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Glossary

synthetic lethal	Genetic interactions where inactivation of multiple genes is inviable (or deleterious) when they are viable if inactivated separately.

Acronyms

AMPK	AMP-activated protein kinase.
BMP	Bone morphogenic protein.
EMT	Epithelial-mesenchymal transition.
GPCR	G protein coupled receptor.
PDE	Phosphodiesterase.
PI3K	Phosphoinositide 3-kinase.
siRNA	Short interfering ribonucleic acid.
SLIPT	Synthetic lethal interaction prediction tool.
TGFβ	Transforming growth factor β.

Chapter 5

Synthetic Lethal Pathway Structure

Aims

- Synthetic Lethal Genes within a Biological Pathway Structure
- Importance and Connectivity of Synthetic Lethal Genes within Pathway Networks
- Upstream and Downstream Relationships between SLIPT and siRNA Candidates

Summary

- Synthetic Lethal genes were explored within a graph structures for key pathways identified previously
- In some cases these graph structures appeared to have relationships between synthetic lethal genes
- However, no existing network metrics of importance and connectivity with the networks were elevated significantly for Synthetic Lethal genes
- Nor was there significant evidence of upstream and downstream relationships between SLIPT and siRNA Candidates in a shortest path permutation analysis

Having identified key pathways implicated in synthetic lethal genetic interactions with *CDH1*, these were investigated for the underlying synthetic lethal genes within them and their relationships to pathway structure in Reactome pathways. This chapter will focus on the pathway structure of biological pathways detected across analyses in Chapter 4. The synthetic lethal genes considered here are those candidates detected by SLIPT (as described in Section 3.1) in TCGA breast cancer expression and mutation data (TCGA, 2012) in comparison to the candidate gene partners from the siRNA screening in breast cell lines (Telford *et al.*, 2015).

The graph structure for Reactome pathways was obtained from Pathway Commons via BioPaX (as described in Section 2.4.2). The pathways describe the (directional) relationships between biomolecules, including proteins (encoded by genes), in biological pathways. These relationships include cell signalling (such as kinase phosphorylation cascades), gene regulation (such as transcription factors, chromatin modifiers, RNA binding proteins), and metabolism (such as the product of an enzyme being the substrate of another). Together these relationships describe the known functional pathways in a human cell with a reasonable resolution, from a curated database supported by publications documenting pathway relationships. While this functional pathway network encapsulates protein complexes and functional modules, protein binding or text-mining alone are not used to determine relationships between genes. The Reactome network is sufficient to test pathway relationships with directional information, although it is not documented whether these relationships are activating or inhibitory.

Pathway structures were derived from the Reactome network (as described in Section 2.4.3) for the graph structure of each biological pathway. The synthetic lethal candidate genes for notable pathways discussed in Chapter 4, including candidate synthetic lethal pathways of *CDH1*, were examined to show the SLIPT and siRNA candidates within these pathways. Thus synthetic lethal genes were identified within a biological context and with further investigations into their relationship with pathway structure and between synthetic lethal candidates detect by each approach. Synthetic lethal gene candidates in the context of pathway structures and additional support for belonging to a synthetic lethal pathway are ideal for triage of targets specfici to *CDH1* deficient tumours and for further experimental validation in preclinical models.

Network analysis metrics (as described in Sections 2.4.4 and 3.5.3) were applied to test whether gene detected by SLIPT, siRNA, or both approaches varied according to these network analysis metrics (of connectivity and importance in the network) to test whether they differed between synthetic lethal genes or approaches to detect them.

Another consideration is the relationships between synthetic lethal candidates detected by either approach: these were tested by both a resampling approach (as described in Sections 3.4.1 and 3.4.1.1) and compared across a ranking based on biological context (Section 3.4.1.2). Together these approaches serve to test the pathway relationships between SLIPT and siRNA synthetic lethal gene candidate partners for *CDH1* within the biological pathways identified and demonstrate a combination of network biology and statistical investigations into structural relationships between genes identified by a Bioinformatics analysis.

5.1 Synthetic Lethal Genes in Reactome Pathways

5.1.1 The PI3K/AKT Pathway

The phosphoinositide 3-kinase (PI3K) cascade signalling pathway exhibited unexpected results with metagene analyses (as discussed in Section 4.3). This pathway is also of interest because mediating signals between the G protein coupled receptors and regulation of protein translation which have both been strongly implicated to be synthetic lethal pathways with loss of *CDH1* function. All three of these pathways have are also subject to dysregulation in cancer and other diseases. Thus the PI3K cascade will be examined along with the most supported synthetic lethal pathways (as identified in Chapter 4).

The phosphoinositide 3-kinase (PI3K) pathway is also an ideal pathway to test pathway structure since it has an established direction of signal transduction from extracellular stimuli (and membrane bound receptors) to the inner mechanisms of the cell, namely the regulation of protein translation. The production of proteins is neccessary for the growth of the cell so it is reasonable to suggest that these processes may be subject to (non-oncogene) addiction in some cancer cells which rely upon them for sustained protein production and cell growth. This is also supported by the oncogenes *PIK3CA* and *AKT1* being involved with the PI3K cascade and related PI3K/AKT pathway which may be subject to oncogene addiction when these proto-oncogenes are activated.

