Retinoic Acid Binding Proteins and Cancer: Similarity or Polarity?

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Abstract

Vitamin A is a precursor for the multiple active metabolites, known as retinoids, among which retinoic acid (RA) is one of the most essential for the embryonic development as well as for the tissue maintenance and renewal in adults. RA upregulates the transcription factors that control the expression of a huge number of genes regulating differentiation, proliferation, cellular death and survival. Potent anticarcinogenic activity of RA has been repeatedly shown for several types of cancer cells. However, the implementation of RA as a therapeutic agent for cancer treatment is limited by the rapid acquisition of RA resistance. Moreover, in some type of tumors RA promotes rather than inhibits cell malignancy. One of the reasons for the development of RA resistance and such distinct functional significance of RA in carcinogenesis is attributed to the proteins, responsible for the delivery of RA to its nuclear receptors regulating transcription and intracellular signaling. The association with the different kind of RA binding proteins largely determines the future fate of RA and its intracellular activity.

Keywords: Retinoic acid; RAR; CRABP-I; CRABP-II; FABP5

Introduction

Retinoic acid (RA) is one of the most active derivatives of vitamin A (retinol), belonging to the huge family of retinoids. RA is the first open morphogen in vertebrates and plays a huge role in embryonic development. In adults RA regulates multiple biological processes including tissue remodeling and regulation of the immune response. The intracellular functions of the RA are also associated primarily with stimulation of differentiation or apoptosis and with negative regulation of proliferation. Due to its pro-differentiation activity RA plays predominantly anti-oncogenic or tumor-suppressive role in the context of carcinogenesis. At present an active attempts are being made to use RA and its derivatives in the therapy of malignant neoplasms [1-5]. However, the use of PA is strongly restricted by the rapid acquisition of cell resistance, as well as by a large number of side effects [5,6].

In addition, in some types of tissues (primarily in skin and in neuronal cells), RA plays an inverse function, stimulating cell survival and proliferation [7-11]. The reasons for such different functional significance of the RA, as well as the mechanisms of cell resistance to the RA, are not fully understood. The growing pool of evidences points to the key role in these processes of the group of proteins that bind PA in cytoplasm and largely determine its further fate as well as its effect on cells. At the same time, the data on the significance of each of these proteins are very contradictory. This review is an attempt to consider current knowledge on the multiple roles that RA-binding proteins play in mediating of the biological activities of retinoic acid, as well as to assess their significance for cancer progression.

RA Nuclear Receptors

The "canonical" activity of the RA is accomplished by regulating the activity of several hundred genes. This activity is mediated by nuclear receptors of RA, ligand-inducible transcription factors belonging to the super family of nuclear hormone receptors that regulate the expression of genes containing retinoid-responsive elements (RARE) in their promoter regions. The main receptors of the RA are RAR (RAR α, β and γ) and RXR proteins, which preferentially bind different isoforms of RA and are capable of forming heterodimers. Besides, RA binds the third nuclear receptor, PPARβ / δ, which functions, like RAR, in a heterodimer with RXR. Importantly, the repertoire of genes under RA control includes different groups of -RAR- and PPARβ / δ-dependent ones.

RA binding proteins.

Intracellular transport of hydrophobic RA and its delivery to the different type of receptors is conducted by the members of lipid-binding proteins (iLBPs) family: CRABP-I and CRABP-II
In fact, there are 2 high-homologous (74% homology) CRABP proteins: CRABP-II and CRABP-I, both bind RA to a similar extent (CRABP-I slightly better than CRABP-II) [12], but the significance of this binding seems fundamentally distinct. Binding of RA with CRABP-II protein causes conformational changes leading to the activation of the nuclear localization signal (NLS) and subsequent translocation of protein into the nucleus where CRABP-II interacts directly with RAR proteins. This interaction significantly facilitates the formation of the active complex of RA-RAR and enhances the transcriptional activity of RAR receptors. In accordance with this activity, the CRABP-II protein is commonly considered as tumor suppressor, and that is confirmed by a number of data [9,26–28]. At the same time there is also some evidence of tumor-promoting role of CRABP-II protein [29–31]. It is not excluded, however, that this role may not be related to its RA binding activity (see below).

The mechanisms of CRABP-I activity are much less understood. Despite that CRABP-I, like CRABP-II could be found in the nucleus [32], this protein does not directly interact with RARs. Accordingly, CRABP-I-mediated transfer of RA to its receptors requires first the dissociation of the RA-CRABP-I complex and the subsequent association of RA with RAR [12,33]. Therefore, even if CRABP-I is able to activate the RAR-dependent transcription, it does this less efficiently than CRABP-II. One of the possible functions of CRABP-I can be protection of cells from the excess of retinoic acid. In support of this hypothesis several studies show a reduction in the effects of RA in the presence of CRABP-I. It is assumed that this protein may sequester RA in the cytoplasm or even contribute to its catabolism in the mitochondria [34,35]. There is also evidence that retention of PK by CRABP-I interfere with its interaction with CRABP-II, thereby suppressing CRABP-II-RAR-dependent signaling [36]. Finally, there is evidence that CRABP-I has no effect on RA effects at all, including on the transcriptional activity of RAR [12,37] and on the expression of retinoid responsive genes, although causes a decrease in intracellular RA concentration [38]. In addition, our own data indicate that CRABP-I can enhance tumorigenicity of transformed cells, regardless to its RA-binding ability [39]. In any case, it seems like most if not all the known functions of CRABP-I are attributed to its activity in the cytoplasm.

