

DIFFERENTIAL EXPRESSION OF TISSUE FACTOR F3 AND NUCLEAR RECEPTORS 4A IN EARLY DEATH ACUTE PROMYELOCYTIC LEUKEMIA PATIENTS

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Acute promyelocytic leukemia early death

- 10-30% suffer an early death (ED)
 - hemorrhagic complications
 - infections
 - differentiation syndrome
- Bleeding risk factors:
 - WBC > $10 \times 10^9/L$
 - blast count > $30 \times 10^9/L$
 - age > 60 years old
 - impaired renal function
 - increased fibrinolysis
 - severe thrombocytopenia
- underlying mechanisms are unclear and successful treatment of ED in APL patients could not be achieved so far
- highly important to identify novel factors implicated in the mechanistic processes in APL-ED patients

RNAseq approach: Comparison APL and APL-ED

- 50 bp single-read RNA sequencing (RNAseq) cohort 1

| | Cohort 1 |
|----------------------|-------------------------|
| No. of APL patients | 16 |
| - APL-ED (BCR1/BCR3) | 6 (1/5) |
| - APL (BCR1/BCR3) | 10 (6/4) |
| Age | Median 59 (Range 37-73) |
| Sex (m/f) | 8/8 |
| Treatment | AIDA2000 (SAL) |
| Sanz Score (No.) | Low/Int 5 High 11 |

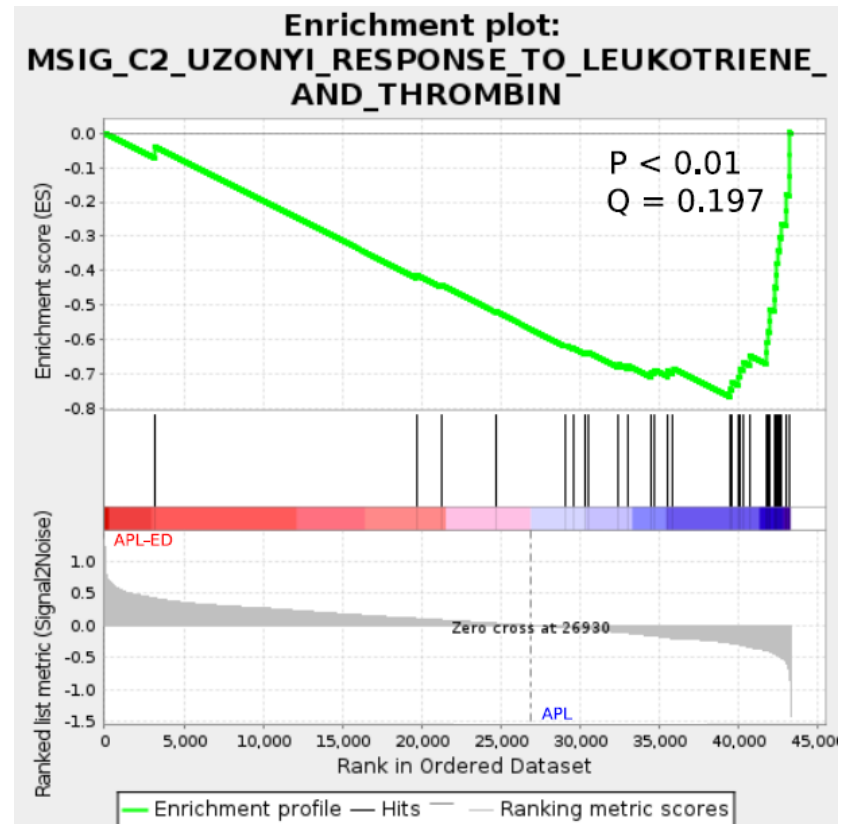
RNAseq approach: Comparison APL and APL-ED

