

MCM2 and the origin licensing complex: A putative node of ER+/HER2- breast cancer therapy resistance

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Abstract

CDK4/6 inhibitors (CDK4/6i) in combination with endocrine therapy (ET) has revolutionized treatment practices for advanced and high-risk ER+/HER2- breast cancer via effective inhibition of cell cycle activation. However, the vast majority of patients eventually progress on these therapies, underscoring the need for new treatment strategies to select patients, monitor response, and target novel therapeutic vulnerabilities. We previously reported that high expression of *MCM2* and the DNA origin licensing complex (LC) is enriched in primary tumors refractory to CDK4/6i¹. We propose that *MCM2*/LC expression may be a biomarker reflecting multiple ET and CDK4/6i resistance mechanisms, due to its role in S-phase activation.

Introduction

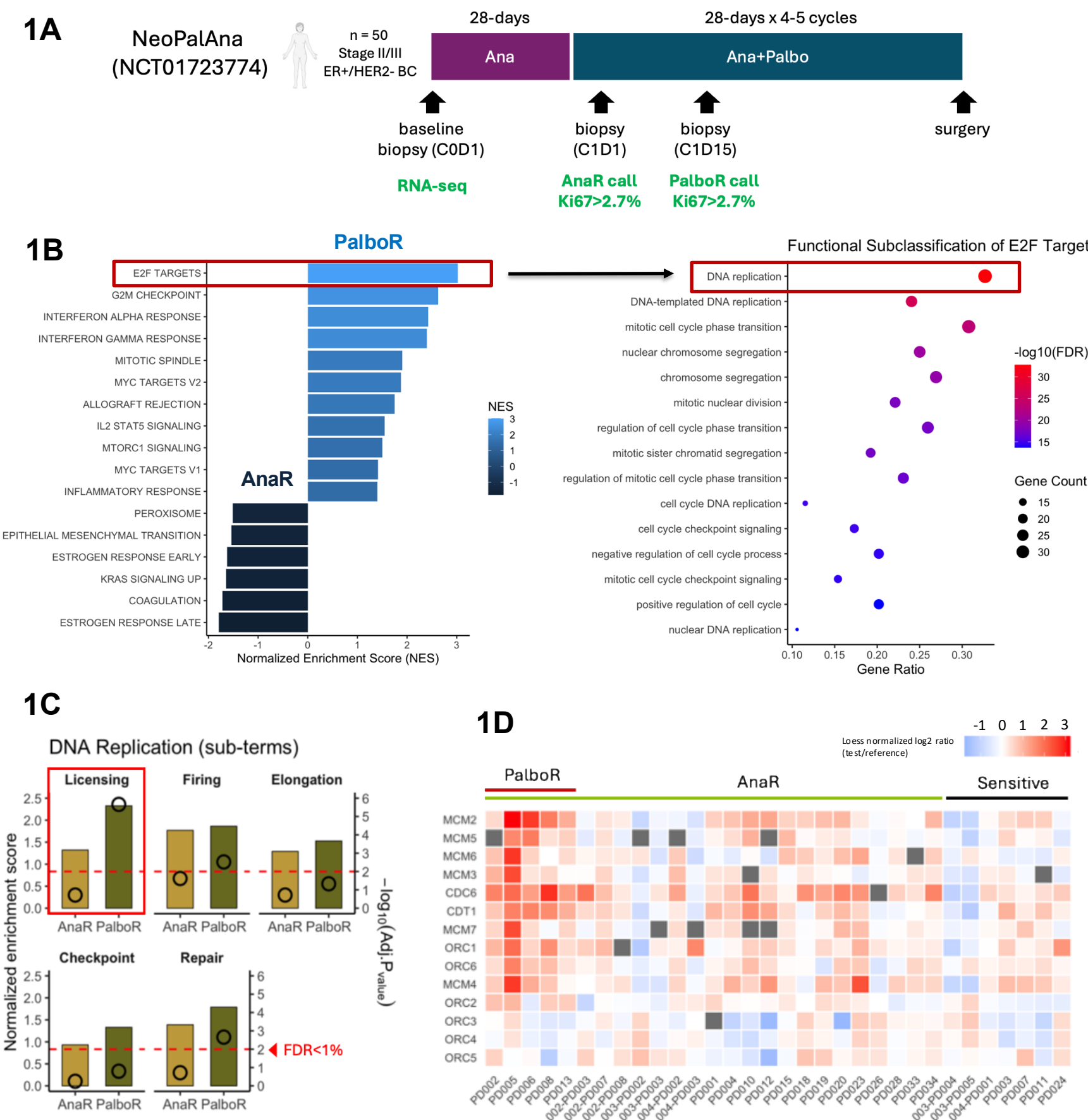


Fig 1. DNA replication origin licensing is associated with resistance to the CDK4/6i, palbociclib (Palbo), vs the aromatase inhibitor, anastrozole (Ana), in the NeoPalAna trial² (A) NeoPalAna study design showing biopsies used for RNA-seq, call of Ana resistance (AnaR) and call for Palbo resistance (PalboR). (B) Baseline GSEA of Hallmark pathways in tumors with resistance to Palbo (vs Ana) and functional GO subclassification of E2F TARGETS gene set. (C) NES of DNA replication sub-terms and (D) heatmap of LC mRNA. (E) Model of the LC.

Methods

- Retrospective review of Caris Life Sciences NGS profiling of 1960 ER+/HER2- tumors (592-gene panel, WES, WTS)
