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New insights into predicting the efficacy of active ingredients in drug development

Drugs consist of molecules developed in the drug laboratory that bind to their target, usually a protein, and thus exert their effect. The actual duration of binding of a drug molecule to its target protein varies depending on the drug. The lifetime of the drug-target complex can play a critical role in the efficacy of a drug, as a long residence time at the target can be crucial for the drug's action in some cases.

Therefore, understanding the underlying causes enables better drug development. In the new study published in the renowned scientific journal Nature Communications, researchers from the University of Eastern Finland and the University of Tübingen have identified the key factors responsible for a long or short residence time at the target site in so-called kinase inhibitors.

Kinases are enzymes that are involved in the transmission of certain signals either on or in cells. For example, they play a role in cell division by passing on "growth signals". Kinase inhibitors are inhibitors that stop these growth signals from the enzymes. Many of these inhibitors are already approved for clinical use, most of them in the treatment of cancer. "Originally, we wanted to know what causes two similar kinase inhibitors to stay on target differently," says lead researcher and first author Dr. Tatu Pantsar of the University of Eastern Finland.

"Identifying which molecules are suitable at an early stage of drug development is a crucial factor, as drug development is extremely time-consuming and costly," says Prof. Dr. Stefan Laufer, Head of Pharmaceutical and Medicinal Chemistry at the Institute of Pharmacy at the University of Tübingen. Prof. Laufer's group has its own academic center for drug discovery and development, the "Tübingen Center for Academic Drug Discovery & Development" (TüCAD2), of which Prof. Laufer is co-founder and spokesman. Prof. Laufer's research group has already designed, synthesized and enzymatically/biologically characterized numerous small molecule kinase inhibitors, which made the current research possible. Inhibitors from previous projects have also found their way to first application in humans.

"In the study, we focused on two small molecule kinase inhibitors that are identical in their inhibitory potency on the isolated enzyme assay, but differ in their residence time on the target enzyme, i.e., how long a single small molecule kinase inhibitor is bound to the target protein. We also found that the inhibitor with a longer residence time was more effective when tested in cells," explains Dr. Pantsar.

In the study, the researchers examined and compared the small-molecule kinase inhibitors together with their target protein using computer simulations performed on Finnish supercomputers. The protein behaved differently depending on the bound inhibitor. "The simulations suggest that when a small molecule inhibitor binds to the protein, the protein is more dynamic when the inhibitor is bound to it with a short residence time. This basically means that the protein moves more when it binds the short-dwell inhibitor and less when it binds the long-dwell inhibitor," Dr. Pantsar explained.

Water molecules have a major influence on the drug's residence time at the target site. "These tiny but abundant water molecules surrounding the protein seem to be crucial. A major component of the inhibitor's binding relies on the displacement of water molecules.

In the simulations, the long residence time inhibitor was less exposed to the water molecules, and the energy required for the water molecules to reoccupy the binding site of the long residence time inhibitor was much higher. This leads to a higher energetic barrier for the separation of the inhibitor from its target and thus to a longer residence time of the drug-target complex. The observations on the behavior of the target protein and the role of water molecules were also confirmed with a structurally diverse small molecule kinase inhibitor with extremely short residence time. Such calculations (MD simulations) were performed for the first time for this type of inhibitor together with water molecules.

The findings may be useful in the early stages of drug development. "Now that we better understand the reasons for drug residence time at the atomic level, we can design more effective molecules that can be used in drug development when long residence time is desired. Of course, it is important to remember that residence time at the target is only one aspect of the very complex and difficult process of drug development, in which a multitude of factors must be taken into account," Dr.

Pantsar concluded.

At the University of Eastern Finland, the research was conducted at the Faculty of Pharmacy and within the DrugTech Research Community. The research was made possible by computing resources provided by CSC - IT Center for Science Finland. The project was an integral part of "TüCAD2", a format of the Tübingen Excellence Strategy, led by Prof. Laufer. It impressively demonstrates the networking of deep basic research with application and direct transfer to drug research.

Publication:

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