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LEARNING BIOLOGY FROM THE STUDY OF GENETIC DISEASES

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More than 6000 human genetic diseases are caused by a mutation in a single gene resulting in a disorder that can be inherited through generations. Furthermore, genetic predisposition plays a major role in a growing group of common human diseases. Understanding the complex series of events leading from a gene mutation (genotype) to disease symptoms (phenotype) is both a challenging and an important task, as it may lead to the identification of novel therapeutic strategies for genetic diseases. In some fortunate cases, studying genetic diseases may lead to the identification of a novel basic biological mechanism, which may have a wide impact in biology and medicine. A recent discovery, made in our laboratory (Sardiello et al. *Science*, June 26, 2009), of a gene network regulating cellular clearance may represent one of such cases. All cells of the human body have a clearance and recycling system by which the byproducts of cellular metabolism are degraded and reutilized. This system relies on intracellular organelles, named lysosomes —the structures that provide a garbage disposal service to the cell— in which degradation processes occur. The efficiency of this system is of crucial importance for a correct cellular function in order to avoid pathological consequences of the accumulation of toxic molecules. Neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases, as well as Lysosomal Storage Disorders, are due to the accumulation of undegraded toxic molecules. We discovered a genetic program that regulates the efficiency of cellular clearance. We identified a "master" gene that acts as a "genetic switch" to turn on genes encoding degradation enzymes. By enhancing the function of this master gene we were able to increase the clearance capacity of the cell and its ability to degrade toxic proteins such as that causing Huntington's disease. This discovery may have important applications for the therapy of neurodegenerative diseases.