Deciphering oncogenic activity of Retinoic acid receptor alpha (RARα) in non-APL-AML

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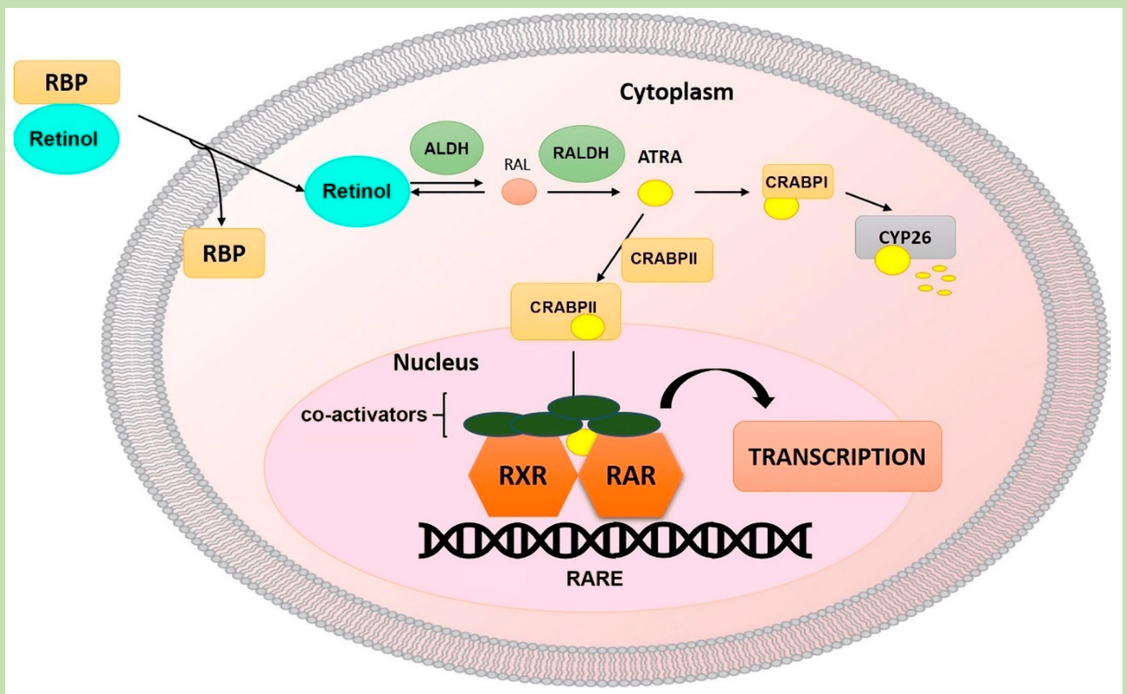
Abstract

Nuclear retinoic acid receptors (RARs), such as retinoic acid receptor alpha (RARA), play a pivotal role in hematopoiesis by modulating gene expression programs that affect hematopoietic progenitor self-renewal and terminal myeloid differentiation in response to retinoic acid (RA). These receptors, acting as ligand-related transcription factors, form heterodimers with retinoid X receptors (RXRs) and bind to specific DNA motifs, called RA-response elements (RAREs), upstream of target genes. The attachment of RA to these receptors triggers the activation of target gene expression (Fig. 1A).

Acute promyelocytic leukemia (APL), a subtype of acute myeloid leukemia (AML), underscores the significance of RARA (Fig. 1B). Here, a fusion protein, PML/RARA, arising from a translocation between chromosomes 15 and 17, acts as an oncoprotein. RARA, a key component of this fusion, initiates the disease and influences responses to RA-based therapies. Elevated RARA levels in primary hematopoietic progenitors can induce self-renewal and immortalization in vitro, akin to PML/RARA. Recent investigations hint at the clinical sensitivity of some non-APL AML cases characterized by RARA overexpression to retinoids, offering a promising avenue for combination therapies.

Our lab research focuses on elucidating how RARA induces progenitor self-renewal through a variety of approaches and tools. The outcomes of this study aim to provide valuable insights into the regulation of hematopoietic cell fate by retinoids and the optimization of RA therapy in non-APL AMLs.

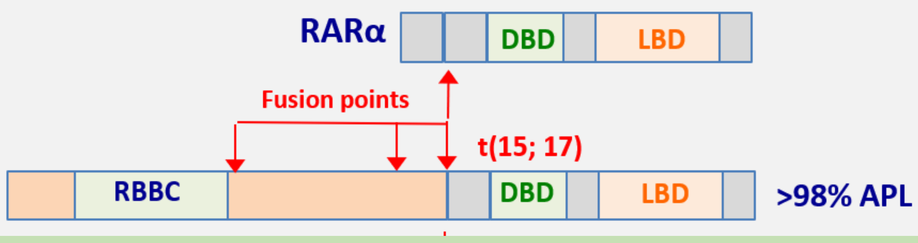
1A



Conserva, M.R et al, 2019, International Journal of Molecular Sciences

1B

Geoffroy & The, 2020, Cancers



What will I do?

Previous studies have shown that RARA promote self-renewal and impair myeloid differentiation.