Despite the PI3K cascade not being supported across SLIPT and siRNA analysis by over-representation (in Section 4.2.1.4) or resampling (in Section 4.2.1.4.1), numerous genes were detected by either Synthetic Lethal Interaction Prediction Tool (SLIPT) in TCGA breast expression data or the short interfering ribonucleic acid (siRNA) primary screen (as shown in Figure 5.1). It is also notable, that of the few genes that

were identified by both approaches, these include genes that are highly conencted in the PI3K cascade and are hubs to information transmission such as *FGF9*,*PDE3B*, and *PDE4A*. The key upstream genes *PIK3CA* and *PIK3CG* were detected by siRNA whereas the downstream *PIK3R1* and *AKT2* genes were detected by SLIPT. Gene detected by either method were also prevalent in the PI3K, phosphodiesterase (PDE), and AMP-activated protein kinase (AMPK) modules, in addition to the downstream translation factors and ribosomal genes (*EIF4B*, *EEF2K*, and *RPS6*). Together these suggest that there may further be structure between the SLIPT and siRNA candidates partners of *CDH1* in pathways such as this example. As such, pathway structure will be tested to detect differences in the upstream and downstream gene candidates of those detected by either method. This may further explain the disparity between SLIPT and siRNA genes, even in pathways such as PI3K where they did not significantly intersect.

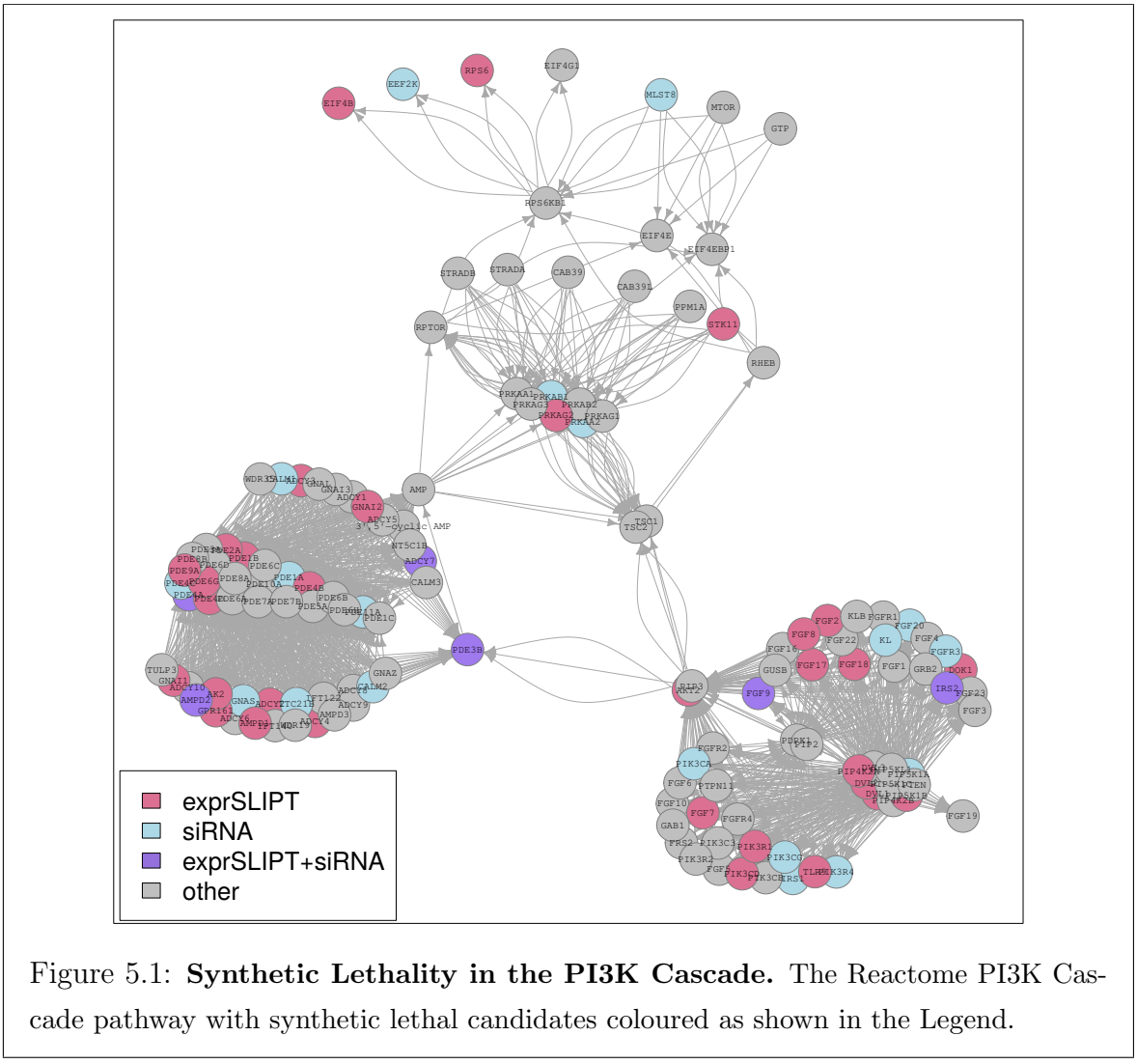

Figure 5.1: **Synthetic Lethality in the PI3K Cascade.** The Reactome PI3K Cascade pathway with synthetic lethal candidates coloured as shown in the Legend.

This disparity between SLIPT and siRNA gene candidate synthetic lethal partners of CDH1, that is a high number of genes detected by either approach with few detected by both, was replicated the related PI3K/AKT pathway and the "PI3K/AKT in cancer" pathway (shown in Figures J.1 and J.2). With many synthetic lethal candidates at the upstream core of these pathway networks and the downstream extremities. It is particularly notable that the many genes important in cell signalling and gene regulation were detected by either sytnhetic lethal detection approach. These include *AKT1*, *AKT2*, and *AKT3*, the Calmodulin signalling genes *CALM1* and *CAMK4*, and the forkhead family transcription factors *FOXO1* (a tumour suppressor) and *FOXO4* and inhibitor of epithelial-mesenchymal transition (EMT).

5.1.2 The Extracellular Matrix

The extracellular pathways elastic fibre formation and fibrin clot formation (shown in Figures 5.2 and 5.3 respectively) were both supported across analyses (in Chapter 4). This includes a significant over-representation and resampling the interaction between SLIPT (for TCGA breast cancer) and siRNA gene candidates showing that SLIPT has identified these pathways in addition to their over-representation in the siRNA screen.

