Vitamin A Metabolism: Challenges and Perspectives
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Abstract
Vitamins set an unprecedented example of the essential environment-gene interactions that are necessary to sustain life. Seventeen Nobel prizes were awarded in the last century for discoveries related to vitamins’ structures, physiology, and functions [1]. These discoveries help to abolish diseases related to vitamin deficiencies in the developed world and offer solutions to eradicate these disorders worldwide [2]. For example, embryonic malformations, night blindness, and immune deficiency in children were effectively treated by vitamin A supplementation [2,3]. In spite of encouraging results in vitamin-deficient subjects, wide applications of vitamin supplements in the nutrient-sufficient populations have been partially discouraging. Many clinical and supplementation trials reported increased mortality in subjects on long-term lipophilic vitamin A and E supplementations [4,5]. Especially striking deleterious effects were reported for lipophilic vitamin A and provitamin A (β-carotene) [4,6]. The answer to safe application of lipophilic vitamins for the treatment and prevention of diseases may lie in the better understanding of their interaction with genes. There are two principal levels of lipophilic vitamin interactions with genes:

1) genes control metabolism of dietary vitamin into derivatives with hormone-like properties, and
2) vitamin-derived metabolites regulate specific gene programs through signaling and transcription pathways (Figure 1).

Keywords: Retinaldehyde dehydrogenase; Raldh-1; Retinol; Abdominal fat; Alcohol dehydrogenases; Retinal
Abbreviations: ADH: Alcohol dehydrogenase; Aldh: Aldehyde dehydrogenase; atRA: All-trans retinoic acid; ARAT: Acyl CoA-retinol acyl transferase; BCMO1: β-Carotene 15,15'-carotene monoxygenase 1; BMP: Bone morphogenetic protein; βLG: Beta-Lactoglobulin; C/EBP: CCAAT enhancer-binding proteins; CRABP-II: Cellular retinoid acid-binding protein II; CRBPII: Cytosolic retinol-binding protein type III (CRBPIII); DR1: Direct repeat motif 1, peroxisome proliferator-activated receptor response element (PPRE); DR5: Direct repeat motif 1, retinoic acid response element (RARE); EBF1: Early B-cell factor; FABP: Fatty acid binding protein; HOX: Homeobox proteins; HSL: Hormone-sensitive lipase; KLF: Krüppel-like transcription factor; L-PGDS: Lipocalin-type prostaglandin (PG) D synthase; LPL: Lipoprotein lipase; MAPK: p38 Mitogen-activated protein kinase; NFATc1: Nuclear factor of activated T cells cl; PGC1α: PPARγ co-activator-1α; PML/RAR: Promyelocytic leukemia/retinoic acid receptor alpha (a); PPARγ: Peroxisome proliferator-activated receptor γ; PPRE: Peroxisome proliferator-activated receptor response element (DR1); pRB: Retinoblastoma protein; RAR: Retinoic acid receptor; RARE: Retinoic acid response element (DR5); RA: Retinoic acid; Raldh: Retinaldehyde/retinaldehyde; Raldh: Retinaldehyde dehydrogenase; RBP: Retinol-binding protein; RDH: Retinol dehydrogenases (microsomal); SDR: Short-chain dehydrogenase/reductase; Shh: Sonic hedgehog; SR-BI: Scavenger receptor class B type I; ZFP423: Zinc finger protein 423, transcription factor

Introduction
Recent groundbreaking discoveries unveiled the complex interactions in the vitamin A pathway that underline differentiation and metabolism in the majority of mammalian tissues during development and in adulthood. A summary of vitamin A metabolites and dependent genes regulating differentiation in some selected tissues is shown in (Figure 2). In this editorial, we briefly discuss some highlights and challenges in the understanding of vitamin A action. References will direct readers to the comprehensive reviews on these topics. Alphabetically-ordered abbreviations are provided in a list.