- 50 bp single-read RNA sequencing (RNAseq) cohort 1

Further validation cohorts

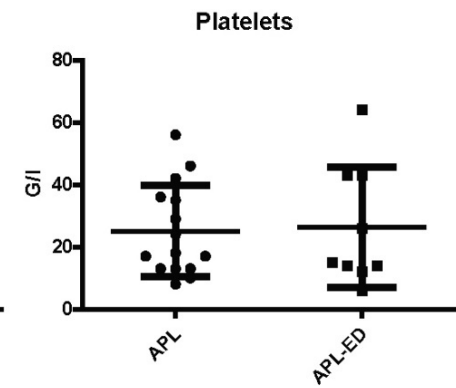
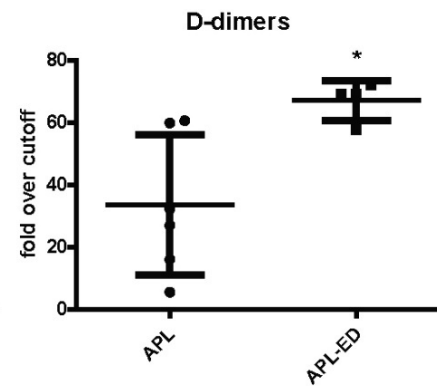
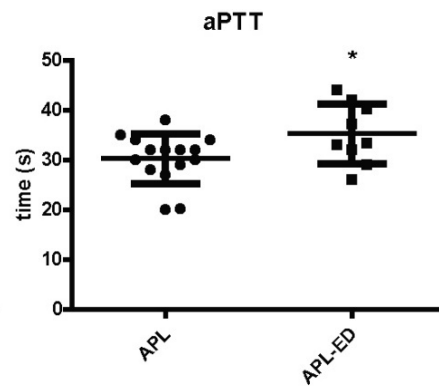
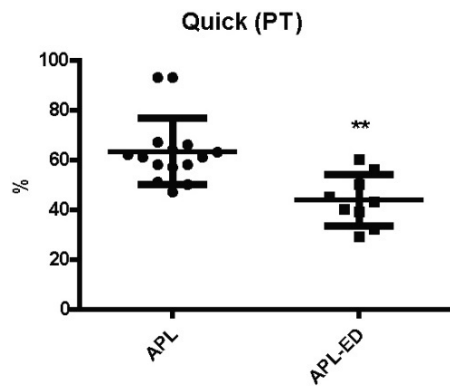
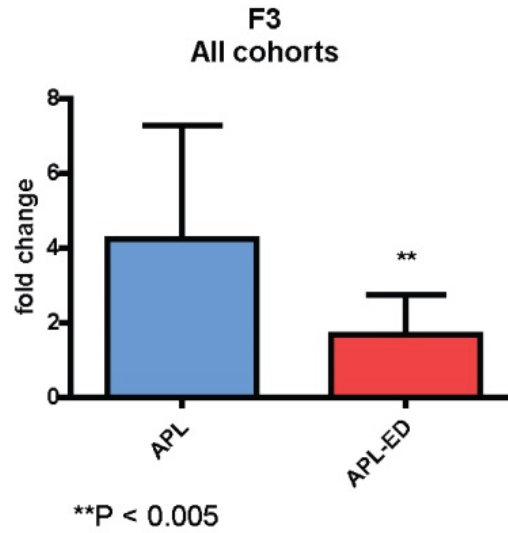
| | Cohort 1 | Cohort 2 | Cohort 3 |
|----------------------------|-------------------------|-------------------------------------|------------------------------|
| No. of APL patients | 16 | 10 | 14 |
| - APL-ED (BCR1/BCR3) | 6 (1/5) | 4 (0/4) | 4 (2/2) |
| - APL (BCR1/BCR3) | 10 (6/4) | 6 (4/2) | 10 (4/6) |
| Age | Median 59 (Range 37-73) | Median 55 (Range 36-79) | Median 55 (Range 37-79) |
| Sex (m/f) | 8/8 | 7/3 | 6/8 |
| Treatment | AIDA2000 (SAL) | mostly AIDA2000 (SAL) or APL0406 | SAL (AIDA, AML, Napoleon) |
| Sanz Score (No.) | Low/Int 5 High 11 | Low/Int 5 High 5 | Low/Int 5 High 3 N/A 4 |

