LRP-LIGAND INTERACTIONS: KINETICS AND STRUCTURAL REQUIREMENTS

High tech applied to better understand clinical treatment of myocardial infarction

Patients struck by myocardial infarction can be treated with tissue-type plasminogen activator (t-PA, a protein). T-PA is an activator of a normally inactive blood protein, which, when activated, can rapidly dissolve blood clots. Immediate administration of t-PA to patients increases the chances of survival enormously. Unfortunately, t-PA is quickly removed from the blood by uptake in the liver. This requires high doses and it leads to bleedings, amongst others in the brain.

An important liver protein (LRP), removes proteins involved in dissolving blood clots. T-PA is one of them and investigating how this molecules binds to LRP was central to the study. Two elegant new technologies were used: *phage display* and *surface plasmon resonance*. These technologies allow researchers to (1) select proteins that are interesting to them and (2) accurately measure how strong these proteins bind to each other. Phage display was recognized as a crucial technology in bioscience and for this reason the dvelopers were awarded the Nobel Prize in chemistry in 2018.

The experiments revealed that a complex of t-PA with a specific inhibitor binds better to LRP than t-PA alone. In addition, the sites where clinically interesting proteins bind to LRP were found as well. The findings support a molecular model how inhibition of binding to LRP can be achieved.

The results of these studies have been described in the thesis and have been published in biochemistry journals.

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