Novel approach to gene regulation can activate multiple genes simultaneously

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By creating a powerful new gene regulation system called CRISPR-on, Whitehead Institute researchers now have the ability to increase the expression of multiple genes simultaneously and precisely manipulate each gene's expression level. The system is effective in both mouse and human cells as well as in mouse embryos.

"CRISPR-on is a tool that will be very useful for studying many biological processes, particularly for studying gene functions and gene networks," says Whitehead Founding Member Rudolf Jaenisch. "In contrast to RNA interference, which is commonly used to inactivate gene activity, the CRISPR-on system allows activation of cellular genes. The technology substantially expands our ability to change gene expression in cultured cells and animals.."

The system, called CRISPR-on, is a modified version of CRISPR/Cas (for "clustered regularly interspaced short palindromic repeat/CRISPR associated"), which taps into a bacterial defense system against viral intruders. CRISPR/Cas relies on an enzyme, Cas9, which cuts DNA at locations specified by single guide RNAs (sgRNAs). For CRISPR-on, the Whitehead team modified the Cas9 enzyme by eliminating its ability to cleave DNA and adding a transcription activation domain. The resulting enzyme can increase gene expression without permanently changing the DNA.

The new system is described this week in the journal *Cell Research*.

CRISPR-on's ability to activate only the desired genes at varying levels could be used to help scientists improve our understanding of transcription network underlying a variety of diseases and potentially find new ways to treat them.

"Many diseases, especially complex diseases, involve multiple genes, and this system could be used therapeutically to target and activate multiple genes together and rescue these disease phenotypes," says Albert Cheng, a graduate student in the Jaenisch lab and co-author of the Cell Research paper. "Or we could use it to study the gene networks in diseases and get a better understanding of how those diseases work."

So far, the researchers have used CRISPR-on to activate up to three native genes concurrently in human cells.

"I think we need to do more work to see if there are any limitations to the number of genes CRISPR-on can activate at a time," says Haoyi Wang, a co-author and postdoctoral researcher in the Jaenisch lab. "We'd like to see if we can get data on activating 10 or more genes, to see if there is an upper limit to what this system can do."

More information: "RNA-guided multiplexed endogenous gene activation" *Cell Research*, online August 27, 2013.

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