Tissue factor F3-containing gene set significantly enriched



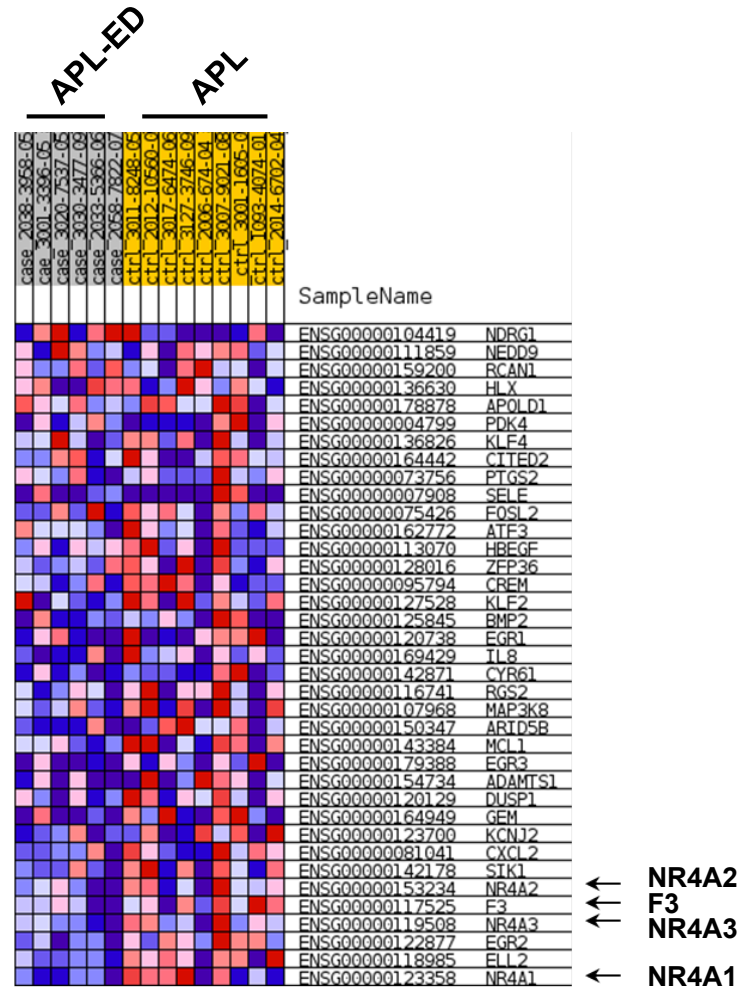
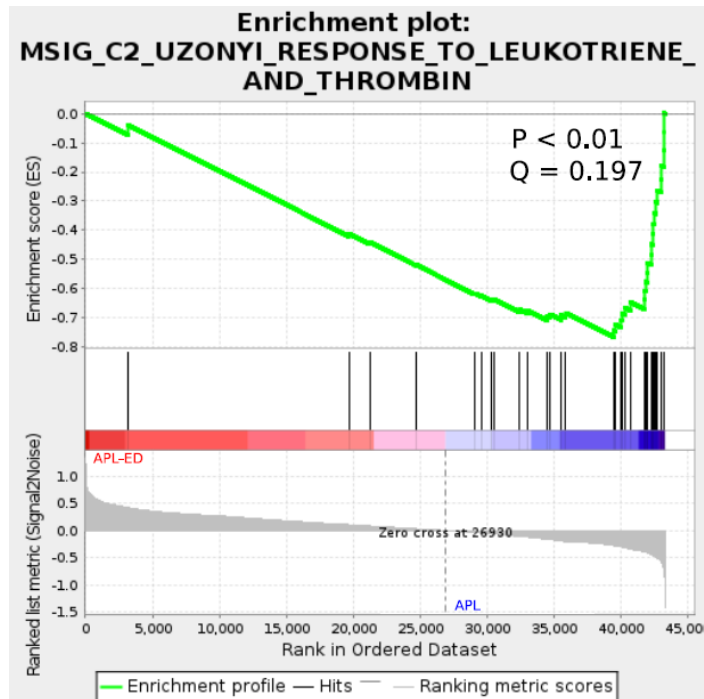
- Negatively correlated with APL-ED
→ Is F3 less expressed in APL-ED than in APL?

