Heterogeneity in Refractory AML: Implications for Drug Resistance

NCI Myelodysplastic Syndromes Symposium

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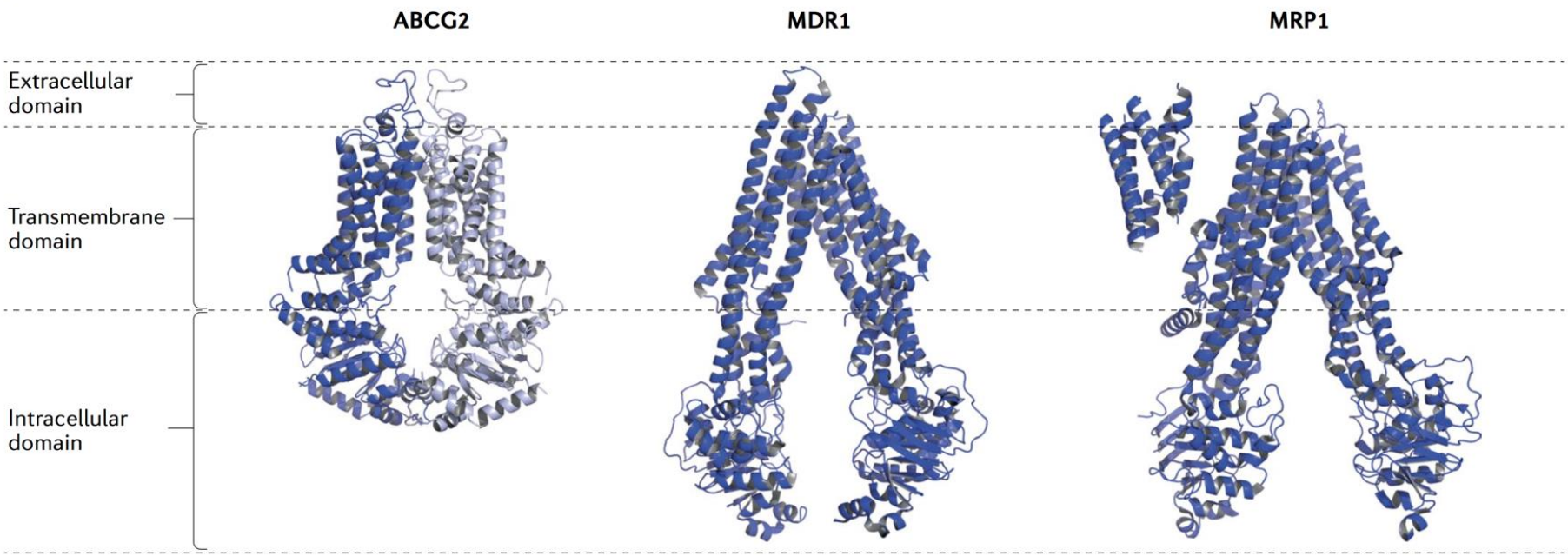
Turning Discovery Into Health

Overall Goals

- **Define molecular mechanisms and physiology of drug resistance in cancer**
- **Determine the clinical relevance of mechanisms derived from *in vitro* studies**
- **Develop new approaches to exploit or circumvent clinically significant resistance mechanisms**

