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Commentary

Integration of CRISPR-Cas9, shRNA with other genomic data provides reliable predicions of gene essentiality

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Recent genome-wide loss-of-function screening studies have provided an unprecedented amount of information to perform functional analysis of the genome. Two main strategies have been followed to perform these experiments: shRNA and, more recently, CRISPR-Cas9.

Both technologies have shown their ability to knock down genes and, in the case of CRISPR-Cas9, the ability to create new cell-line strands with different phenotypes.

Surprisingly, both technologies are non-coherent in certain cases: genes that appear to be essential using one technology are not essential for the other and vice versa. In their article, Wang et al. [1] studied 42 cell-lines -corresponding to 10 different cancers- with paired experiments using shRNA and CRISPR-Cas9 in order to measure the coherence between both approaches.

The results showed that, for 12 cell-lines out of 42, the correlation of essentiality scores was non-significant or even negative. This finding is intriguing since both technologies showed stronger gene essentiality for housekeeping genes (n = 3804) compared to others (median score −0.02 vs 0.14 for CRISPR screen and −0.08 vs. 0.09 for the shRNA screen, Wilcoxon test p-value < 2e−16 in both cases). Therefore, the explanation is more complex than a simple difference in efficiency. Both technologies work but behave differently with different genes. On the other hand, in some cases, the two technologies are coherent: 9 out of 10 leukemia cell lines showed moderately positive correlations ranging from 0.12 to 0.20, suggesting that leukemia cells tend to respond similarly to these two screen technologies.

Wang et al. performed a functional enrichment analysis of essential genes that are specific for each technology. In the case of CRISPR-Cas9, the sensitive pathways are related with DNA repair, response to DNA damage stimulus or, in general, DNA processing. On the contrary, the sensitive pathways for shRNA are mainly related with immune response. Their analysis shed some light on the essentiality of "technology-specific" genes. Since the CRISPR experiment induces a rupture in the DNA, the cell is especially sensitive to DNA repair pathways. On the contrary, the process of transfection of plasmids for shRNA triggers several immune response pathways, and cells are particularly sensitive to the alteration of genes involved in these pathways.

Even though the functional analysis is quite informative on why each of technology shows different essentiality results, there is still an open question: is there a way to integrate shRNA and CRISPR-Cas9 screens to get "the best of both worlds"?. For this, Wang et al. proposed the CES score. This score integrates gene expression, mutational load and copy number alteration together with the shRNA and CRISPR screens using a multiple linear regression to obtain a combined score.

Despite its simplicity, the results of their algorithm outperform previous attempts. In order to compare their method, they built a set of true positives genes (genes that are known to be essential) and true negative genes (genes that are known to be non-essential). CES outperformed any other state of the art methods including CERES, DEMETER, DEMETER2, etc. [2–4]. Besides, the linear model allows to investigate the internal characteristics of the predictions. For example, the coefficient for copy number is negative showing that genes with amplifications tend to be essential -and therefore, that genes with deletions tend to be non-essential.

In addition, the authors showed some examples of translational applications of the CES method. For instance, AGR2 was identified to be essential for the T47D cell line – an ER+ breast cancer cell-line – using the CES score and was not detected by any other method; SRGN was predicted to be a potential drug target for AML cell lines and was neither predicted by other methods. They showed, using clinical data, that AGR2 upregulation is predictive of poor survival in ER-positive breast cancer patients and that SRGN upregulation is associated with poor AML prognosis.

As genome-wide loss-of function screening experiments become widely available, the scope of CES-like scores will be improved and these approaches will be indispensable to analyze genetic dependencies. This work opens a fresh approach to integrate functional and genomic data that might provide important clues for drug discovery in personalized medicine, as the authors highlighted in their conclusion.

Declaration of Competing Interest

The author declared no conflicts of interest.

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