has been shown to participate in leptin's metabolism in both mice and human tissue[87–90]. Different isomers of RA seem to have different effects on leptin expression and adipogenesis. *In vitro*, leptin expression is inhibited by both 9-*cis*- and all-*trans*-RA [89,90]. However, Menendez *et al.*[90] found that all-*trans*-RA has a more potent inhibitor of leptin secretion compared with 9-*cis*-RA. In addition, all-*trans*-RA increases adipogenesis in a dose-dependent way through the activation of RXR and PPARγ, while 9-*cis*-RA has no effect[89].

Vitamin A deficiency and the immune response in obesity

Vitamin A deficiency

Vitamin A deficiency is a major public health concern worldwide. Clinical signs of vitamin A deficiency include xerophthalmia, and also an increase of infectious diseases[1,3,91,92]. According to the World Health Organisation, the global prevalence of vitamin A deficiency, defined as serum retinol concentrations $<0·7\,\mu mol/l$ ($<20\,\mu g/dl$), is 33·3 (95 % CI 31·1, 35·4) % for preschool children and 15·3 (95 % CI 7·4, 23·2) % for pregnant women[93]. These numbers represent 190 million children and 19·1 million pregnant women worldwide.

The clinical manifestations of vitamin A deficiency are due to its effect on the immune system, mainly lymphopenia, impairment of the mucosal barriers and a decrease of the T-cell response[3,19,94]. Since the immune response is compromised, vitamin A deficiency increases the risk of parasites, bacterial and viral infections. In vitamin A deficiency, normal regeneration of the mucosal epithelial barriers is impaired and the resistance to infections is diminished. In animal models, vitamin A deficiency impaired both the humoral and cellular immunity of the intestinal mucosa probably through the modulation of the dendritic cells[95].

Vitamin A deficiency and T-helper types 1 and 2 response

Vitamin A deficiency impairs both Th1 and Th2 response[3,96]. However, Th2 immune response is affected the most. Vitamin A deficiency down-regulates the Th2 response and up-regulates Th1 response[21,23,52,96]. In vitamin A deficiency, the antibody-mediated immunity is impaired and there is an increase of pro-inflammatory cytokines that promotes a Th1 type inflammatory response, while the production of anti-inflammatory cytokines, such as IL-4 and IL-10, is reduced[21,52,97,98]. It has been observed that vitamin A-deficient children had a markedly Th1 response with low concentrations of IL-10 compared with non-deficient children[25]. In Indonesian children, for example, vitamin A deficiency was associated with a Th1 response[99]. A population of children in Venezuela with a high prevalence of vitamin A subclinical deficiency had lower IL-10 concentrations, an anti-inflammatory cytokine, compared with a group with adequate vitamin A status[100].

Table 1. Vitamin A functions, major roles in the immune system and effects of vitamin A deficiency in undernutrition and obesity (adapted from Maggini and Stephen[94] and Maggini and co-workers[54])

Vitamin A functions	Vitamin A functions in the immune system	Vitamin A deficiency and obesity
Vision	Innate and cell immunity	Down-regulation of leptin expression
Development	Antibody response	Down-regulation of resistin expression
Epithelial integrity	Epithelial tissue differentiation	Increased Th1 type response
Tissue cell growth and differentiation	Gene expression	Increased pro-inflammatory cytokines
Reproductive function	Critical for Th1 and Th2 lymphocytes differentiation	Increased UCP mRNA and reduced thermogenesis in BAT
Gene expression	T- and B-cell differentiation in the intestine	Promote adipogenesis
Immune function	Supports a Th2 anti-inflammatory response	
	Supplementation decreases morbidity and mortality due to infectious diseases	
	Supplementation improves vaccine response	

Th1, T-helper type 1 response; Th2, T-helper type 2 response; UCP, uncoupling protein; BAT, brown adipose tissue.

Thus, even in subclinical vitamin A deficiency, Th2 response is compromised. The elevated Th1:Th2 ratios observed in vitamin A deficiency lead to inflammation and low capacity of the body to fight infections. In animal models, vitamin A deficiency shifts from a Th2 response to a Th1 response, decreasing antibody production and Ig maturation[21]. This increase in the inflammatory response is due to a higher production of IFN-γ by T lymphocytes[101,102].