ABC transporters that confer MDR: Domain organization

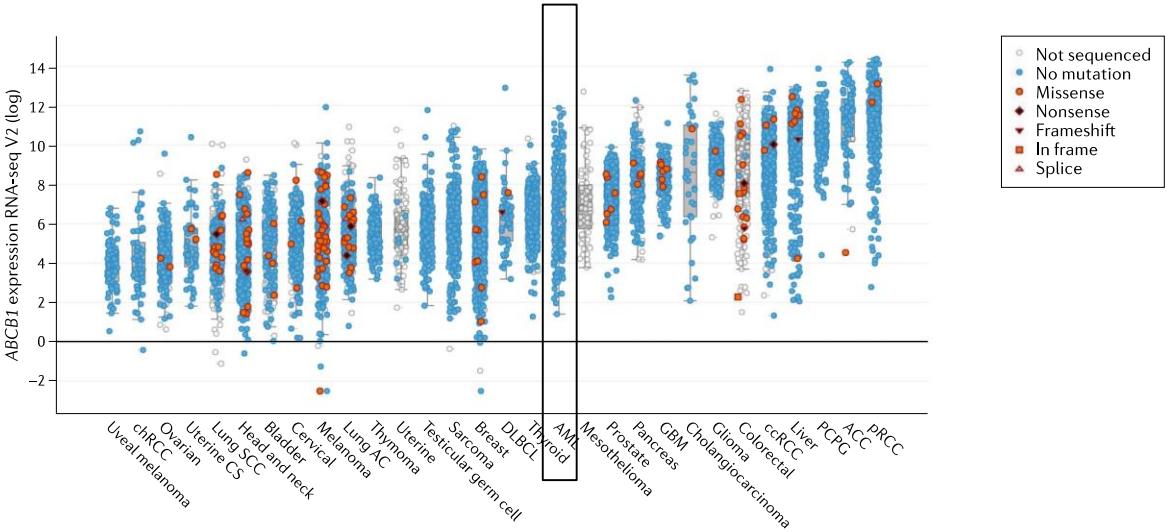


A likely role for ABC Transporters in AML

- **Some AMLs express ABC transporters, including ABCB1 and ABCG2 consistent with a role in intrinsic and acquired resistance**
- **Anthracyclines used to treat AML, such as daunorubicin, are substrates for efflux by ABC transporters**
- **In a classic SWOG study, addition of cyclosporine A, an inhibitor of both ABCB1 and ABCG2, improved response of high-risk AML to chemotherapy with cytosine arabinoside and daunorubicin (List et al., *Blood* 98, 3212-3220, 2001)**
- **<u>But</u> subsequent studies with more potent inhibitors of ABCB1 (P-glycoprotein) failed to show benefit and exhibited increased toxicity, leading to the editorial suggestion that inhibition of ABC transporters was not of clinical benefit (Libby, E. and Hromas, R., *Blood*, 116, 4037-4038, 2010). Unfortunately, no studies were stratified to identify AMLs likely to express specific ABC transporters, and inhibitors for these transporters were not carefully chosen.**

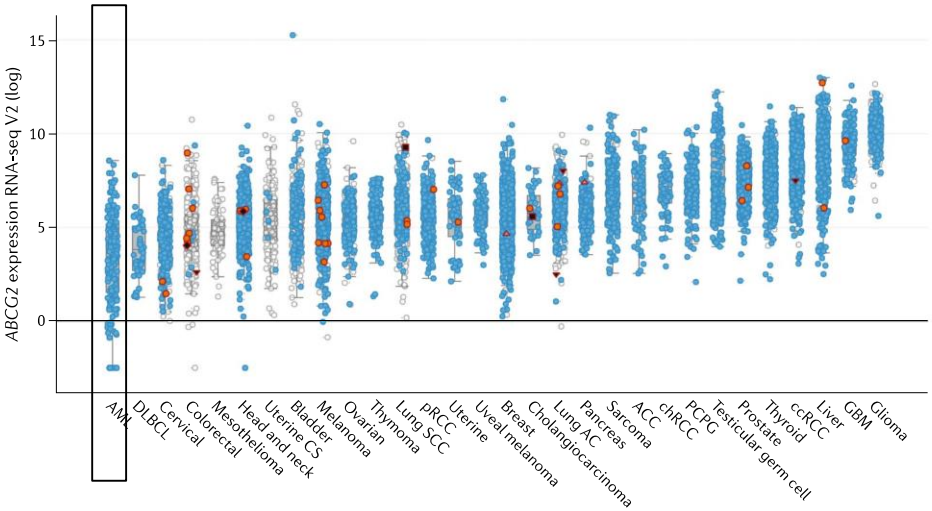
ABCB1 and ABCG2 are expressed in some AMLs

ABCB1



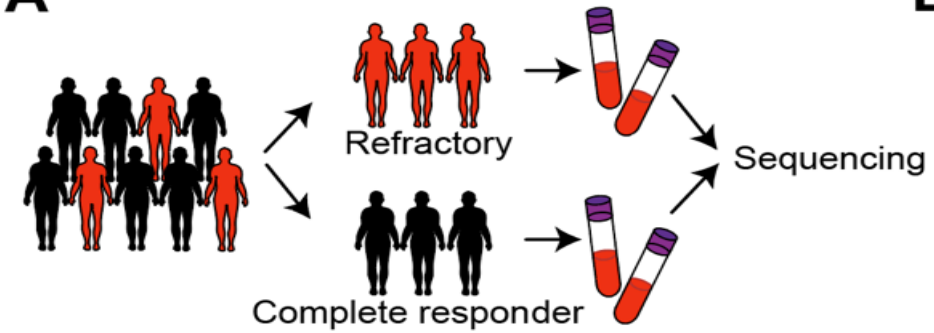
The Cancer Genome Anatomy Project (TCGA)

ABCG2



Stratification of Refractory AML reveals a subset of AML expressing ABC transporters

