Are all APLs created equal?

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Background

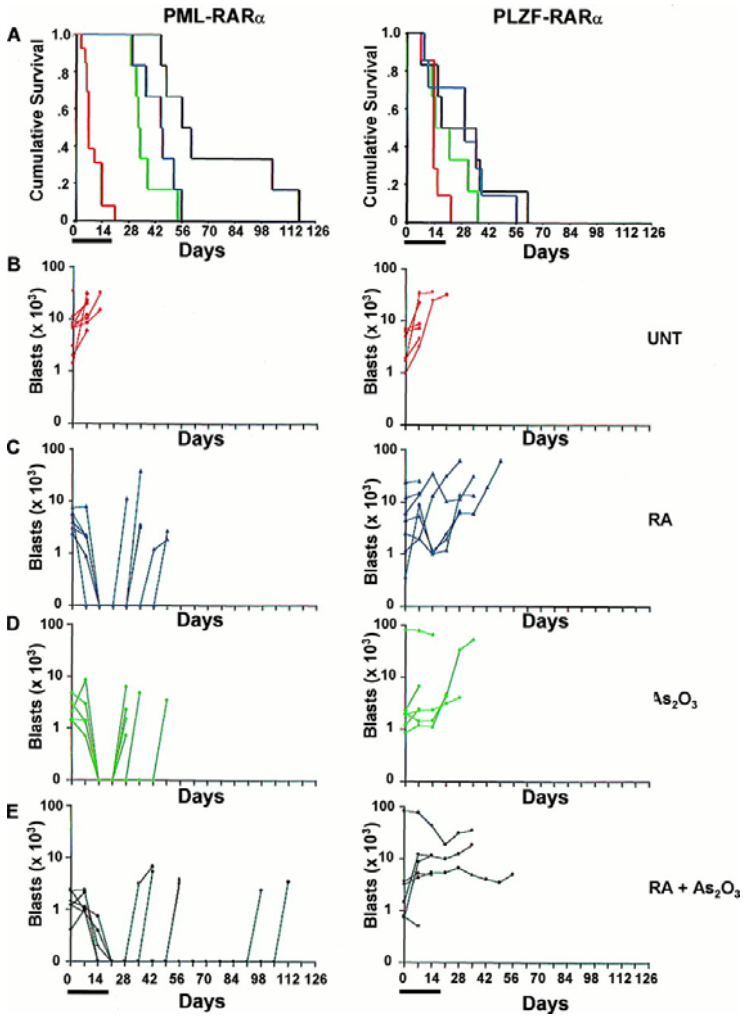
- RARα translocations in acute promyelocytic leukemia (APL)
- Mouse models recapitulate the human phenotype
- Current treatments utilize retinoic acid (RA) to induce differentiation and arsenic trioxide to induce apoptosis
- Human patients have variable response to therapy

Retinoic acid (RA) and As_2O_3 treatment in transgenic models of acute promyelocytic leukemia (APL) unravel the distinct nature of the leukemogenic process induced by the PML-RARα and PLZF-RARα oncoproteins

Eduaro M. Rego, Li-Zhen He, Raymond P. Warrell, Jr., Zhu-Gang Wang, and Pier Paolo Pandolfi

Proc. Natl. Acad. Sci. USA 97, 10173-10178

Fig. 1. Effects of treatment with As2O3, RA, or As2O3 + RA on the survival of leukemic TM PML-RAR[alpha] and PLZF-RAR[alpha]



Rego, E. M., et al. "Retinoic Acid (RA) and As2O3 Treatment in Transgenic Models of Acute Promyelocytic Leukemia (APL) Unravel the Distinct Nature of the Leukemogenic Process induced by the PML-RARalpha and PLZF-RARalpha Oncoproteins." *PNAS* 97, no. 18 (August 29, 2000): 10173-8. Copyright 2000 National Academy of Sciences, U.S.A. Used with permission.

