

Systems biology of epistasis

Shedding light on genetic interaction network “hubs”

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Genetic (or epistatic) interactions occur when the phenotypic effect of a mutation depends on the presence of other mutations in the genome. Genetic interactions have long fascinated biologists as they are the key to understand how genes relate functionally, why and how organisms tolerate mutations and also, how complex genetic diseases arise. Recent high-throughput screens have constructed comprehensive maps of genetic interactions between pairs of genes in budding yeast (*Saccharomyces cerevisiae*) and provided the first glimpse into the organizational principles of epistatic networks.¹ A striking pattern has emerged from these studies: consistent with other biological networks, the vast majority of genes show few genetic interactions, whereas a small number of ‘hub’ genes are epistatically highly connected. For example, 1% of all genes tested contributed to almost 6% of all genetic interactions. Thus, activities of these hub genes are expected to modulate the phenotypic effects of mutations in many other genes. Although they do not belong to a single functional module, hubs do have distinguishing physiological and evolutionary properties: they tend to exhibit severe fitness defect when deleted, are highly pleiotropic (that is, multifunctional), and evolve slowly.¹ How to explain these observations?

Given the sheer complexity of the cell’s molecular circuitry, we need computational systems biology models to understand how these genetic phenomena emerge from the operation of molecular networks. Intermediary metabolism, the best characterized molecular circuit of the cell, is amenable to mathematical modeling and therefore suitable to elucidate

the genotype-phenotype relationship.² Particularly, genome-scale metabolic models can successfully calculate the phenotypic impact of gene deletions, and deliver mechanistic insight into why most genes appear to be non-essential for cell growth.³ Thus, to understand the link between epistatic interaction degree, pleiotropy and gene’s functional importance, we have recently explored the genetic interaction map of yeast metabolism using automated genetic analysis, and compared it with predictions derived from a metabolic model.⁴

Remarkably, the metabolic network model can explain the above-mentioned basic principles of epistatic networks. First, it successfully captured the high epistatic connectivity of genes with large fitness contribution. As the model contains information only on the reaction stoichiometry and growth requirements of the metabolic network, but does not account for gene regulatory and enzyme kinetic details, this finding indicates that genetic interaction hubs are primarily dictated by the structure of metabolism. Second, the computational analysis revealed why genetic interaction degree and pleiotropy are connected to each other. By definition, pleiotropic enzymes contribute to multiple biological processes, for example by producing metabolites that are needed for multiple biosynthetic routes. Accordingly, the phenotypic effect upon their deletion can potentially be modulated by many other genes, resulting in numerous genetic interactions (Fig. 1A). Thus, epistatic hubs can emerge as a result of multifunctionality of certain metabolic pathways, a prediction that should deserve future empirical testing.

A case study from our genetic interaction map can further illuminate why pleiotropy correlates with epistatic connectivity (see Fig. 1B). Consider two genes, one involved in NAD biosynthesis (*BNA6*, encoding quinolinate phosphoribosyl transferase) and the other encoding fumarase in TCA cycle (*FUM1*). While the metabolic network model suggests that *BNA6* is only required for NAD biosynthesis, removal of *FUM1* affects the production of over two dozen central compounds required for growth (including various amino acids, phospholipids and polysaccharides). In line with expectations, *BNA6* exhibits only a few genetic interactions, and mostly with genes involved in NAD metabolism, while *FUM1* is an epistatic hub connected with a large number of other genes involved in various other pathways.

Why are these results important? One might speculate that evolutionary loss or condition-dependent downregulation of epistatic hub genes may dramatically alter the effects of mutations at various genomic locations and thus exert a strong influence on the accessibility of evolutionary paths. Finally, it is becoming increasingly clear that epistatic interactions are generally plastic across environmental conditions.^{5,6} How far hubs and their interaction partners change with the environment is currently a terra incognita.