- Tumor stratification by *MCM2* or LC-score: Q1 (low) mRNA \leq 25th percentile, Q4 (high) mRNA $>$ 75th percentile
- Clinical characterization: age, Tx exposure, tumor histology, PAM50
- Molecular characterization: GSEA, mutational/copy number analysis
- Chi-square, Fisher's Exact, or Mann-Whitney U tests (p-/q-)

Results

MCM2 Cohort Clinical Characteristics			LC Cohort Clinical Characteristics		
	Q1 (low)	Q4 (high)		Q1 (low)	Q4 (high)
Histology	Lobular 17.1%	Lobular 6.1%	Histology	Lobular 15.5%	Lobular 8%
	Ductal 43.7%	Ductal 47.6%		Ductal 42.2%	Ductal 49.2%
PAM50 subtype	LumA 56.3%	LumA 5.3%	PAM50 subtype	LumA 48.6%	LumA 4.3%
	LumB 39.8%	LumB 85.5%		LumB 46.9%	LumB 85.7%

Fig 2. Tumors with high *MCM2* or LC-score expression are less lobular and more Luminal B. Table of histology and PAM50 intrinsic subtype frequencies in (A) *MCM2* and (B) LC-score Q1 versus Q4 tumors. Histologic enrichment calculated by Fisher's Exact test (p<0.05), and PAM50 enrichment calculated by Chi-Square test (p<0.05).

MCM2 P/LP Variant Frequency			LC-score P/LP Variant Frequency		
	Q1	Q4		Q1	Q4
PIK3CA	52	41	PIK3CA	53	41
CDH1	25	15	CDH1	25	17
TP53	17	33	TP53	19	30
MAP3K1	12	8	CBFB	4.6	1.5
KMT2C	11	7.4	RB1	1.9	4.9
AKT1	6	2.6	MEN1	0.7	2.4
FOXA1	5.5	2.3			
CBFB	5.1	2.1			
SE3B1	4.2	1.9			
ERBB2	3.3	1.3			
ERBB3	2.2	0.6			
FGFR2	2.2	0.6			
RB1	1.2	5.8			
MEN1	0.7	3.2			

Fig 3. Tumors with high *MCM2* or licensing complex expression harbor enrichment of *TP53* and *RB1* mutations. Pathogenic or likely pathogenic gene variant (P/LP) frequency in (A) *MCM2* and (B) LC-score Q1 versus Q4 tumors. Each comparison shown is p<0.05 by Chi-square test.

