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Glossary

bioinformatics	Statistical or computational approaches to biological data or research tools.
chemoprevention	The use of drugs to prevent early-stage cancers, generally applied to high-risk mutation carriers.
E-cadherin	Epithelial cadherin (calcium-dependent adhesion), a cell-adhesion protein encoded by *CDH1*.
essential	A gene which is required to be functional or expressed for a cell or organism to be viable, grow or develop.
familial	A trait recurrently occurring in families, not necessarily with a genetic cause.
functional redundancy	Genes which perform a common function, also known as genetic redundancy.
gene expression	A measure of the relative expression of each gene from the mRNA extracted from (pooled) cells.
genome	All of the DNA sequence in the genome.
genomic	The use of data from all genes in the genome.
graph or network	A mathematical structure modelling or depicting the relationships between elements.
metagene	A consistent signal of expression for a collection of genes such as a biological pathway, derived from singular value decomposition.
mutant	A variant or dysfunctional phenotype arising from a mutation in a gene.
mutation	A change in DNA sequence that disrupts gene function.

oncogene	A gene that potentially causes cancer, typically by over-expression or mutant gene variants.
pleiotropy	When a gene has multiple biological functions.
sporadic cancer	Cancers which do occur in patients with a family history or carry a high-risk genetic variant.
synthetic lethal	Genetic interactions where inactivation of multiple genes is inviable (or deleterious) which are viable if inactivated separately.
targeted therapy	Cancer treatment that specifically acts against a molecular target, in contrast to standard chemotherapy.
treatment	Medical procedures for a disease to improve patient outcomes.
tumour suppressor	A gene potentially causes cancer, typically by disruption of functions which protect the cell from cancer.

Acronyms

ANOVA	Analysis of Variance.
DNA	Deoxyribonucleic Acid.
GPCR	G Crotein Coupled Receptor.
HDGC	Hereditary Diffuse Gastric Cancer.
mtSLIPT	Synthetic Lethal Interaction Prediction Tool (against mutation).
NMD	Nonsense-Mediated Decay.
RNAi	RNA Interference.
siRNA	Short Interfering RNA.
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 partners of *CDH1*. Together these findings further elucidate the functions of *CDH1* in the cell, functional redundancy in cancer, and represent potential therapeutic targets against loss of *CDH1* function. These candidate synthetic lethal genes were further investigated for relationships within synthetic lethal pathways, and in the process a network-based approach to compare genes identified in genomics experiments was developed.

The synthetic lethal detection methodology, SLIPT, was applied to gene expression data throughout this thesis and was evaluated with simulated data. A procedure was developed to stringently generate gene expression data from known synthetic lethal partners in simulated data. These simulations included 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 made available) 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* tumour suppressor gene was the focus of identifying synthetic lethal partners to demonstrate the novel SLIPT methodology. This gene is important in sporadic breast and stomach cancers, in addition to familial syndromes, such as hereditary diffuse gastric cancer (HDGC). The analysis of synthetic lethal partners of *CDH1* in breast and stomach cancers was enabled by the availability of molecular data (Bass

et al., 2014; Koboldt *et al.*, 2012) and a synthetic lethal screen conducted in MCF10A breast cells (Chen *et al.*, 2014; Telford *et al.*, 2015).

Synthetic lethal interactions 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* indicate the wide-ranging biological functions that E-cadherin is involved in. The diverse synthetic lethal pathways identified support the known pleiotropic nature of the *CDH1* gene (Kroepil *et al.*, 2012), 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 was also consistent with *CDH1* being a tumour suppressor gene.

7.1.1 Established Functions of *CDH1*

CDH1 has established functions in cell-cell communication and maintaining the cytoskeleton, specifically with cell-cell adhesion by forming tight junctions and the adherens complex (Jeanes *et al.*, 2008). More recently, additional functions of *CDH1* in the extracellular matrix and fibrin clotting have also been identified (Cardiff *et al.*, 2011; Tunggal *et al.*, 2005; Wojtukiewicz *et al.*, 2016). 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 (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 important in cancers as it indicates a mechanism by which *CDH1* loss may affect the tumour microenvironment, contributing to its role as a tumour and invasion suppressor. Furthermore, perturbations in the extracellular matrix and tumour microenvironment present a means by which to specifically inhibit (cancerous) *CDH1*-deficient cells, in addition to those currently being considered. 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 the growth of *CDH1*-deficient cancers and present a poten-

tial 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 siRNA screen (Telford *et al.*, 2015), they were 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 lethality 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 pathways represent downstream targets regulated by the putative synthetic lethal signalling pathways which cancer cells are dependent on to proliferate and evade host defense processes such as apoptosis and immune responses (Gao and Roux, 2015) .

