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A Bioinformatics Approach to Synthetic Lethal Interactions in Breast Cancer with Gene Expression Data

S. Thomas Kelly

a thesis submitted for the degree of

Doctor of Philosophy

at the University of Otago, Dunedin,

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Abstract

Background

Synthetic lethal genetic interactions are re-emerging in the post-genomics era due to their potential for precision medicine against cancers. Synthetic lethal drug design exploits the functional redundancy of genes disrupted in cancers (including tumour suppressors) to develop specific treatments against them. *CDH1*, which encodes E-cadherin, is a tumour supressor gene with loss of function in breast and btomach cancers. Experimental screens have identified candidate synthetic lethal interactions for drug target triage, which can be further supported with bioinformatics analysis. Furthermore, gene expression data enables investigation of synthetic lethal pathways and graph structure of synthetic lethal genes within them.

Approach

A computational methodology, the Synthetic Lethal Prediction Tool (SLIPT) has been developed to detect synthetic lethal interactions in gene expression data. This methodology was demonstrated on interactions with *CDH1* in breast and stomach cancer data from The Cancer Genome Atlas (TCGA) project. Synthetic lethal genes and pathways were further investigated with unsupervised clustering, gene set over-representation analysis, metagenes, and permutation resampling. In particular, analyses focused on comparing SLIPT gene candidates to an experimental siRNA screen Telford *et al.* (2015). Network analysis methods were applied to the most supported pathways to test for pathway structure among between synthetic lethal candidates. Simulation and modelling was used to assess the statistical performance of SLIPT, including simulated data with correlation structures derived from graph stuctures.

Findings

Many candidate synthetic lethal partners of *CDH1* were detected in both TCGA breast cancer. These genes clustered into several distinct groups, with distinct biological functions and elevated expression in different clinical subtypes. While the number of genes detected by both approaches was not significant, these contained significantly enriched pathways. In particular, $G_{\alpha i}$ signalling, cytoplasmic microfibres, and extracellular fibrin clotting were robustly supported by both approaches, which is consistent with the known cytoskeletal and cell signalling roles of E-cadherin and validation of GPCR pathways performed by Telford *et al.* (2015). Many of these pathways were replicated in stomach cancer data. The pathways supported only by SLIPT included regulation of immune signalling and translational elongation which were not expected to be detected in an isogenic cell line model but are still candidates for further investigation.

Synthetic lethal candidates detected by SLIPT and siRNA were compared within graph structures of the candidate synthetic lethal pathways. These genes did not differ with respect to network metrics of importance or connectivity in the pathway. There was little support, across pathways, that SLIPT gene candidates were consistently upstream or downstream of siRNA gene candidates with pathways.

A model of synthetic lethality was used to simulate gene expression data with synthetic lethal partners of a gene. The SLIPT methodology had high statistical performance, detecting few synthetic lethal partners, which diminished with more synthetic lethal partners or lower sample size. The SLIPT methodology performed better than Pearson correlation or the χ^2-test. In particular, it performed well with high specificity for datasets containing thousands of genes or genes positively correlated with the query gene (as expected to occur in expression data). SLIPT was robust across correlation structures, including those derived from complex pathway structures and often distinguished synthetic lethal genes from those positively or negatively correlated with them. Therefore SLIPT is appropriate to identify synthetic lethal genes within pathways and use candidate synthetic lethal genes (and their correlates) to identify synthetic lethal pathways.

Summary

Thus my thesis has developed, evaluated, and refined a bioinformatics approach to discovery of synthetic lethal genes solely from gene expression data. This approach has been demonstrated to detect biologically informative and clinically relevant candidate partners for *CDH1* in breast and stomach cancers. These investigations have also involved the development of network analysis and simulation procedures which may be more widely applicable.

Research Contributions During Candidature

Publications

Kelly, S. T. and Spencer, H. G. (2017) Population-Genetics Models of Sex-Limited Genomic Imprinting. *Theoretical Population Biology* **115**:35-44 doi:10.1016/j.tpb.2017.03.004

Manuscripts Submitted

Kelly, S. T., Single, A. B., Telford, B. J., Beetham, H. G, Godwin, T. D., Chen, A., Black, M., A., and Guilford, P. J. (2017) Towards HDGC chemoprevention: vulnerabilities in E-cadherin-negative cells identified by genomic interrogation of isogenic cell lines and whole tumors. Submitted to *Cancer Prevention Research*.