In addition to its effect on the T-cells response, vitamin A deficiency also diminishes the activity of neutrophils, macrophages and natural killer cells[1,3,103]. Animal models have shown that chronic marginal vitamin A status decreases number of natural killer cells and lymphocytes, affects both T-cells distribution and function, and thus increases the risk of infections with aging[103–105].

Vitamin A deficiency and the adipose tissue

The increase of the adipose tissue observed in obesity produces an increased secretion of adipocytokines, such as leptin, that, as mentioned earlier, induces an inflammatory response. Vitamin A deficiency is highly prevalent in obesity and this may produce inadequate Th1:Th2 ratio, increased leptin concentrations, and elevate pro-inflammatory cytokines levels[18,106,107]. Vitamin A deficiency reduces not only RA levels but also retinaldehyde, and therefore may be contributing to fat deposition.

In a mouse model, vitamin A deficiency increases the expression of UCP-1 mRNA and UCP-2 mRNA expressions, thus promoting reduced thermogenesis in BAT, increased body weight and increased leptin concentrations[108]. In addition, vitamin A deficiency might promote adipogenesis, adipocyte differentiation through PPAR and increased preadipocyte survival time.

Vitamin A deficiency might increase leptin expression and thus, increase the production of cytokines, contributing with the low-grade systemic inflammation observed in obesity. For example, in mice, vitamin A deficiency increased body weight, BAT, adiposity and leptin mRNA expression[108]. Low RA concentrations increase leptin and resistin expressions in brown and white adipocytes[108,109].

Resistin is an adipocytokine that inhibits adipocyte differentiation and an insulin resistance factor in both cell and animal models. *In vitro*, RA inhibits resistin expression in both brown and white adipocytes through RAR and RXR pathways[109].

Thus, vitamin A deficiency in obesity increases Th1 type response, increases the expression of leptin, resistin and UCP, and promotes adipogenesis. Vitamin A deficiency in obesity might be increasing the risk of fat deposition and also the risk of chronic inflammation associated with obesity.

The main activities of vitamin A, the role of vitamin A in the immune function and the effect of vitamin A deficiency on the immune function in obesity are summarised in Table 1.

Vitamin A supplementation and the immune response in obesity

Supplementation of vitamin A has proven to be an effective strategy to reduce specific mortality from diarrhoea[12,13]. Pooled results of twelve trials showed that preventive vitamin A supplementation reduced diarrhoea mortality by 30 % in children aged between 6 and 59 months[13]. A meta-analysis that included seven trials found a 28 % reduction in specific mortality from diarrhoea when supplementing vitamin A in children aged 6 months to 5 years of age and a decrease in the incidence of diarrhoea mortality[12].

The effect of vitamin A supplementation on leptin and inflammatory cytokines has been studied in both *in vitro* and in animal studies. *In vitro*, vitamin A supplementation has been shown to down-regulate the inflammatory response inducing a Th2 response, with a dose-dependent increase of mRNA and protein levels of IL-4, IL-5 and IL-13[98,110]. Leptin expression is inhibited by RA supplementation. Supplementing mice with RA reduces leptin mRNA concentrations, in both BAT and WAT independently of adiposity and the fat content of the diet[27,87,111]. Similarly, in human adipose tissue, RA inhibits both leptin expression and secretion[88,90]. Furthermore, it has been observed that RA supplementation and dietary vitamin A reduce both resistin mRNA and resistin circulating

concentration in animals[109]. Also, RA supplementation and vitamin A status are involved in the expression of transcription factors involved in adipogenesis and UCP in WAT and BAT in animal studies[65,108,111–112]. In rats, a high-fat diet down-regulated PPARγ and RAR mRNA expression and up-regulated cyclooxygenase-2[51]. When supplementing with RA, production of cyclooxygenase-2 was inhibited.

