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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

ANOVA	Analysis of Variance.
GPCR	G protein coupled receptor.
HDGC	Hereditary diffuse gastric cancer.
NMD	Nonsense-mediated decay.
RNAi	Ribonucleic acid interference.
siRNA	Short interfering ribonucleic acid.
SLIPT	Synthetic lethal interaction prediction tool.
TCGA	The Cancer Genome Atlas (genomics project).
UTR	Untranslated region (of mRNA).

Chapter 7

Discussion

This thesis combines analysis of gene expression data from The Cancer Genome Atlas (TCGA) with experimental screening results (Telford *et al.*, 2015) to demonstrate synthetic lethal discovery for *CDH1* in expression data generated by genomics technologies with comparisons to existing experimental candidates. Together these findings further elucidate the functions for *CDH1* in the cell, functional redundancy in breast cancer, and potential targets against cancers with loss of *CDH1* function. These candidate synthetic lethal genes were further investigated for relationships within synthetic lethal pathways, developing a network-based approach to comparing genes identified in genomics experiments and analyses in the process.

The synthetic lethal detection methodology, Synthetic Lethal Interaction Prediction Tool (SLIPT), that was applied to gene expression data throughout this thesis was evaluated with simulated data. A simulation procedure was developed to stringently generate gene expression data from known synthetic lethal partners in simulated data, including simple and complex correlation structures and modelling synthetic lethal genes within pathways. Together, these results demonstrate SLIPT as a robust widely applicable gene expression analysis procedure (for which an R package has been released) for discovery of synthetic lethal partner genes. Performance of SLIPT on simulated data also highlights the strengths of the procedure and future directions to improve upon it.

7.1 Synthetic Lethality and *CDH1* Biology

The *CDH1* gene was selected to identify synthetic lethal partners to demonstrate the novel SLIPT methodology as an important tumour suppressor gene in cancers. These include sporadic breast and stomach cancers and the familial syndromes such as hered-

itary diffuse gastric cancer (HDGC). The analysis of synthetic lethal partners of *CDH1* in breast and stomach cancers was also enabled by the availability of molecular data (Bass *et al.*, 2014; TCGA, 2012) and a synthetic lethal screen conducted in MCF10A breast cells (Chen *et al.*, 2014; Telford *et al.*, 2015).

Synthetic lethal interactions are generally regarded to arise due to functional redundancy (Boone *et al.*, 2007; Fece de la Cruz *et al.*, 2015; Kaelin, Jr, 2005) and as such the synthetic lethal partners of *CDH1* indicates the wide-ranging biological functions that E-cadherin is involved in. The diverse synthetic lethal pathways identified supports the known pleiotropic nature of the *CDH1* gene by detecting established functions of *CDH1*, replicating candidates from an experimental screen (Telford *et al.*, 2015), and identifying novel interactions with candidate genes and pathways for further investigation. The highly pleiotropic functions of E-cadherin as also consistent with *CDH1* being a tumour suppressor gene for which epithelial cells are significantly disrupted at the molecular level and prone to becoming cancerous.

7.1.1 Established Functions of *CDH1*

The *CDH1* has established functions in cell-cell communication and maintaining the cytoskeletion, specifically with cell-cell adhesion by forming tight junctions and the adherens complex. More recently, additional functions of *CDH1* in the extracellular matrix and fibrin clotting have also been identified. Synthetic lethal interactions within biological pathways (i.e., partners in the same pathway as the query gene) are expected according to previous synthetic lethal experiments and (Boone *et al.*, 2007; Kelley and Ideker, 2005). Synthetic lethal interactions identified in these pathways are consistent with these being functions of *CDH1*, in addition to potentially actionable targets against cancers.

7.1.2 The Molecular Role of *CDH1* in Cancer

The involvement of *CDH1* in the extracellular matrix is also important in cancers as it indicates a mechanism by which *CDH1* loss may affect the tumour microenvironment, contributing to it's role as a tumour and invasion suppressor. Furthermore, perturbations in the extracellular matrix and tumour microenvironment present an potential means by which to specifically inhibit (cancerous) *CDH1*-deficient cells in addition to those currently being considered. Few genes in extracellular pathways were detected in an experimental screen (Telford *et al.*, 2015) conducted in an isolated cell model (Chen *et al.*, 2014) but these are not expected to be detected in such as system. These

may be further supported in further investigations with 3D cell culture, "organoid", or mouse xenograft cancer models.