Disrupted coagulation cascade in APL-ED

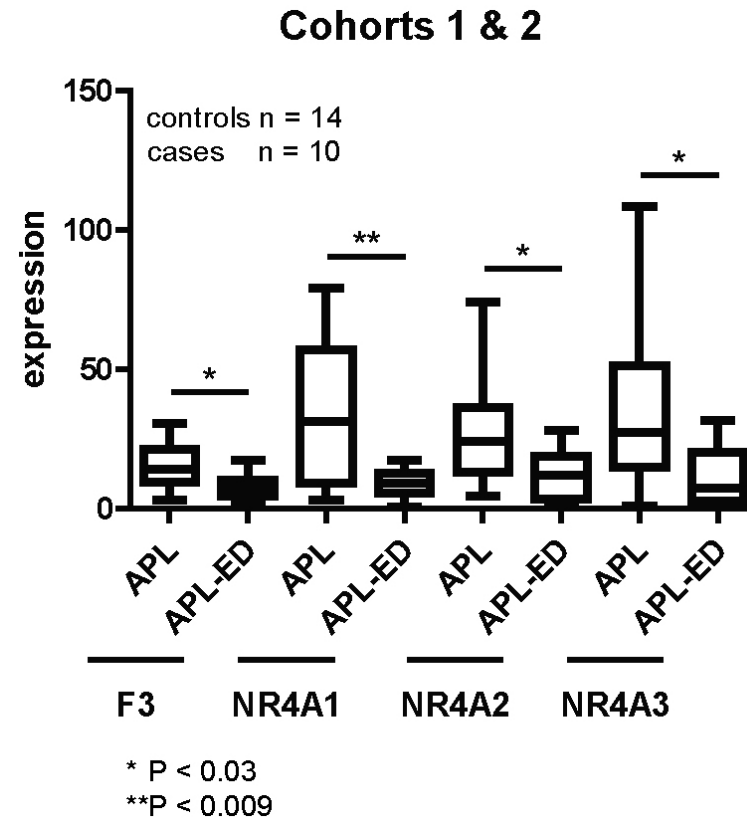


* P ≤ 0.04
**P ≤ 0.001

Downregulation of F3 is accompanied by downregulation of NR4A family members