Kelly, S. T., Chen, A., Guilford, P. J., and Black, M. A. (2017) Synthetic lethal interaction prediction of target pathways in E-cadherin deficient breast cancers. Submitted to *BMC Genomics*.

Conference Presentations

Consortium of Biological Sciences 2017 (Kobe) December TBC

eResearch 2017 (Queenstown) February 20^{th}-22^{nd}

Research Bazaar 2016 (Dunedin) February 2^{nd}-4^{th}

eResearch 2016 (Queenstown) February 9^{th}-11^{th}

Genetics Otago Symposium 2016 (Dunedin) March 7^{th}-8^{th}

DunDead: Zombie Science and Culture Festival 2014 (Dunedin) August 16^{th}-17^{th}

eResearch 2014 (Hamilton) June 30^{th}-July 2^{nd} (Supported by Google)

Poster Presentations

Next Generation Sequencing Asia 2016 (Singapore) October 11^{th}-12^{th} (Supported by the University of Otago Division of Health Sciences; Maurice and Phyllis Paykel Trust)

Research Bazaar 2015 (Melbourne) February 16^{th}-18^{th} (Supported by the New Zealand eScience Infrastructure)

Otago School of Medical Sciences Postgraduate Symposium 2015 (Dunedin) April 28^{th}-29^{th}

QMB Cancer Drugs Satellite 2014 (Queenstown) August 24^{th}-25^{th}

Seminar Presentations

University of Otago Department of Biochemistry 2017 (Dunedin) November TBC

Tōhoku University 2016 (Sendai) November 11th

Okinawa Institute of Science and Technology 2016 (Onna) November 1st

Sōkendai Graduate University 2016 (Hayama) October 25th

Tōkyō University Institute of Medical Science 2016 (Shirokanedai) October 24th

National Institute of Genetics 2016 (Mishima) October 21st

RIKEN Division of Genomic Technologies 2016 (Yokohama) October 20th

Software Packages

Software packages in the R language have been released. Please refer to the appropriate GitHub repository for more information (including documentation, vignettes, and installation instructions), on the following account: https://github.com/TomKellyGenetics

- `slipt` to accompany the synthetic lethal publication above and release SLIPT (Synthetic Lethal Interaction Prediction Tool)
- `vioplotx` to provide enhanced violin plots
- `heatmap.2x` to provide annotated heatmaps
- `igraph.extensions` metapackage for the packages for iGraph objects:
  - `plot.igraph` to provide plotting for directed graphs
  - `info.centrality` to compute network analysis metrics
  - `pathway.structure.permutation` for resampling within pathways
  - `graphsim` to simulate expression (`mvtnorm`) from pathway structures

The `slipt-app` GitHub repository also hosts an application for Synthetic Lethal Interaction Prediction Tool (SLIPT) developed in the R `shiny` environment as part of a related project. There is a digital copy of this thesis, including high resolution full-colour figures, hosted at:

https://github.com/TomKellyGenetics/thesis/blob/master/thesis.pdf

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- Otago Division of Health Sciences, Oxford Global, and Maurice and Phyllis Paykel Trust (NGS Asia 2016, Singapore)
- RIKEN Division of Genomic Technologies and the Okinawa Institute of Science and Technology (seminar visits in Japan)

Thanks most of all to my fianceé, Dr Yui Kawagishi, you've been an inspiration. Thank you for your support and encouragement, every day, even from afar: it has always made a difference. It's been incredible to see you flourish in your career and I look forward to joining you again soon. May the next chapter of our adventures involve a bit less Skype across timezones.