Particularly for elastic fibres (in Figure 5.2), the vast majority of genes were detected by either approach in addition to a significant proportion of genes detected by both approaches (as determined in Section 4.2.1.4). The genes detected by both approaches also appeared to have a non-random distribution in the network with *TFGB1*, *ITGB8*, and *MFAP2* exhibiting high connectivity and a cental role in their respective pathway modules. In addition to a structural role in the extracellular matrix and connective tissue (including the tumour microenvironment), these proteins including Furin, transforming growth factor β (TGFβ), and the bone morphogenic proteins (BMPs), are also involved in responses to endocrine signals and interacting with the cellular receptors for signalling pathways. Therefore it is plausible that *CDH1* deficient tumours will be subject to non-oncogene addiction to the extracellular environment and growth signals arising from this pathway. The pathway structure is also worth further investigation into whether the genes detected by siRNA or both approaches are downstream of those detected by SLIPT in addition to whether they have higher connectivity or centrality than other genes in the pathway.

Genes detected as synthetic lethal partners of *CDH1* by SLIPT or siRNA screening were also common in the Fibrin clot formation pathway (shown in Figure 5.3). This is consistent with the established pleiotropic role of *CDH1* in regulating fibrin clotting. It

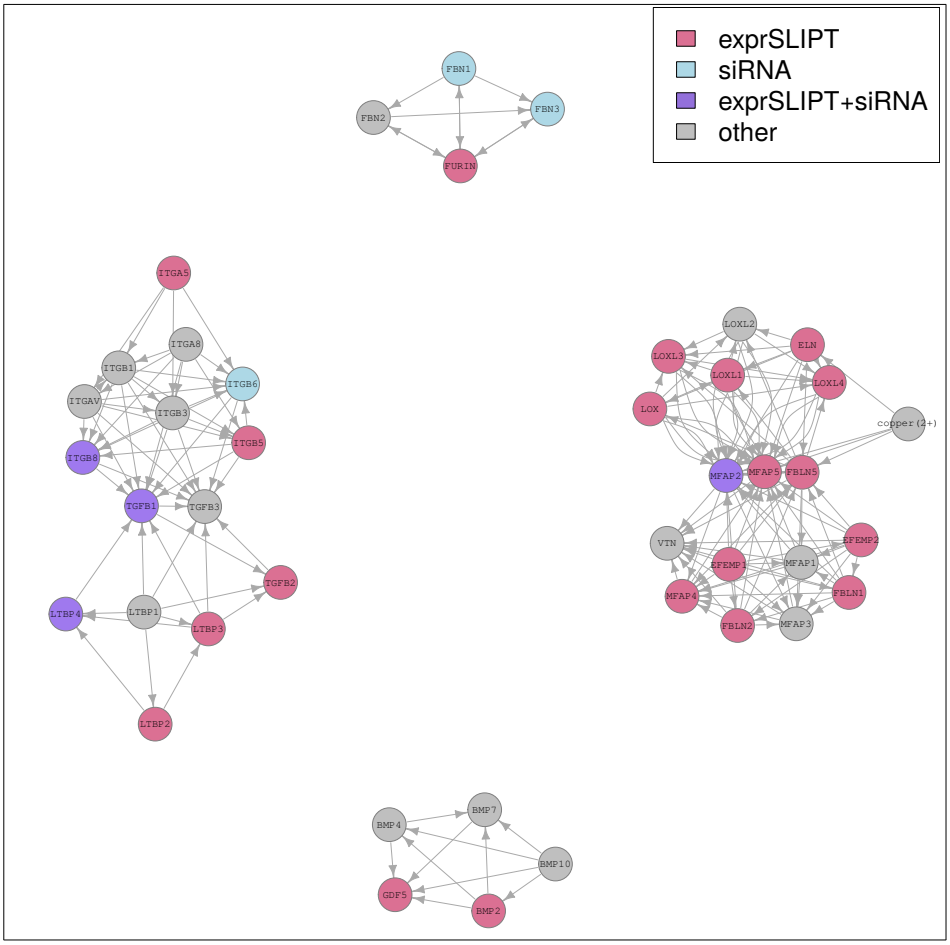

Figure 5.2: **Synthetic Lethality in the Elastic Fibre Formation Pathway.** The Reactome Elastic Fibre Formation pathway with synthetic lethal candidates coloured as shown in the Legend.

is also notable that the genes detected by either method appear to be highly connected such as *C1QBP KNG1*, *F8*, *F10*, *F12*, *F13A*, and *PROC* (including many of the coagulation factors). Synthetic lethal candidates also include *SERPINE2* and *PRCP*, which only affect downstream genes, in addition to *PROCR* and *VWF*, which are only affected by upstream genes.

Many of these genes are involved in the larger Extracellular Matrix pathway (shown in Figure J.3), including many of the synthetic lethal candidates discussed for elastic fibres. The number of SLIPT candidate genes outnumbers those identified by siRNA as expected from an isolated cell model. However, the endocrine response genes (such as *TGFB1* and *LTBP4*) which are potentailly artifacts of the cell line growth process were replicated with SLIPT analysis in patient tumours (TCGA breast cancer data).

There is also additional support for synthetic elthal genes such as *ITGB2*, *MFAP2*, and *SPARC* being highly connected networks hubs of the pathway. Although the complexity of extracellular matrix pathway lends credence to the need for formal network analysis approaches to aid interpretation of the structure and relationships among synthetic lethal candidates in a pathway network, in addition to statistical approaches to determine whether such relationships are unlikely to be observed by sampling error.