Results

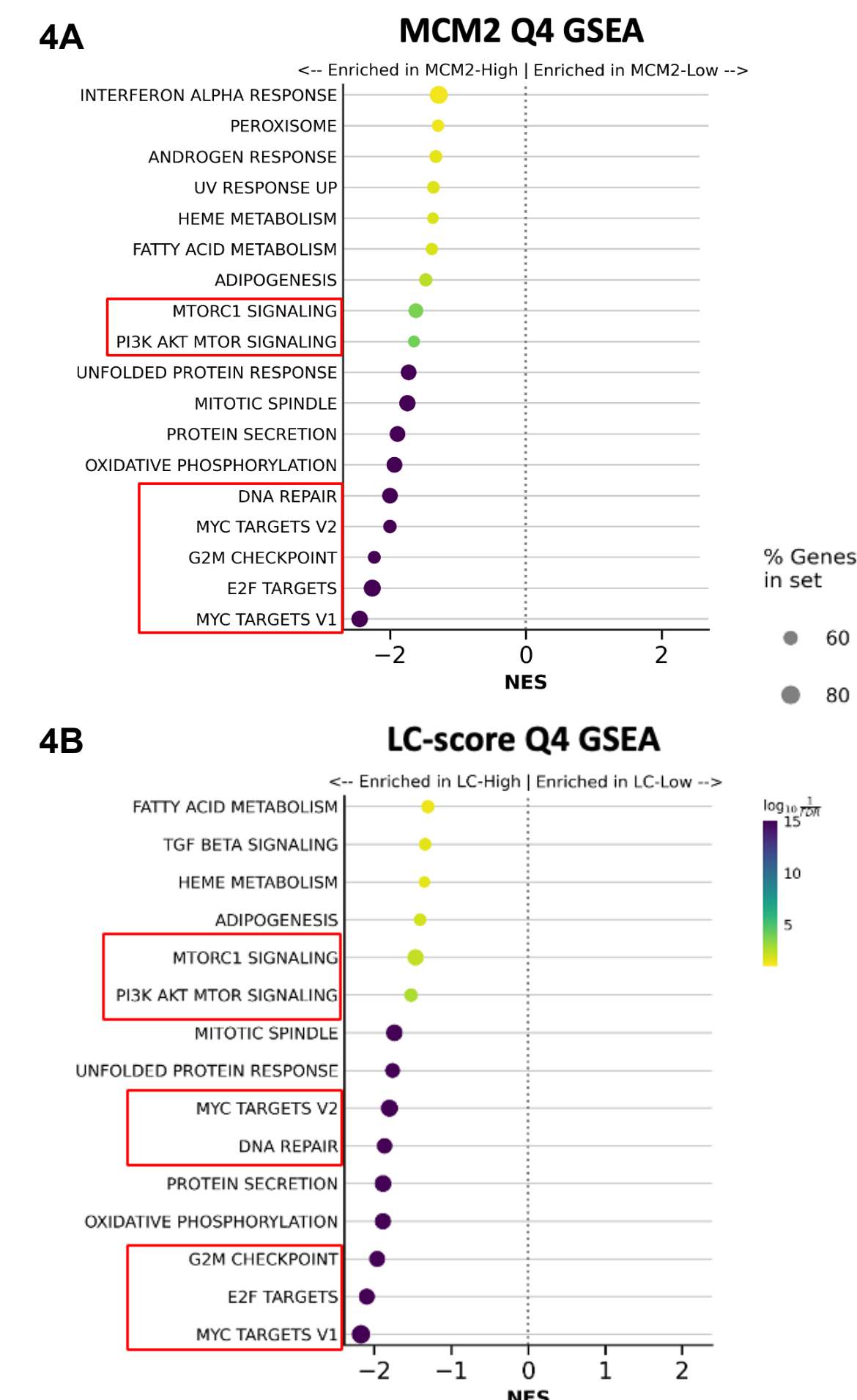


Fig 4. Tumors with high *MCM2* or LC-score expression display transcriptomic enrichment of Hallmark pathways previously identified to drive ET and CDK4/6i resistance. GSEA dot plot showing significant (FDR q<0.05) pathways enriched in (A) *MCM2*-high or (B) LC-high tumors.

