A Crucial Role for Cellular Retinol-Binding Protein I in Retinoid Signaling

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Retinol (the prototypic vitamin A) and its metabolites called retinoids play important physiologic roles in embryonal development, vision, maintenance of epithelial differentiation, immune functions, and reproduction (1). Many of these functions are mediated by retinol metabolites such as all-trans-retinoic acid (ATRA) (2). ATRA modulates gene expression by means of nuclear receptors that are members of the steroid hormone gene superfamily. These receptors, retinoic acid receptors (RARs) and retinoid X receptors (RXRs), appear in at least three subtypes, designated α, β, and γ. The receptors function as ligand-activated heterodimeric DNA-binding transcription enhancing factors and regulate the transcription of various genes, which play important roles during development and in adult tissues. Aberrant expression and function of specific retinoid receptors, primarily RARβ, have been associated with cancer development and progression (3,4). However, recent studies have highlighted additional mechanisms for abrogation of retinoid signaling in carcinogenesis. These involve abnormalities located upstream of retinoic acid and its nuclear receptors. These defects interfere with retinol storage and its metabolism to retinoic acid and result in a localized retinoid deficiency. Interestingly, we have suggested that decreased levels of RARβ may be, at least in part, caused by local vitamin A deficiency (5).

Dietary retinol is stored in the liver in specialized cells and delivered to various target tissues via a retinol-binding protein...
(6). However, retinol is also stored in various extra-hepatic tissues including breast epithelial cells. Retinyl esters are the major storage form of retinol as they can be concentrated in lipid droplets that serve as a storage organelle from which retinol can be mobilized rapidly for further metabolism to ATRA or other retinoids (7). The esterification of retinol in preparation for storage is catalyzed by the enzyme lecithin:retinol acyltransferase (LRAT), which is also localized in the lipid droplets.

L. Gudas and her colleagues have shown that retinol esterification is diminished in various human carcinoma cell lines, including oral cavity, kidney, skin, breast, and prostate, relative to their respective normal cell counterparts (8,9). They provided evidence that the reduced esterification was associated with a lower expression of LRAT in the tumor cells and tissue relative to the corresponding normal cells or tissue (9). Because LRAT expression is regulated by retinoids, the decrease in stored retinol and the consequent decline in free retinol and its metabolite ATRA may be a reason for the decrease in LRAT levels. Thus, lower storage of retinol in malignant tissues would result in a state of local retinoid deficiency despite adequate dietary vitamin A intake and liver storage.

R. Mira-y-Lopez and colleagues have previously shown that cellular retinol-binding protein I (CRBP-I) level decreased in breast cancer cells and its restored expression resulted in tumor suppressive effects (10). Others have shown that CRBP-I expression is silenced by DNA methylation in many tumors (11) as are several tumor suppressor genes including RARβ2 (12).

In this issue of the Journal, the same group (13) addressed the question of the role of CRBP-I in retinoid signaling focusing on breast cancer. Specifically, they investigated whether decreased CRBP-I expression leads to a corresponding decline in retinoid-dependent effects on differentiation and tumor progression. The interest in CRBP-I in the context of retinoid signaling is plausible given that it facilitates the esterification and storage of retinol, because LRAT is much more active when its substrate retinol is presented in a complex with CRBP-I (14).

Farias et al. (13) summarized a series of elegant studies combining complementary approaches, which have shown that in mammary epithelial cells, CRBP-I is localized primarily in lipid droplets, which are the organelles where retinol is stored. Furthermore, they provide evidence linking the presence of CRBP-I in these droplets with enhancement of retinol storage, increased activity of retinoic acid receptor (RAR), and stimulated acinar differentiation. This stimulation of differentiation could be evoked by retinoic acid treatment and diminished by RAR antagonist treatment. Finally, CRBP-I suppressed tumorigenicity of mouse mammary gland malignant cells and human breast cancer xenografts in athymic mice. Based on these results they have concluded that CRBP-I plays a pivotal role in retinoid signaling in that physiologic activation of RAR is dependent on ATRA level and ATRA level depends on the availability of stored retinol its precursor. Their findings support the model in which CRBP-I mediates retinol storage and a sustained decrease in CRBP-I would lead to lowering of ATRA production and abrogate RAR level and activity, leading to loss of cell differentiation and tumor progression.

It has been suggested that physiologic retinoids may act as endogenous chemopreventive factors, suppressing the expansion of early abberant clones, thus preventing the formation of premalignant lesions. This contention is supported by the finding that retinoid signaling can be compromised at different levels at early stages of cancer development. Several groups have demonstrated that RARβ levels decrease at early stages of carcinogenesis (i.e., in premalignant lesions in vivo and in vitro) (3). It would be interesting to determine whether the decreased levels of CRBP-I and LRAT also occur in the premalignant stages of cancers shown to have decreased levels of these proteins. Any one of these changes could be sufficient to abrogate retinoid signaling as they all appear to be related—ATRA level depends on retinol level, retinol level is dependent on both CRBP-I and LRAT, and the expression of both LRAT and CRBP-I is controlled at least in part by ATRA. RARβ silencing by methylation of CpG islands in its promoter has been demonstrated in many different cancers as has CRBP-I silencing. Four of five breast carcinoma cases that did not express CRBP-I also did not express RARβ (15). The mechanism of LRAT suppression in cancer cells has not yet been elucidated. It would be interesting to determine whether the three genes, CRBP-I, LRAT, and RARβ, are down regulated coordinately and to explore the prognostic value of each of these aberrations alone and in combination. Estrogen receptor positive (ER+ / breast cancer cell lines are growth inhibited by ATRA and 4-oxoretinol, whereas only 4-oxoretinol is effective against ER− tumors (16). Therefore, the decrease in retinol storage due to CRBP-I and LRAT downregulation is expected to affect the development of both ER+ and ER− breast cancers.

REFERENCES