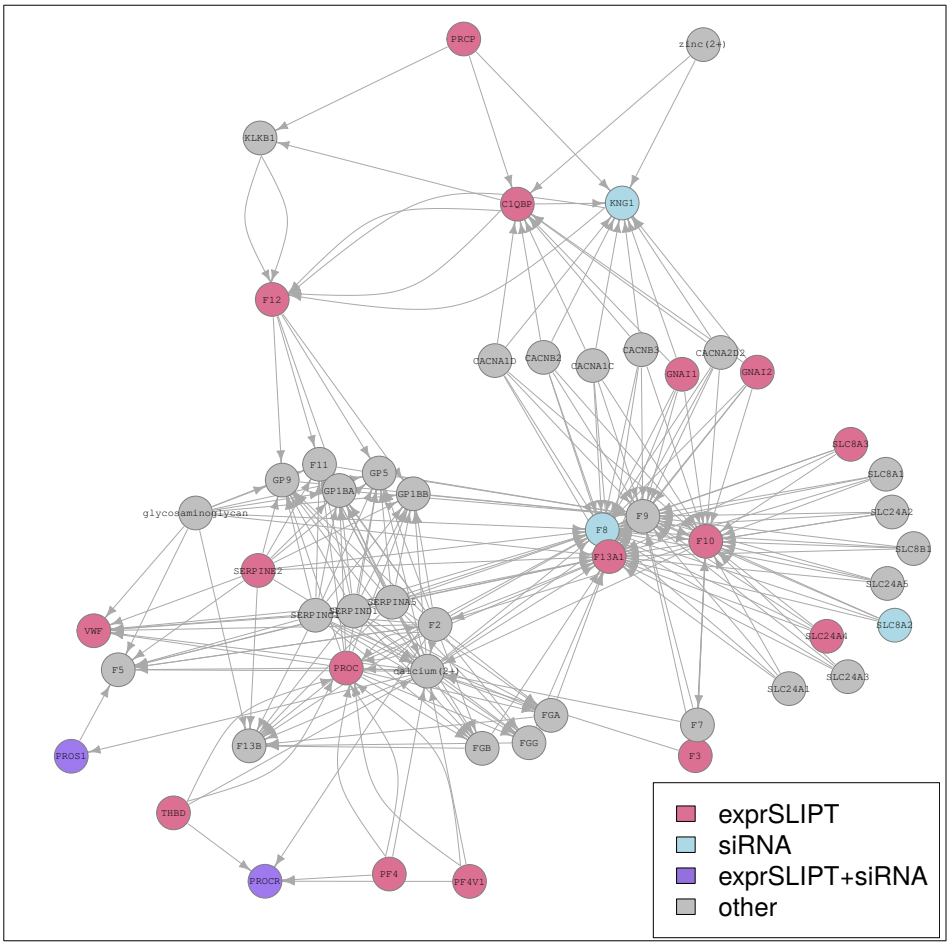

Figure 5.3: **Synthetic Lethality in the Fibrin Clot Formation.** The Reactome Fibrin Clot Formation pathway with synthetic lethal candidates coloured as shown in the Legend.

5.1.3 G Protein Coupled Receptors

Similarly, G protein coupled receptor (GPCR) pathways are highly complex (as shown in Figures J.4 and J.5). Many of these were synthetic lethal candidates by eith SLIPT pr siRNA screening with many detected with both approaches, consistent with these path-

ways being supported by prior analyses (in Sections 4.2.1.4 and 4.2.1.4.1). Synthetic lethal candidates include the PDE and Calmodulin genes (as discussed in Section 5.1.3) in addition to others such as the regulators of G-protein signaling (RGS), chemokine receptors (CXCR), Janus kinase (JAK), and the Ras homolog family (RHO) genes. These are important regulatory signalling pathways necessary for cellular growth and cancer proliferation. Thus the GPCR pathways (and downstream PI3K/AKT signals) are a potentially actionable vulnerability against *CDH1* deficient cancers, particularly since many existing drug targets exist among these signalling pathways, some of which have been experimentally validated (Kelly *et al.*, 2017b; Telford *et al.*, 2015). However, the complexity of GPCR networks containing hundreds of genes requires the relationships between SLIPT and experimental candidates to be tested with a network based statistical approach, although a statistically significant intersection of these approaches has been established (in Sections 4.2.1.4 and 4.2.1.4.1).

5.1.4 Gene Regulation and Translation

While very few synthetic lethal genes were detected in translational pathways in an experimental screen against *CDH1* Telford *et al.* (2015), these were highly over-represented in translational elongation (as shown in Figure J.6). These SLIPT genes include many ribosomal proteins and the regulatory "elongation factors" which may be subject to responses in the upstream signalling pathways. This observation lends support the notion of pathway structure among synthetic lethal candidates detected by SLIPT in comparison with siRNA as the computational approach with SLIPT has demonstrated the ability to detect downstream genes in the core translational processes which experimental screening did not identify. Although it is possible that the experimental screening may detect upstream regulatory genes less sensitive inactivation, that is genes which are less likely to be indiscriminately lethal to both genotypes at high doses of inactivation.

Many of these SLIPT candidate genes are also among the nonsense-mediated decay (NMD) pathway (shown in Figure J.7) or $3'$ untranslated region (UTR) mediated translational regulation (shown in Figure J.8). While genes in these pathways were also supported by experimental screening with siRNA, there was clear pathway structure. In particular, *UPF1* was detected in the siRNA screen and is the focal downstream gene for the entire NMD pathway showing that (in this case) siRNA genes are downstream effectors of those detected by SLIPT. $3'$ UTR mediated translational regulation has a similar structure with two modules connected solely by *RPL13A*, giving an ex-

ample of SLIPT candidates genes with high connectivity, although there were many ribosomal proteins detected by SLIPT. However, *EIF3K* a regulatory elongation factor (not essential to ribosomal function) that was detected by SLIPT was replicated with siRNA screening while the majority of the elongation factors were not detected by either approach. Regulatory genes being more amenable to experimental validation also support further investigation into pathway structure as the SLIPT candidates may support them by structural relationships and the downstream genes not being detectable by experimental screening with high dose inhibitors may explain the greater number of SLIPT candidate partners of *CDH1* than those experimentally identified.

