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APL: Retinoic Acid and Retinoid Pharmacology, A Breakthrough Trials Today

George Zhu*

The Institute of Oncology, Tehran University of Medical Sciences, Iran

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***Corresponding author:** George Zhu, The Institute of Oncology, Tehran University of Medical Sciences, Iran

Short Communication

Acute promyelocytic leukemia (APL), a specific characteristic of t (15;17) chromosomal translocation, molecular gene analyses are conclusive in vivo evidence that oncogenic pml/RARa fusion plays a crucial role in APL leukemogenesis [1-3]. Since the introduction of initial 13-cis retinoic acid (13-cis RA) [4], and currently all-trans RA(ATRA) and tamibarotene [5,6] RA plus chemotherapy or RA plus As2O3 regimen is currently the standard of care [7]. APL has a very good prognosis, with long-term survival rates up to near 70%-90%. The elucidation of the molecular basis of retinoic acid and retinoid pharmacology in APL has been illustrated in several publications [8-11], the detail molecular model of gene regulation had also been proposed by Zhu in 1990s [12-14]. From the following figure clear shown, oncogenic pml/RARa is a constitutive transcriptional repressor to differentiation block at the promyelocyte stage whereas retinoic acid overcome the transcriptional repressor activity of pml/RARa, including the dissociation of corepressor complexes N-CoR, SMAT and HDACs from oncogenic pml/RARa. Consequentially, pml/RARa chimera converted receptor from a repressor to a RA-dependent activator of transcription. This transcriptional derepression occurs at RARE on pml/RARa DNA binding. The resulting pml/RARa oncoprotein proteolytic degradation occurs through autophagy or the proteasome system (UPS) or caspase 3 or/and E1-like ubiquitin-activating enzyme (UBE1L) induction. An effect is to relieve the blockade of pml/RARa-mediated RA dependent promyelocyte differentiation and induce promyelocyte maturation. This earliest proposal has now been demonstrated by structure and functional analysis of oncogenic pml/RARa chimera protein in vitro and in vivo studies [15-27]. This is first described in eukaryotes. Moreover, this oncogenic receptor pml/RARa is locked in its "off" regular mode thereby constitutively repressing transcription of genes or key enzymes (for examples AP-1, PTEN, DAPK2, PU.1) that are critical for differentiation of hematopoietic cells [28-32]. Whether silencing of these RARE-responsive target genes such as myeloid transcription factors such as C/EBPa, PU.1 or other unknown key enzymes that are critical for neutrophil differentiation needs to be further identification and under investigation (Figure 1).

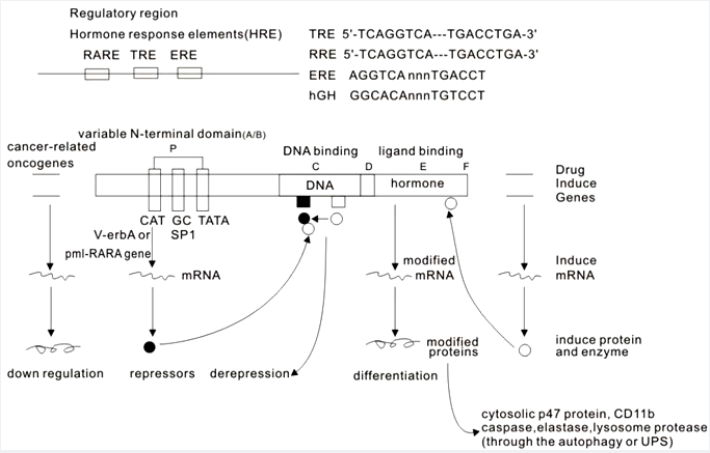

Figure 1: Molecular model of the gene regulation of retinoic acid (RA) action.

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