

**Brief Communication**

**Interaction between cellular retinoic acid-binding protein II and histone hypoacetylation in renal cell carcinoma**

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**Abstract:**

Renal cell carcinoma is a rare but serious malignancy. Since a reduction in the level of retinoic acid receptor beta 2 (RARbeta2) expression in cancer cells due in part to histone hypoacetylation which is controlled by histone deacetylase (HD), the study on the interaction between cellular retinoic acid-binding proteins II (CRABP II), which is proposed to have its potential influence on retinoic acid (RA) response, and HD can be useful. Comparing to CARBP II and HD, the CARBP II-HD poses the same function and biological process as HD. This can confirm that HD has a significant suppressive effect on the expression of CARBP II. Therefore, reduction in the level of RARbeta2 expression in cancer cells can be expected and this can lead to failure in treatment of renal cell carcinoma with RA. The author hereby propose that additional HD inhibitor should be added into the regimen of RA to increase the effectiveness of treatment.

**Key Words:** Retinoic acid, Cellular retinoic acid-binding proteins, Histone deacetylase, Renal cell carcinoma

## Introduction:

Renal cell carcinoma or kidney cancer, although relatively rare when compared to other malignancies, occurs not uncommonly in patients with renal disease and is often discovered incidentally during the initial nephrologic work-up.[1] While surgical approaches are generally curative when the disease is confined to the kidney, one-third of the cases that present in the metastatic form and require conventional medical therapy are associated with a truly dismal patient survival rate.[1] Recently, several novel and promising therapeutic approaches to renal cell carcinoma are emerging.

Retinoic acid (RA) and its derivatives possess antiproliferative and tumor-suppressive abilities and are successfully used in the treatment of various malignancies. However, in metastatic renal cell carcinoma, its application did not meet first expectations.[2] As the exact mechanisms of RA action and especially the role of the cellular retinoic acid-binding proteins (CRABP) still remain unclear. CRABP II is proposed to have its potential influence on RA response in renal cell carcinoma [2]. Touma et al said that the retinoid-induced up-regulation of retinoic acid receptor beta (RARbeta) correlated with antitumor effects in renal cell carcinoma [3]. They also noted that there was a reduction in the level of RARbeta2 expression in cancer cells due in part to histone hypoacetylation which is controlled by histone deacetylase (HD).[3]

To study the interaction between two proteins is hard. Luckily, the new development in bioinformatics can be applied in nanoscale genomics and proteomics research. Here, the author used a recent gene ontology technology to predict the molecular function and biological process due to the interaction between CRABP II and HD.

## Materials and Methods:

### A. Getting the sequence

The database Pubmed was used for data mining of the amino acid sequence for CRABP II and HD.

### B. Prediction of molecular function and biological process

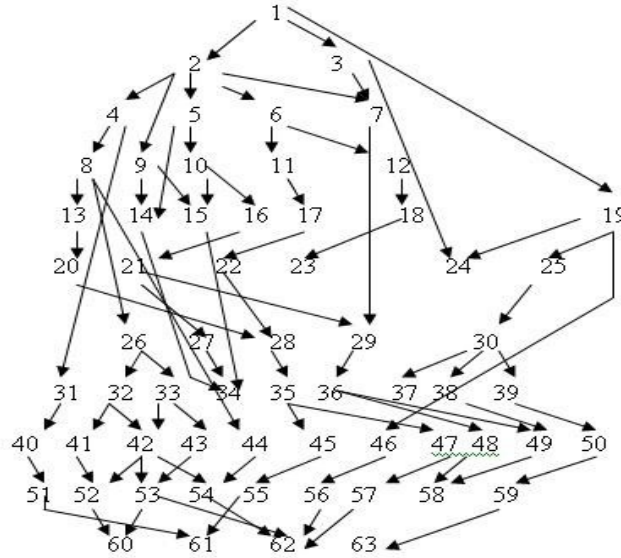
The author performs prediction of molecular function and biological process of CRABP II, HD as well as combination between CRABP II and HD (CRABP II-HD) using a novel gene ontology prediction tool, GoFigure. [4] GoFigure is a computational algorithm tool which is recently developed in gene ontology.[4] The tool accepts an input DNA or protein sequence, and uses BLAST to identify homologous sequences in gene ontology annotated databases.[4] The approach is to use a BLAST search to identify homologs in public databases that have been annotated with gene ontology terms.[4] These include: SwissProt, Flybase (Drosophila), the Saccharomyces Genome Database (SGD), Mouse Genome Informatics (MG) and Wormbase (nematode).[4] The contents of the results will show results for molecular function as well as biological process of the studied protein.[4] The prediction of molecular function and biological process were presented and compared.