The internship project aims to:

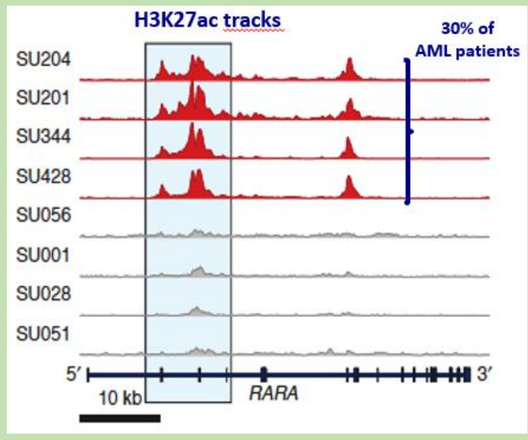
1. Identify candidate RARA target genes linked to progenitor self-renewal or terminal myeloid differentiation

2. Perform individual silencing and overexpression experiments for the identified master genes to uncover their roles in RARA-mediated immortalization.

Why is it important ?

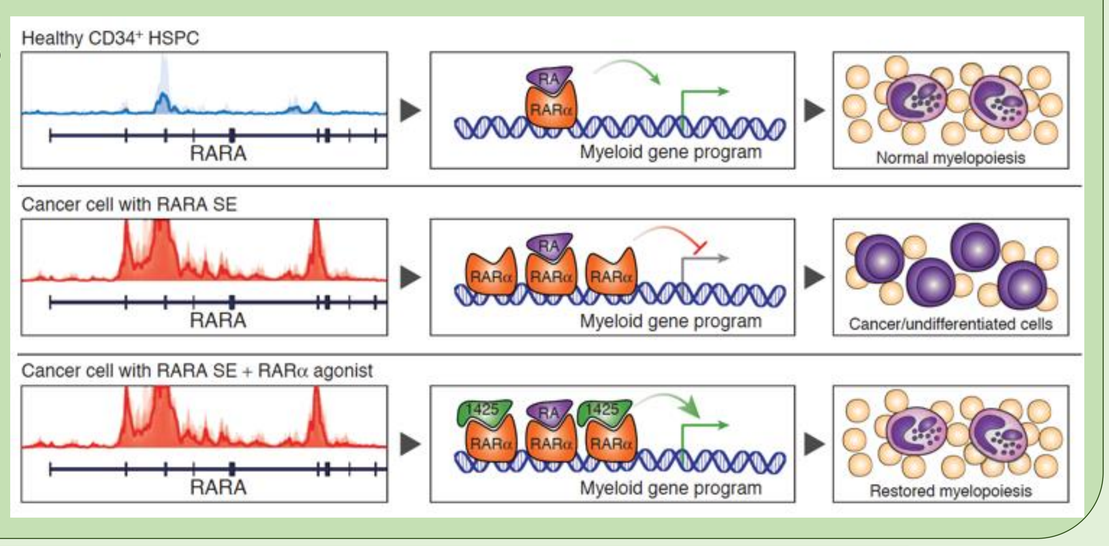
Previous studies have identified an upstream super-enhancer at the RARA locus (Fig. 2A). Additionally, a model has been proposed for RARA's oncogenic role in progenitors, where RARA can form dimers with various partners, potentially contributing to different types of AML beyond APL/AML. This implies that non-APL/AML cases may also respond to RA therapy approaches, as depicted in the model (Fig. 2B).

2A



The primary objective remains to understand how RARA induces progenitor self-renewal, with various research avenues being explored.

2B

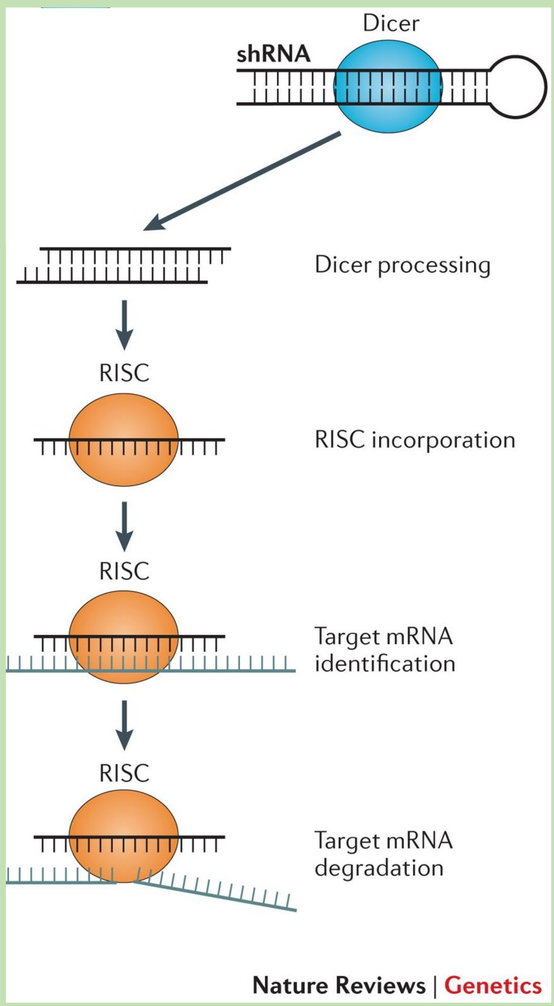


How we're going to do it?

1. To Identify candidate RARA target genes linked to progenitor self-renewal or terminal myeloid differentiation :
Cut and Tag, ATAC-seq, ChIP, transcriptome analysis, RNA-seq, and single-cell RNA-seq.

2. To uncover the role of identified master genes in RARA-mediated immortalization:
ShRNA-induced gene suppression, and CRISPR-mediated methods to individual silencing and overexpression of the genes.

ShRNA-induced gene suppression



Cut and Tag