

GNA13/S1P Pathway in DLBCL

Integrating Mutations and Expression with Clinical Outcome

DLBCL Bioinformatics Analysis

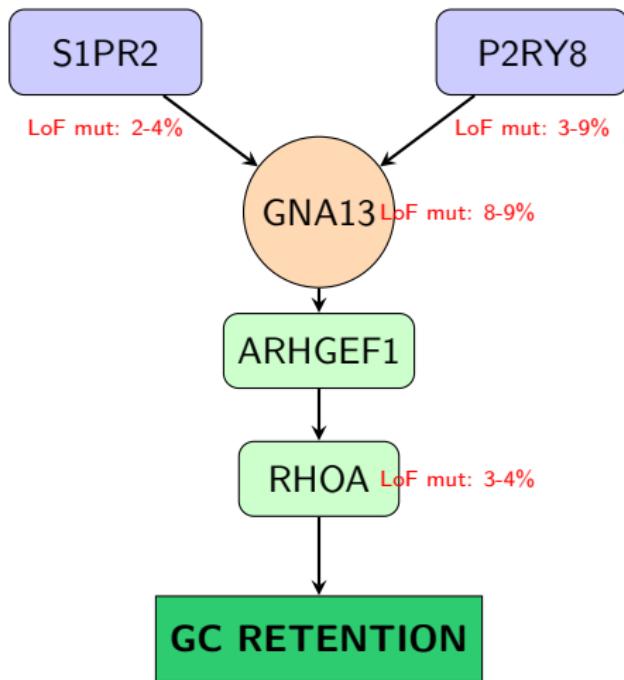
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Section 1

Background

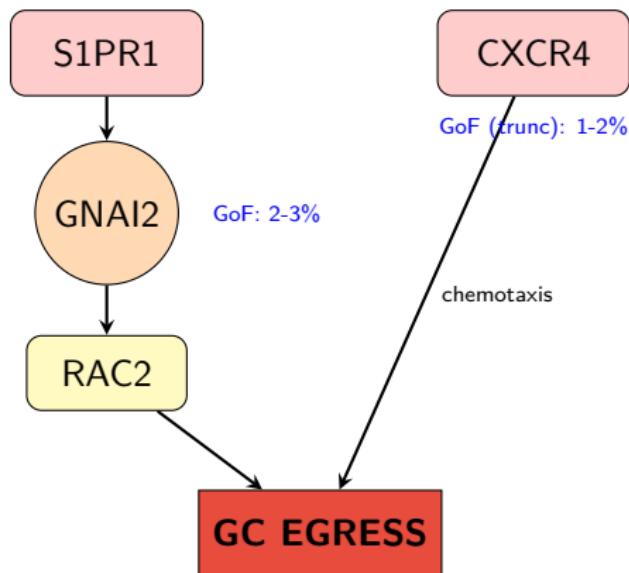
The S1P/GNA13 Signaling Axis

RETENTION PATHWAY



Egress Pathway

EGRESS PATHWAY



Gain-of-function mutations (e.g., CXCR4 truncating) enhance chemotaxis and promote egress from germinal center

Biological Context

Germinal Center (GC) Biology:

- B cells normally retained in GC for affinity maturation
- S1P gradient controls trafficking
- S1PR2/GNA13 = "stay" signal
- S1PR1 = "go" signal

DLBCL Relevance:

- GCB-DLBCL arises from GC B cells
- Loss of retention → dissemination
- GNA13 mutations define EZB subtype
- Therapeutic vulnerability?

Question: Do mutation patterns and expression levels predict clinical outcome?

