Universität Basel

Research Project

Functional dry cavities in proteins

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The interior of experimentally determined protein structures often contains cavities, which are not filled by protein atoms. Such cavities are generally thought to be filled by water. However, in few proteins completely empty voids, devoid of any water molecules have been detected by X-ray crystallography or NMR spectroscopy. The most recent example is a 141 Å3-sized, dry pocket in thermolysin, which was unambiguously detected by high-resolution X-ray crystallography using an absolute-scale electron density map (Krimmer et al. JACS 2017, 139, 30, 10419-10431). This hydrophobic cavity could then be filled by noble gases as also detected by X-ray crystallography. These observations are limited to a few model systems, and it is unclear how abundant dry voids are in proteins, and whether such voids are connected to protein function and structural stability.Such a functional role may exist in the medically highly relevant G protein-coupled receptors (GPCRs), which constitute the most abundant class of membrane proteins in the human genome. Indeed, a recent study on the ß 1-adrenergic receptor (ß 1AR, Warne et al. Science 2019, 364, 775-778) showed that its extracellular ligand binding pocket shrinks by 20-40% upon activation by an intracellular G protein mimic. This compression of the ligand pocket explains the affinity increase of G protein-coupled receptors (GPCRs) for agonist ligands in their G protein-bound state. From the 2.8 Å-resolution crystal structure, it remained unclear to what extent the extracellular ligand binding cavity is filled by water. However, a recent pressure NMR study (Abiko et al. JACS 2019, 141, 42, 16663-16670) showed quantitatively that the same receptor experiences a volume reduction of 100 Å3 upon transition to the active state. This shrinking can only be explained by the collapse of empty, non-hydrated cavities, but the location of these empty cavities remained unknown from the NMR study.We hypothesize that the external ligand pocket of ß 1AR is at least partially empty and that this void plays a crucial role in GPCR activation. We propose to determine the location of these empty cavities by X-ray crystallography. In contrast to previous studies, we will incubate the crystals of ß 1AR in different functional states at mild pressures with xenon. If empty hydrophobic cavities are present, they should incorporate xenon, which is then easily located in the electron density by its high scattering power.These experiments may reveal the first dry pocket in a membrane protein and connect its existence to a crucial function in GPCRs. More generally, such a proof of existence may establish dry voids as a new interaction principle in proteins. Thus, dry pockets may serve as structural motifs that confine protein movements during folding and function or which specifically recognize distinct hydrophobic moieties of a ligand. This may have major implications on protein folding research, the structure-based explanation of protein function, and the development of new drugs.

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Published results

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