No studies have looked at the effect of vitamin A supplementation alone in inflammation markers in obese populations. Our group found that supplementing with low-fat milk with added micronutrients, including vitamin A, of women from rural communities in Mexico with a high prevalence of micronutrient deficiencies, reduced more body weight, BMI and total body fat compared with a control group[113]. Similarly, supplementing obese women in China with micronutrients, that also included vitamin A, resulted in less body weight and body fat than women receiving Ca supplementation alone[114]. In both studies, vitamin A and the other micronutrients may be having an effect on leptin concentrations, and also may be reducing pro-inflammatory cytokine concentrations. Supplementing obese individuals with vitamin A may be important in populations with high vitamin A deficiency, high prevalence of obesity and chronic inflammation.

Conclusions

Retinoids are important to regulate critical pathways of the immune functions. Vitamin A deficiency has important consequences on the immune response. In obesity, vitamin A deficiency seems to increase a Th1 response and elevate adipocytokine levels, and thus, may participate in the inflammatory process involved in chronic inflammation and fat deposition. The metabolism of leptin and other adipocytokines may play a critical role in the effect of vitamin A deficiency in the inflammatory response observed in obesity. To understand how vitamin A deficiency affects the immune system in obese populations provides new insights into treatment of chronic inflammation processes.

Acknowledgements

References

1. Cunningham-Rundles S, McNeeley DF & Moon A (2005) Mechanisms of nutrient modulation of the immune response. *J Allergy Clin Immunol* **115**, 1119–1128.
2. Castellani ML, Shaik-Dasthagirisaheb YB, Tripoid D *et al.* (2010) Interrelationship between vitamins and cytokines in immunity. *J Biol Regul Homeost Agents* **24**, 385–390.
3. Stephensen CB (2001) Vitamin A, infection, and immunity. *Annu Rev Nutr* **21**, 167–192.
4. Villamor E & Fawzi WW (2005) Effects of vitamin A supplementation on immune responses and correlation with nutritional outcome. *Clin Microbiol Rev* **18**, 446–464.
5. Amann PM, Eichmüller SB, Schmidt J *et al.* (2011) Regulation of gene expression by retinoids. *Curr Med Chem* **18**, 1405–1412.
6. Jarrett A & Spearman RI (1970) Vitamin A and the skin. *Br J Dermatol* **82**, 197–199.
7. Ross SA, McCaffery PJ, Drager UC *et al.* (2000) Retinoid in embryonal development. *Physiol Rev* **80**, 1021–1054.
8. Ziouzenkova O, Orasanu G, Sharlack M *et al.* (2007) Retinaldehyde represses adipogenesis and diet-induced obesity. *Nat Med* **13**, 695–702.
9. Rivera MT, De Souza AP, Araujo-Jorge TC *et al.* (2003) Trace elements, innate immune response and parasites. *Clin Chem Lab Med* **41**, 1020–1025.
10. Fraker PJ & Lill-Elghanian DA (2004) The many roles or apoptosis in immunity as modified by aging and nutritional status. *J Nutr Health Aging* **8**, 56–63.
11. Guerrant RL, Lima AA & Davidson F (2000) Micronutrients and infection: interactions and implications with enteric and other infections and future priorities. *J Infect Dis* **182**, S134–S138.
12. Imdad A, Herzer K, Mayo-Wilson E *et al.* (2010) Vitamin A supplementation for preventing morbidity and mortality in children from 6 months to 5 years of age. *Cochrane Database Syst Rev* **12**, CD008524.
13. Imdad A, Yakoob MY, Sudfeld C *et al.* (2011) Impact of vitamin A supplementation on infant and childhood mortality. *BMC Public Health* **11**, Suppl. 3, S20.
14. García OP, Long KZ & Rosado JL (2009) Impact of micronutrient deficiencies on obesity. *Nutr Rev* **67**, 559–572.
15. Strauss RS (1999) Comparison of serum concentrations of alpha-tocopherol and beta-carotene in a cross-sectional sample of obese and nonobese children (NHANES III). National Health and Nutrition Examination Survey. *J Pediatr* **134**, 160–165.
16. Switzer BR, Atwood JR, Stark AH *et al.* (2005) Plasma carotenoid and vitamins a and e concentrations in older African American women after wheat bran supplementation: Effects of age, body mass and smoking history. *J Am Coll Nutr* **24**, 217–226.
17. Vaughan LA, Benyshek DC & Martin JF (1997) Food acquisition habits, nutrient intakes, and anthropometric data of Havasupai adults. *J Am Diet Assoc* **97**, 1275–1282.
18. Villaça Chaves G, Pereira SE, Saboya CJ *et al.* (2008) Non-alcoholic fatty liver disease and its relationship with the nutritional status of vitamin A in individuals with class III obesity. *Obes Surg* **18**, 378–385.
19. Viroonudomphol D, Pongpaew P, Tungtrongchitr R *et al.* (2003) The relationships between anthropometric measurements, serum vitamin A and E concentrations and lipid profiles in overweight and obese subjects. *Asia Pac J Clin Nutr* **12**, 73–79.
20. Rocha VZ & Folco EJ (2011) Inflammatory concepts of obesity. *Int J Infl* **2011**:529061.
21. Cantorna MT, Nashold FE & Hayes CE (1994) In vitamin A deficiency multiple mechanisms establish a regulatory T helper cell imbalance with excess Th1 and insufficient Th2 function. *J Immunol* **152**, 1515–1522.
22. Halevy O, Arazi Y, Melamed D *et al.* (1994) Retinoic acid receptor-alpha gene expression is modulated by dietary vitamin A and by retinoic acid in chicken T lymphocytes. *J Nutr* **124**, 2139–2146.
23. Long KZ & Nanthakumar N (2004) Energetic and nutritional regulation of the adaptive immune response and trade-offs in ecological immunology. *Am J Hum Biol* **16**, 499–507.