Section 2

Mutation Analysis

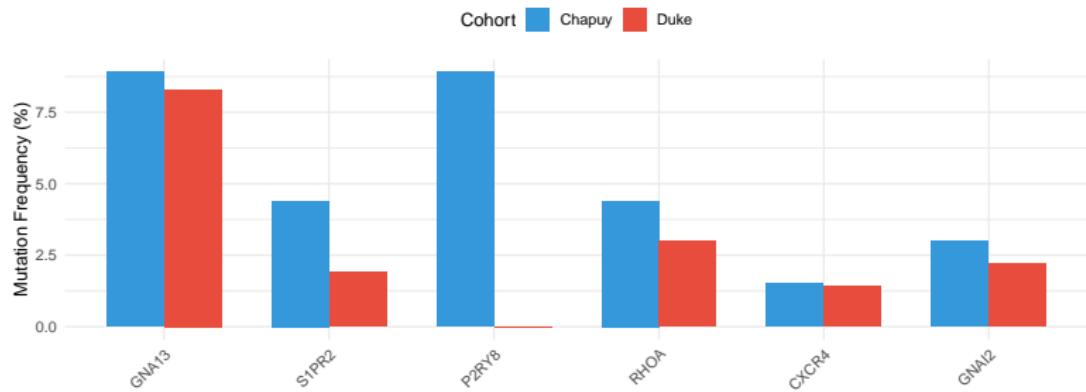
Pathway Gene Mutations in DLBCL

Table 1: Mutation frequencies across cohorts

Gene	Pathway	Chapuy (%)	Duke (%)
S1PR2	Retention LoF	4.4	1.9
GNA13	Retention LoF	8.9	8.3
P2RY8	Retention LoF	8.9	0.0
RHOA	Retention LoF	4.4	3.0
CXCR4	Egress GoF	1.5	1.4
GNAI2	Egress GoF	3.0	2.2

- **GNA13** most frequently mutated retention gene (8-9%)
- **P2RY8** (orphan GPCR) mutated in 3-9%
- Egress pathway mutations less common

Cross-Cohort Mutation Comparison

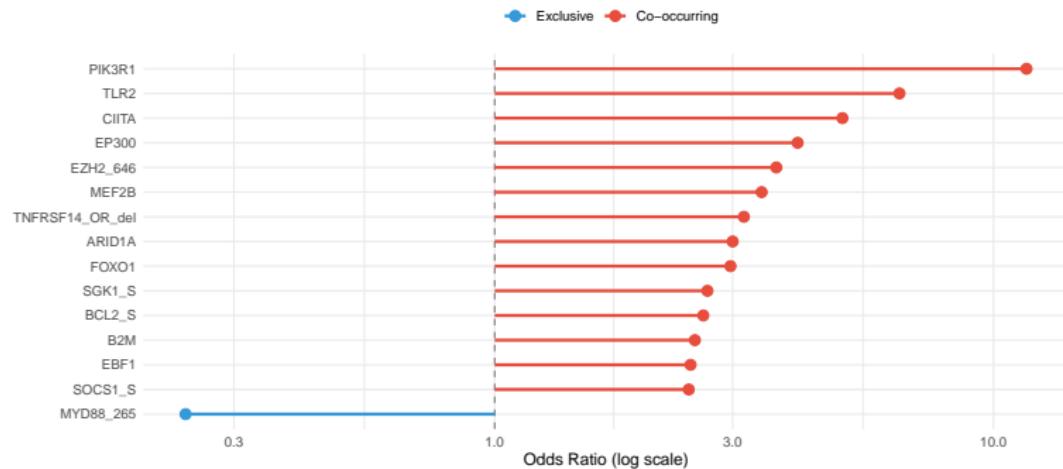


GNA13 Mutation Co-occurrence

Table 2: Top GNA13 co-occurring mutations

Gene	GNA13+ (%)	GNA13- (%)	OR	P-value
PIK3R1	7.7	0.7	11.65	1.8e-04
TLR2	5.1	0.8	6.48	9.7e-03
CIITA	10.3	2.2	4.98	1.0e-03
EP300	14.1	3.9	4.05	5.7e-04
EZH2_646	28.2	9.6	3.67	1.1e-05
MEF2B	19.2	6.5	3.43	3.3e-04
TNFRSF14_OR_del	38.5	16.5	3.16	1.1e-05
ARID1A	16.7	6.2	3.00	2.0e-03
FOXO1	12.8	4.7	2.97	6.3e-03
SGK1_S	29.5	13.5	2.67	6.5e-04