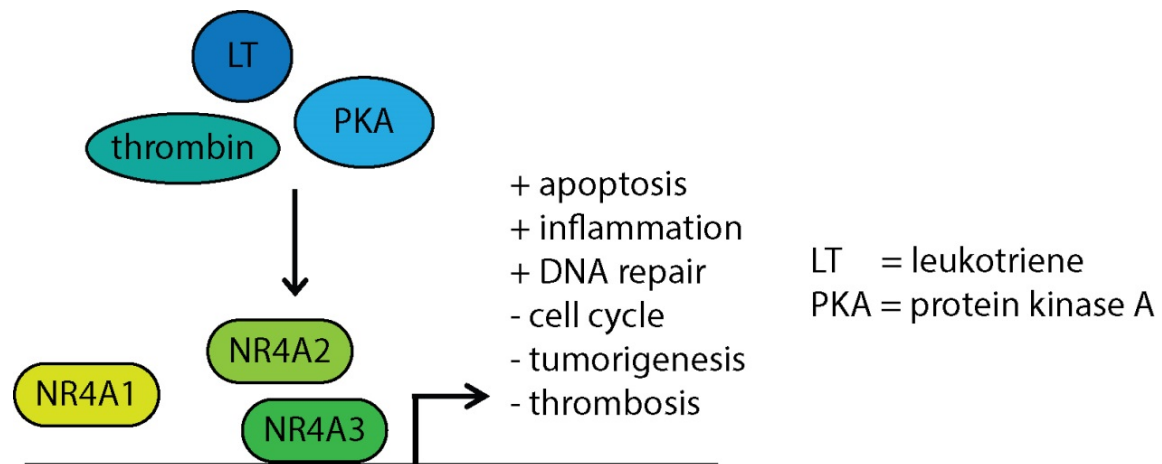


NR4A1, NR4A2 and NR4A3 are downregulated in ED-APL

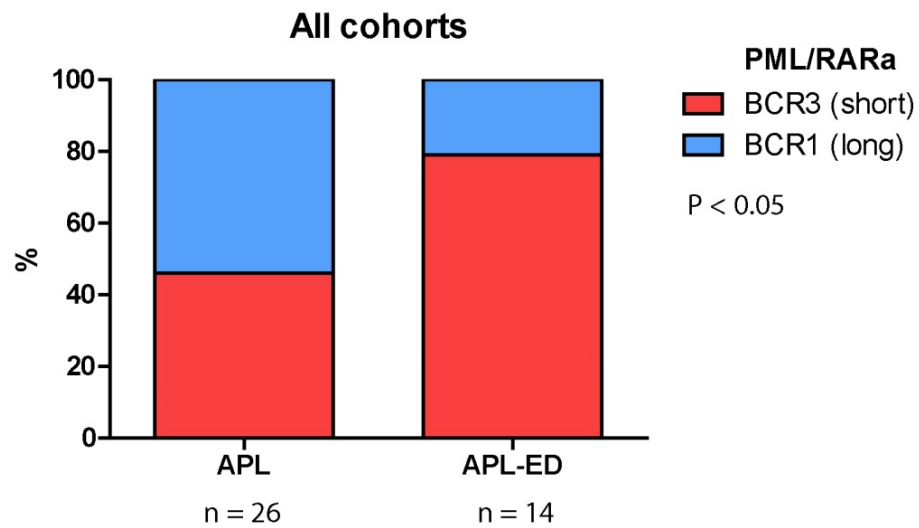
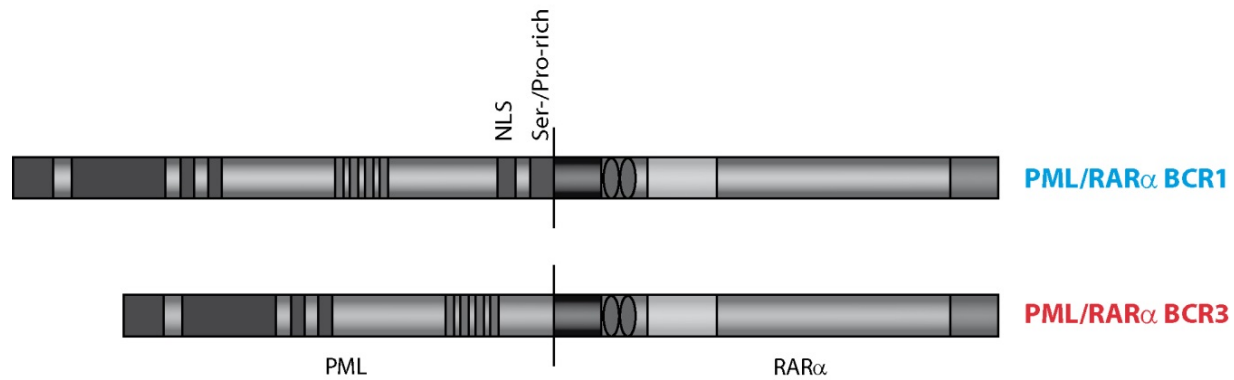


