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

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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 nutriture 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]retinoid 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 retinoid acid in the brain (88%) and liver (78%), but for <10% of the retinoid 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 retinoid 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, or stellate 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 probably not identical, myofibroblastic cell types in the liver, lung, and several other organs.

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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 dietary precursors because such mechanisms may well be part of a finely tuned, steady-state, homeostatic system in which retinoid metabolism and retinoid-regulated gene expression are spacially and functionally linked. The new information presented on retinol metabolism by lung LIC (5) is a step in this direction.

REFERENCES