Fig. 3. Effects of treatment with As2O3, RA, or As2O3 + RA on the induction of apoptosis in leukemic cells sorted from the liver of transplanted NM

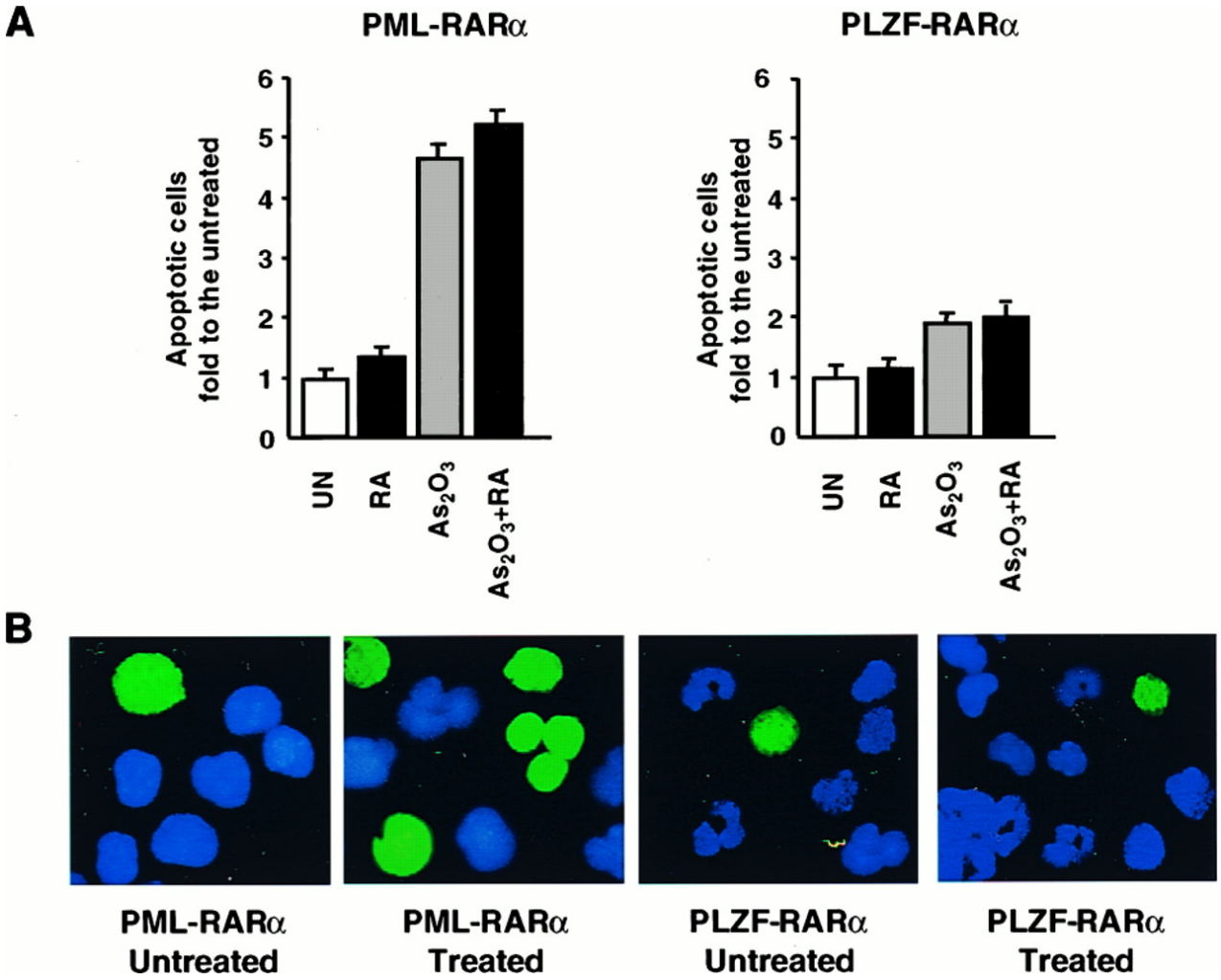


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Fig. 4. Effects of treatment with As2O3, RA, or As2O3 + RA on the induction of differentiation in leukemic cells sorted from the liver of transplanted NM