NR4A family - nuclear receptor subfamily 4, group A

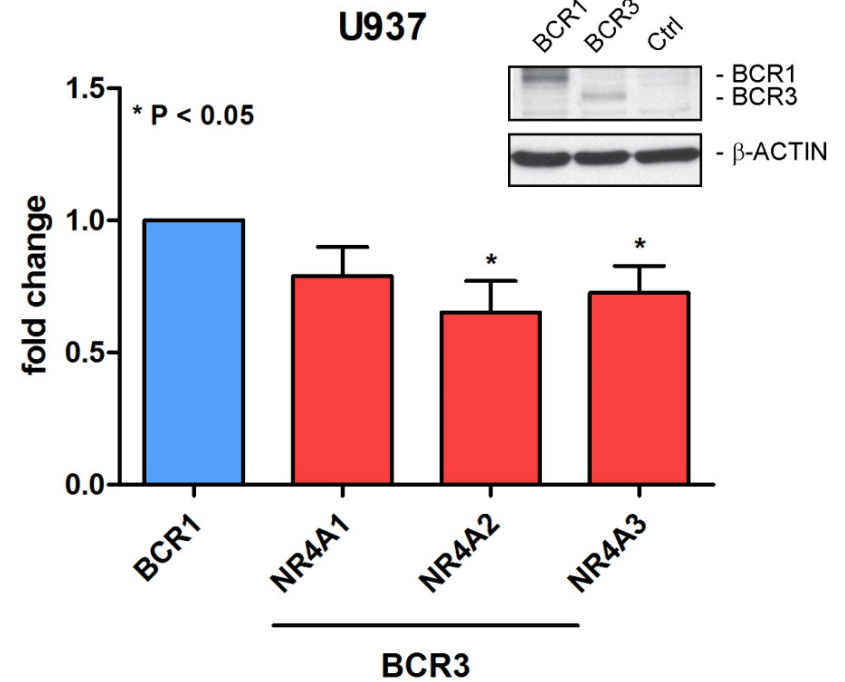
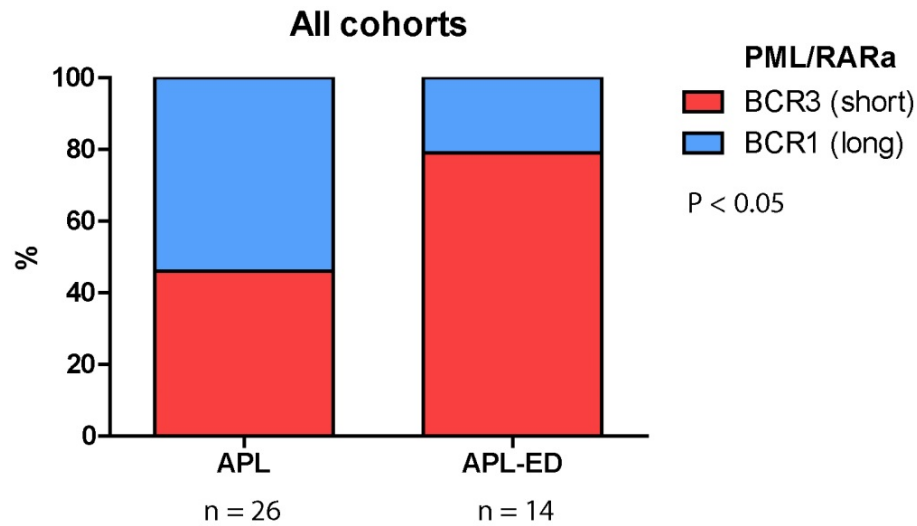
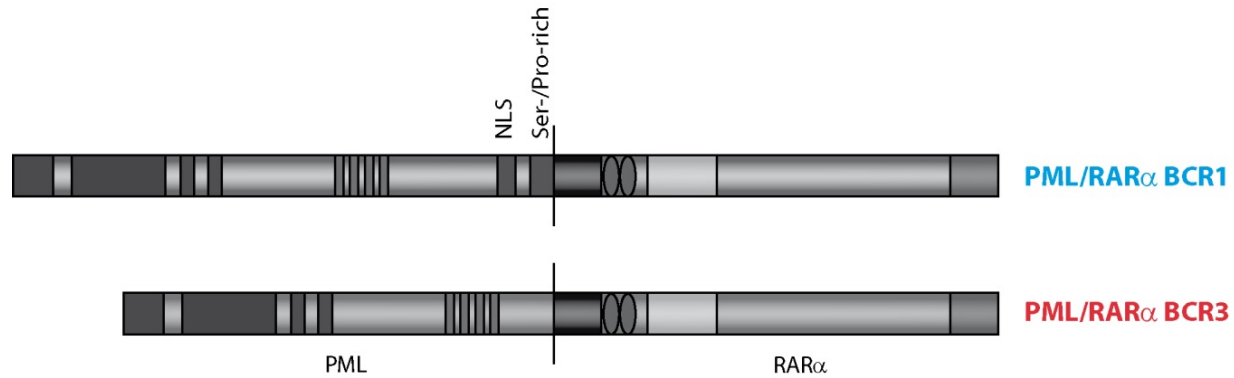
- Nuclear transcription factors
- NR4A1 and NR4A3 tumor suppressors in AML
→ abrogation causes AML development in a mouse model Mullican *et al.*, 2007
- NR4A2/3 induced by PKA
→ PKA important for ATRA-induced differentiation Zhao *et al.*, 2004; Nguyen *et al.*, 2013; Prince *et al.*, 2017
- NR4A1/2 heteromerization with RXR Perlman & Jansson, 1995, Zetterstrom *et al.*, 1996
- NR4A1/3 act antithrombotic via upregulation of thrombomodulin Morser, 2012; Yang *et al.*, 2016