24. Berger A (2000) Th1 and Th2 responses: what are they? *Br Med J* **321**, 424.
25. Jason J, Archibald LK, Nwanyanwu OC *et al.* (2002) Vitamin A levels and immunity in humans. *Clin Diagn Lab Immunol* **9**, 616–621.
26. Dawson H, Solano-Aguilar G, Beal M *et al.* (2009) Localized Th1-, Th2-, T regulatory cell-, and inflammation-associated hepatic and pulmonary immune responses in *Ascaris suum*-infected swine are increased by retinoic acid. *Infect Immun* **77**, 2576–2587.
27. Kumar M, Sunvold G & Scarpace P (1999) Dietary vitamin A supplementation in rats: Suppression of leptin and induction of UCP1 mRNA. *J Lipid Res* **40**, 824–830.
28. Kim CH (2009) FOXP3 and its role in the immune system. *Adv Exp Med Biol* **665**, 17–29.
29. Luo XM & Ross AC (2005) Physiological and receptor-selective retinoids modulate interferon gamma signaling by increasing the expression, nuclear localization, and functional activity of interferon regulatory factor-1. *J Biol Chem* **280**, 36228–36236.
30. Giguere V, Ong ES, Segui P *et al.* (1987) Identification of a receptor for the morphogen retinoic acid. *Nature* **330**, 624–629.
31. Petkovich M, Bran NJ, Krust A *et al.* (1987) A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* **330**, 444–450.
32. Mangelsdorf DJ, Thummel C, Beato M *et al.* (1995) The nuclear receptor super family: The second decade. *Cell* **83**, 835–839.
33. Aranda A & Pascual A (2001) A nuclear hormone receptors and gene expression. *Physiol Rev* **81**, 1269–1304.
34. Robinson-Rechavi M, Escriva GH & Laudet V (2002) The nuclear receptor superfamily. *J Cell Sci* **116**, 585–586.
35. Blomhoff R & Blomhoff HK (2006) Overview of retinoid metabolism and function. *J Neurobiol* **66**, 606–630.
36. Elder JR, Aström A, Pettersson U *et al.* (2002) Retinoic acid receptors and binding proteins in human skin. *J Invest Dermatol* **98**, 36S–41S.
37. Mcrane MM (2007) Vitamin A regulation of gene expression: Molecular mechanism of a prototype gene. *J Nutr Biochem* **18**, 497–508.
38. Montrone M, Martorelli D, Rosato A *et al.* (2009) Retinoids as criticals modulators of immune functions: new therapeutic perspectives for old compounds. *Endocr Metab Immune Disord Drug Targets* **9**, 113–131.
39. Ziuzenkova O & Plutzky J (2008) Retinoid metabolism and nuclear receptor responses: New insights into coordinated regulation of the PPAR-RXR complex. *FEBS Lett* **582**, 32–38.
40. Mongan NP & Gudas LJ (2007) Diverse actions of retinoids receptors in cancer prevention and treatment. *Differ Res Biol Diver* **75**, 853–870.
41. Kim CH (2011) Retinoic acid, immunity, and inflammation. *Vitam Horm* **86**, 83–101.
42. Ross AC, Chen Q & Ma Y (2011) Vitamin A and retinoic acid in the regulation of B-cell development and antibody production. *Vitam Horm* **86**, 103–126.
43. Allan LL, Stax AM, Zheng DJ *et al.* (2011) CD1d and CD1c expression in human B cells is regulated by activation and retinoic acid receptor signaling. *J Immunol* **186**, 5261–5272.
44. Gudas LJ & Wagner JA (2011) Retinoids regulate stem cell differentiation. *J Cell Physiol* **226**, 322–330.
45. Du X, Tabeta K, Mann N *et al.* (2005) An essential role for RXR alpha in the development of Th2 responses. *Eur J Immunol* **35**, 3414–3423.