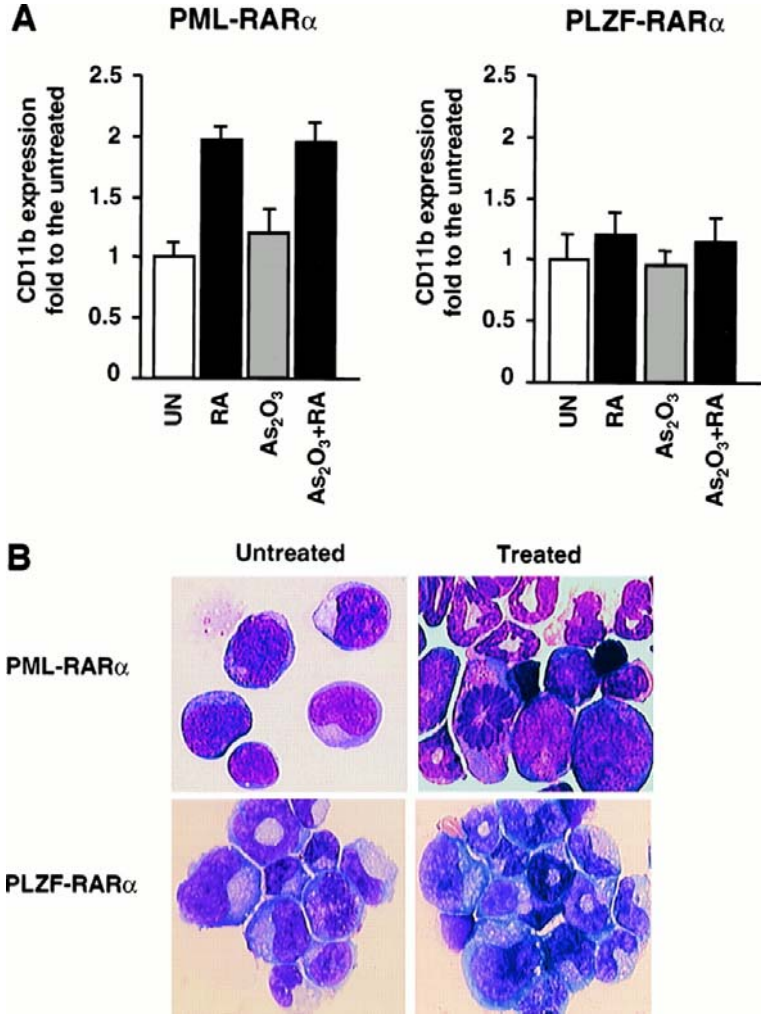

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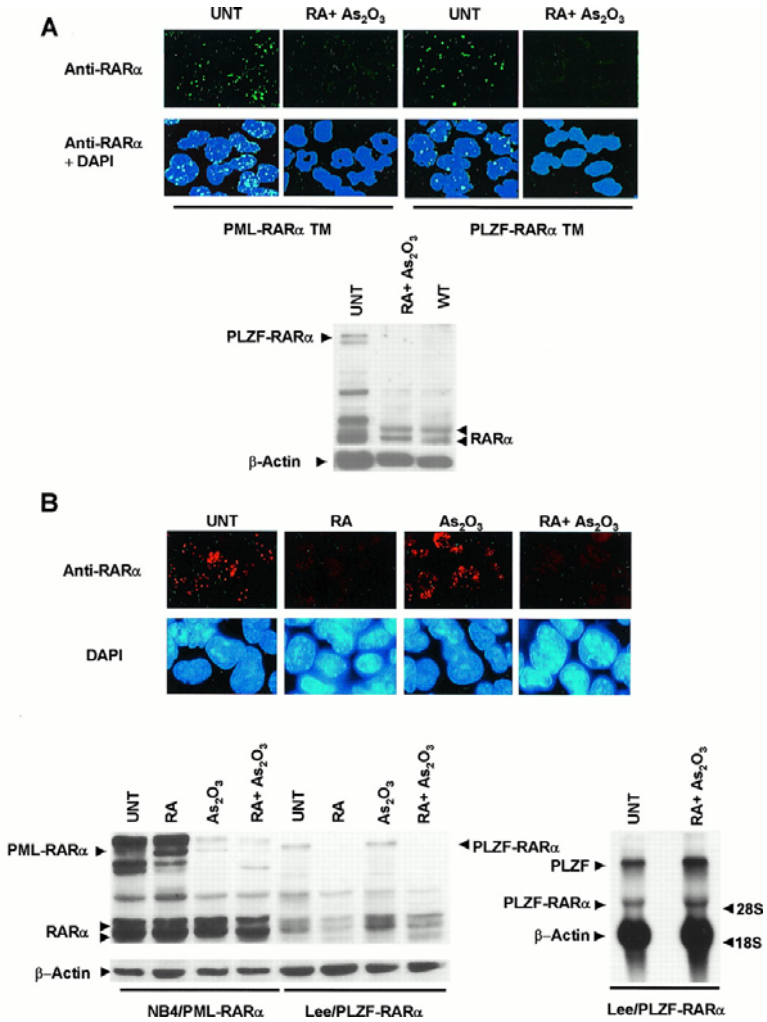
Fig. 5. In vivo and in vitro effects of RA or RA + As2O3 treatments on the PML-RAR[alpha] and PLZF-RAR[alpha] oncoproteins



Rego, E. M., et al. "Retinoic Acid (RA) and As2O3 Treatment in Transgenic Models of Acute Promyelocytic Leukemia (APL) Unravel the Distinct Nature of the Leukemogenic Process induced by the PML-RARalpha and PLZF-RARalpha Oncoproteins." *PNAS* 97, no. 18 (August 29, 2000): 10173-8. Copyright 2000 National Academy of Sciences, U.S.A. Used with permission.

Questions remaining:

- What are the inherent differences/similarities between PML-RARα and PLZF-RARα at the molecular level?
- How/why does PLZF-RARα respond differently to RA?
- Is expression of PLZF-RARα required for tumor maintenance?

What are the inherent differences between PML-RARa and PLZF-RARa at the molecular level?

- Gene expression analysis on random APLs from humans followed by identification of the fusion gene
- Correlate gene expression in PML-RARα vs. PLZF-RARα vs. normal myeloid cells