7.2 Significance

7.2.1 Synthetic Lethality in the Genomic Era

Development of an effective synthetic lethal discovery tool for bioinformatic 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 (Boone *et al.*, 2007; Nowak *et al.*, 1997; Tischler *et al.*, 2008).

Developmental genes in particular, are highly evolutionarily conserved and subject to high rates of redundancy (Fromental-Ramain *et al.*, 1996; Kockel *et al.*, 1997; Nowak

et al., 1997). 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 genomic 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 pharmacogenomic investigations. These may elucidate the impact of genotypes at multiple loci, which lead to adverse effects in a subset of the population due to variants in synthetic lethal genes.

Furthermore, redundant functions and synthetic lethal interactions also present a means to expand upon the concept of the "minimal" genome (Hutchison *et al.*, 2016). It is important to account 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. An essential gene approach is likely to produce an underestimate that does not account for synthetic lethal interactions.

Synthetic lethal interactions are fundamentally important throughout genetics. Further understanding of them in a genomic context, facilitated by methods such as SLIPT, would contribute towards deeper understanding of gene functions and their role in traits or diseases in the post-genomic era. Genes do not function in isolation and understanding them in the context of the complexity of a cell and across genetic

backgrounds is essential to further characterise their functions and ensure that findings can be validated or applied 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). Synthetic lethal drug design against cancer mutations, including gene loss or over-expression, could lead to a revolution in cancer therapy and chemoprevention. Such therapeutics would enable personalised treatment for cancer patients 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 (McLachlan *et al.*, 2016). Many large-scale RNA interference (RNAi) screens have been conducted recently, aiming to discover gene function and drug targets for similar application with other cancer genes, including cancers in other tissues (Fece de la Cruz *et al.*, 2015).

While SLIPT analysis and 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 false positives may occur in SLIPT analysis or siRNA screens. 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 to develop developed or repurposed against the synthetic lethal partner. Drug targets could be triaged from synthetic lethal genes by functions known to be amenable to drugs or structure with conserved specific sites that are not homologous to other genes, or those with existing drugs approved in trial for other applications. Both structure-aided drug design and compound screening are viable ways to target synthetic lethal partners.

Targeted therapeutics designed based on synthetic lethal interactions could expand the applications of "precision medicine" against molecular targets. 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*. Oncogenes with disrupted functions that are over-expressed or highly homologous to non-cancerous proto-oncogenes,

such as *MYC*, *EGFR* or *KRAS*, may also be targeted by synthetic lethality. Applications against tumour suppressor genes is particularly important, as these cannot be approached by careful dosing. Synthetic lethal drug design has the benefit of being highly specific against a particular genotype (such as $CDH1^{-/-}$) with the potential for targeted 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 in HDGC patients (Guilford *et al.*, 2010), as an alternative to monitoring or surgery.

7.3 Future Directions

While further validation and pre-clinical testing 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 be 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. In particular, DNA copy number and mutations have been demonstrated by other approaches to synthetic lethal analysis (Jerby-Arnon *et al.*, 2014; Lu *et al.*, 2015; Srihari *et al.*, 2015; Wappett *et al.*, 2016), although some of these have not been released for wider application.

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 computes relatively quickly in R (R Core Team, 2016), 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` R package has been documented and released as open-source software (as described in Section 3.5) to facilitate further development, wider adoption, or comparison with other scientific software for similar purposes.

Alternative methods may be also 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 fitting a linear relationship 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 (Friedman *et al.*, 2000; Imoto *et al.*, 2004; Jansen *et al.*, 2003) 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 the velopment of highly specific targeted cancer treatments. In particular, synthetic lethality could expand the repertoire of applications for precision cancer medicine to include 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. Thus there is a need for a bioinformatics tool to predict synthetic lethal interactions from gene expression data, which would facilitate the rapid identification of synthetic lethal candidates, and augment functional genetic screens and triage of cancer drug targets. This thesis develops the Synthetic Lethal Interaction Prediction Tool (SLIPT) methodology as a statistically robust procedure perform this analysis.

The SLIPT methodology has been demonstrated to identify biologically relevant genes and pathways. A comprehensive analysis of synthetic lethal partners of the *CDH1* gene was performed in TCGA breast cancer data (Koboldt *et al.*, 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 synthetic lethal candidates in the $G_{\alpha i}$ signalling, cytoplasmic microfibres, and extracellular fibrin clotting pathways which were supported by an siRNA screen performed by Telford *et al.* (2015) and were consistent with the known cytoskeletal and cell signalling roles of E-cadherin. SLIPT also identified synthetic lethal partners in novel pathways for *CDH1*, including the regulation of immune signalling and translational elongation, which extend the range of established functions of *CDH1* and present further biological mechanisms that can be investigated to exploit the 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 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. However, it could be shown that

SLIPT genes had lower centrality and we upstream of siRNA candidates, specifically in the $G_{\alpha i}$ signalling pathway.

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 known 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 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.

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