A



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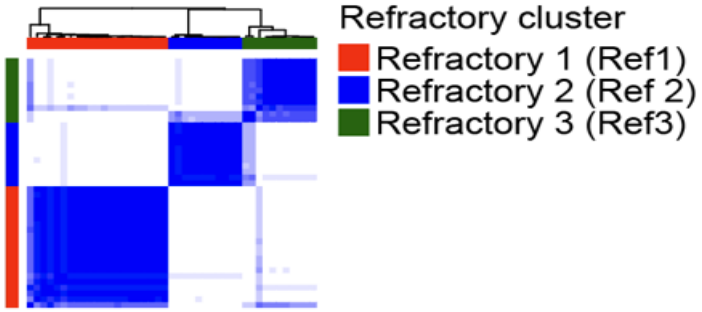

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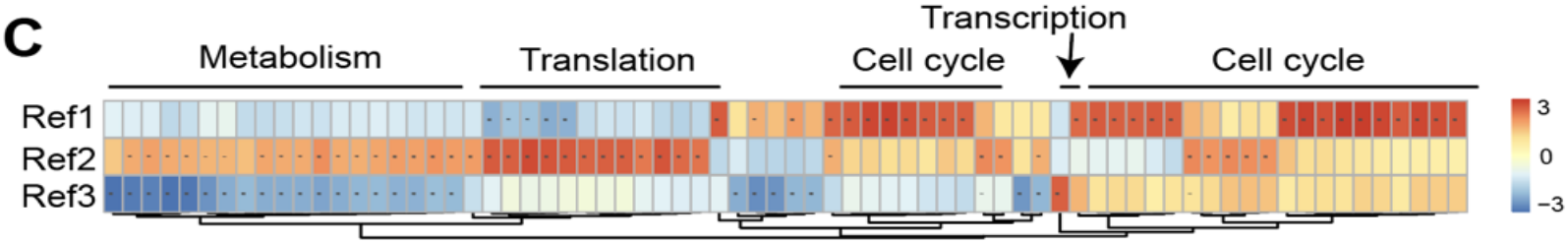
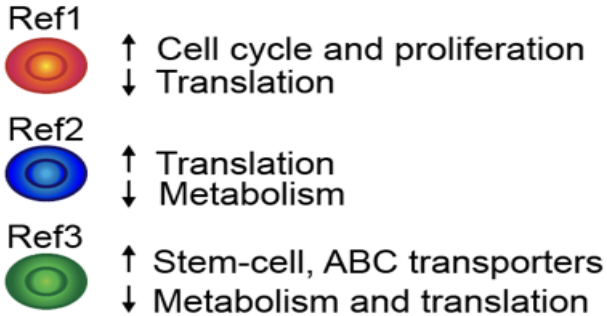


D

Genes	FC	P-value	Adj. p-value
ABCG2	5.56	<0.001	0.002
ABCA2	1.96	0.001	0.023
ABCA9	3.81	0.002	0.033
ABCA6	3.68	0.003	0.036

E



Fold-change of 10 ABC transporters known to be involved in chemotherapy resistance, in AML samples taken after relapse compared with their counterparts taken at diagnosis

Genes	P11	P 2	P 3	P 7	P 10	P 1	P 5	P 8	P 6	P 4	P 9
	M0	M1	M1	M1	M2	M4	M4	M4	M5a	M5b	M5b
ABCA3	-2.2	NA	NA	2.1	NA	NA	NA	NA	2.6	NA	NA
ABCB1	3.5	-9.4	2.5	-6.0	-2.2	NA	5.7	3.8	-2.4	-4.6	24.6
ABCB4	4.6	-14.9	NA	NA	NA	-10.7	2.5	NA	NA	NA	-13.3
ABCC1	NA	NA	NA	NA	NA	NA	2.0	-2.5	NA	4.3	5.4
ABCC2	NA	3.8	-2.9	-2.0	NA	NA	NA	NA	NA	NA	-2.9
ABCC3	25.9	NA	13.3	NA	NA	-3.8	-6.4	NA	NA	-5.1	-43.5
ABCC4	NA	-3.0	NA	NA	NA	NA	NA	-10.0	-3.2	3.4	3.2
ABCC5	NA	NA	NA	NA	NA	NA	NA	NA	-2.4	NA	NA
ABCC6	11.4	2.7	NA	NA	NA	NA	NA	-2.9	NA	NA	3.2
ABCG2	NA	3.8	-7.4	NA	3.3	NA	NA	2.5	2.0	NA	8.3

Conclusions

- **Stratification of AML at presentation reveals heterogeneity in gene expression, including heterogeneous expression of ABC transporters in refractory leukemias that could be targeted to improve therapy (Horibata et al., PNAS, 116, 10494-10503, 2019).**
- **ABCG2, not ABCB1, is statistically more likely to be expressed in the Ref 3 subset of refractory AML could be specifically targeted**
- **Relapsed AML is also extremely heterogenous in expression of ABC transporters, and determination of which transporters are expressed at relapse could improve choice of inhibitors (Patel et al., Cancer, 119, 3076-3083, 2013).**

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