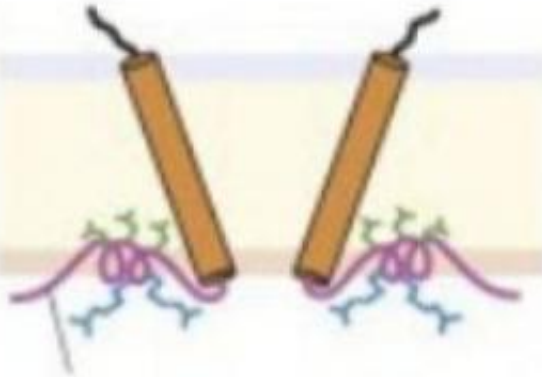


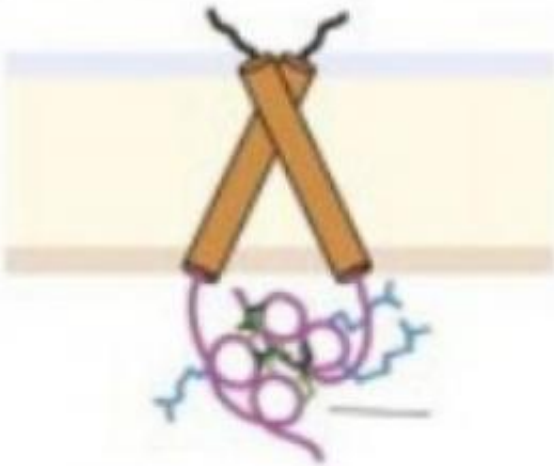
New details on the molecular machinery of cancer

February 11 2013

Inactive



Active



This shows a structural coupling that allows intracellular kinase domains to undergo dimerization is a key to EGFR activation. Credit: Jay Groves, et. al, Berkeley Lab

Researchers with Lawrence Berkeley National Laboratory (Berkeley Lab) and the University of California (UC) Berkeley have provided important new details into the activation of the epidermal growth factor receptor (EGFR), a cell surface protein that has been strongly linked to a large number of cancers and is a major target of cancer therapies.

"The more we understand about EGFR and the complex molecular machinery involved in the growth and proliferation of cells, the closer we will be to developing new and more effective ways to cure and treat the many different forms of cancer," says chemist Jay Groves, one of the leaders of this research. "Through a tour-de-force of quantitative biology techniques that included cutting edge time-resolved fluorescence spectroscopy in living cells, [Nuclear Magnetic Resonance](#), and computational modeling, we've determined definitively how EGFR becomes activated through to its epidermal growth factor (EGF) ligand."

Groves, who holds joint appointments with Berkeley Lab's Physical Biosciences Division and UC Berkeley's Chemistry Department, and is also a Howard Hughes Medical Institute (HHMI) investigator is one of two corresponding authors of a paper in the journal *Cell* that describes this research. The paper is titled "Conformational Coupling across the Plasma Membrane in Activation of the EGF Receptor." The other corresponding author is John Kuriyan, who also holds joint appointments with Berkeley Lab, UC Berkeley and HHMI.

In high school biology classes we learn that genes contain coded instructions that are translated into the assembly of specific proteins.

Many proteins, however, must be activated by post-translational processes such as autophosphorylation, the addition of phosphate. Protein activation can impact many important cellular processes including proliferation, differentiation and migration. Cancer is essentially a case of these cellular functions gone wild, often the result of problems with the EGFR. However, despite its well-established links to cancer, EGFR activation has only been partially understood.

"As a member of the large class of cell surface receptors known as receptor tyrosine kinases, EGFR features a ligand-binding domain on its extracellular side and a kinase domain on its intracellular side," Groves says. "The text-book explanation for EGFR activation is that the binding of EGFR's ligand, EGF, to its extracellular side induces dimerization of the receptor, which in turn brings together the kinase domains on the intracellular sides of the dimer, allowing them to phosphorylate one another."

Groves says while the picture is accurate, it is an oversimplification of the mechanics behind the process because isolated intracellular kinase domains in solution can be active on their own at relatively low concentration without EGF ligand-induced dimerization. Dimerization is the combining of two identical molecules into a single compound molecule.

Measuring autophosphorylation as a function of EGFR surface density in cells, Groves, Kuriyan and their colleagues found that structural coupling between the EGFR transmembrane helix and extracellular juxtamembrane modules in addition to EGF ligand-engagement is required for EGFR activation. This structural coupling permits dimerization to take place in the presence of the EGF ligand.

"The un-ligated EGFR sits in a structural configuration that prevents the intracellular kinase domains from being able to reach each other,"

Groves says. "When the EGF ligand binds, this restraint is removed, dimerization occurs, and one kinase phosphorylates the other."

The inclusion by Groves and his colleagues of time-resolved fluorescence spectroscopy on living cells is another new advance in bringing a quantitative approach to the biological sciences. By combining picosecond light pulses from two different colors of lasers into a single beam, then genetically modifying EGFRs to carry either a red or green fluorescent protein, the researchers were able to monitor in real time how EGFRs move and assemble into dimers during activation by the EGF ligands.

"Focusing on the cell membrane and monitoring each fluorescent photon emitted, then determining both its color and precise time of arrival at the detector, allows unambiguous assignment of which photon was triggered by which color light pulse," Groves says. "All of this can be done in real time and in living cells."

With the mechanics behind the activation of EGFR now fully explained, Groves and his colleagues are now applying their quantitative biology techniques to another group of receptor tyrosine kinases, the Eph receptors, as well as T cell receptors that are so important to the immune system.

"Our broader goal with these quantitative biology techniques is to transform biology into a hard physical science," Groves says. "The idea is to move from simply describing a collage of observations to being able to understand how biological systems work based on fundamental physics."

More information: www.cell.com/abstract/S0092-8674%2812%2901554-1

Provided by Lawrence Berkeley National Laboratory

Citation: New details on the molecular machinery of cancer (2013, February 11) retrieved 26 April 2024 from <https://medicalxpress.com/news/2013-02-molecular-machinery-cancer.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.