References

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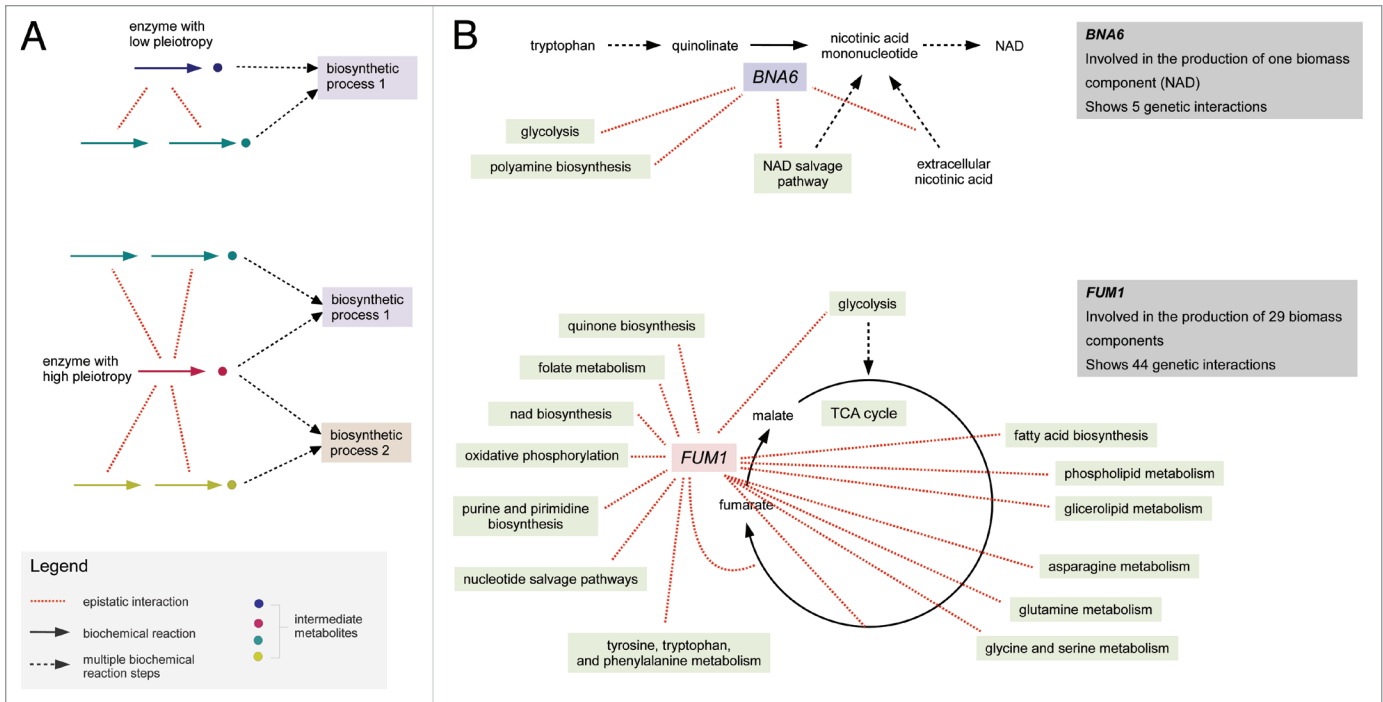


Figure 1. Epistatic interactions and pleiotropy. (A) A conceptual model to explain why highly pleiotropic genes exhibit many epistatic interactions with other genes in the metabolic network. The phenotypic effect of mutation in a gene that contributes to numerous biosynthetic processes can potentially be modulated by a large number of other enzyme-encoding genes, each of them negatively or positively affecting different aspects of functionality. (B) An example. *BNA6* encodes an enzyme that catalyzes a crucial step in NAD biosynthesis. A computational analysis revealed that removal of this gene only influences the production of NAD. In agreement with its specialized cellular role, it shows epistatic interactions with only few other genes. In sharp contrast, *FUM1*, which is involved in the TCA cycle, shows both high degree of pleiotropy and a large number of epistatic interactions.