Scientists develop a general 'control switch' for protein activity

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Our bodies could not maintain their existence without thousands of proteins performing myriad vital tasks within cells. Since malfunctioning proteins can cause disease, the study of protein structure and function can lead to the development of drugs and treatments for numerous disorders.

For example, the discovery of insulin's role in diabetes paved the way for the development of a treatment based on insulin injections. Yet, despite enormous research efforts led by scientists worldwide, the cellular function of numerous proteins is still unknown. To reveal this function, scientists perform various genetic manipulations to increase or, conversely, decrease the production of a certain protein, but existing manipulations of this sort are complicated and do not fully meet the researchers' needs.

Prof. Mordechai "Moti" Liscovitch and graduate student Oran Erster of the Weizmann Institute's Biological Regulation Department, together with Dr. Miri Eisenstein of Chemical Research Support, have recently developed a unique "switch" that can control the activity of any protein, raising it several-fold or stopping it almost completely. The method provides researchers with a simple and effective tool for exploring the function of unknown proteins, and in the future the new technique may find many additional uses.

The switch has a genetic component and a chemical component: Using genetic engineering, the scientists insert a short segment of amino acids

into the amino acid sequence making up the protein. This segment is capable of binding strongly and selectively to a particular chemical drug, which affects the activity level of the engineered protein by increasing or reducing it. When the drug is no longer applied, or when it is removed from the system, the protein returns to its natural activity level.

As reported recently in the journal *Nature Methods*, the first stage of the method consists of preparing a set of genetically engineered proteins (called a “library” in scientific language) with the amino acid segment inserted in different places. In the second stage, the engineered proteins are screened to identify the ones that respond to the drug in a desired manner. The researchers have discovered that in some of the engineered proteins the drug increased the activity level, while in others this activity was reduced. Says Prof. Liscovitch: “We were surprised by the effectiveness of the method – it turns out that a small set of engineered proteins is needed to find the ones that respond to the drug. With their greater resources, biotechnology companies will be able to create much larger sets of engineered proteins in order to find one that best meets their needs.”

The method developed by the Weizmann Institute scientists is ready for immediate use, both in basic biomedical research and in the pharmaceutical industry, in the search for proteins that can serve as targets for new drugs. Beyond offering a potent tool that can be applied to any protein, the method has an important advantage compared with other techniques: It allows the total and precise control over the activity of an engineered protein. Such activity can be brought to a desired level or returned to its natural level, at specific locations in the body and at specific times – all this by giving exact and well-timed doses of the same simple drug.

In addition, the method could be used one day in gene therapy. It may be possible to replace damaged proteins that cause severe diseases with

genetically engineered proteins, and to control these proteins' activity levels in a precise manner by giving appropriate doses of the drug. Another potential future application is in agricultural genetic engineering. The method might make it possible, for example, to create genetically engineered plants in which the precise timing of fruit ripening would be controlled using a substance that increases the activity of proteins responsible for ripening. Moreover, numerous proteins are used in industrial processes, as biological sensors and in other applications. The possibility of controlling these applications – strengthening or slowing the rate of protein activity in an immediate and reversible manner – can be of great value.

Source: Weizmann Institute of Science