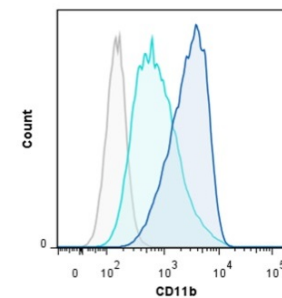
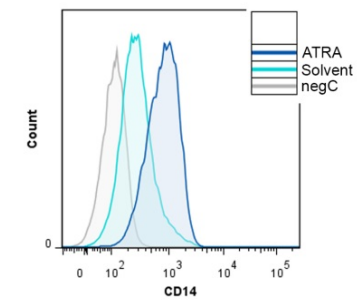
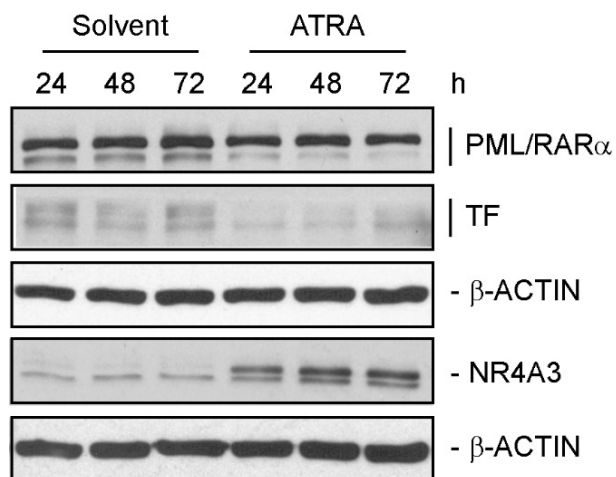
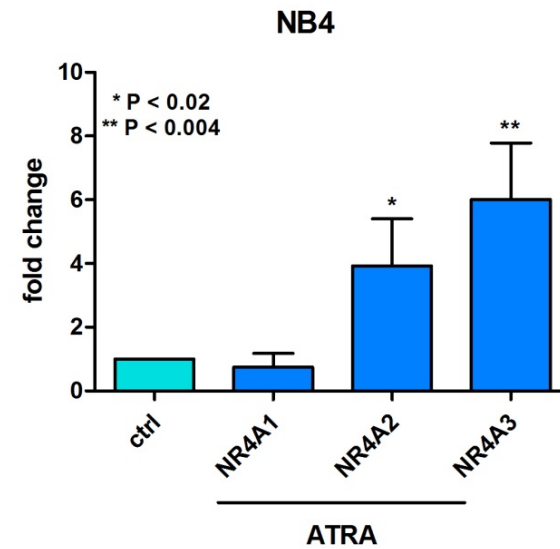
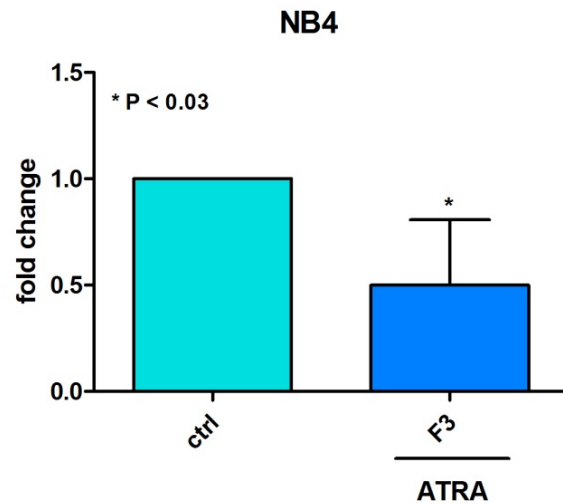
Expression of short variance BCR3 of translocation t(15;17) associated with lower expression of NR4A2 and NR4A3