46. Stephensen CB, Jiang X & Freytag T (2004) Vitamin A deficiency increases the *in vivo* development of IL-10-positive Th2 cells and decreases development of Th1 cells in mice. *J Nutr* **134**, 2660–2666.
47. Austenaa LM, Carlsen H, Hollung K *et al.* (2009) Retinoic acid dampens LPS-induced NF-kappaB activity: results from human monoblasts and *in vivo* imaging of NF-kappaB reporter mice. *J Nutr Biochem* **20**, 726–734.
48. Andela VB, Gingold BI, Souza MD *et al.* (2003) Clinical relevance of increased retinoid and cAMP transcriptional programs in tumor cells rendered non-malignant by dominant negative inhibition of NFkappaB. *Cancer Lett* **194**, 37–43.
49. Na SY, Kang BY, Chung SW *et al.* (1999) Retinoids inhibit interleukin-12 production in macrophages through physical associations of retinoid X receptor an NFkappaB. *J Biol Chem* **274**, 7674–7680.
50. Otsuki T, Sakaguchi H, Hatayama T *et al.* (2003) Effects of all-trans retinoic acid (ATRA) on human myeloma cells. *Leuk Lymphoma* **44**, 1651–1656.
51. Delage B, Bairras C, Buaud B *et al.* (2005) A high-fat diet generates alterations in nuclear receptor expression: prevention by vitamin A and links with cyclooxygenase-2 and beta-catenin. *Int J Cancer* **116**, 839–846.
52. Garbe A, Jochen B & Hämmerling U (1992) Retinoids are important cofactors in T cell activation. *J Exp Med* **176**, 109–117.
53. Hammerschmidt SI, Friedrichsen M, Boelter J *et al.* (2011) Retinoic acid induces homing of protective T and B cells to the gut after subcutaneous immunization in mice. *J Clin Invest* **121**, 3051–3061.
54. Maggini S, Wintergerst ES, Beveridge S *et al.* (2007) Selected vitamins and trace elements support immune functions by strengthening epithelial barriers and cellular and humoral immune responses. *Br J Nutr* **98**, S29–S35.
55. Kang SG, Wang C, Matsumoto S *et al.* (2009) High and low vitamin A therapies induce distinct FoxP3 + T-cell subsets and effectively control intestinal inflammation. *Gastroenterology* **137**, 1391–1402.
56. Zovich DC, Orolonga A, Okuno M *et al.* (1992) Differentiation dependent expression of retinoid-binding proteins in BFC-1beta adipocytes. *J Biol Chem* **267**, 13884–13889.
57. Villarroya F, Giralt M & Iglesis R (1999) Retinoids and adipose tissues: Metabolism, cell differentiation and gene expression. *Int J Obes* **23**, 1–6.
58. Bonet ML, Ribot J, Felipe F *et al.* (2003) Vitamin A and the regulation of fat reserves. *Cell Mol Life Sci* **60**, 1311–1321.
59. Yasmeen R, Jeyakumar SM, Reichert B *et al.* (2012) The contribution of vitamin A to autocrine regulation of fat depots. *Biochim Biophys Acta* **1821**,190–197.
60. Xue JC, Shwarz EJ, Chawla A *et al.* (1996) Distinct stages in adipogenesis revealed by retinoid inhibition of differentiation after induction of PPARgamma. *Mol Cell Biol* **16**, 1567–1575.
61. Tsutsumi C, Okuno M, Tannous L *et al.* (1992) Retinoids and retinoid-binding protein expression in rat adipocytes. *J Biol Chem* **267**, 1805–1810.
62. Villarroya F (1998) Differential effects of retinoic acid on white and brown adipose tissue: an unexpected role for vitamin A derivatives on energy balance. *Ann N Y Acad Sci* **839**, 190–195.
63. Alvarez R, De Andrés J, Yubero P *et al.* (1995) A novel regulatory pathway of brown fat thermogenesis. Retinoic acid is a transcriptional activator of mitochondrial uncoupling protein gene. *J Biol Chem* **270**, 5666–5673.