5.2 Network Analysis of Synthetic Lethal Genes

5.2.1 Gene Connectivity and Vertex Degree

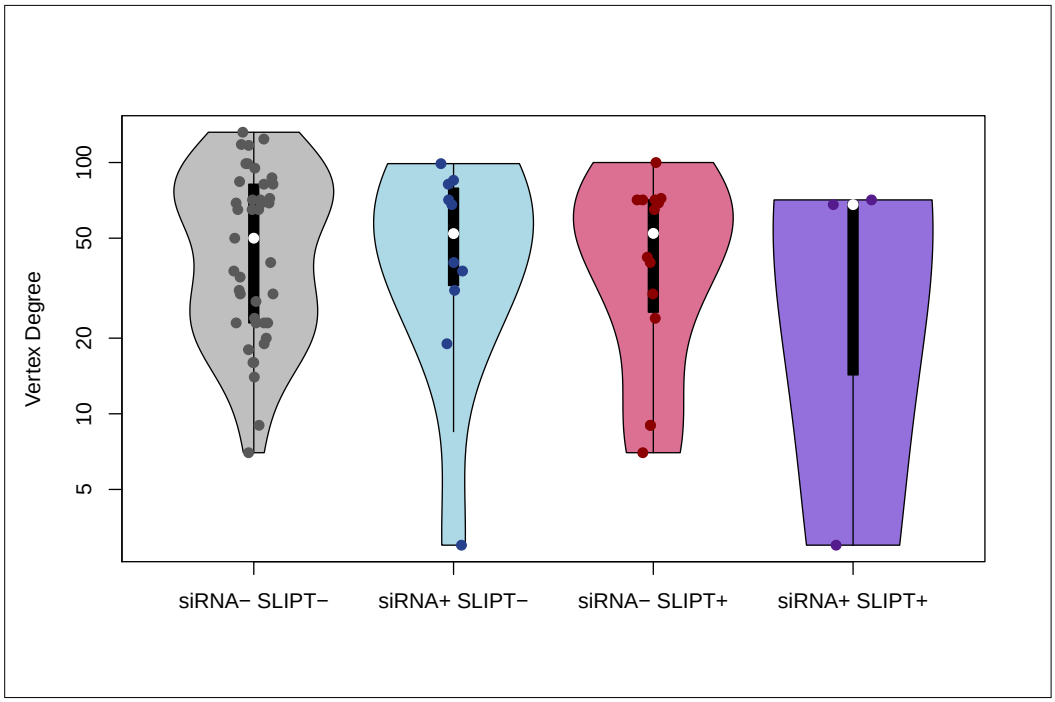

Figure 5.4: **Synthetic Lethality and Vertex Degree.** Synthetic Lethality and Vertex Degree

Table 5.1: ANOVA for Synthetic Lethality and Vertex Degree

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	15	15.50	0.0134	0.9082
SLIPT	1	506	506.01	0.4378	0.5105
siRNA×SLIPT	1	0	0.05	0.0000	0.9947

ANOVA for Synthetic Lethality and Vertex Degree

5.2.2 Gene Importance and Centrality

5.2.2.1 Information Centrality

Information centrality is a measure of the importance of nodes in a network but how vital they are to the transmission of information throughout the network. This naturally applies well to biological pathways, partcularly gene regulation and cell signalling. The nodes with the highest information centrality are not necessarily the most connected as they may also include nodes which pass signals between highly connected netwprk hubs.

Information centrality has also been suggested to indicate essentiality of genes or proteins (Kranthi *et al.*, 2013). See also Appendix M on gene essentiality.

Table 5.2: ANOVA for Synthetic Lethality and Information Centrality

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	0.000256	0.0002561	0.1854	0.6682
SLIPT	1	0.003827	0.0038275	2.7717	0.1008
siRNA×SLIPT	1	0.000804	0.0008036	0.5820	0.4483