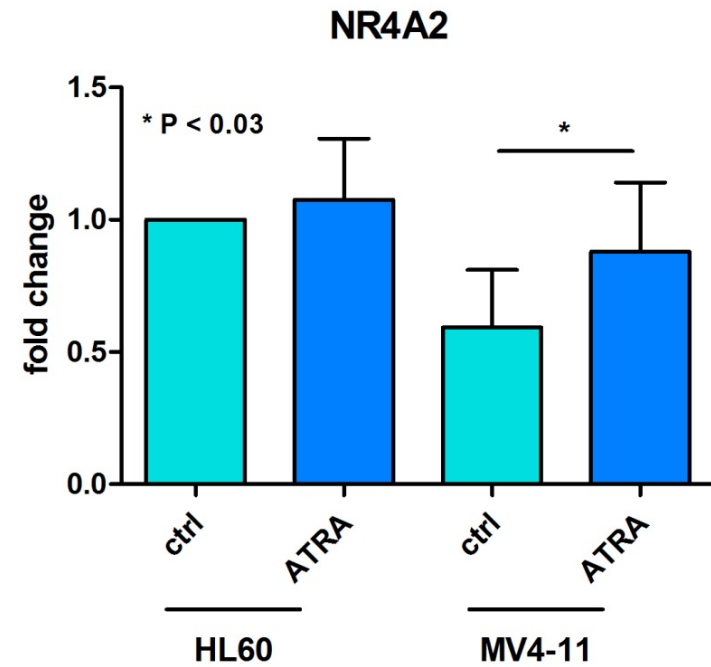
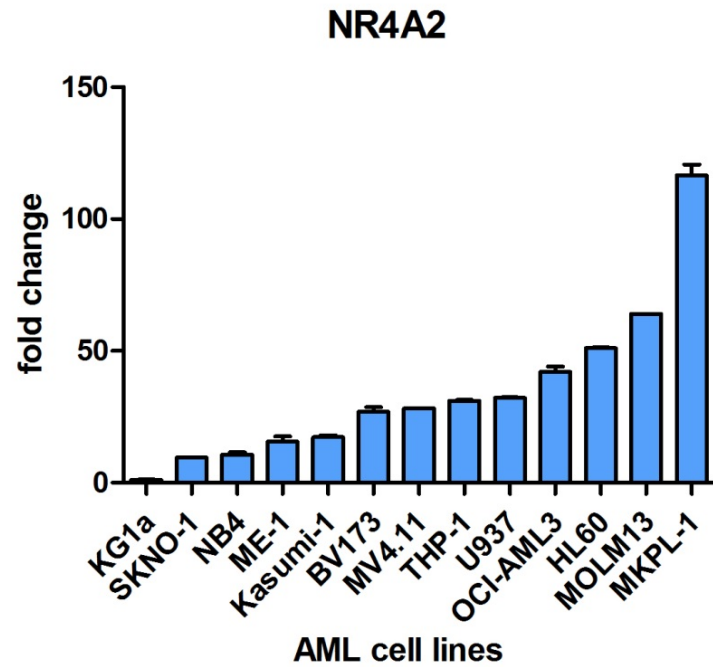
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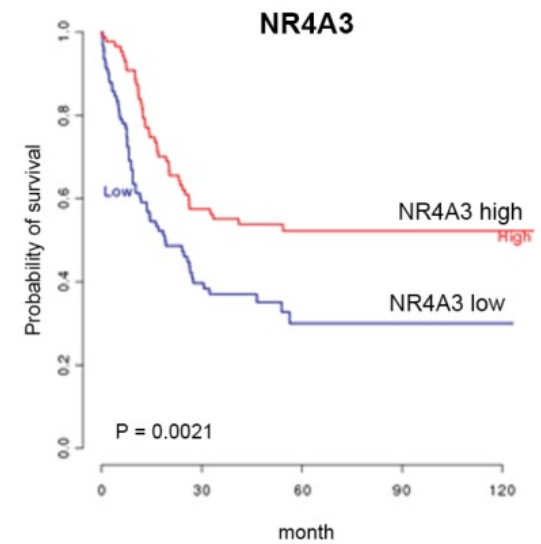
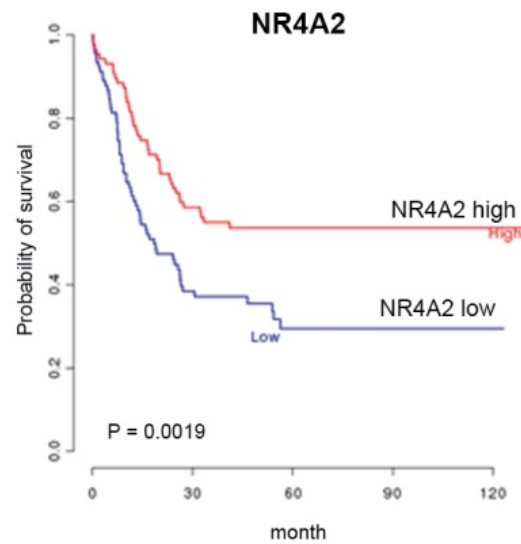
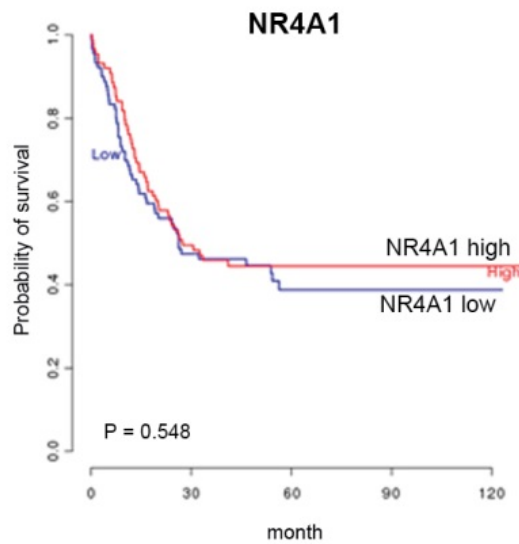
ATRA treatment in NB4 cells inhibits F3 expression but induces NR4A2 and NR4A3 expression



ATRA treatment may induce NR4A expression in other AML subtypes



In AML low expression of NR4A2 and NR4A3 is associated with decreased OS



Summary

- F3 and NR4A1/2/3 are downregulated in APL-ED
- decreased expression of NR4A2/3 is associated with short PML-RAR α variant BCR3
- NR4A members may contribute to APL-ED phenotype
- NR4A2/3 expression can be induced by ATRA and this may have therapeutic implications for other AML subtypes

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