どうもありがとう由ちゃん。また来月。頑張った！行きます！

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Glossary

allele	A gene variant with a specific sequence and phenotype.
bioinformatics	Statistical or computational approaches to biological data or research tools.
Bisulfite-Seq	Methylome data from sequencing bisulfite treated DNA.
CAGE-Seq	Transcriptome data from cap analysis of gene expression.
cancer	A class of diseases, formally "malignant neoplasm", of abnormal cellular growth and spread to other organs.
cancer gene	A gene which is involved in the malignancy of some cancers, encompassing oncogenes and tumour suppressors, which have molecular aberrations in cancer and variants which predispose individuals to cancer.
centrality	A network metric which identifies the most important vertices in a network.
chemoprevention	The use of cytotoxic drugs to prevent cancers from forming, generally applied to high-risk mutation carriers.
chemotherapy	The use of cytotoxic drugs to treat cancers, in combinations, generally applied to advanced stage cancers.
ChIP-Seq	Epigenome data from chromatin immunopreciptation sequencing.
compound screen	A high-throughput screen performed using a library of chemical compounds.
computational biology	Applying computational or mathematical modelling to understanding biological systems and relationships.

conditional essentiality	A gene becoming essential to viability under certain environmental conditions, including presence of compounds which inactivate other genes.
copy number	The number of copies of DNA, typically two copies for diploid organisms but subject to variation.
de novo	A bioinformatics sequence assembly conducted entirely from raw genomics data without a reference sequence.
diagnosis	The identification of disease by clinical, cellular, and molecular characteristics.
driver mutation	A mutation which promotes cancer growth.
E-cadherin	Epithelial cadherin (calcium-dependent adhesion), a cell-adhesion protein encoded by the tumour suppressor gene, *CDH1*.
edge or link	A relationship connecting a pair of elements of a graph structure or network, may weighted or directional.
epigenome	An analysis of epigenetic modifications of all genes in the genome.
epistasis (biological)	The effects of a gene modifying or masking the phenotype of another gene.
epistasis (statistical)	A divergence of the observed double mutant phenotype from that expected based on the respective phenotypes of single mutant (Fisher, 1919).
essential	A gene which is required to be functional or expressed for a cell or organism to be viable, grow or develop.
exome	A sequencing approach designed to generate data enriched for coding genes within the genome.
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.
genetic robustness	A system of biological pathways which (has evolved to) continue to function as a whole under various conditions, including the inactivation of various individual genes.
genome	An analysis of all of the DNA sequence in the genome.
genomic	An approach or technology designed to generate or use data from all genes in the genome.
genomic medicine	The use of genomic information to tailor medicine treatment to the genetics of an individual.
germline mutation	A mutation that occurred in germline cells and is passed between generation.
graph or network	A mathematical structure modelling or depicting the relationships between elements.
hallmark of cancer	An underlying characteristic of cancer as part of a rational approach devised by (Hanahan and Weinberg, 2000).
hereditary	A trait or disease which has a genetic cause and is inherited from family members.
high-throughput screen	An experimental procedure to perform a large scale series of chemical, genetic, or pharmacological tests.
hub	A central or highly connected component of a network.
in silico	An investigation conducted using computations, typically simulations or analyses.
in vitro	An investigation conducted using a controlled experimental system to examine biomolecules.
in vivo	An investigation conducted using in the context of a biological cell or organism, including pre-clincal models and clinical trials.
induced essentiality	A gene becoming essential to viability under certain conditions, including inactivation of a synthetic lethal partner.

information centrality	A network centrality metric which uses the impact of removing a vertex or node on connections in the network.
intrinsic subtype	Distinguishing cancer by molecular and genetic features.
MCF10A cell line	A non-tumorigenic epithelial cell line derived from breast tissue.
metabolome	An analysis of all the metabolites and enzymes in the cell.
metagene	A consistent signal of expression for a collection of genes such as a biological pathway, derived from singular value decomposition.
metagenome	An analysis of all of the genes and genomes in a community.
metastasis	A secondary growth of a tumour or spread of cancer to other organs.
microarray	A high-throughput technique to measure presence or abundance of nucleic acid sequences from binding to probes.
microRNA	Short RNA molecules generally regarded to regulate gene expression by binding to mRNA.
molecular profile	A combination of genetic and biochemical measures which identifies characteristic traits of a tumour.
molecular subtype	A classification of cancers based on an identification using molecular properties.
mutant	A variant or dysfunctional phenotype arising from a mutation in a gene.
mutation	A change in DNA sequence that disrupts gene function.
network biology	The application mathematical and computational approaches to networks in understanding biological relationships.
network medicine	The use of network biology to understand, prevent, or treat diseases.
non-oncogene addiction	The dependence of a cancer cell on functioning non-mutant genes.
'omics	A combination of approaches to generating biological data with high-throughput procedures such as genomics, proteomics or metabolomics.

