Mechanisms of genetic interactions and cancer treatment

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Genetic interaction between two or more genes is an observation of unexpectedly large or small effect on a phenotype from the perturbed activity of a group of genes, compared to their individual effects.

Knowledge of genetic interactions can be used to infer signalling pathways, to predict cell fates and to find therapeutic intervention points in human disease. Some types of synthetic interactions are used as an approach for treatment of some cancer types: synthetic lethality (SL) is used to target mutated tumour suppressor genes (such as BRCA1), while masking alleviating interactions can be used to predict if targeting an oncogene will bring a therapeutic effect [1].

Despite significant progress in data collection, especially in model organisms [2], there is still a lack of mechanistic understanding of genetic interactions. The classical paradigm explains aggravating genetic interactions by existence of redundant pathways performing the same essential function, while alleviating interactions are expected to happen within the same pathway. This view is tightly linked to the historical image of a pathway as a linear chain of reactions, which is clearly outdated now. Usage of computational modelling allowed getting mechanistic insight into more complex scenarios leading to genetic interactions.

We investigated the role of genetic interactions in DNA repair cellular machinery. This is particular important for cancer treatment since many somatic and inherited mutations in cancer are in the genes involved in DNA repair.

First, we propose a novel mechanism leading to within-pathway SL involving two genes functioning in a single *non-essential* pathway [3]. This type of SL termed

within-reversible-pathway SL involves reversible pathway steps, catalyzed by different enzymes in the forward and backward directions, and *kinetic trapping* of a potentially toxic intermediate. Experimental data with recombinational DNA repair genes validate the concept. Mathematical modeling recapitulates the possibility of kinetic trapping and revealed the potential contributions of synthetic, dosage-lethal interactions in such a genetic system as well as the possibility of within-pathway positive masking interactions. Analysis of yeast gene interaction and pathway data suggests broad applicability of this novel concept.

Second, we use a comprehensive reconstruction of the molecular interactions involved in DNA repair, created by us, in order to predict those combinations of genes whose deactivation can lead to inability for a cell to repair some specific types of DNA damage. We validated some of these predictions using existing databases of genetic interactions. In addition, using large-scale profiling of cancer genomes in cell lines or tumour samples, we show how these interactions either create pre-disposition for successful treatment of cancer cells by some types of genotoxic treatment or make them insensitive to treatment.

These findings extend the canonical interpretation of synthetic-lethal or synthetic-sick interactions with direct implications to reconstruct molecular pathways and improve therapeutic approaches.

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2. M. Costanzo, A. Baryshnikova, J. Bellay, Y. Kim, E.D. Spear, et al. (2010) The genetic landscape of a cell. *Science* **327**: 425-431.

3. A. Zinovyev, I. Kuperstein, E. Barillot and W.-D. Heyer (2003) Synthetic lethality between gene defects affecting a single non-essential molecular pathway with reversible steps, *PLoS Computational Biology, In press*.