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Structure of atypical cancer protein paves way for drug development

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A team of researchers from Case Western Reserve University School of Medicine has helped uncover the elusive structure of a cancer cell receptor protein that can be leveraged to fight disease progression. Previous studies have showed blocking the receptor can slow tumor growth and metastasis in certain cases. However, the development of drugs (inhibitors) has been slowed by an absence of structural information on this highly unstable membrane protein. Armed with the new study, drug developers can now design molecules that nestle into the receptor's binding sites to modulate its function or outcompete native ligands.

The research team, including Mark Chance PhD, professor and vice dean for research at Case Western Reserve School of Medicine, identified for the first time regions where the receptor interacts with other molecules, including investigational drugs. The findings, published in *Nature Communications*, provide the first complete structural model for an important class of proteins that sit in the membranes of several types of normal and cancer cells, and are critical mediators of cell-cell communication.

Chance and the team, including investigators at Case Western Reserve University and the University of San Diego, used multiple biochemical and bioinformatics approaches, including novel mass spectrometry techniques, to produce models of "atypical chemokine receptor 3," or ACKR3, alone and in complex with a drug currently in phase 2 trials for treatment of glioblastoma tumors. The researchers also created models

of ACKR3 interacting with chemokines, small molecules naturally circulating in the body that control cell movement. The feat required mapping ACKR3 in multiple states, as it dramatically changes shape when bound by these molecular triggers of cell movement.

Said Chance, "ACKR3 is considered an important anti-cancer and immune system target for drug development. ACKR3 can signal cells to grow and move accelerating their cancer potential. By mapping the protein's interactions with known activators as well as drugs that can manipulate function, we can understand its mechanism of action including where the drugs bind and what changes occur in ACKR3 as a result of these interactions."

Chance and his research team used over 100 molecular probes to cover all the static and dynamic regions of ACKR3. The probes helped the team visualize ACKR3 in the laboratory and piece together its structure. "Drug binding results in a conformational change in ACKR3 similar to those of other proteins in its class," said Chance. "We were surprised that the mechanism is so consistent across many types of receptors."

The state-of-the-art techniques used by the team are helping to map other types of cancer-related cell proteins to guide drug development. Information from the study may also allow refinement of compounds currently under development to treat a multitude of cancers.

More information: Martin Gustavsson et al, Structural basis of ligand interaction with atypical chemokine receptor 3, *Nature Communications* (2017). DOI: 10.1038/ncomms14135

Provided by Case Western Reserve University