CXCL12 AND CXCR3 MAY IDENTIFY COMPLETE RESPONSE IN ACUTE MYELOID LEUKEMIA PATIENTS TREATED WITH TIPIFARNIB

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**HIGH CXCL12 AND BONE MARROW HOMING ARE MARKERS OF TIPIFARNIB’S ACTIVITY**

- Pre-treatment high tumor CXCL12 expression identifies potential responders to tipifarnib therapy but the relationship between farnesylation and CXCL12 is poorly understood.
- Hypothesis: Because CXCL12 expression and bone marrow homing are associated with the activity of tipifarnib in AML, expression of the farnesylated target(s) of tipifarnib could be expected to correlate with the expression of CXCL12 in AML. Expression of a farnesylated target should also be associated with bone marrow homing.
- Method: Determine the strength of the relationship between the expression of genes encoding farnesylated proteins and that of CXCL12 using the Spearman’s rank order test. Database: TCGA AML, Provisional, N=173, RNA Seq V2 RSEM.
- Genes screened were identified using PRENbase (Parameters: KNOWN FT required, GGT1-GGT2 excluded, Eukaryotic Mammalia, Minimum cluster=3): RAB28, RASD1, RASD2, NAP1L1, GNGT1, PTP4A2, RILP, PRICKLE1, PRICKLE2, LMO6, INPP5A, INPP5E, Gbp5, Gbp1, PLA2G4C, PTGIR, CLN3, TIMAP, MYPT3, RHOQ, TC10, RHOU, RHOD, RHOE, HRAS, RAP2A, RAP2C, ERAS, DNAJA4, Lmnb2, Lmnb3, CENPF, CENPE, STK11, GRK1, PHKB, RHEB, PTPRB, PDE6C, PDE6A/C.
- Results: Spearman’s rho ~500 (highly significant) observed for RHOE (RND3, 0.723), PRICKLE2 (0.628).

**SCREENING FOR FARNESYLATED TARGETS OF TIPIFARNIB IN AML**

- Concurrent RHOE/PRICKLE2 Expression Identifies Bone Marrow Samples with High CXCL12
- Working Model of Modulation of the CXCL12/CXCR4 Pathway by De-farnesylation of PRICKLE2/RHOE
- In this model, de-farnesylation of PRICKLE2/RHOE triggers a downstream switch from activation of full-length CXCL12 to activation of the CXCR3 and induction of cell death by a 5-67 CXCL12 fragment

**HIGH PRICKLE2/RHOE EXPRESSION ASSOCIATED WITH BONE BLAST MARROW HOMING**

- High bone marrow RHOE, CXCL12, CXCR3 and homing of AML blasts to the bone marrow are observed in AML patients who respond to tipifarnib therapy.

**REFERENCE 3’UTR/INTRON CXCL12 LYMPHOMA RESPONDERS**

- In AML, bone marrow expression of farnesylated RHOD and PRICKLE2 strongly correlated with CXCL12 expression and homing of AML blasts to the bone marrow.
- CXCL12, RHOD and CXCL12 appear to be of stromal origin based on its strong correlation with VCAM1.
- CXCL12 expression in lymphoma is determined in part by 3’UTR/intron polymorphisms.
- High bone marrow RHOD, CXCL12, CXCR3 and homing of AML blasts to the bone marrow are observed in AML patients who respond to tipifarnib therapy.
- These data provide a working model by which farnesylation regulates the activity of the CXCL12 pathway.

**CONCLUSIONS**

- The presence of a CXCL12 3’UTR gene variant (rs1801157) has previously been shown to be associated with decreased CXCL12 levels (Soriano 2002) and to decrease bone marrow homing of blasts and increase extramedullary disease in AML (Dommange 2006).
- We observed that the presence of the rs2839696 A>G 3’UTR/intron CXCL12 gene sequences translated to lower levels of CXCL12 gene expression in T-cell lymphoma (AITL, NOS).
- Mutation of CXCL12 3’UTR/intron sequences translated to lower CXCL12 expression in B-lymphoma (DLBCL). Most CXCL12 variants in DLBCL were due to mutation.


**GLOBAL GENE EXPRESSION DATA WAS GENERATED USING THE AFFYMETRIX U133A GENE CHIP**

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