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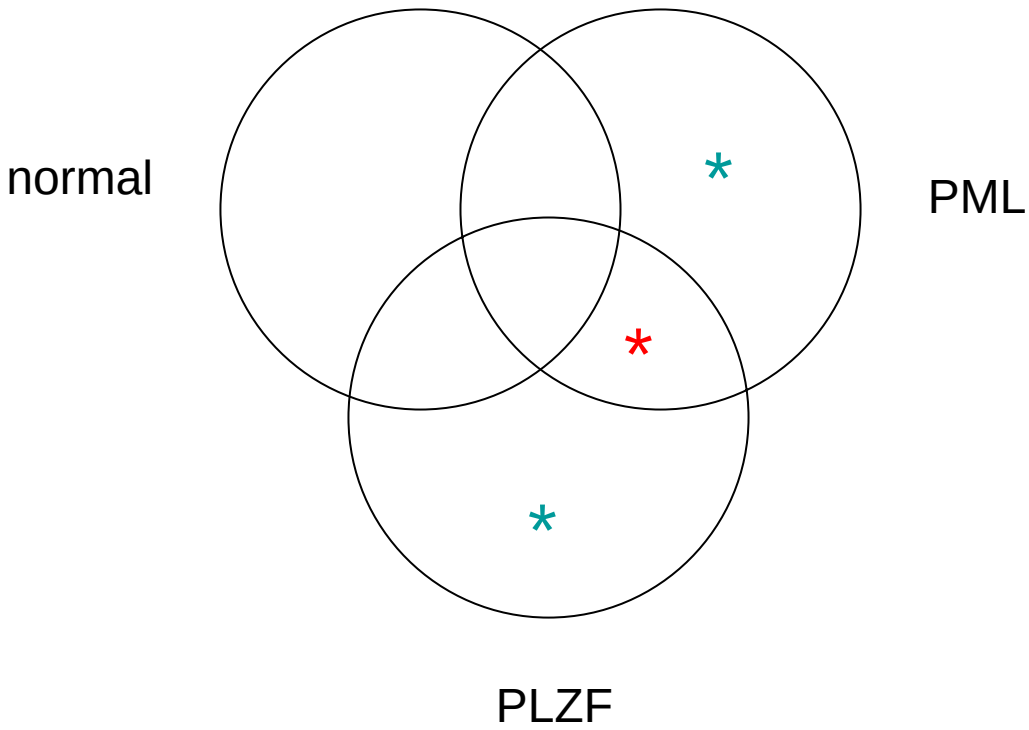
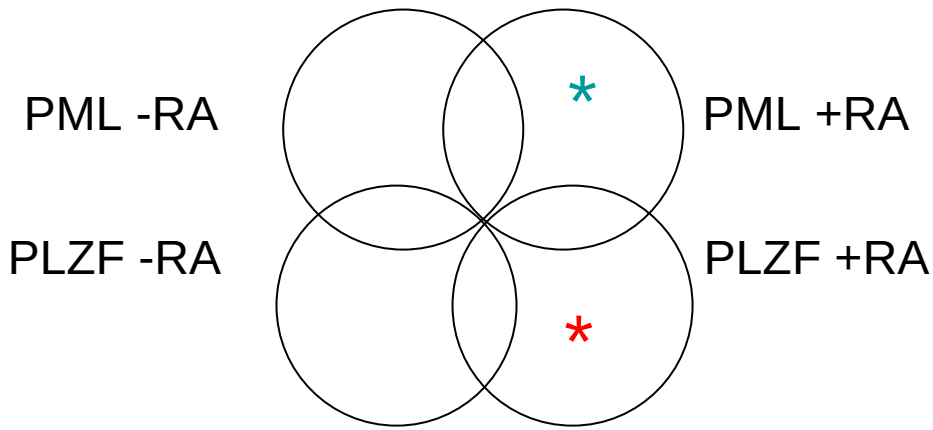
Possible results: Common genetic pathways upregulated

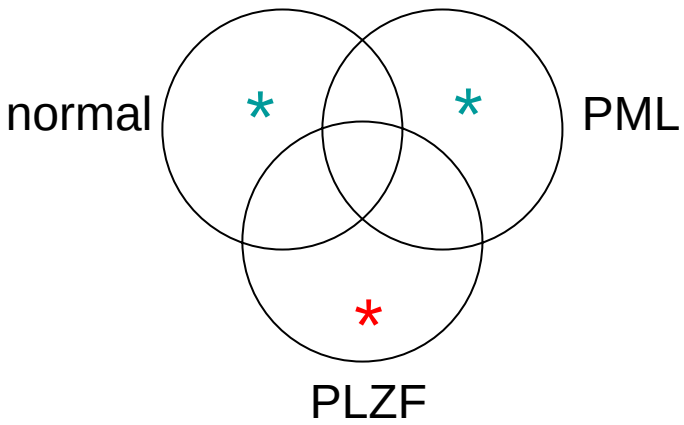


How/why does PLZF-RARa respond differently to RA?

- Additional analysis of gene expression profiles generated in previous section.
- New gene expression analysis comparing cultured PML-RARα ± RA and PLZF-RARα ± RA.