Genes Participating in Vitamin A Metabolism
Vitamin A is a generic term for retinol and retinyl esters present in the diet [7]. All metabolites emerging from these compounds are known as retinoids. Beta-carotene is defined as provitamin A because its central cleavage can potentially yield retinoids [7,8]. Metabolism of vitamin A results in the production of three major metabolites: retinol (ROH), retinaldehyde (retinal/Rald), and retinoic acid (RA) (Figure 1) [9]. In the course of vitamin A/β-carotene metabolism, a broad range of other metabolites could be produced (e.g. dihydroretinol, 4-oxo-RA and other oxidized RA derivatives, and apocarotenoids) [7,8,10]; however, their physiologic or therapeutic relevance await further investigation [11].

Vitamin A metabolism is encoded by genes participating in the absorption, uptake, transport (Figure 1, boxes), and enzymatic modification of retinoids, including major SDH/RDH and ADH families of Rald-generating enzymes and Aldh1 and AKR families [12-16]. Dysregulation of these genes has been reported in association with cancerogenesis or differentiation in different tissues (some of them are outlined in Figure 2). The key roles of RDH10, Aldh1a2, and Cyp26 enzyme in embryogenesis were demonstrated in genetically deficient mice [17,18]. The embryonic lethal phenotype in these mice limits studies on the possible causal role of these genes in tissue differentiation in adulthood. Currently, the role of vitamin A metabolizing enzymes is studied in greater detail during embryogenesis. The emerging studies on differentiation during in adulthood underscore the role of Aldh1a2-dependent RA production in antigen presentation [19], of Aldh1 enzymes in the formation of fat depots [20], RBP4/STRA6 in adipogenesis and insulin sensitivity [21], DHRS9, Aldh1, CRABP2, and

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each enzyme needs to be analyzed in conjunction with the presence of enzymes that function redundantly [12,27]. Therefore, the function of ROH, and RA from Rald (Figure 1) are mediated by a family of challenging. Hydrolysis of ROH from RE, generation of Rald from [25,26], and other differentiation and metabolic processes. The stem cell differentiation [23,24], ADH/Aldh1/AKR in cancerogenesis CRABPII in hair follicles/sebaceous glands [22], RDH, ADH, Aldh1 in metabolism are expressed in a tissue- and activity of other enzymes from this family as well as enzymes providing substrates (e.g. Rald generation for RA synthesis by Aldh1a1, a2, and a3 enzymes). Although the enzymes from the same family have common enzymatic actions, many of them exert specific functions. For instance, the Aldh1a1 enzyme can utilize other substrates if they are present at high concentrations. In contrast, Aldh1a2 and a3 enzymes utilize only Rald as a substrate [28,29]. The presence of other substrates for Aldh1a1 may potentially alter the balance of retinoid production.

Vitamin A-metabolizing enzymes are expressed in a tissue- and/
or sex-specific manner; however, the functional relevance of such expression is understudied. Recently, we showed that fat formation in detrimental visceral vs. unhealthy subcutaneous fat depots is determined by the fat-depot-specific expression of Aldh1a1 and Aldh1a3, which produce depot-specific levels of RA for adipogenesis [20]. Whether the changes in Aldh1 enzymes also influence divergent properties of visceral and subcutaneous fat remains to be investigated.

Redox properties of retinoids are another challenge hindering the investigation of vitamin A-related pathways. The majority of retinoids, but especially intermediate metabolites like Rald, undergo rapid reduction to ROH or oxidation to RA (Figure 1). Moreover, the conversion rate may depend on the redox status in the cells, since all ADH, RDH/SDH, and Aldh1 enzymes are NADH- or NADP+-dependent [16]. It is expected that several retinoid metabolites, such as Rald, RDH10, ADH4, and Aldh1 enzymes are NADH- or NADP+-dependent [16]. 9-cis RA activates PPARβ/δ [39], and all-trans RA activates PPARγ [40]. Figure 1 depicts examples of multiple other transcription factors that are under control of RA [40]. Many transcription factors, such as ZFP423, are RA-sensitive, by yet unknown mechanisms of action [33].

