

# RETINOIDS AS THERAPEUTIC AGENTS AGAINST NEUROBLASTOMA

Marta Garcia Forn  
Ciències Biomèdiques, Universitat Autònoma de Barcelona



## INTRODUCTION

Retinoids are lipophilic vitamin A derivatives that have an important role throughout life, since they are essential in normal embryo development and in the maintenance of physiological processes such as reproduction, vision, immunomodulation, and tissue repair. At a cellular level, they present pro-differentiating, anti-proliferative, pro-apoptotic, and anti-oxidant effects. These characteristics make them attractive potential chemopreventive and chemotherapeutic agents for cancer's therapy. The aim of this study is to unravel the mechanisms of action of retinoids in normal cells and in one of the most lethal cancers of childhood, neuroblastoma.

## METHODS

The main source of information was PubMed database. A first search of reviews about retinoids and "retinoids AND neuroblastoma" was followed by a search of those original articles which seemed more relevant.

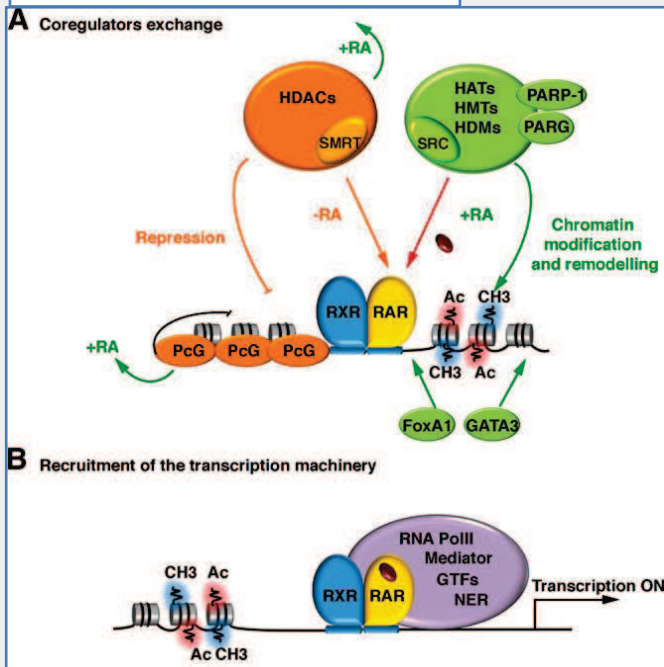
## RESULTS

### General mechanisms of action of retinoids

ATRA (all-trans retinoic acid), 13-cis-RA and 9-cis-RA are natural retinoids that have both genomic and nongenomic effects:

- **Genomic effects:** by binding to two nuclear receptors that act mostly as heterodimers, RAR (retinoic acid receptor)/RXR (retinoid x receptor), retinoids induce the transcription of their target genes. The interaction ligand-receptor leads to the recruitment of chromatin modifiers that decondense the chromatin of the promoter region of these genes, the called RARE (RA response elements) region. Consequently, transcription is activated. When there are no ligands, condensation of chromatin in RARE occurs, turning off the transcription. (Figure 1).
- **RA target genes:** important role in controlling cell proliferation, differentiation and apoptosis. *MYC*, *FOXA1*, *GATA3*, and *HOX* genes, among many others.
- **Nongenomic effects:** activation of several kinases cascades, such as p38MAPK/MSK1 and ERK/MAPK pathways.

Figure 1. General genomic mechanisms of retinoids<sup>1</sup>



## Retinoids in neuroblastoma

### Neuroblastoma (NB):

- Most common extracranial solid malignant tumor in childhood
- Cause of 15% of cancer-related deaths in children<sup>2</sup>
- Undifferentiated neuroectodermal cells → sympathetic nervous system affected
- High – risk NB:
  - Most of them, amplification of *MYCN* oncogene
  - Long – term survival rate without RA: <20%<sup>3</sup>
  - Long – term survival rate with RA: <40%<sup>3</sup>
  - Actual treatment: myeloablative chemotherapy + bone marrow transplantation + 160 mg/m<sup>2</sup>/day 13-cis-RA (maintenance therapy)