oncogene	A gene that potentially causes cancer, typically by over-expression or mutant gene variants.
oncogene addiction	The dependence of a cancer cell on a specific oncogenic pathway.
PageRank centrality	A network centrality metric which uses eigenvectors with a scaling factor (Brin and Page, 1998).
pan cancer	A focus on the molecular and genetic features across cancers in different tissues.
passenger mutation	A mutation that occurs in cancers but does not affect the growth of cancers.
pathway	A series of biomolecules that produces a particular product or biological function.
pleiotropy	A gene which has multiple biological functions.
polypharmacology	The design of drugs to target multiple molecular targets or biological pathways.
precision medicine	The application of prevention and treatment measures to target diseases by molecular and genetic features.
prognosis	The estimation of disease progression and patient outcome.
proteome	An analysis of all the proteins expressed from the genome.
proto-oncogene	The non-mutant variant or precursor to a mutant oncogene.
recurrent mutation	The repeated occurrence of mutations in a particular gene across cancers.
RNAi screen	A high-throughput screen performed using a RNA interference (RNAi).
RNA-Seq	Transcriptome data from sequencing RNA.
Sanger sequencing	A dideoxy chain termination method for DNA sequencing (named after Fred Sanger).
scale-free	A property of a network which has a power law vertex degree distribution, that is several highly connected hub genes and many with very few connections.

shortest path	A path with the fewest possible edges which connects two particular vertices.
small world	A property of a network which is highly connected and has a low characteristic path length, derived from the mean shortest path length across all pairs of nodes.
somatic mutation	A mutation that occurs in somatic cells, during a patient's lifespan.
sporadic cancer	Cancers which do occur in patients with a family history or carry a high-risk genetic variant.
synergy	When multiple drugs have more effect than expected from the effect of each separately.
synthetic dosage lethal	A synthetic genetic interaction (SGI) analogous to synthetic lethality where genes are disrupted by a change in dosage, typically where one gene is inactivated and the other overexpressed.
synthetic lethal	Genetic interactions where inactivation of multiple genes is inviable (or deleterious) which are viable if inactivated separately.
synthetic lethal screen	A high-throughput screen performed on isogenic cell lines to detect genes for which inhibition specifically deleterious to the null mutant genotype.
synthetic rescue	A synthetic genetic interaction when the combined mutations restores the wild-type the phenotype of one of the mutations.
synthetic sick	Genetic interactions where inactivation of multiple genes is deleterious which are viable if inactivated separately.
synthetic suppression	A synthetic genetic interaction when the combined mutations (partially) suppresses the mutant phenotype of one of the mutations.
targeted therapy	Cancer treatment that specifically acts against a molecular target, in contrast to standard chemotherapy.
transcriptome	An analysis of all of the genes expressed in the genome.
treatment	Medical procedures for a disease to improve patient outcomes.

tumour	An abnormal lump of tissue or growth of cells, may be cancerous.
tumour suppressor	A gene potentially causes cancer, typically by disruption of functions which protect the cell from cancer.
vertex degree	A network metric of connectivity of vertices which uses the number of edges connected to each vertex or node.
vertex or node	An element of a graph structure or network.
wild-type	A natural phenotype of a trait or the normally functional allele which encodes it.