ANOVA for Synthetic Lethality and Information Centrality

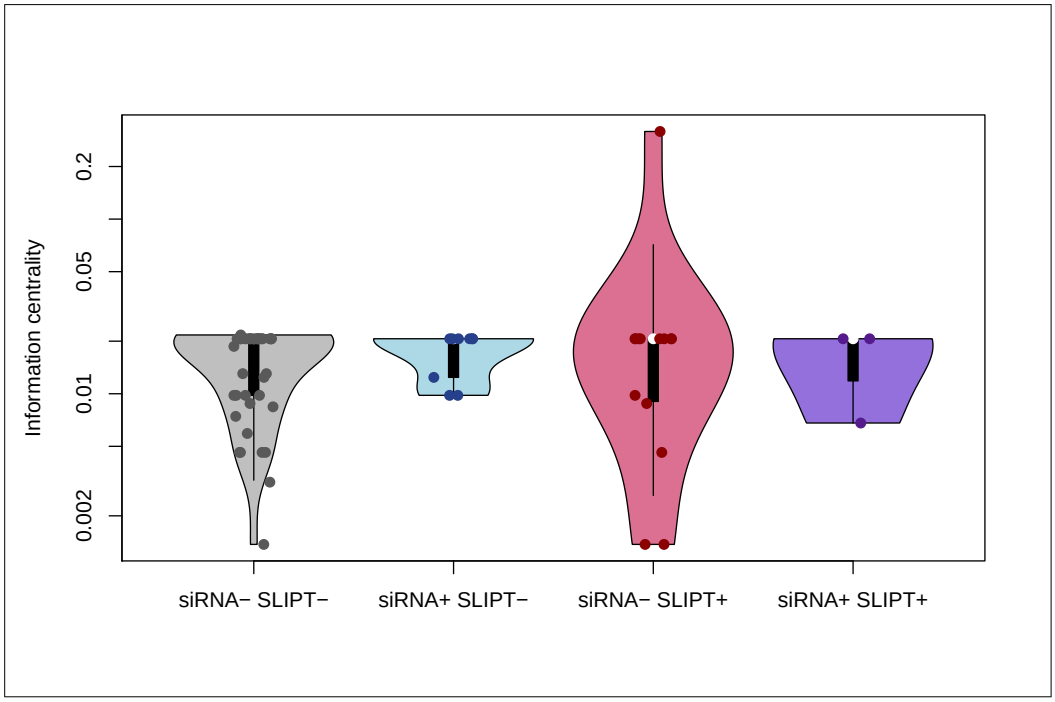

Figure 5.5: **Synthetic Lethality and Centrality.** Synthetic Lethality and Information Centrality (log-scale).

5.2.2.2 PageRank Centrality

Table 5.3: ANOVA for Synthetic Lethality and PageRank Centrality

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	0.0002038	2.0385×10^{-4}	1.1423	0.2892
SLIPT	1	0.0000208	2.0752×10^{-5}	0.1163	0.7342
siRNA×SLIPT	1	0.0000208	2.0752×10^{-5}	0.1163	0.7342

ANOVA for Synthetic Lethality and PageRank Centrality

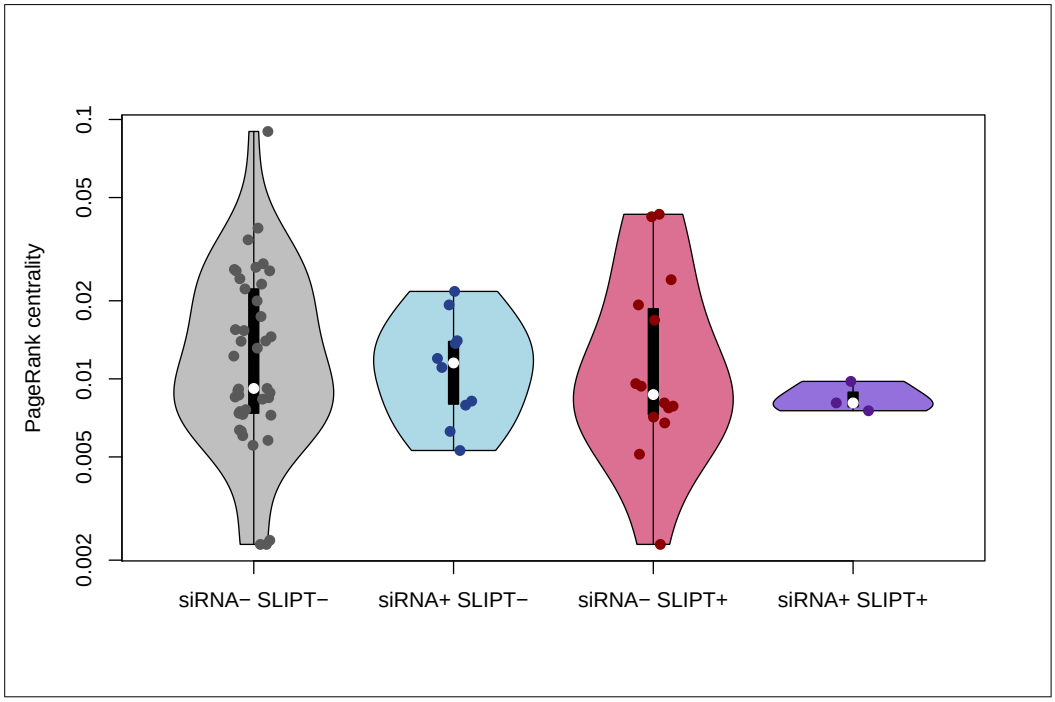

Figure 5.6: **Synthetic Lethality and PageRank.** Synthetic Lethality and PageRank.

