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Clinical Image

APL:Retinoic Acid and Retinoid Pharmacology, a Breakthrough Today

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1. Clinical Image

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) [5] and tamibarotene [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 repressor 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 depression 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[28-31]. 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 really critical for neutrophil differentiation needs to be further identification and under investigation.

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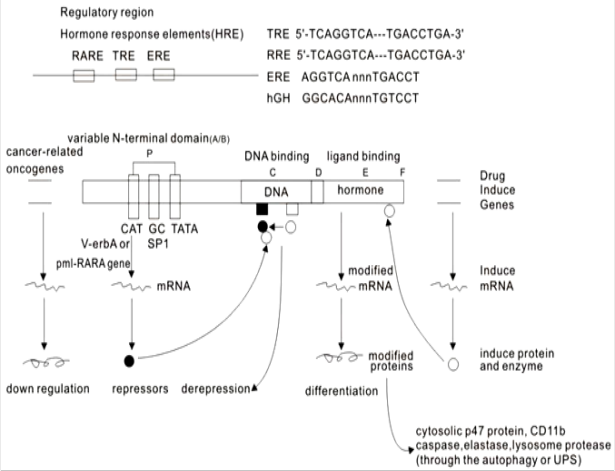

Figure: Molecular model of the gene regulation of retinoic acid(RA) action(George Zhu,January 1991,revised in 2012 [12], further revised in 2018 [31])

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