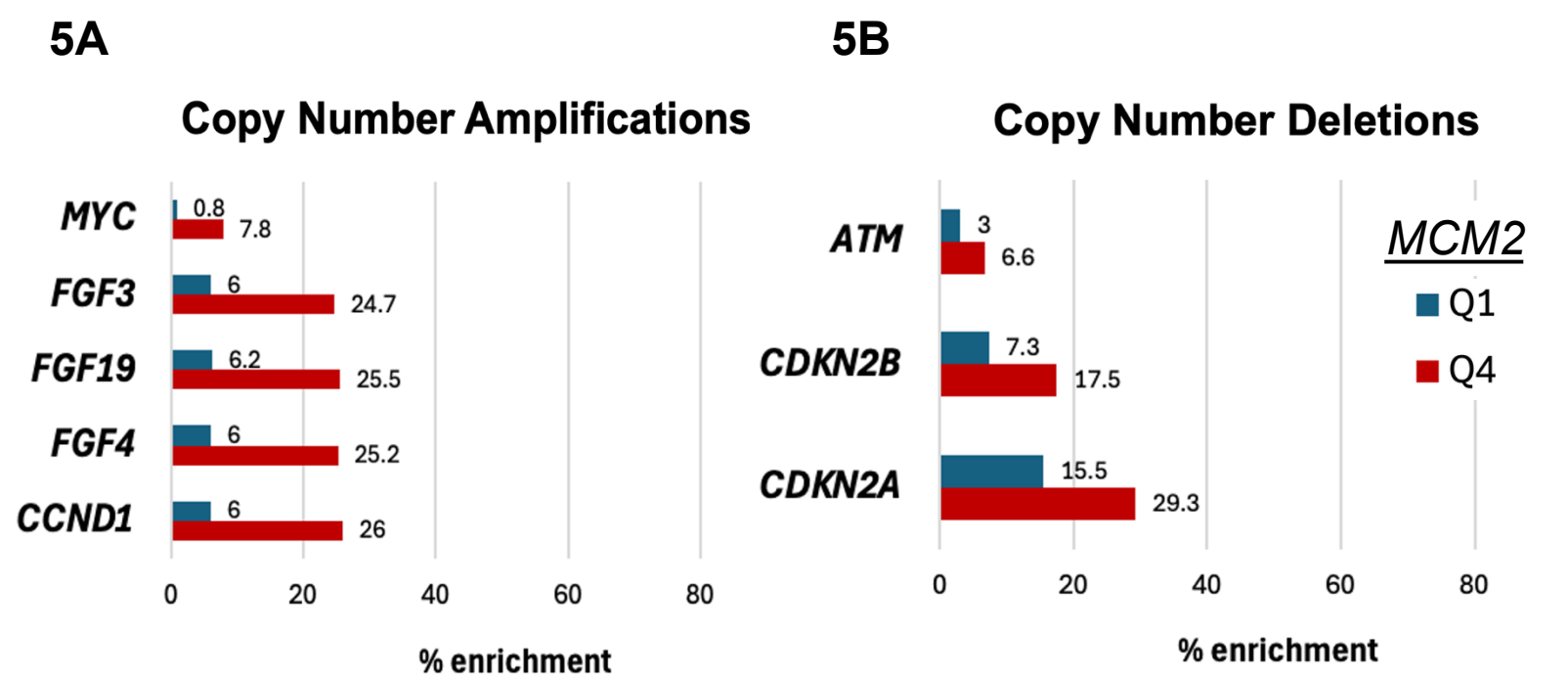


Fig 5. DNA copy number alterations associated with high *MCM2* expression. (A) Copy number amplifications and (B) deletions enriched in *MCM2* Q4 versus Q1 tumors. p-values calculated by Chi-Square test (p<0.05). *Very similar results for LC-score Q1 and Q4.*