GNA13 Co-occurrence Forest Plot



GNA13 Defines the EZB Subtype

Strong Co-occurrence:

- EZH2 mutations (OR = 3.67)
- TNFRSF14 deletions (OR = 3.16)
- BCL2 translocations
- GCB cell-of-origin

Mutual Exclusivity:

- MYD88 L265P (OR = 0.06)
- CD79B mutations
- ABC-associated alterations

GNA13 mutations are a hallmark of the **EZB/GCB molecular subtype**, characterized by epigenetic dysregulation and germinal center phenotype

Section 3

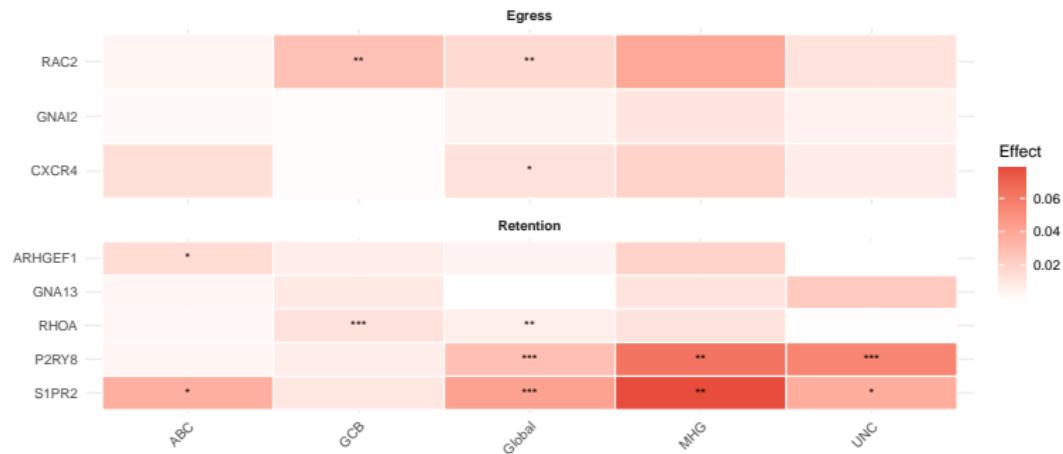
Expression-Survival Analysis

Expression Predicts Survival

Table 3: Expression-survival associations (Global cohort)

Gene	Pathway	Log2FC	P-value	Direction	
P2RY8	Retention	-0.029	1.5e-06	GOOD	***
S1PR2	Retention	-0.043	1.7e-06	GOOD	***
RAC2	Egress	-0.017	3.9e-03	GOOD	**
RHOA	Retention	-0.008	4.8e-03	GOOD	**
CXCR4	Egress	0.013	2.8e-02	POOR	*
GNAI2	Egress	-0.005	1.2e-01	GOOD	
ARHGEF1	Retention	-0.005	2.3e-01	GOOD	
GNA13	Retention	0.000	9.9e-01	POOR	

Expression Effects by COO Subtype



Green = protective (high expr → better survival); Red = adverse

Key Expression Findings

Retention Genes:

- S1PR2: Protective ($p = 1.7e-6$)
- P2RY8: Protective ($p = 1.5e-6$)
- RHOA: Protective ($p = 0.005$)
- GNA13: Not significant ($p = 0.99$)
- ARHGEF1: Not significant

Egress Genes:

- CXCR4: Adverse ($p = 0.03$)
- GNAI2: Not significant
- RAC2: Paradoxically protective ($p = 0.004$)

The GNA13 Paradox

GNA13 is the most frequently mutated gene in this pathway (8-9%), yet its **expression is not prognostic**. Possible explanations: transcriptional compensation, post-translational regulation, or pathway redundancy.

