Scenic Biotech | Evolution Inspired Medicine

Exploiting genetic modifiers to treat disease

Genetic modifiers can explain why some people with inherited diseases have mild or no symptoms, whilst others – even family members – have a severe, fully expressed disease. Here at Scenic Biotech, we are taking a functional genomics approach to identifying modifier genes as starting points for radically new ways of treating patients.

Mendelian disorders are inherited disorders generally caused by changes in a single gene. To date, more than 6,000 Mendelian disorders have been described and yet only a handful of effective treatments have been developed. One reason for this is the difficulty of restoring protein activity in the presence of loss-of-function mutations. Therefore, treatment of Mendelian disorders often focuses on relieving symptoms rather than on true cures. However, not all patients with a disease mutation experience the same outcome – there is substantial variation in terms of the age-of-onset, rate of progression and severity of disease. While some of this variation may be due to environmental factors, much is likely due to the action of so-called modifier genes.

For example, genetic diseases in nonidentical twins who have grown up in the same environment and who carry the same primary mutation can manifest very differently. Indeed, mutations in modifier genes may even suppress the disease phenotype altogether.

One of the first large-scale studies to look for such genetic exceptions analyzed data from over half a million healthy people and identified 13 individuals who should have had serious childhood diseases based on their genetic sequence, but did not develop the disease (Chen et al, Nat Biotech 2016). Pinpointing the genes responsible for suppression/modulation of disease represents a promising route to intervening in disease initiation and progression.

However, several difficulties are associated with identifying genetic modifiers in human populations. As illustrated by the study above, individuals who 'escape' Mendelian disorders are rare, limiting the statistical power required to identify genetic modifiers. Furthermore, the disorders themselves are generally rare, so that disease population sizes are often small. Diseases with relatively high incidence, such as cystic fibrosis, have therefore shown most promise for identification of modifier genes that drive phenotypic variability. Another issue is the genetic heterogeneity of human populations, which makes it difficult to pinpoint which gene is responsible for any modifying effects. This limitation can be partially overcome by studying related individuals in extended families. However, clinical descriptions are often incomplete, so that it is difficult to provide accurate descriptions of disease onset, rate of progression and severity. Finally, non-genetic factors like environmental variables further confound the genotype-phenotype relationship.

Many of these limitations can be overcome by using model organisms, which offer

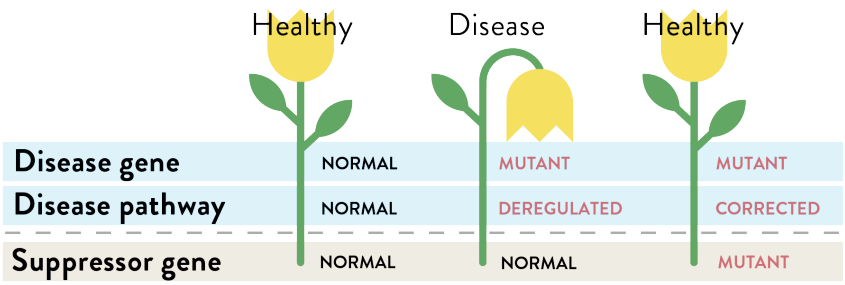

Figure 1. Schematic overview of the interaction between "suppressor genes" with disease gene/pathway

a controlled, systematic approach to studying variation, and include the option of artificially introducing mutations. One of the simplest model organisms, budding yeast, has been used to assemble a global network of genetic suppression interactions (van Leeuwen et al, Science 2016), and the principles gained from such studies have the potential to guide the identification of modifier genes in human disease. In mice, linkage crosses, specialized inbred strains and mutagenesis screens have been used to identify and map modifier genes. However, such model systems are very difficult to scale making it hard to routinely employ, and provide limited relevance to humans.

Although human genes can be studied in a laboratory setting using cell lines, the diploid genome and inability to set up genetic crosses long precluded the use of mutagenesis approaches for linking genotype and phenotype. However, recent developments have made it possible to study the human genome using knockout alleles. On the one hand, human haploid cells carrying single alleles for each gene have enabled the generation of knockout alleles for most human genes. On the other hand, CRISPR-Cas technology can target mutation anywhere in the genome. The impact of mutations on a range of readouts – e.g., gene expression, protein state and cell viability – can then be studied.

Taking advantage of human haploid cell lines, we are using Cell-Seq, screening technology that is proprietary to Scenic, to identify genetic modifiers (e.g., Brockmann et al, Nature 2017). In contrast to diploid cells, haploid cells carry a single copy of its genes making them highly suited for genomic studies. Specifically, we subject the cells to random mutagenesis, then fluorescently stain with antibodies against a disease-relevant readout (e.g., protein, metabolite). Mutated cells with higher or lower abundance of the protein of interest can then be sorted by FACS and sequenced to identify the mutation(s). The result is a high-resolution "map" that highlights all genes that affect the disease trait. Importantly, such maps can be generated in cells that have been engineered to contain disease-causing mutations thus yielding genetic modifiers that suppress the disease phenotype. For example, we have performed sets of Cell-Seq maps with various relevant readouts to identify genes that may influence lysosomal storage diseases, a group of severe, inherited disorders with an incidence of ~1:5,000. One such disorder, Niemann Pick Type C disease, is caused by cholesterol accumulation. We are currently investigating a modifier that suppresses cholesterol accumulation specifically in Niemann Pick patient-derived cells.

In summary, genetic modifiers are genes that can suppress or even completely block the effect of a disease-causing mutated gene. Scenic is at the forefront of identifying new drug targets to enable the development of disease modifying therapeutics that will offer hope for patients with devastating diseases including inherited rare diseases and cancer.

References

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