Cytosolic action of RAR has also been revealed. RAR appears to participate in the activation of critical signaling pathways, such as mTOR, and protein translation, at least in the neurons [40,44]. These findings raise important questions about partition of RA between cytosolic and nuclear compartments or among different transcription factors dependent on RA. The answer may lie in the binding proteins. Dr. Noy’s laboratory showed that RA binding to CRABPII activates RAR, whereas expression of KLF5 leads to activation of PPARγ [45]. Obviously, the specificity of RA responses in different tissues will also depend on the expression of different transcription factors. The dynamic changes in transcription factors during differentiation, could, potentially, alter responses to RA in the same experimental system, such as adipogenesis in 3T3-L1, which can be inhibited or facilitated by RA [20]. In adipogenesis, RA responses are also markedly influenced by RA concentration, circadian cycle, and the presence of metabolizing enzymes. Debates about RA effects in obesity continue, because vitamin A supplementation/RA administration can promote obesity or weight loss in different experimental models [20,46]. Often these experiments do not account for endogenous vitamin A metabolism and mobilization of retinoids from internal storage. RA can also mediate paracrine effects in tandem with other transcription factors: RA induces HOX transcription factors that in turn regulate RAR and Aldh1 expression in organogenesis [9]. More studies are needed to establish the hierarchy in transcription factor activation by RA [20]. Chromosome-wide studies of hormone actions led to the surprising conclusion that regulation of promoters occurred only in a minor portion of hormone-sensitive genes [47]. Such studies have not been performed for RA. Even less is known about RA epigenetic effects. Comprehensive studies on RA action will unravel molecular targets for RA responsible for the therapeutic effects and toxicity of this potent metabolite.

Retinoids participate in their own regulation. In adipocytes, the addition of RA to the cells leads to a dose-dependent inhibition of Aldh1a1 expression by a negative feedback mechanism [33]. However, this regulation could differ in other tissues and be gender-dependent. In fact, many vitamin A metabolizing enzymes are expressed in a tissue-specific manner in males and females [34] by marginally understood mechanisms. Aldh1a2 expression appears to be regulated directly by estrogen receptor in its promoter region [35], whereas other Aldh1 enzyme levels are sensitive to sex-hormones by other, undefined mechanisms [36]. The sex-specific expression of RBP4 is linked to different levels of leptin in males and females [34]. Many mice genetically deficient in vitamin A metabolizing enzymes exhibit pronounced sex differences [37]. Undoubtedly, vitamin A metabolism in men and women may determine their responses to nutrients, vitamin supplements, and retinoid therapies. Understanding of vitamin A metabolizing gene regulation is a necessary step for the development of personalized, safe, and effective therapies with retinoids.

**Retinoid-dependent Regulation of Specific Signaling and Transcriptional Pathways**

The major breakthrough in the molecular mechanisms of retinoid action came from the Dr. Chambron’s laboratory, reporting the discovery of the retinoic acid receptor (RAR) in 1987 [38], followed by identification of its heterodimerization partner RXR [39]. These receptors act as transcription factors upon binding of RA [40,41]. All RA isoforms, 4-oxo RA, ROH, and Rald, can activate RAR isoforms [42]; 9-cis RA activates RXR [39], and all-trans RA activates PPARγ/δ [43]. Figure 1 depicts examples of multiple other transcription factors that are under control of RA [40]. Many transcription factors, such as ZFP423, are RA-sensitive, by yet unknown mechanisms of action [33].

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and have been detected in vivo [49], however, their specific molecular targets remained to be discovered.

Conclusion

Possibly, vitamin A regulates the broadest range of gene programs in mammalian development, tissue differentiation, and metabolism (Figure 1). Incomplete understanding of genes participating in vitamin A metabolism and retinoid interactions with signaling and transcription pathways is a major drawback in the safe application of vitamin A. OMICS open access journal, ‘Vitamins & Trace Elements’ will foster reports, discussions, opinions, and reviews to facilitate the development of the vitamin A research field.

References


