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Researchers make major signal transduction discovery

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The chemical process known as acetylation plays a central role in cytokine receptor signal transduction – a fundamental biochemical cascade inside cells that controls the activity of antiviral and tumor-suppressing genes.

A team of cell biologists led by Eugene Chin, M.D., a research professor at The Warren Alpert Medical School of Brown University and a staff researcher at Rhode Island Hospital, reports its findings in the journal *Cell*. Their results are surprising.

Scientists have long known that phosphorylation, an amino acid modifying process in proteins, is critical for switching receptors on and off on the surface of cells. Chin and his team studied how type 1 interferon binds to a receptor complex, known as the IFN-α receptor, on the cell surface to trigger an immune response. Chin and his team found that acetylation, another chemical process that modifies amino acids, plays a central role in activating interferon receptors.

Interferons play a crucial role in the body's defense against infection and uncontrolled cell growth. Type 1 interferon is widely used to treat hepatitis B and C and cancers such as melanoma and leukemia.

"This is a major discovery in the field of signal transduction," Chin said. "Tyrosine phosphorylation has so far been considered the major player in signal transduction. But what we discovered challenges this concept. We found another player – acetylation – in the process."

In their experiments, Chin and his team looked at how cells respond to type 1 interferon, a protein produced in response to a viral infection or other immune trigger. The researchers found that type 1 interferon receptors, which are found in every cell in the body, call up cytoplasmic CREB-binding protein, or CBP, to move up to the cell surface. CPB acetylates these receptors. That, in turn, sparks a biochemical cascade that attracts more proteins to create a complex called ISGF3. To activate this protein complex, Chin found, acetylation is required. Once that occurs, the complex travels to the cell nucleus to switch on anti-viral or tumor-suppressing genes.

The discovery of the acetylation of cytokine receptors marks a milestone in the study of signal transduction, the process of how cells receive and respond to chemical messages.

Many diseases, such as diabetes, cancer and heart disease, occur when signal transduction goes awry. That is why some drugs either inhibit or amplify signaling inside cells by targeting tyrosine phosphorylation. By showing that another chemical process is critical to signal transduction, Chin's findings may explain why some anti-cancer or anti-viral drugs do not work for everyone. The findings provide an important new target for therapies that fight cancer and viral infectious diseases.

Source: Brown University