In contrast, many of the pathways involved in cell signalling, including G protein coupled receptors, were identified by SLIPT in addition to the experimental screen (Telford *et al.*, 2015). These support the previous results in cell line models, that these pathways are essential to growth of *CDH1*-deficient cancers and present a potential vulnerability specific to these (cancerous) cells. Furthermore, the replication of synthetic lethality of *CDH1* with cell signalling pathways in TCGA data across cancer types and genetic backgrounds robustly supports these pathways being clinically applicable beyond the genetic background of the model system of *CDH1*$^{-/-}$ MCF10A cells (Chen *et al.*, 2014). While the specific synthetic lethal genes were not as consistently detected between the SLIPT analyses and short interfering ribonucleic acid (siRNA) screen (Telford *et al.*, 2015), the was sufficient to identify synthetic lethal pathways for further experimental investigation which are more likely to be replicated between genetic backgrounds (Dixon *et al.*, 2008). Together these results demonstrate how SLIPT can be integrated with an experimental screen to triage potential therapeutic targets for further pre-clinical investigation.

The analysis of expression data with SLIPT is also indicative of additional biological mechanisms of synthetic lethal in pathways beyond those identified in screening experiments (Telford *et al.*, 2015). In particular, translation and regulatory pathways, involving 3′ untranslated regions (UTRs) and nonsense-mediated decay (NMD), were identified as candidate synthetic lethal pathways with *CDH1* by SLIPT. These present downstream target regulated by the putative synthetic lethal signalling pathways which cancer cells are dependent on for sustained protein expression (Gao and Roux, 2015) to proliferate and evade host defense processes such as apoptosis and immune responses.

7.2 Significance

7.2.1 Synthetic Lethality in the Genomic Era

Development of an effective synthetic lethal discovery tool for bioinformatics analysis has a wide range of applications in genetics research including functional genomics, medical and agricultural applications. The SLIPT approach demonstrated in this thesis is widely applicable to other genes and biological questions. In addition to further query of cancer genes, including other tissues, synthetic lethal gene functions are also of wider interest for their implications for genetic redundancy. Highly redundant genes and the

genetically robust systems they give rise to are of further relevance to evolutionary, developmental, and systems biology to understand how these change over time and play a role in fundamental development of cell types, in addition to cancers.

Developmental genes in particular, are highly evolutionary conserved and subject to high rates of redundancy. These are often difficult to study with conventional functional genetics since individual knockouts of redundant genes do not necessarily have a mutant phenotype. Identifying genes with a common function is therefore also important to the study of developmental genes with unknown functions. Synthetic lethal discovery methods such as SLIPT provide a genomic approach to further systematic characterisation of gene function including such highly redundant developmental genes.

Similarly, variants of unknown significance and modifier loci are a major concerns in human genetics, including "monogenic" and "rare" diseases. Many of these could potentially be difficult to characterise individually due to synthetic lethal interactions where additional loci contribute to the disease (or only compensate for some variants). As such systematic identification of synthetic lethal interactions also has applications in the study of such "oligogenic" diseases along with similar applications in the study of heritability for traits including agricultural genome-based selection.

Genetic redundancy is also a concern in pharmacology. Polypharmacology and network medicine are rationales to account for this by using drugs with multiple (known and specific) targets (Barabási *et al.*, 2011; Hopkins, 2008). Further characterisation of synthetic lethal genes will be valuable to the design of effective multi-target drugs or combination therapies in a range of therapeutic applications including molecular targeted therapies against cancer for which combination therapies are a popular solution for acquired resistance against individual targeted therapies. Characterisation of genetic interactions and combination therapies also has the potential to expand pharmacogenomics investigations to understanding the impact of genotypes at multiple loci leading to adverse effects in a subset of the population or accounting for why the rest of the population does not experience this adverse effects since their synthetic lethal partner genes do not share the same variants.

Furthermore, redundant functions and synthetic lethal interactions also present a means to expand upon the concept of the "minimal" genome by accounting for essential gene functions that are performed by redundant genes (or in combination with pleiotropic) genes rather than simply those that are perturbed by individual genes as an essential gene approach is likely an underestimate that does not account for synthetic lethal interactions.

Therefore synthetic lethal interactions are a fundamentally important part of genetics and further understanding of them in a genomics context, facilitated by methods such as SLIPT, shows great potential to contribute a deeper understanding of gene functions and their role in traits or diseases in the post-genomic era. Genes do not function in isolation and so understanding them in the context of the complexity of a cell and across genetic backgrounds (such as the data provided by TCGA) is essential to further characterise their functions and ensure that further applications are reproducible beyond experimental systems.