Possible results: Inhibition of Hox signaling



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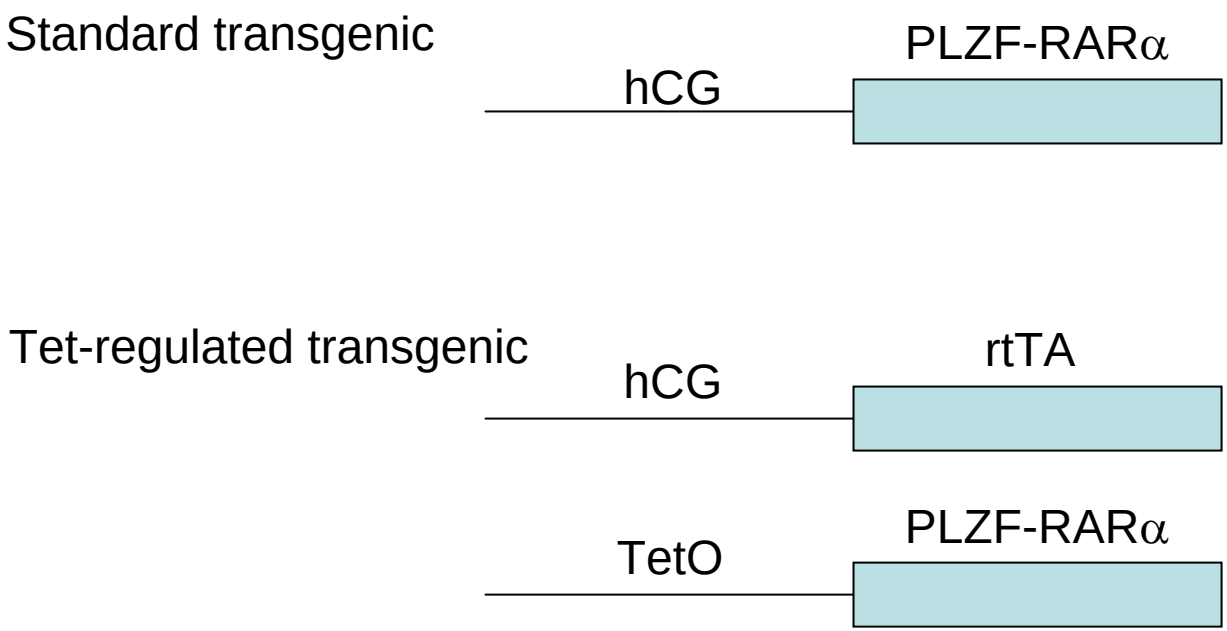
* : HoxB3 inhibits differentiation → normal & PML do not express B3

* : HoxD4 promotes differentiation → PLZF does not express D4 or B4

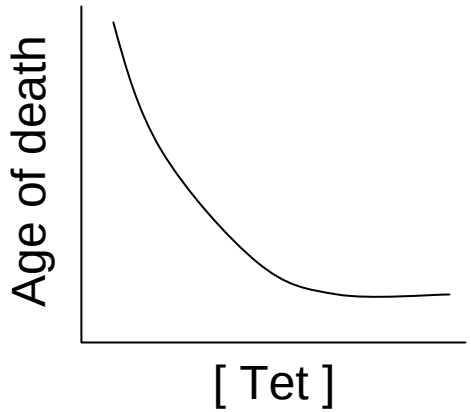
Is expression of PLZF-RARa required for tumor maintenance?

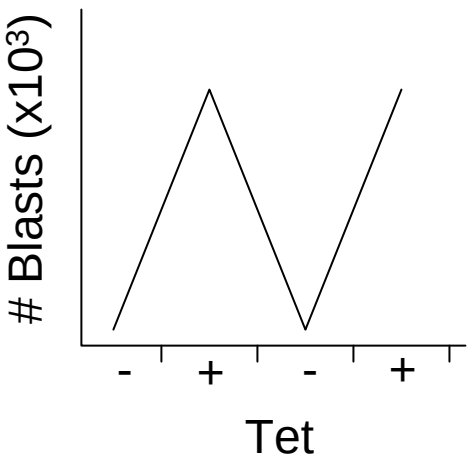
- Tetracycline-regulated transgenic expression



Possible results

Expression of PZLF-RARα required





Expression of PZLF-RARα not required