5.3 Testing Pathway Structure of Synthetic Lethal Genes

5.3.1 Hierarchical Pathway Structure

5.3.1.1 Contextual Ranking of PI3K

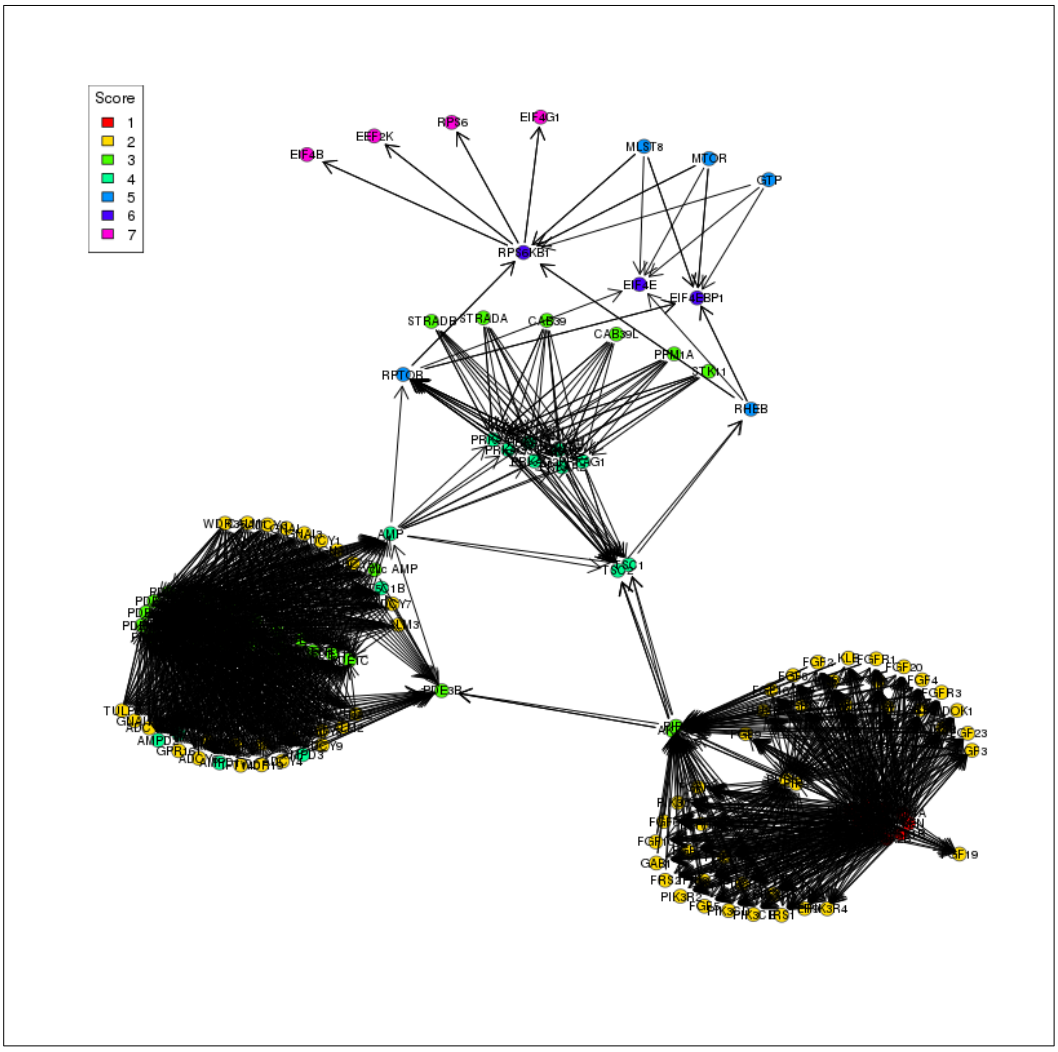

Figure 5.7: **Structure of PI3K Ranking.** Structure of PI3K Ranking.

5.3.1.2 Testing Contextual Ranking of Synthetic Lethal Genes

- Are there more SL genes of a particular rank?
- Is there an association with SLIPT (Chi-sq) or siRNA (viability) score?

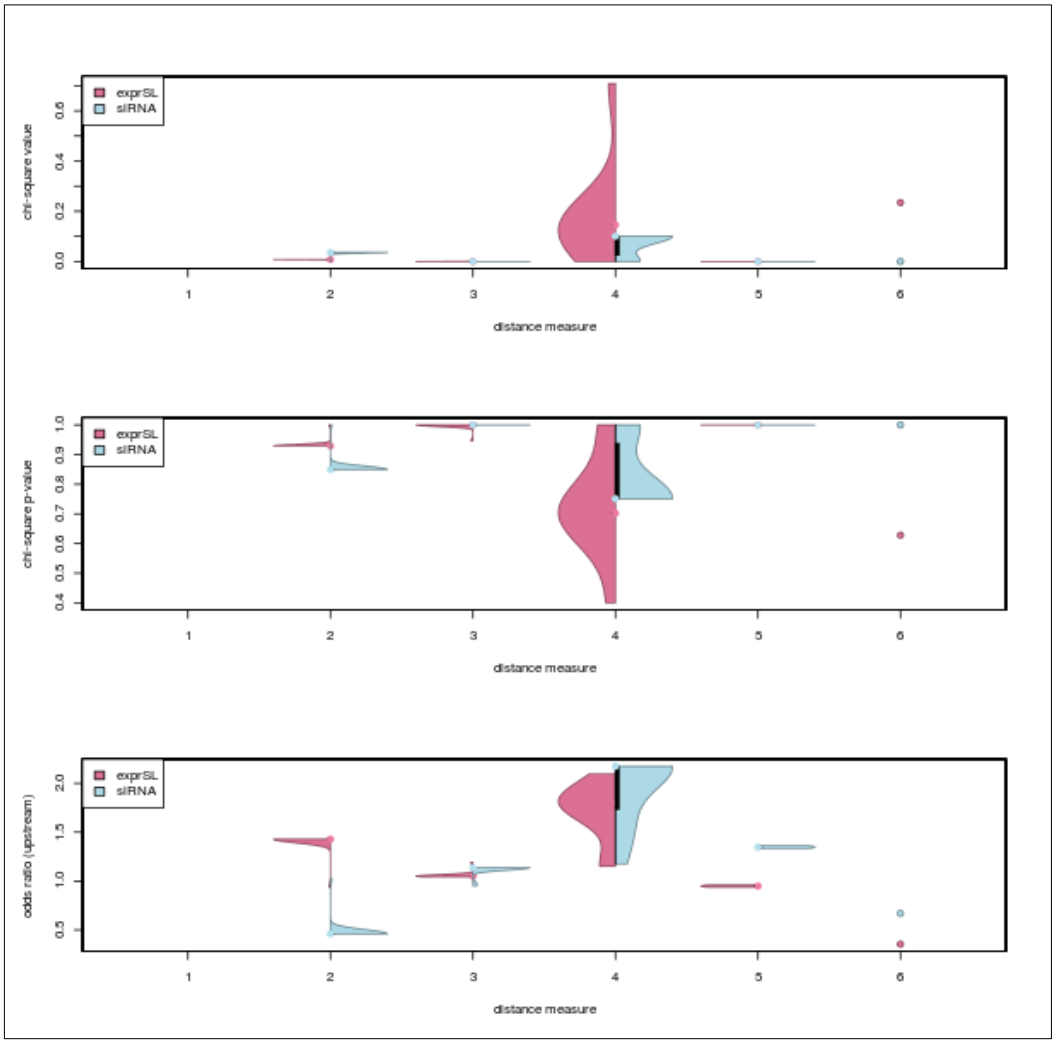

Figure 5.8: **Structure of Synthetic Lethality in PI3K.** Structure of Synthetic Lethality in PI3K.