In this respect, recently published data on “non-canonical” activity of RA, in the mediating of which CRABP-I can participate, seems very interesting. Thus, it was shown, that RA can stimulate non genomic activation of the key signaling pathways such as MAPK- and Akt-dependent cascades. Particularly, all-trans retinoic acid (atRA) promoted activation of the PI3k/Akt pathway via transcription-independent mechanisms by translocation of RARs to the plasma membrane and association of RARs with Akt [40]. The same group also recently reported the transcription-independent mechanisms of Erk1/2 activation by atRA [41]. Importantly, CRABP-I can contribute to this non-canonical activity of the RA, what has been demonstrated in two studies. The authors have found that CRABP-I mediates the non-canonical, RAR- and membrane signal-independent activation of ERK1/2 by atRA in various cellular backgrounds [42]. Noteworthy, in this case CRABP-I-dependent activation of Erk1/2 resulted in the stimulation of apoptosis and correspondingly, CRABP-I demonstrated anti-oncogenic activity [43]. In general, the functional significance of CRABP-I in carcinogenesis remains poorly understood, and the data on this issue are highly controversial - some testify to its tumor suppressing activity [44–48] while others indicate its association with cancer or with poor prognosis for cancer patients [36,49].

The situation is further complicated by the fact that both CRABP homologs apparently have activities and target proteins independent from RA and its receptors. In particular, for CRABP-II, the direct interaction with the members of Hu group of proteins has been shown recently [50]. These proteins are involved in post-transcriptional regulation of gene expression and mRNA stability. Interestingly, the protein-protein interaction of CRABP-II with HuR markedly increases the affinity of HuR for certain target transcripts. CRABP-II thus enhances the stability and increases the expression levels of these transcripts including mRNAs for the certain proapoptotic genes, such as Apaf-1 and Casp7 as well as for HuR itself. Therefore CRABP-II can realize anticarcinogenic activity using both mechanisms – RAR-dependent stimulation of transcription and up regulation of HuR [51]. However, in neuroblastoma cells CRABP-II apparently plays an opposite role, promoting cell malignancy. Notably, this activity is also associated with Hu proteins. In this case, CRABP-II through not well understood mechanism stimulates the production of HuD and HuB proteins, causing an increase in MycN expression, which is one of the main criteria for poor prognosis in neuroblastomas [52].

In glioblastomas (GBM), the accumulation of CRABP-II in the cytoplasm has been also determined as a factor of poor prognosis. The authors of this study showed, that CRABP-II accumulates in the cytoplasm of GBM cells, attenuating the transcriptional activity of RARs and thereby promoting tumor cells survival [31].
These data are in good agreement with the results of CRABP proteins study in breast cancer cells, where it has been shown that nuclear but not cytoplasmic, CRABP-II was positively associated with patient survival, while cytoplasmic CRABP-I was associated with a poor prognosis. Moreover, the authors of this research propose that CRABP-I accumulation in the cytoplasm prevents RAR activation in the nucleus. Noteworthy, this is one of the very few articles where all three RC binding proteins CRABP-I, CRABP-II as well as FABP5 were studied simultaneously in the same cells. The authors found that CRABP-I negatively regulates CRABP-II expression and also suppress CRABP-II activity via CRABP-I-dependent sequestration of RA in cytoplasm and repression of RA-mediated nuclear translocation of CRABP-II [36]. Given that expression of genes encoding described above RA-binding proteins, in turn, are themselves controlled by RAR transcriptional factors, the possibility of their mutual regulation seems very similar to the truth.

Conclusion

Summing up, it should be noted that many aspects of the functional activity of the RA-binding proteins remain unexplained. For example, the role of CRABP-I in the nucleus remains completely unclear. The question of similar or (more likely) the opposite role of CRABP-I and CRABP-II homologs with respect to carrying out RC-dependent signaling is also left open. The same concerns their role in cancerogenesis in general. It is likely that these proteins could be at least partially responsible for the different effects of RA in different types of cancer, and also could contribute to the formation of the resistance to RA treatment. The only thing that seems obvious is the great importance of these proteins in carcinogenesis and the need for their further research. This should include the simultaneous study of all RA-binding proteins in the same cells, an analysis of their activity both in the cytoplasm and in the nucleus, and estimation of their effects on the canonical and non-transcriptional activity of RA.

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