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64. Carmona MC, Valmaseda A, Iglesias R *et al.* (1998) 9-*cis* retinoic acid induces the expression of the uncoupling protein-2 gene in brown adipocytes. *FEBS Lett* **441**, 447–450.

65. Puigserver P, Vázquez F, Bonet ML *et al.* (1996) *In vitro* and *in vivo* induction of brown adipocyte uncoupling protein (thermogenin) by retinoic acid. *Biochem J* **317**, 827–833.

66. Rabelo R, Reyes S, Schifman A *et al.* (1996) A complex retinoic acid response element in the uncoupling protein gene defines a novel role for retinoids in thermogenesis. *Endocrinology* **137**, 3488–3496.

67. Alvarez R, Checa M, Brun S *et al.* (2000) Both retinoic-acid-receptor- and retinoid-X-receptor-dependent signalling pathways mediate the induction of the brown-adipose-tissue-uncoupling-protein-1 gene by retinoids. *Biochem J* **1**, 91–97.

68. Lehr L, Canola K & Léger B (2009) Differentiation and characterization in primary culture of white adipose tissue brown adipocyte-like cells. *Int J Obes (Lond)* **33**, 680–686.

69. Chawla A & Lazar MA (1994) Peroxisome proliferator and retinoid signaling pathways co-regulate preadipocyte phenotype and survival. *Proc Natl Acad Sci USA* **91**, 1786–1790.

70. Safonova I, Darimont C, Amri EZ *et al.* (1994) Retinoids are positive effectors of adipose cell differentiation. *Mol Cell Endocrinol* **104**, 201–211.

71. Kuri-Harcuch W (1982) Differentiation of 3T3 F442A cells into adipocytes is inhibited by retinoic acid. *Differentiation* **23**, 164–169.

72. Berry DC, Soltanian H & Noy N (2010) Repression of cellular retinoic acid-binding protein II during adipocyte differentiation. *J Biol Chem* **285**, 15324–15332.

73. Friedman JM (2002). The function of leptin in nutrition, weight, and physiology. *Nutr Rev* **60**, S1–S14.

74. Leibel RL (2002) The role of leptin in the control of body weight. *Nutr Rev* **60**, S15–S29.

75. La Cava A & Matarese G (2004) The weight of leptin in immunity. *Nat Rev Immunol* **4**, 371–379.

76. Sarraf P, Frederich RC, Turner EM *et al.* (1997) Multiple cytokines and acute inflammation raise mouse leptin levels: Potential role in inflammatory anorexia. *J Exp Med* **185**, 171–175.