Acronyms

1KGP	1000 genomes project.
ADP	Adenosine Diphosphate.
AMP	Adenosine Monophosphate.
AMPK	AMP-activated Protein Kinase.
ANOVA	Analysis of Variance.
ATP	Adenosine Triphosphate.
AUROC	Area Under the Receiver Operating Characteristic (curve).
BioPAX	Biological Pathway Exchange.
BiSEp	Bimodal Subsetting Expression.
BMP	Bone Morphogenic Protein.
cAMP	Cylic AMP.
CCLE	Cancer Cell Line Encyclopaedia.
cDNA	Complementary Deoxyribonucleic Acid (from mRNA).
CGP	Cancer Genome Project.
ChIP	Chromatin Immunopreciptation.
ChIP-Seq	Chromatin Immunopreciptation Sequencing.
CNV	Copy Number Variation.
COSMIC	Catalogue Of Somatic Mutations In Cancer.
CpG	5′–C–phosphate–G–3′.
CRAN	comprehensive R archive network.
CXCR	Chemokine Receptor.
DAISY	Data Mining Synthetic Lethal Identification Pipeline.
DDBJ	DNA Data Bank of Japan.
DNA	Deoxyribonucleic Acid.
EMBL	European Molecular Biology Laboratory.
EMT	Epithelial-Mesenchymal Transition.
ENA	The European Nucleotide Archive.

ENCODE	Encyclopaedia of DNA Elements.
ER	Estrogen Receptor.
exprSL	Synthetic Lethality (expression).
FANTOM	Functional Annotation Of Mammalian genome.
FDR	False Discovery Rate.
GEO	Gene Expression Omnibus.
GO	Gene Ontology.
GPCR	G Crotein Coupled Receptor.
HDAC	Histone Deacetylase.
HDGC	Hereditary Diffuse Gastric Cancer.
HLRCC	Hereditary Leiomyomatosis and Renal Cell Carcinoma.
HPC	High Performance Computing.
ICGC	International Cancer Genome Consortium.
InDel	Insertion or Deletion (in DNA sequence).
JAK	Janus Kinase.
lncRNA	Long Non-Coding Ribonucleic Acid.
METABRIC	Molecular Taxonomy of Breast Cancer International Consortium.
microRNA	Micro RNA.
mRNA	Messenger Ribonucleic Acid.
MSI	Microsatellite Instability.
mtSL	synthetic Lethality (mutation).
mtSLIPT	Synthetic Lethal Interaction Prediction Tool (against mutation).
NCBI	National Center for Biotechnology Information (in the USA).
NCI	National Cancer Institute (in the USA).
NeSI	New Zealand eScience Infrastructure.
NGS	Next-Generation Sequencing.
NHGRI	National Human Genome Research Institute (in the USA).

NIG National Institute of Genetics (in Japan).
NIH National Institutes of Health (in the USA).
NMD Nonsense-Mediated Decay.

PAM50 Prediction Analysis of Microarray 50.
PARP Poly-ADP-Ribose Polymerase.
PCR Polymerase Chain Reaction.
PDE Phosphodiesterase.
PI3K Phosphoinositide 3-kinase.
PIP_2 Phosphatidylinositol-(4,5)-bisphosphate.
PIP_3 Phosphatidylinositol-(3,4,5)-trisphosphate.
PPI Protein-Protein Interaction.
PR Progesterone Receptor.

qPCR Quantitative (real-time) Polymerase Chain Reaction.

RFLP Restriction Fragment Length Polymorphism.
RGS G-protein Signalling.
RHO Ras Homolog Family.
RMA Robust Multiarray Averaging (normalisation.
RNA Ribonucleic Acid.
RNAi Ribonucleic Acid Interference.
ROC Reciever Operating Characteristic (curve).
RPPA Reverse Phase Protein Arrays.
RRBS Reduced Representation Bisulfite Sequencing.
rRNA Ribonucleic acid.
RSEM RNA-Seq by Expectation Maximization (normalisation.

SGA Synthetic Gene Array (technique).
SGI Synthetic Genetic Interaction.
shRNA Short Hairpin Ribonucleic Acid.
siRNA Short Interfering Ribonucleic Acid.
SL Synthetic Lethal.
SLIPT Synthetic Lethal Interaction Prediction Tool.
Slurm Simple Linux Utility for Resource Management.
SNP Single Nucleotide Polymorphism.
SR Synthetic Rescue (or viability).
SS Synthetic Suppression.

SSL Synthetic Sick.

TCGA The Cancer Genome Atlas (genomics project).
TGFα Transforming Growth Factor α.
tRNA Transfer Ribonucleic Acid.

UCSC University of California, Santa Cruz.
UTR Untranslated Region (of mRNA).

WNT Wingless-Related Integration Site.

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