New method to tinker cell surface proteins can help design new drugs

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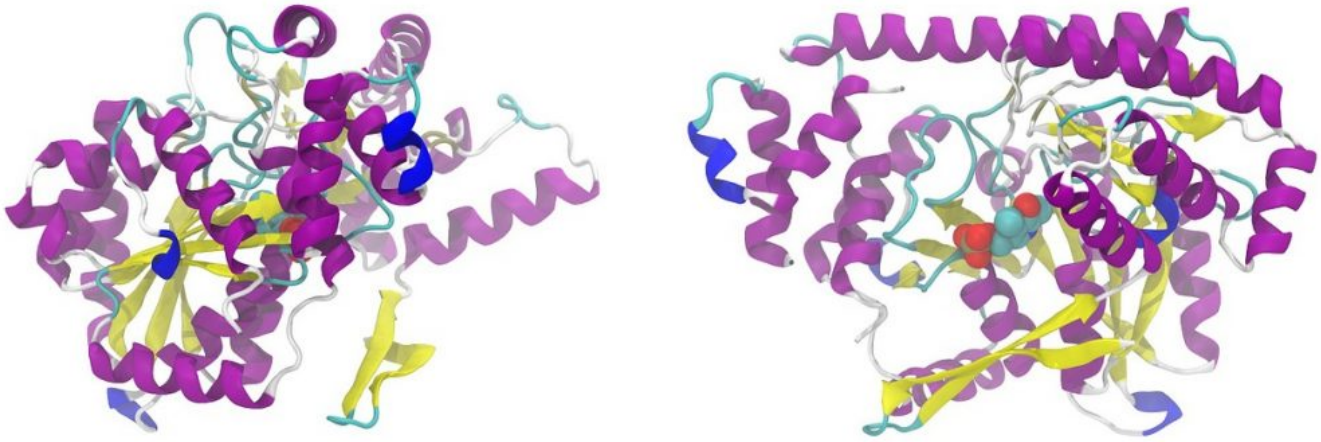

By Ratneshwar Thakur

New Delhi: A group of Indian scientists has found a new way to modulate specific cellular functions by tinkering with proteins that play a role in cells' response to external chemicals like drugs.

The new finding, described in a paper published this week in journal *Nature Nanotechnology*, makes it convenient for researchers to study the workings of a large family of sensor proteins called G-protein-coupled receptors (GPCRs) and to develop potential synthetic antibody-based drugs.

Research teams led by Dr Arun K. Shukla at IIT Kanpur have engineered synthetic antibody fragments that target beta-arrestin (a class of proteins inside the cell). GPCRs are mobile proteins that sit in the cell membranes and support cells to respond to chemical signals from body parts or external world. GPCRs are the most sought-after drug targets in modern medical research. Drug companies are investing heavily to identify new drug molecule that can target key GPCRs involved in several pathophysiological conditions. Beta-arrestin regulates actions of GPCRs by attenuating its signaling.

"There are more than 800 GPCRs and only limited beta-arrestin which controls its functioning, therefore, targeting beta-arrestin will enable us with a greater handle over the desired signaling across all GPCR types. So, we developed synthetic Fabs (fragment antigen-binding) that targets beta -arrestin and have potential to modulate their functioning," explained Dr Shukla.

According to the study, small molecule-based drugs, which either bind to stimulate or inhibit

GPCR, remains a traditional way of tweaking the GPCRs. Dr Shukla says that beta-arrestin functions are usually studied by either knocking the gene out or turning their expression down by silencing of protein coding genes). But synthetic Fab molecules can specifically target a particular part of the protein and selectively offset its function without interfering with its any other function, attributed to its other domains. “Our finding is the first demonstration of targeting a specific function of beta-arrestins without altering its other functions,” said Eshan Ghosh, first author of this paper.

Dr Shukla and members of the research team.

This study was an ambitious project to design a generic tool to study GPCRs. “Initially, in vitro studies, we found very encouraging results but the real deal was to replicate the study in cellular systems, where we can really see the molecule in action by monitoring its cellular readouts,” said Dr Shukla. Interestingly, during microscopic experiments, Dr Shukla’s team members could observe that this fab in form of an intrabody (an antibody that works within the cell) was clearly blocking the endocytosis (pulling in of a GPCR from the surface to inside of a living cell).

“Synthetic intrabody we have identified has the potential to treat many diseases implicating GPCRs if its delivery vehicle is well devised,” said Mithu Baidya, one of the authors of this study.

“Our approach has the potential to take antibody-based drug discovery to the next level, where we can dissect to compartmentalize the functioning of a protein and thereby modulate it. This study will flag off a new direction for future drug discovery,” said the study leader.

Research team included Eshan Ghosh, Ashish Srivastava, Mithu Baidya, Punita Kumari, Hemlata Dwivedi, Kumari Nidhi, Ravi Ranjan and Arun K. Shukla (Indian Institute of Technology, Kanpur), Shalini Dogra Prem N. Yadav (CSIR-Central Drug Research Institute,

Lucknow), Akiko Koide, Shohei Koide (Laura and Isaac Perlmutter Cancer Center, USA), Sachdev S. Sidhu (University of Toronto, Canada).

(Indian Science Wire)