7.2.2 Clinical Interventions based on Synthetic Lethality

Synthetic lethal discovery with SLIPT is of particular interest in cancer research as a complementary approach to discovery of synthetic lethal drug targets. The cancer research community relies on cell line and mouse models for screening and validation experiments (Fece de la Cruz *et al.*, 2015) which would benefit from integration with gene expression analysis as demonstrated for *CDH1* and the screen conducted by Telford *et al.* (2015). The potential for synthetic lethal drug design against cancer mutations including gene loss or overexpression could lead to a revolution in cancer therapy and chemoprevention with personalised treatment of cancers and high risk individuals. Examples of the synthetic lethal strategy (Bryant *et al.*, 2005; Farmer *et al.*, 2005) for cancer treatment have been shown to be clinically effective with many large-scale RNAi screens recently conduced to aiming discover gene function and drug targets for similar application with other cancer genes, including cancers in other tissues.

While SLIPT analysis and RNA interference (RNAi) screens represent a significant step towards anti-cancer medicines, further validation is required to ensure that the synthetic lethal candidate genes and pathways identified for *CDH1* in breast and stomach cancer are applicable against *CDH1*-deficient cancers in the clinic. Validation with RNAi or pharmacological inhibitors is needed since both the SLIPT analysis and siRNA screen are susceptible to false positives. These candidates will need to be tested in pre-clinical models (cell lines and mouse xenografts) before proceeding to clinical trials. A therapeutic intervention will also require a targeted therapeutic against the synthetic lethal partner if one has not been developed against another disease (for which it van be re-purposed). Drug targets must be feasible to have effective anti-cancer interventions designed against them, which raises the need for targets with existing drugs in the clinic, trials, or feasible to development with structural analysis or screening. Druggable targets could be selected by gene functions known to be amenable to drugs,

with a structure amenable with development, with conserved specific sites without homology to other genes, or with known approval or developing drugs which could be repurposed from other disease applications. Both structure-aided drug design and compound screening are viable ways to accompany genetic screens and computational analysis with pharmacological investigations.

Targeted therapeutics designed based on synthetic lethal interactions have potential to vastly expand the applications of "precision medicine" against molecular targets, particularly in cancer where many have been cancer genes have been identified. Synthetic lethality expands the range of cancer genes which can be (indirectly) targeted to include tumour suppressor genes with loss of function (such as *CDH1*) and oncogenes with disrupted functions that are dysregulated or highly homologous to non-cancerous proto-oncogenes (such as *MYC*, *EGFR* or *KRAS*). Applications against tumour suppressor genes is a particularly important application as these cannot be approached by careful dosing. Synthetic lethal drug design also has the added benefit of being highly specific against a particular genotype (such as $CDH1^{-/-}$) with the potential for target therapies with a wide therapeutic index and few adverse effects, in contrast to many current anti-cancer drug regimens (Hopkins, 2008; Kaelin, Jr, 2009). These properties are highly desirable for chemoprevention applications such as treatment against *CDH1*-deficient early cancers in HDGC patients (Guilford *et al.*, 2010) before they are detectable during screening.

7.3 Future Directions

While further validation and pre-clinical tested is required to translate the findings for *CDH1* to cancer therapy or prevention, there are also further avenues for research into the detection of synthetic lethality in gene expression and other genomics data. The SLIPT methodology is amenable to wider application against a range of genes for which loss of function is deleterious, including other cancer genes in breast cancer or other tissues. Synthetic lethal interactions are functionally informative, particularly for mode-of-action of known drug targets, and are also relevant for identifying functions of newly characterised genes in genomics studies and designing specific interventions against cells with loss of function in cancer and other diseases. Thus synthetic lethal detection using SLIPT in expression data could be further used for many other genes, including others relevant to human health and disease.

These investigations do not need to limited to expression data. While expression as a measure of gene function has been the focus of this thesis, other genomics data

could be used for a similar purpose for SLIPT analysis. These include DNA copy number, DNA methylation, histone activation, mutation status, protein abundance, and protein activation state. For some applications or genes these molecular profiles may be more informative of gene function and synthetic lethal relationships. However, expression was the focus of the investigations thus far as a widely accepted measure of gene function which has widely available genomics data. SLIPT is compatible with each of these data types (if the thresholds are selected appropriately) and may perform better for some applications with these molecular profiles or a weighted combination of these. As demonstrated, SLIPT is also suitable for future investigations with pathway metagenes and other summary data as well.

It may also be possible to improve the performance of SLIPT with refinements to the statistical or computational approach. This thesis has focused on rational query-based approach which relatively computes quickly (even in R) and is relatively intuitive to interpret. These computations are compatible with parallel computing and the computational resources may be further reduced by using a different computing language. The `slipt` has been documented and release open-source to facilitate further development, wider adoption, or comparison with other scientific software for similar purposes.

