Molecular Systems Biology 7; Article number 463; doi:10.1038/msb.2010.117
Citation: *Molecular Systems Biology* 7:463

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molecular systems biology

NEWS AND VIEWS

Rewiring makes the difference

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Molecular Systems Biology **7**: 463; published online 18 January 2011; doi:10.1038/msb.2010.117

While canonical pathways and regulatory networks provide a representation of molecular interactions in the cell that appears static and immutable, actual regulatory pathways are anything but. Rather, they appear to reconfigure dynamically as a function of the specific molecular context in which they operate. This was shown initially in yeast (Luscombe *et al*, 2004) and more recently in mammalian cells (Mani *et al*, 2008; Wang *et al*, 2009). Now, in an elegant study recently published in Science, Trey Ideker, Nevan Krogan, Michael-Christopher Keogh and colleagues show that the cellular response to environmental stress is also associated with massive rewiring of genetic interaction networks (Bandyopadhyay *et al*, 2010).

Specifically, the authors tested 80 000 genetic interactions, both under standard laboratory conditions and upon perturbation by the DNA damaging agent methyl methanesulfonate (MMS). Using the epistatic miniarray profiles technique (Schuldiner *et al*, 2006), strains carrying systematical pairwise deletions (for non-essential genes) or hypomorphic alleles (for essential genes) were tested to quantitatively assess genetic interactions between 418 genes selected to broadly cover transcriptional and post-translational regulation in budding yeast.

Surprisingly, the genetic interaction map obtained upon MMS treatment was not enriched in interactions between known components of the DNA damage response. On the other hand, closer examination of both the untreated and the MMS 'static' networks revealed that the vast majority of interactions identified under one condition could not be identified under the other. For instance, 70% of positive genetic interactions (i.e., those resulting in increased cell viability) under MMS treatment were not identified in the untreated samples, suggesting that viability under DNA damage is affected by mechanisms that are not in play in the absence of DNA damage.

To perform a systematical comparison between the two 'static' maps, the authors introduce the concept of differential epistatic mini-array profile by computing a difference score that quantifies the change of genetic interaction across two conditions. Strikingly, subtracting the untreated map from the MMS map resulted in a 'differential' network that turned out to be highly enriched for DNA damage response genes, in marked contrast to the static maps. Furthermore, several differential interaction hub genes, including *SLT1*, *CBF1* and *HTZ1*, were shown to be part of the DNA damage response machinery.

These findings suggest that differential interaction networks may reveal the processes that are dynamically engaged during cellular responses to stress. More broadly, differential functional networks may shed light on the regulation of cell type, tissue-specific or disease-related pathways.

Genetic interactions reflect synergistic or antisynergistic regulation in the cell and may or may not correspond to actual physical interactions at the molecular level. It is thus intriguing that molecular interactions appear to be similarly rearranged across distinct conditions or biochemical perturbations, such as following CD40 stimulation in human B cells (Mani *et al*, 2008). If genetic interaction maps are the result of the context-dependent wiring of regulatory networks in the cell, this suggests that changes in one layer are reflected in the other and vice versa, opening a number of exciting and interesting possibilities. For instance, if dynamical changes in the topology of molecular interactions could be used to predict the corresponding changes in genetic interactions, this could pave the way to predictive combination therapy, to reduce cancer cell viability using negative interactions, for instance, or to increase cell viability in neurodegenerative diseases using positive interactions.

The analysis of DNA damage-induced epistasis in yeast may also be relevant to the study of oncogenesis, as increased proliferation following dysregulation in DNA damage response pathways is a hallmark of human cancer (Smith *et al*, 2010). More importantly this approach may offer a broadly applicable conceptual framework for the discovery of cancer-specific dependencies, such as oncogene addiction (Weinstein and Joe, 2008). While the mechanism of oncogene addiction is not currently fully understood, this phenomenon remains key to the successful identification of specific genetic targets for cancer treatment. The approach proposed by Bandyopadhyay *et al* (2010) and the fact that profiles of gene essentiality in untreated cells differ from those in cells treated with MMS (Brown *et al*, 2006) suggest that cancer-specific mechanisms, including oncogene addiction, could similarly be unraveled by

systematically mapping conditional phenotypic profiles resulting from single gene as well as pairwise gene inhibition.

Finally, it is remarkable, although somewhat counter-intuitive, that genes that are not directly related to DNA damage response emerged from this study as being involved in MMS treatment-specific genetic interactions. In the context of cancer, for instance, this suggests that malignancies may be addicted to genes that are not directly involved in tumorigenesis. Such non-oncogene addiction (Schreiber *et al*, 2010) may some day provide highly specific and, more importantly, oncogene-independent therapeutic targets for combination therapy, thus potentially broadening the spectrum of cancer patients who can be treated with targeted therapy.

Conflict of interest

The author declares that he has no conflict of interest.

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