

Opposite effects of retinoic acid in cancer

Objective

The aim of this work is to make a review of the role of retinoic acid in cancer. Also to understand the problems of the retinoic acid (RA) therapy used in many cancers.

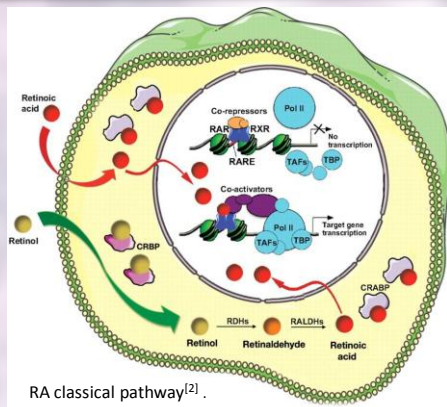
Roger Flores Costa
rogerflorescosta@gmail.com
 Bachelor's Thesis, Degree in
 Biochemistry
 Universitat Autònoma de
 Barcelona
 June 2014



Introduction

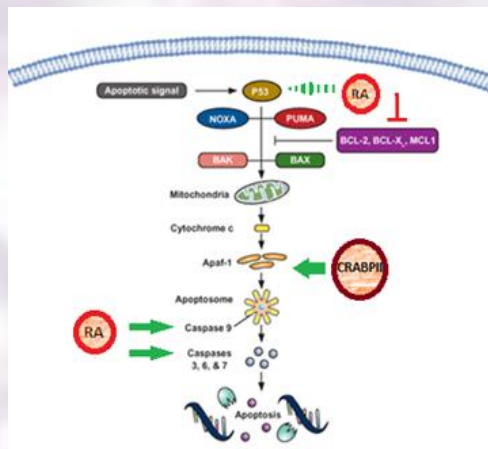
Retinoic acid (RA), which is a vitamin A derivative, has been used as a therapy against cancer thanks to its antiproliferative activity. The problem is that some cancers show resistance to the treatment, not even no effect, but also contrary actions, the overcoming of these actions would be very useful for therapy. We will study these functions and what determines if apoptotic or antiapoptotic action is found in the cancer^[1].

RA Classical Pathway



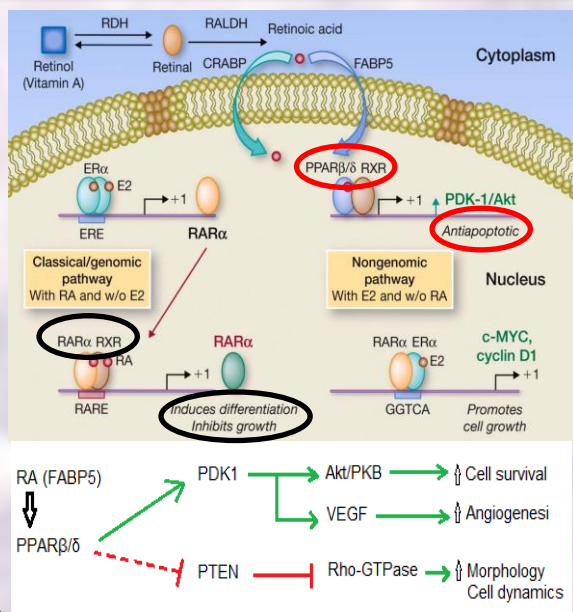
RA can be synthesized from retinol bound to cellular retinol-binding protein (CRBP) in the cytosol. RA binds cellular RA binding protein (CRABP) in cytosol and it drives RA to the nucleus, where it activates the receptors RXR-RAR dimers that control different gene expression through RA response elements (RAREs), multiple co-activators and co-repressors participate in the process^[2].

RA Antiproliferative Activity



RA upregulates caspase 9 and p53 expression and downregulates Bcl-2 proteins, increasing apoptotic pathway, it also increases the expression of caspases 3, 6 and 7, increasing the susceptibility to apoptosis. CRABP-II can also be involved, upregulating Apaf-1, the main component of the apoptosome^[3].

RA Antiapoptotic Activity as compared with the classical pathway



Top image: RA pathways (modified from [4]).
 Bottom image: PPARβ/δ target genes and effects (self-created).

Conclusions

- More knowledge about the RA target genes is still needed, this could provide new therapeutic targets.
- The control of CRABP-II/FABP5 ratio could overcome the RA treatment opposite effects. Inhibitors or siRNA against FABP5 could be a good strategy.
- Retinoic Acid treatment could be very useful and effective against some cancer types if the actions are completely understood and the current problems are solved.

References

- [1] Das, B. C. (2014). Retinoic acid signaling pathways in development and diseases. *BIOORGAN MED CHEM*, 22(2), 673–83.
- [2] Rhinn, M., & Dollé, P. (2012). Retinoic acid signalling during development. *Development*, 139(5), 843–58.
- [3] Noy, N. (2010). Between death and survival: retinoic acid in regulation of apoptosis. *ANNU REV NUTR*, 30, 201–17.
- [4] Connolly, R. M., Nguyen, N. K., & Sukumar, S. (2013). Molecular pathways: current role and future directions of the retinoic acid pathway in cancer prevention and treatment. *CLIN CANCER RES*, 19(7), 1651–9.
- [5] <http://www.bioncology.com>.