5.3.2 Upstream or Downstream Synthetic Lethality

5.3.2.1 Measuring Structure of Candidates within PI3K

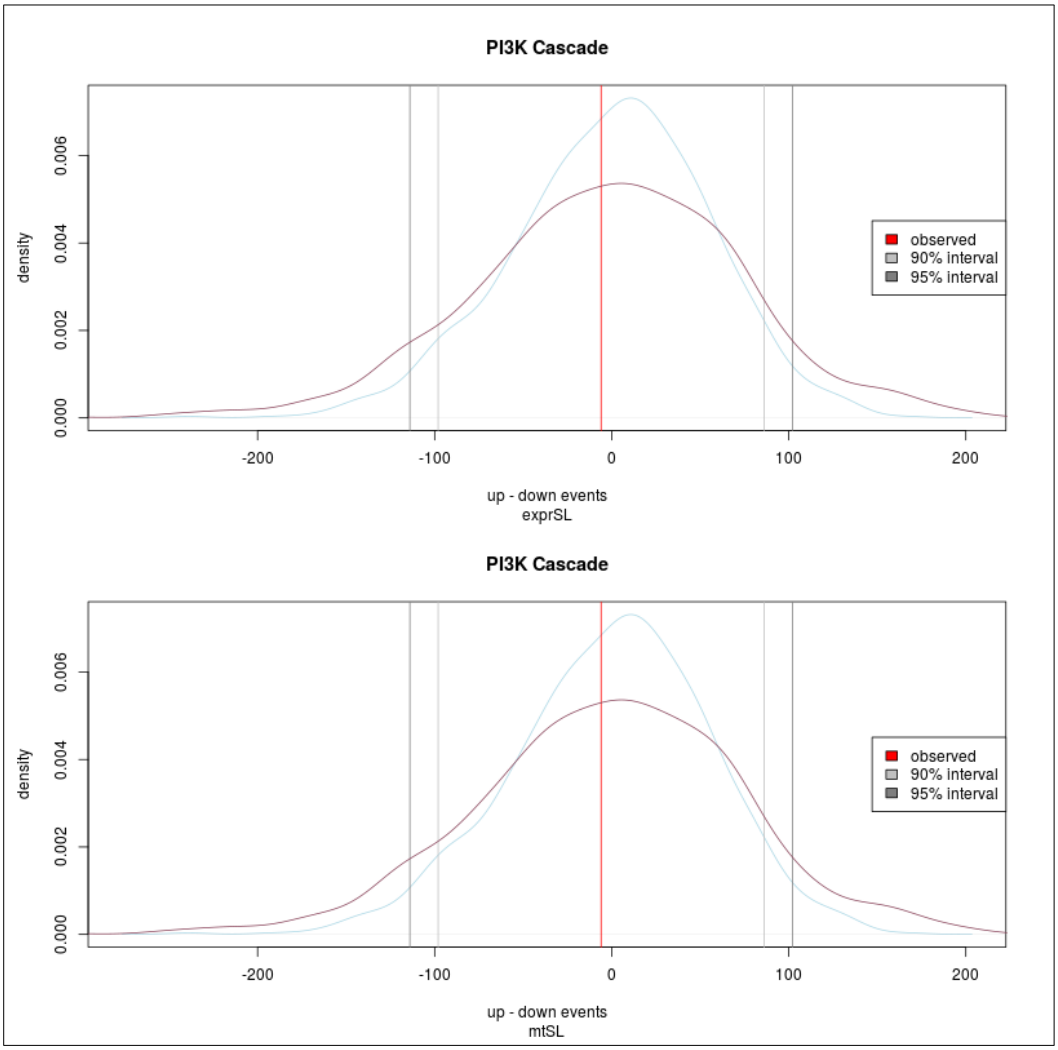

Figure 5.9: **Structure of Synthetic Lethality Resampling.** Structure of Synthetic Lethality Resampling.

5.3.2.2 Resampling for Synthetic Lethal Pathway Structure

Table 5.4: Information centrality for genes and molecules in the Reactome network

	Graph:		States:		Observed:				Permutation p-value:	
Pathway	Nodes	Edges	SLIPT	siRNA	Up	Down	Up−Down	Up/Down	Up−Down	Down−Up
PI3K Cascade	138	1495	38	25	122	128	-6	0.953	0.5326	0.4606
PI3K/AKT Signaling in Cancer	275	12882	98	44	779	679	100	1.147	0.3255	0.6734
$G_{\alpha i}$ Signaling	292	22003	95	58	836	1546	-710	0.541	0.9971	**0.0029**
GPCR downstream	1270	142071	312	160	9755	9261	494	1.053	0.3692	0.6305
Elastic fibre formation	42	175	24	7	1	2	-1	0.500	0.5461	0.3865
Extracellular matrix	299	3677	127	29	547	455	92	1.202	0.3351	0.6636
Formation of Fibrin	52	243	18	5	12	17	-5	0.706	0.6198	0.3564
Nonsense-Mediated Decay	103	102	74	2	0	74	-74	0	1.0000	**0.0000**
3' -UTR-mediated translational regulation	107	2860	77	1	0	0	0	NaN	0.4902	0.5027
Eukaryotic Translation Elongation	92	3746	76	0	0	0	0	NaN	0.4943	0.4933

Pathways in the Reactome network tested for structural relationships between SLIPT and siRNA genes by resampling (raw p-value)

Significant resampling in bold

Sampling only within target pathway

Number of siRNA+SLIPT matched to observed

siRNA+SLIPT kept for up/down evaluation

5.4 Discussion

5.5 Conclusion

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