Restoration of Cell Growth with Small Molecule Surrogates for Missing Proteins

Alexander G. Cioffi, Jennifer Hou, Anthony S. Grillo, and Martin D. Burke

Human diseases caused by an excess of protein function can often be treated with small molecules that inhibit the corresponding proteins. In contrast, many diseases caused by a deficiency of protein function are refractory to this approach and remain incurable. Small molecules can at least partially replicate many protein functions, but it has remained unclear if this partial functional replication can be sufficient to restore physiology in the setting of a protein deficiency. To answer this question, we designed a new type of functional complementation experiment in which small molecules are tested for the capacity to rescue growth deficiency in a cell lacking a protein. Strikingly, vigorous restoration of cell growth was observed upon treating yeast cells lacking highly selective and extensively regulated ion transporter proteins with inherently much less selective and unregulated small molecule surrogates. Extensive mechanistic studies, including those with ion transport-deficient synthetic derivatives of these small molecules, established that the observed restoration of cell growth is caused by small molecule-mediated ion transport. These findings collectively suggest that the inherent robustness of living systems stands to enable small molecule surrogates for missing proteins to operate as prostheses on the molecular scale.