### Effects of ATRA and 13-cis-RA in neuroblastoma cells:

- Inhibition of proliferation: via decreasing *MYCN* levels (Figure 2)
- Neuronal differentiation: via activating ERK1/2 pathway (Figure 3)
- 13-cis-RA less toxic and more effective than ATRA → 13-cis-RA in NB treatment

Figure 2. Inhibition of NB cells proliferation by RA

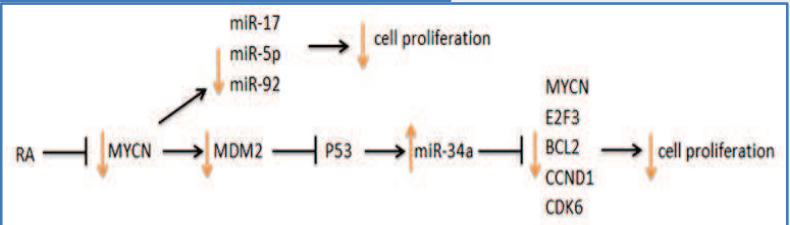
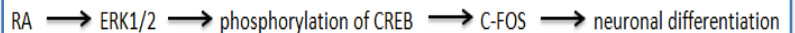


Figure 3. Stimulation of neuronal differentiation by RA



### Acquisition of drug resistance:

- NB cells eventually develop resistance to 13-cis-RA (Figure 4).
- Alternative: N-(4-hydroxyphenyl)-retinamide (fenretinide or 4-HPR) (Table 1)

Figure 4. Mechanisms of drug-resistance development

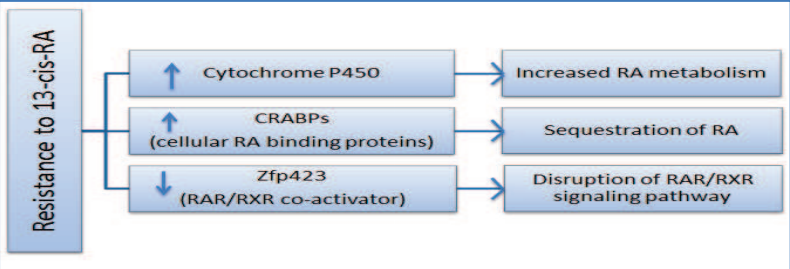


Table 1. Characteristics and mechanisms of action of fenretinide

Characteristics
Synthetic retinoid
Low systemic toxicity
Promising clinical trials
Mechanisms of action
Active against 13-cis-RA – resistant NB cells
Kills by apoptosis and necrosis
Generates reactive oxygen species (ROS), free radicals, ceramide and cytochrome c

## CONCLUSION

Retinoids act as anti-proliferative agents in neuroblastoma cells by decreasing the amount of the *MYCN*, an oncogene which is frequently amplified in high-risk neuroblastoma. By a nongenomic mechanism, they also stimulate neuronal differentiation. Thus, retinoids seem promising chemotherapeutic agents against this type of cancer. Although the long-term survival is still low, the incorporation of natural retinoids as maintenance therapy has supposed a step forward in the fight against high-risk neuroblastoma and the good results of the synthetic retinoid fenretinide are encouraging.

1. Al Tanoury Z, Piskunov A, Rochette-Egly C. Vitamin A and retinoid signaling: genomic and nongenomic effects. *J. Lipid Res.* 2013;54(7):1761–75.
2. Park, J. R., Eggert, A., & Caron, H. Neuroblastoma: biology, prognosis, and treatment. *Pediatric clinics of North America.* 2008; 55(1): 97–120.
3. Matthey KK, Reynolds CP, Seeger RC, Shimada H, Adkins ES, Haas-kogan D, et al. Long-Term Results for Children With High-Risk Neuroblastoma Treated on a Randomized Trial of Myeloablative Therapy Followed by 13-cis-Retinoic Acid: A Children's Oncology Group Study. *J. Clin. Oncol.* 2014;27(7):1007–13.