### Results:

From searching of the database PubMed, sequence of CRABP II and HD were derived. Using GoFigure server, the molecular function and biological process in CRABP II, HD as well as CRABP II-HD are predicted. The molecular function and biological processes of CRABP II, HD as well as CRABP II-HD are similar as presented in presented in Table 1. The function and biological process of HD and CARBP II-HD are same.

**Table 1. The summary on the molecular function and biological process of CRABP II, HD as well as CRABP II-HD.**

	<b>Molecular function</b>	<b>Biological process</b>
CARBP II	1.Lipid binding 2.Retinoid binding	1.Epidermal differentiation 2.Regulation of transcription, DNA- dependant 3.Transport 4.Signal transduction
HD	1.Transcription corepressor activity 2.Specific transcriptional repressor activity 3.Histone deacetylase activity	1.Negative regulation of transcription from Pol II protomor 2.Histone deacetylation 3.Chromatin silencing 4.B cell differentiation 5.Neurogenesis 6.Negative regulation of myogenesis
CARBP II and HD	1.Transcription corepressor activity 2.Specific transcriptional repressor activity 3.Histone deacetylase activity	1.Negative regulation of transcription from Pol II protomor 2.Histone deacetylation 3.Chromatin silencing 4.B cell differentiation 5.Neurogenesis 6.Negative regulation of myogenesis



**Figure 1. Expected biological process of CRABP II-HD**

**Discussion:**

New developments have forced a re-evaluation of our understanding for diagnosis and treatment of renal cell carcinoma. RA is a new agent used for cancer therapy. [5,6] However, the application of RA in renal cell carcinoma is not favorable. Reduction in the level of RARbeta2 expression is believed to be an important factor.[3] To access the interaction between CRABP II and HD is therefore useful for renal cell carcinoma treatment.

Based on the recent advance in the genomics technology, current microarray technologies permit the examination of gene expression patterns of tens of thousands of genes.[4] While one can check the literature, a rapid means to get some idea of potential function of a gene product is to obtain the ontology terms that describe the gene.[4] The gene ontology is developed for this specific purpose. Here, the author used a gene ontology tool to predict the function aberration due to the interaction between CRABP II and HD.

Comparing to CARBP II and HD, the CARBP II-HD poses the same function and biological process (Figure 1) as HD. Lost of all CARBP II after interaction can be seen. This can confirm that HD has a significant suppressive effect on the expression of CARBP II. Therefore, reduction in the level of RARbeta2 expression in cancer cells can be expected and this can lead to failure in treatment of renal cell carcinoma with RA. The author hereby purpose that additional HD inhibitor should be added into the regiment of RA to increase the effectiveness of treatment. Indeed, HD inhibitor is proved to elicit an inhibition of cell proliferation in renal cell carcinoma cell lines. [7] Of interest, such combination is noted for the effectiveness in leukemia [8] as well as prostate cancer [9] treatment. However, further experimental studies are

needed before making a conclusion on this topic. The finding in this study is not only supports the previous knowledge on RA regimen but also gives the new view on the treatment of renal cell carcinoma.

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