Fail-Safe System May Lead to Cures for Inherited Disorders

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Scientists at the University of California, San Diego School of Medicine have uncovered a previously unknown fail-safe (compensatory) pathway that potentially protects the brain and other organs from genetic and environmental threats. The discovery could provide new ways to diminish the negative consequences of genetic mutations and environmental toxins that cause neurological diseases and other maladies.

The findings are published in the Sept. 16 issue of the journal Molecular Cell.

Messenger ribonucleic acid (mRNA) is an essential molecule that "reads" genetic information contained within the human genome, and based on this information, generates proteins essential for life. A key inherent feature of mRNA is its "stop signal," which tells cellular machinery to stop reading the mRNA because it has produced a full-length protein. Importantly, in some aberrant mRNAs, the stop signal is displayed too early, resulting in the production of a shorter-than-normal protein. Some of these short proteins can be highly toxic to cells. To avoid their production, cells use a quality control pathway called nonsense-mediated mRNA decay or NMD, which rapidly degrades "bad" mRNAs with early stop signals.

In research published earlier this year, Miles Wilkinson, PhD, professor of reproductive medicine and a member of the UCSD Institute for Genomic Medicine, and colleagues, revealed that NMD is important for the normal development of the brain and the nervous system. Jozef Gecz, PhD, professor of pediatrics at the University of Adelaide, showed that when NMD doesn't work correctly, neurological conditions arise, ranging from mental retardation and attention-deficit disorder to schizophrenia and autism. These conditions are likely due to the production and accumulation of short proteins in the brain.

Like all components of the body, the NMD pathway is vulnerable to insults, such as environmental toxins or gene mutations. "If such events prevent the NMD pathway from working, there will be an accumulation of short proteins, some of which are likely toxic, resulting in bad consequences to the individual," Wilkinson said.

In their present work, Wilkinson and colleagues report the discovery that human cells have evolved a way to overcome attacks on the NMD pathway. If any molecule of the pathway is injured, the cell sends reinforcement molecules to compensate for the loss.

"These reinforcements are not sent out from all cells of our body but only selectively in certain cells; in some cases they appear to be sent from cells that need reinforcements the most," Wilkinson said.

"This is an important feature of this compensatory ("buffering") response that could potentially be relevant for clinical application," Wilkinson said. "To appreciate this, one first needs to realize that a very large proportion of people with genetic diseases—one-third, in fact—have a faulty gene with a mutation that leads to an early stop signal. As a consequence, most of these genes will give rise to an mRNA that is degraded by NMD and hence the encoded protein is never made. A key point is that a proportion of these mutant proteins—although shorter than normal—is actually still functional. So, if clinicians could inhibit NMD, this would potentially ameliorate the symptoms of some of these diseases because this treatment would increase the production of these short, but still functional, proteins."

"Unfortunately, a global NMD blockade would also lead to the production of lots of other short proteins, some of which would be toxic," Wilkinson noted. As a result, "in the past, there has been little interest in 'NMD-inhibition therapy.'" The new discovery makes NMD-inhibition therapy much more attractive because the tissue-specific compensatory response has the potential to greatly dampen the side effects. "By choosing a branch of the NMD pathway that is subject to compensation only in the appropriate tissues, a highly selective effect can potentially be achieved" said Wilkinson.

"For example, there is a need to come up with better treatments for cystic fibrosis—a heritable chronic lung disease—that is currently being treated in some patients with drugs that act by blocking recognition of the premature stop signal in the mutant CFTR gene," he said. "There has been some success with this approach, but there are concerns with side effects." The finding that NMD is buffered by a tissue-specific regulatory system means that one could design a different type of drug—a tissue-specific NMD-inhibition drug—that increases the level of the CFTR protein primarily in its main cellular site of action: the lung. "This could potentially increase the efficacy and drastically reduce the side effects of NMD-inhibition drugs" says Wilkinson.

Lead author of the study is Lulu Huang, with co-authors Chih-Hong Lou, Wai-kin Chan, Eleen Y. Shum, Hye-Won Song, Ada Shao and Rachid Karam in the Department of Reproductive Medicine, UCSD School of Medicine. Also contributing is Erica Stone in the Department of Cellular and Molecular Medicine at UCSD.

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