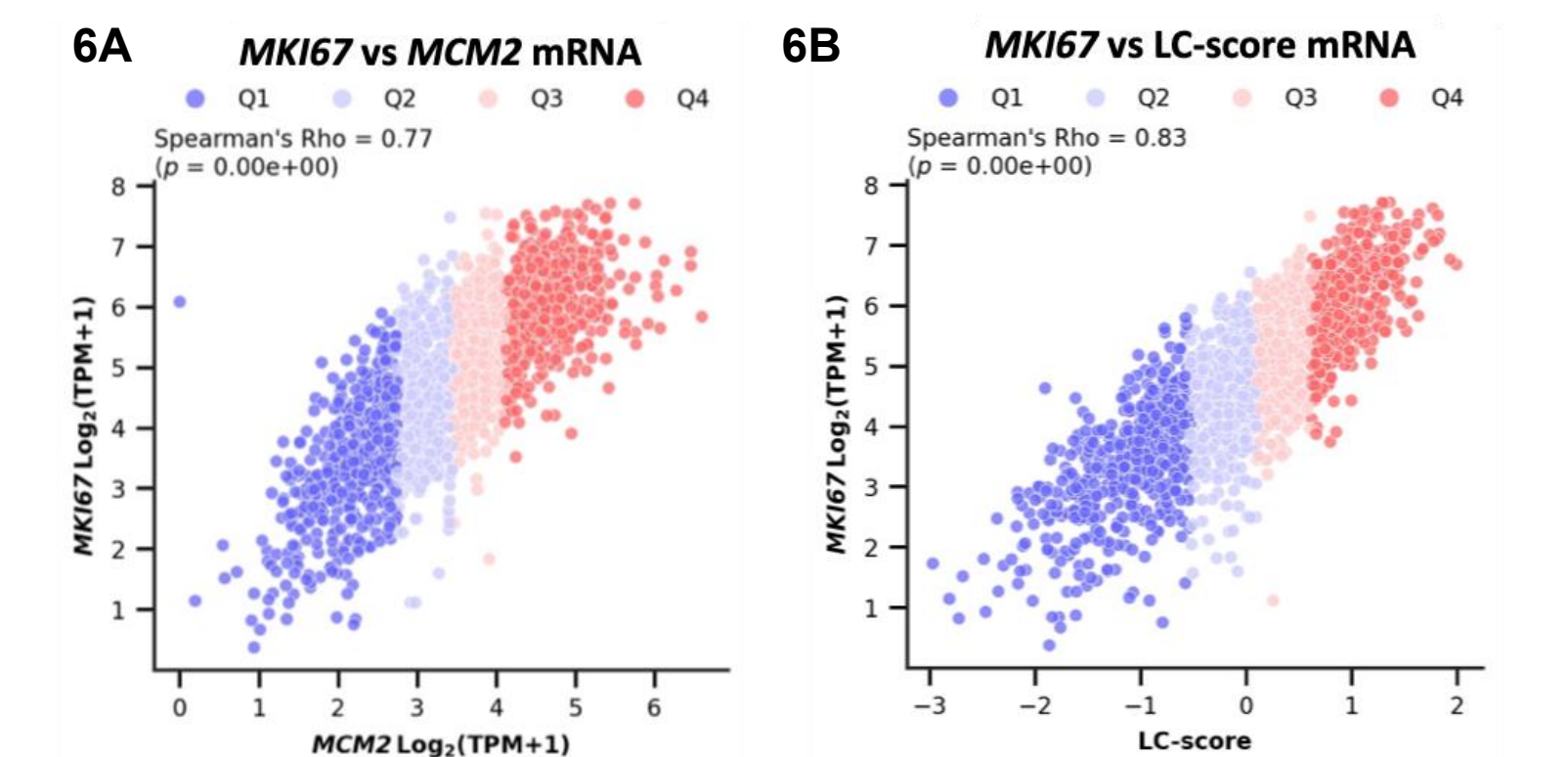
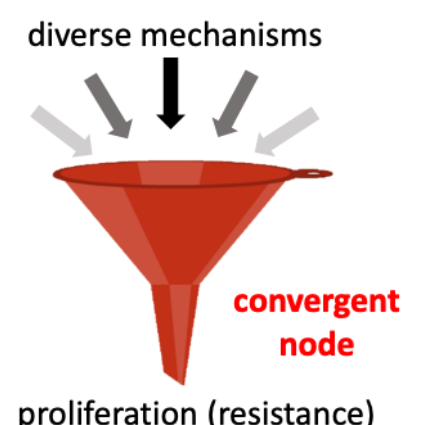


Fig 6. *MCM2* and LC-score are highly positively correlated with Ki-67 gene expression in treatment-naïve ER+/HER2- tumors. Correlation plot of *MKI67* mRNA versus (A) *MCM2* and (B) LC-score mRNA. Rho and p-value calculated by Spearman's rank correlation. *MCM2*/LC quartiles: dark blue = Q1, light blue = Q2, pink = Q3, red = Q4.

Conclusions

In ER+/HER2- BC, high *MCM2*/LC is associated with:

- LumB subtype and less lobular histology
- TP53* and *RB1* mutations
- CCND1*, *MYC*, *FGF* amplifications (cell cycle activating)
- CDKN2A/B* and *ATM* deletions (cell cycle inhibitory)
- increased expression of E2F, MYC, and cell cycle activation, and DNA repair genes



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