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Discovery of EGF Receptor Activation Mechanism Yields Insights for Future Drug Development

The discovery of how the epidermal growth factor receptor (EGFR) is activated offers insight into how current EGFR-blocking drugs interact with the receptor and an important avenue for the development of novel anticancer drugs, said Howard Hughes Medical Institute investigator John Kuriyan.

Mutations that permanently switch on EGFR have been associated with a broad range of cancers, including cancers of the breast, lung, and pancreas.

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Researchers designing new cancer therapeutics have taken two approaches to shutting down aberrant EGFRs. One approach is to make antibodies that target the portion of the receptor exposed to the outside of the cell. A second strategy involves creating molecules that inhibit the kinase domain inside the cell.

Some of these molecules — such as erlotinib (marketed as Tarceva), which is used to treat lung and pancreatic cancers — attach to the active conformation of the kinase domain of EGFR and block it. Other drugs — such as the experimental drug lapatinib (trade name Tykerb), which is used against breast cancer — block the receptor by attaching to its inactive conformation.

Treatment with these drugs is not effective for all patients. Closely related drugs such as gefitinib (marketed as Iressa), however, can be effective in such cases. Those patients who have activating mutations of EGFR are responsive to gefitinib (and possibly to the closely related drug erlotinib), whereas patients with wild-type EGFR are resistant to this class of drugs. The underlying mechanism for this phenomenon is that these drugs specifically

target the active conformation of the EGFR kinase, which is favored by EGFR containing the activating mutations.

When structural biologists created crystals of the EGFR kinase domain complexed with lapatinib to study their interaction, they could only find the receptor in its inactive conformation, Kuriyan noted. In contrast, crystals of erlotinib and the EGFR kinase domain showed an active conformation of the receptor.

The argument could always be made that binding of this high-affinity drug lapatinib somehow distorted the kinase domain into an inactive conformation, and that normally it is active, said Kuriyan. Perhaps that's one reason why the significance of that structure in terms of the activation mechanism was not fully appreciated.

However, Xuewu Zhang, Kuriyan, and their colleagues demonstrated that lapatinib was not needed to force EGFR into an artificially inactive state. They found that by introducing a single mutation into a part of the receptor that interacts with the paired EGFR during dimerization, they could produce crystals of EGFR in an inactive state without lapatinib.

From a structural point of view, this is a very nice experiment because Xuewu made a single mutation in the kinase domain — very far from the active site, but one that is involved in this activation interaction — and achieved the inactive conformation previously seen complexed only with lapatinib, he said.

We've shown that when EGFR forms a dimer, one molecule in the dimer acts on the other one, forcing it out of this inactive conformation that is recognized by lapatinib, into the active conformation, which is recognized by drugs such as erlotinib and gefitinib.

The EGFR activation mechanism they discovered will have implications for development of new EGFR-blocking drugs, said Kuriyan. This mechanism provides an unexpected, alternate route to controlling the activation of the EGF receptor that is likely to be a very important avenue for further studies, potentially with clinical implications, he said. It's quite obvious that if you can somehow block this interaction you would block the activation of the EGF receptor.