77. Conde J, Scotece M, Gómez R *et al.* (2010) At the cross-road between immunity and metabolism: focus on leptin. *Expert Rev Clin Immunol* **6**, 801–808.

78. Stofkova A (2009) Leptin and adiponectin: From energy and metabolic dysbalance to inflammation and auto-immunity. *Endocr Regul* **43**, 157–168.

79. Lord GM, Matarese G, Howard J *et al.* (2001) The bioenergetics of the immune system. *Science* **292**, 855–856.

80. Rodriguez E, Perea JM, Lopez-Sobaler AM *et al.* (2009) Obesidad, resistencia a la insulina y aumento de los niveles de adipoquinas: Importancia de la dieta y el ejercicio físico. *Nutr Hosp* **24**, 415–421.

81. De Rosa V, Procaccini C, Cali G *et al.* (2007) A key role of leptin in the control of regulatory T cell proliferation. *Immunity* **26**, 241–256.

82. Zarkesh-Esfahani H, Pockley AG, Wu Z *et al.* (2004) Leptin indirectly activates human neutrophil via induction of TNF-alpha. *J Immunol* **172**, 1809–1814.

83. Caldefie-Chezet F, Poulin A & Vasson MP (2003) Leptin regulates functional capacities of polymorphonuclear neutrophils. *Free Radic Res* **37**, 809–814.

84. Lord GM, Matarese G, Howard JK *et al.* (1998) Leptin modulates the T-cell immune response and reverses starvation induced immunosuppression. *Nature* **394**, 897–901.

85. Siegmund B, Lehr HA & Fantuzzi G (2002) Leptin, a pivotal mediator of intestinal inflammation in mice. *Gastroenterology* **122**, 2011–2025.

86. Xiao E, Xia-Zhang L, Vulliémoz NR *et al.* (2003) Leptin modulates inflammatory cytokine and neuroendocrine responses to endotoxin in the primate. *Endocrinology* **144**, 4350–4353.

87. Felipe F, Mercader J, Ribot J *et al.* (2005) Effects of retinoic acid administration and dietary vitamin A supplementation on leptin expression in mice: lack of correlation with changes of adipose tissue mass and food intake. *Biochem Biophys Acta* **30**, 258–265.

88. Hollung K, Rise CP, Drevon CA *et al.* (2004) Tissue-specific regulation of leptin expression and secretion by all-trans retinoic acid. *Cell Biochem* **92**, 307–315.

89. Hong SE, Ahn IS, Jung HS *et al.* (2004) Effect of retinoic acid on leptin, glycerol, and glucose levels in mature rat adipocytes *in vitro*. *J Med Food* **7**, 320–326.

90. Menendez C, Lage M, Peino R *et al.* (2001) Retinoic acid and vitamin D(3) powerfully inhibit *in vitro* leptin secretion by human adipose tissue. *J Endocrinol* **170**, 425–431.

91. Sommer A, Katz J & Tarwotjo I (1984) Increases risk of respiratory disease and diarrhea in children with preexisting mild vitamin A deficiency. *Am J Clin Nutr* **40**, 1090–1095.

92. Barreto ML, Santos LM, Assis AMO *et al.* (1994) Effect of vitamin A supplementation on diarrhoea and acute lower-respiratory tract infections in young children in Brazil. *Lancet* **344**, 228–231.

93. World Health Organization (2009) Global prevalence of vitamin A deficiency in populations at risk 1995–2005. WHO Global Database on Vitamin A Deficiency. Geneva:- WHO.

94. Maggini S & Stephen B (2011) Vitaminas y oligoelementos que mejoran la función inmunitaria mediante el refuerzo de barreras epiteliales y las respuestas celular y humoral. In *Inmunonutrición: en la salud y en la enfermedad*, 1st ed., pp. 181–199 [A. Marcos, editor]. España: Editorial Médica Panamericana.

95. Yang Y, Yuan Y, Tao Y *et al.* (2011) Effects of vitamin A deficiency on mucosal immunity and response to intestinal infection in rat. *Nutrition* **27**, 227–232.

