On the sources of retinoic acid in the lung: understanding the local conversion of retinol to retinoic acid

A. Catharine Ross
Department of Nutritional Sciences and the Huck Life Sciences Institute,
The Pennsylvania State University, University Park, Pennsylvania 16802

Submitted 17 July 2003; accepted in final form 17 July 2003

Vitamin A (retinol) is the dietary precursor of several biologically active retinoids of which all-trans retinoic acid (ATRA) is the most potent known metabolite. Extensive research has characterized ATRA as the physiological ligand for the retinoic acid receptor (RAR) family of nuclear hormone receptors, and numerous reports have documented roles for retinoic acid, the RAR, and their related RXR partners in the differentiation of many types of cells, tissues, and organs (9), including the lungs (4, 7). Specific retinoid receptors have been implicated in both normal and aberrant lung development (11–13, 20). In utero, either a deficiency of vitamin A or an excess of exogenous retinoid can cause developmental abnormalities, including dysmorphogenesis of the cardiovascular and visceral organs (1). It is well established that vitamin A nutriure in the perinatal period significantly affects lung retinoid contents (19) and functional maturation (21), whereas vitamin A deficiency in the postnatal period results in pathological changes in lung parenchyma (2). Both vitamin A status and exogenous retinoid acid are significant factors in the expression of cellular and extracellular components of lung tissue (14), regulatory enzymes (22), and surfactant proteins (3).

Despite a great deal of interest in the pleiotropic effects of retinoids in many tissues, the physiological sources of tissue retinoids are poorly understood. With the use of a steady-state tracer dilution approach, Kurlandsky et al. (8) determined the proportions of retinoid acid in 10 tissues of normal rats that were derived from the uptake of plasma [3H]retinoic acid or the local production of retinoid acid from unlabeled precursors. A surprising result was the wide range of values observed in various tissues, with uptake of retinoid acid from plasma accounting for the majority of tissue retinoic acid in the brain (88%) and liver (78%), but for <10% of the retinoic acid in the epididymis, pancreas, and testis. Lung was not among the tissues reported in their study. The report from Dirami et al., one of the current articles in focus (Ref. 5, see p. L249 in this issue), makes a significant advance toward elucidating the sources of lung retinoic acid by demonstrating that isolated lung lipid interstitial cells (LIC) are capable of converting all-trans retinol to an acidic retinoid with properties that are similar and possibly identical to those of ATRA. The lung LIC (also referred to as lipocytes, Ito cells, vitamin A-storing cells, orstellate cells in the liver) have previously been identified by morphological and biochemical criteria as vitamin A-storing cells; they are thought to be part of a vitamin A-storing system that comprises similar, but possibly not identical, myofibroblastic cell types in the liver, lung, and several other organs (15). As Dirami et al. (5) have reviewed, the LIC in postnatal rat lung are concentrated at septal junctions, sites from which septa emanate. The coincidence of the anatomic location and vitamin A-storing nature of the LIC (14a), together with previous demonstrations that retinoids promote septation (10), led the authors to propose that the lung’s LIC may be a site of retinol oxidation and production of more biologically active metabolites, which could produce downstream effects on gene expression in LIC or neighboring cells. To test their proposal, the authors used a series of morphological, biochemical, and molecular methods which, together, have demonstrated: 1) the vitamin A-storing nature of the lung LIC, 2) their ability to take up and oxidize all-trans retinol, and 3) the induction by medium transferred from retinoid-enriched LIC to cultured pulmonary microvascular cells of the gene for cellular retinol-binding protein (CRBP), which is proposed to represent a functionally relevant outcome of increased retinoic acid biosynthesis and secretion. These new data help to fill a significant gap in understanding the sources of retinoic acid in the lungs. The demonstration that LIC secrete most of the acidic retinoid they produce, and that other cells can take up and respond to the newly synthesized retinoid, suggests that the LIC play at least a paracrine role, and possibly autocrine and endocrine roles as well, in the biological activities of acidic retinoids in lung alveoli.

One or more types of the cytoplasmic/CRBP are known to function in the conversion of all-trans retinol to retinyl esters, the major storage form of vitamin A, and the oxidation of retinol to retinal for retinoic acid biosynthesis (16–18). In some but not all tissues, the level of CRBP is increased after exposure to retinoic acid. Dirami et al. (5) showed that conditioned medium from retinoid-enriched LIC can, upon transfer to cultured pulmonary microvascular cells, produce an increase in the level of CRBP mRNA. This result constitutes a proof of principle that the retinoid(s) metabolized by LIC is capable of exerting a biological effect previously demonstrated for authentic retinoic acid. To solidify these interesting results, it is important that further analysis be conducted of the conditioned medium from retinol-incubated LIC to firmly establish the identity of the acidic retinoid metabolite or metabolites they produce. The tentative identification of the newly formed retinol metabolite as retinoic acid is based on comigration on reverse-phase HPLC of the 3H-labeled acidic metabolite with a standard of ATRA. However, due to the existence of several geometric isomers of retinoic acid and the possible comigration of more than one retinoid metabolite, a more detailed characterization of the newly produced endogenous metabolite is a necessary next step.

In the normal state, retinoic acid circulates in plasma at nanomolar concentrations, bound to albumin, and turns over...
very rapidly with a typical half-life, in rodents, of less than an hour (6). Most studies of retinoid-regulated gene expression have used supraphysiological concentrations of retinoic acid added to cultured cells or, less frequently, administered to animals in vivo. Although such experiments have demonstrated the potential scope of retinoic acid-regulated gene expression, they may not be informative concerning the regulation of gene expression when retinoic acid is produced locally from diet-derived precursors. It is important to elucidate when, where, and how retinoic acid is produced from its precursors. Lung LIC (5) is a step in this direction. The new information presented on retinol metabolism by lung LIC (5) is a step in this direction.

REFERENCES