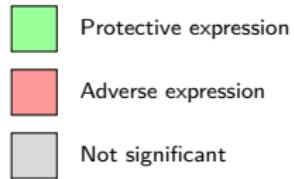
Section 4

Integrated Analysis

Mutations vs Expression: Integrated View

RETENTION

S1PR2	Mut: 2-4% Expr: Protective
P2RY8	Mut: 3-9% Expr: Protective
GNA13	Mut: 8-9% Expr: NS
RHOA	Mut: 3-4% Expr: Protective

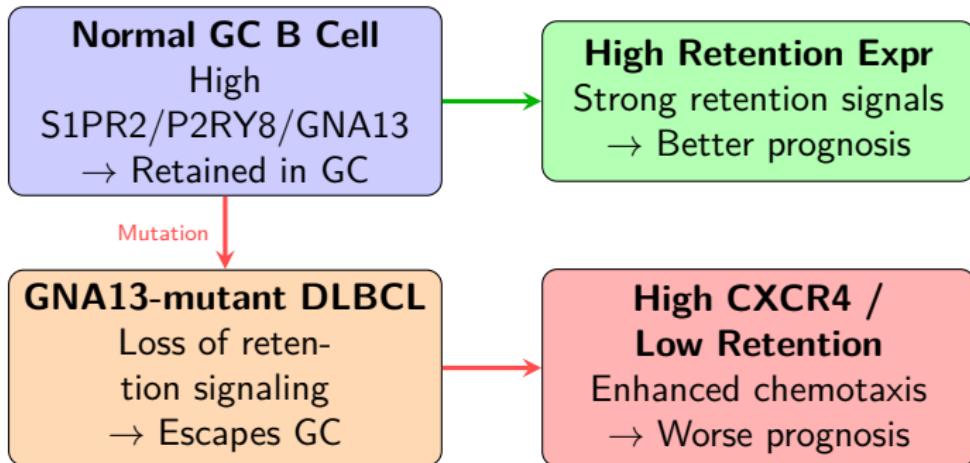


*Paradoxical

EGRESS

CXCR4	Mut: 1-2% Expr: Adverse
GNAI2	Mut: 2-3% Expr: NS
RAC2	Mut: 3% Expr: Protective*

Biological Model



Summary of Key Findings

- ① **Retention pathway mutations** (GNA13, P2RY8, RHOA) are recurrent in DLBCL, especially GCB subtype
- ② **Expression of retention genes** (S1PR2, P2RY8, RHOA) is protective – high expression correlates with better survival
- ③ **GNA13 paradox:** Most frequently mutated but expression not prognostic
- ④ **CXCR4** is the key egress gene – high expression predicts worse outcome
- ⑤ **GNA13 mutations co-occur** with EZH2 and TNFRSF14, defining the EZB molecular subtype
- ⑥ **Mutual exclusivity** with MYD88 L265P confirms pathway specificity to GCB-DLBCL

Clinical Implications

Prognostic Value:

- S1PR2/P2RY8 expression as biomarkers
- CXCR4 expression identifies high-risk patients
- Potential for retention/egress gene signature

Therapeutic Opportunities:

- CXCR4 antagonists (plerixafor)
- S1PR modulators (fingolimod)
- EZH2 inhibitors for GNA13-mutant tumors

Future Directions

- Validate retention/egress signature in independent cohorts
- Explore combination of mutation + expression features
- Investigate mechanism of GNA13 expression paradox

Acknowledgments

Data Sources:

- Lacy/HMRN cohort (n=928) – Expression and survival
- Chapuy et al. (2018) – Mutation frequencies
- Duke cohort – Cross-validation

Analysis Pipeline:

R/Bioconductor, survival analysis, ggplot2 visualization

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