Alternative methods may be also be able to improve on the statistical performance of SLIPT. In particular, the sensitivity was generally as issue with higher numbers of synthetic lethal partners in simulated data. While approaches using continuous data such as Pearson correlation and linear regression did not perform as well as SLIPT, they could be improved. A least squares regression approach in particular, enables multiple measures of relationships such as the coefficients of the fitted curve and significance of the fit (computed from the residuals). A linear modelling approach using regression is also amenable to refinement such as extending from a fitting a linear relationships to a polynomial or logistic regression. Another benefit to fitting linear models is that these would enable the conditioning of known synthetic lethal partners to identify subtle signatures of further interacting partners.

This approach could also be applied iteratively on the strongest candidates from previous synthetic lethal analyses in further rounds of prediction conditioned upon them. Similarly, synthetic lethal prediction could also be approached with a Bayesian framework which is also amenable to Bayesian priors on known or previously predicted synthetic lethal partners. Either of these approaches has the potential to improve upon the synthetic lethal predictions which have been demonstrated as possible and biologically relevant by SLIPT.

7.4 Conclusions

Synthetic lethal interactions are important for understanding gene function and development of highly specific targeted anti-cancer treatments. Synthetic lethality potential expanding the repertoire of applications for precision cancer medicine to indirectly targeting loss of function in tumour suppressor genes. Synthetic lethal discovery with experimental screening is error prone and limited by the model systems in which it is performed. There is a need for bioinformatics tool to predict synthetic lethal interactions from gene expression data facilitates rapid identification of synthetic lethal candidates to augment functional genetic screens and cancer drug target triage. I present the original Synthetic Lethal Interaction Prediction Tool (SLIPT) methodology as a statically robust procedure which performs this analysis.

The SLIPT methodology has been demonstrated to identify biologically relevant genes and pathways. An comprehensive analysis of synthetic lethal partners of the *CDH1* was performed in TCGA breast cancer data (TCGA, 2012) with many of these findings replicated in stomach cancer data (Bass *et al.*, 2014). These genes clustered into several distinct groups, with distinct biological functions and elevated expression in different clinical subtypes. These analyses identified of synthetic lethal candidates in the $G_{\alpha i}$ signalling, cytoplasmic microfibres, and extracellular fibrin clotting pathways which were validated in an siRNA screen performed by Telford *et al.* (2015) and consistent with the known cytoskeletal and cell signalling roles of E-cadherin. These findings support interventions against these pathways being applicable to specific cancer therapeutics beyond the pre-clinical cell line models in which they were validated. SLIPT has also identified synthetic lethal partners in novel pathways for *CDH1* including the regulation of immune signalling and translational elongation which extend the range of pleiotropic functions of *CDH1* and present further biological mechanisms to investigate the malignancy and vulnerabilities of *CDH1*-deficient cancers.

While some of these pathways are not expected to be detected in an isolated experimental cell line model, pathway structure may have accounted for this disparity. Thus synthetic lethal candidates detected by SLIPT and siRNA were compared within graph structures of the candidate synthetic lethal pathways. However, this did not generally account for differences between detection by these approaches. Neither synthetic lethal detection methodology preferentially detected genes of more importance or connectivity in pathway structures using established network metrics. Nor could it

be generally established that SLIPT gene candidates were upstream or downstream of siRNA gene candidates in pathway structures across biological pathways.

Pathway graph structures were also included in investigations with simulated data to ascertain whether the SLIPT procedure performed desirably in data with complex correlation structures derived based on biological pathways. A simulation procedure was developed based on a statistical model of synthetic lethality which generates multivariate normal data with known synthetic lethal partners and correlation structures. The SLIPT methodology had high statistical performance, particularly when detecting few synthetic lethal genes, with large sample sizes, and a background of many non synthetic lethal genes to distinguish true partners from. This method had high specificity, performed better than Pearson's correlation or the χ^2-test, and had had optimal performance across simulation parameter combinations for the thresholds used throughout this thesis. These findings were robust across correlation structures, including those derived from complex pathway structures containing strong positive and negative correlations between genes. Together these findings support the release of the SLIPT software R packages and the application of the method to identify synthetic lethal genes within pathways and use candidate synthetic lethal genes to identify synthetic lethal pathways as demonstrated in this thesis.

Therefore, I present a widely applicable synthetic lethal procedure using gene expression data for wider use in genomics research, including the development of precision cancer medicine. This methodology is supported by the release of a software package in R, simulation results based on a statistical model of synthetic lethality, the demonstration of bioinformatics and network biology investigations into interactions with the *CDH1* gene in breast and stomach cancers.

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