Researchers discover cell's 'quality control' mechanism

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Researchers in Japan and Canada have discovered a key component of the quality control mechanism that operates inside human cells – sometimes too well. The breakthrough has significant implications for the development of new treatments for cystic fibrosis (CF) and some other hereditary diseases, the researchers say. Their results were published July 25 in the journal *Science*.

Dr. Kazahiro Nagata and colleagues at Kyoto University and the Japan Science Technology Agency, and Dr. David Thomas and Dr. Gregor Jansen at McGill University in Montreal, have discovered the important role played by an enzyme called ERdj5 inside the cell's endoplasmic reticulum (ER). The ER acts as a sort of packaging plant that folds and prepares proteins for distribution inside or outside the cell. But when proteins are misfolded in the ER, they must be destroyed in a degradation process – and that is where ERdj5 comes into play.

"ERdj5 is like a quality control inspector," explained Dr. Thomas, McGill's Chair of Biochemistry and Canada Research Chair in Molecular Genetics. "If you ever owned an AMC Pacer and you now drive a BMW, you know the difference quality control can make. That's what ERdj5 does, it recognizes when a protein has 'manufacturing defects' and degrades it before it can be distributed."

The ERdj5 enzyme is the first protein found to be capable of breaking the disulfide bonds that hold the misfolded proteins together in the ER. Once those bonds are broken, the researchers say ERdj5 also helps other

enzymes and molecules break down the misfolded proteins completely so that the constituent amino acids can be recycled for further protein synthesis.

"Unfortunately, the mechanism sometimes works a little too well," Dr. Thomas said. "It insists on BMW quality when a Honda would do. For example, some people carry a mutated version of the protein CFTR. The mutated protein is damaged but would still work fine if it were distributed, but in some individuals, the quality control mechanism insists on degrading it. It's the degradation of the protein, not the mutation itself, which causes cystic fibrosis. We're hoping this discovery will open up new avenues of research into treatments for CF."

Source: McGill University