96. Stephensen CB, Rasooly R, Jiang X *et al.* (2002) Vitamin A enhances *in vitro* Th2 development via retinoid X receptor pathway. *J Immunol* **168**, 4495–4503.

97. Long KZ & Santos JL (1999) Vitamins and the regulation of the immune response. *Pediatr Infect Dis J* **18**, 284–290.

98. Aukrust P, Mueller F, Ueland T *et al.* (2000) Decreased vitamin A levels in common variable immunodeficiency: Vitamin A supplementation *in vivo* enhances immunoglobulin production and downregulates inflammatory response. *Eur J Clin Invest* **30**, 252–259.

99. Wieringa FT, Dijkhuizen MA, West CE *et al.* (2004) Reduced production of immunoregulatory cytokines in vitamin A- and zinc-deficient Indonesian infants. *Eur J Clin Nutr* **58**, 1498–1504.

100. Leal JY, Castejón HV, Romero T *et al.* (2004) Serum values of cytokines in children with vitamin A deficiency disorders. *Invest Clin* **45**, 243–256.

101. Wiedermann U, Chen XJ & Enerback L *et al.* (1996) Vitamin A deficiency increases inflammatory responses. *Scand J Immunol* **44**, 578–584.

102. Cantorna MT & Hayes CE (1996) Vitamin A deficiency exacerbates murine Lyme arthritis. *J Infect Dis* **174**, 747–751.

103. Dawson HD, Li NQ, DeCicco KL *et al.* (1999) Chronic marginal vitamin A status reduces natural killer cell number and function in aging Lewis rats. *J Nutr* **129**, 1510–1517.

104. Dawson HD & Ross AC (1999) Chronic marginal vitamin A status affects the distribution and function of T cells and natural T cells in aging Lewis rats. *J Nutr* **129**, 1782–1790.
105. Nauss KM, Mark DA & Suskind RM (1979) The effect of vitamin A deficiency on the *in vitro* cellular immune response of rats. *J Nutr* **109**, 1815–1823.
106. Maffei M, Funicello M, Vottari T *et al.* (2009) The obesity and inflammatory marker haptoglobin attracts monocytes via interaction with chemokine (C-C motif) receptor 2(CCR2). *BMC Biol* **7**, 1–14.
107. Harford KA, Reynolds CM, McGillicuddy FC *et al.* (2011) Fats, inflammation and insulin resistance: Insights to the role of macrophage and T-cell accumulation in adipose tissue. *Proc Nutr Soc* **12**, 1–10 (Epub ahead of print version).
108. Bonet ML, Oliver J, Picó C *et al.* (2000) Opposite effects of vitamin A deficient diet-feeding and retinoic acid treatment on brown adipose tissue UCP1, UCP2 and leptin expression. *J Endocrinol* **166**, 511–517.
109. Felipe F, Bonet ML, Ribot J *et al.* (2004) Modulation of resistin expression by retinoic acid and vitamin A status. *Diabetes* **53**, 882–889.
110. Dawson HD, Collins G, Pyle R *et al.* (2006) Direct and indirect effects of retinoic acid on human Th2 cytokine and chemokine expression by human T lymphocytes. *BMC Immunol* **7**, 27.
111. Felipe F, Bonet ML, Ribot J *et al.* (2003) Up-regulation of muscle uncoupling protein 3 gene expression in mice following high fat diet, dietary vitamin A supplementation and acute retinoic acid-treatment. *Int J Obes Relat Metab Disord* **27**, 60–69.
112. Ribot J, Felipe F, Bonet ML *et al.* (2001) Changes of adiposity in response to vitamin A status correlate with changes of PPAR gamma 2 expression. *Obes Res* **9**, 500–509.
113. Rosado JL, García OP, Ronquillo D *et al.* (2011) The inclusion of milk added with micronutrients increases the effectiveness of a calorie restricted diet to reduce obesity in women. *J Am Diet Assoc* **111**, 1507–1516.
114. Li Y, Wang C, Zhu K *et al.* (2010) Effects of multivitamin and mineral supplementation on adiposity, energy expenditure and lipid profiles in obese Chinese women. *Int J Obes* **34**, 1070–1077.