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ASLW and RSVM at positions 1-4 functioned as allosteric agonists for CXCR4, where RSVM and ASLW acted as partial and super agonists, respectively. In this study, using the recently published computational model of the CXCR4 in complex with its endogenous ligand CXCL12, we investigate the mechanism of the super and partial peptide agonists binding to the CXCR4 through novel Peptide Gaussian accelerated molecular dynamics (PepGaMD) simulations. We explore representative conformations of the structural clusters for each system and analyze the peptide-receptor conformations to define the mechanisms of activation of the super agonist versus the partial agonist. The obtained mechanistic insights provide a significant framework for design and development of new peptide allosteric modulators targeting the CXCR4 receptor.

1631-Pos

Affecting antibody-antigen binding affinity through dynamic allosteric mutations

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The usual goal of antibody engineering is to affect the binding affinity of antibodies with their antigens or other ligands through directed mutation. Experiments in engineered ScFv antibody fragments have shown that mutations entirely distant from the active site can have very significant affects on binding affinity[1]. A method based on molecular dynamics simulations and normal mode analysis is used to predict and test allosteric mutations in engineered antibodies and antibody fragments. A course grained carbon-alpha covariance matrix is extracted from an all atom MD simulation. Under a quasi-harmonic approximation, this covariance matrix is inverted to form a Hessian matrix which defines an effective elastic network model. Localized perturbations to the ENM are used to simulate the dynamic effects of mutations and antigen binding which are usually small localized reductions in residue mobility. Changes in normal mode frequencies which occur due to these perturbations are used to compute estimates of dynamic allosteric effects between each residue and the antigen binding site[2]. Residue locations which show a strong allosteric effect when perturbed are potential mutation targets or dynamic allosteric binding sites. These targets are mutated in simulation and the antigen binding affinities of the mutated antibodies are computed using umbrella sampling simulations.

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1632-Pos

Examining the donor effect on FRET efficiency in macromolecular crowding sensors

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Macromolecular crowding influences many biological processes in living cells such as protein folding, protein-protein interactions, translational diffusion, and biochemical reaction kinetics. In order to investigate the correlation between the heterogenous, dynamic macromolecular crowding and cell physiology, site-specific biosensors and noninvasive, quantitative methodology are critically needed. Here, we investigate the effects of donor identity (mCerulean3, mTurqoise2.1, and mTurqoise2.0) on the environmental sensitivity of genetically encoded sensors (donor-linker-mCitrine) using time-resolved two-photon fluorescence measurements. The linker region in these constructs consists of flexible, neutral amino acid sequences. These measurements were carried out in controlled environment as a function of Ficoll-70 concentration in a buffer. Our working hypothesis is that the sensor with mTurquoise2.0 as a donor will exhibit a higher energy transfer efficiency (i.e., higher environmental sensitivity) as compared to mCerulean3 constructs due to their enhanced spectral overlap, excitation cross-section, and fluorescence quantum yield. Control experiments will be carried on enzymatically-cleaved sensor (i.e., donor alone) under the same experimental conditions. The measured fluorescence decays of cleaved and intact sensors, detected at magic-angle polarization, will be deconvoluted using the measured system response function under the same experimental conditions. These results will allow for the development of a rational strategy for designing more effective environmental biosensors for *in vivo* studies on.

1633-Pos

Structure and dynamics of the acyl carrier protein linker in the fungal fatty acid synthase

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Fatty acid synthesis is a central pillar of metabolism, providing essential molecules for energy storage, cell wall integrity and signal transduction. Fatty acids are synthesized in an iterative cycle of reactions, carried out by multiple enzymes. In fungi, the capabilities of these enzymes are combined in a single heterododecameric complex. The fungal fatty acid synthase (FAS) provides six catalytic units in two semispherical reaction chambers. Nascent fatty acids are covalently linked to an integral acyl carrier protein (ACP), confined in the reaction chambers. ACP is necessary for the efficient transfer of reaction intermediates between consecutive catalytic domain. However, the dynamics of ACP are poorly understood, mainly due to the lack structural information about the two intrinsically disordered linker regions, tethering ACP to the FAS scaffold. Here we combine recent CryoEM results and exhaustive molecular dynamics, to provide the first complete structural model of the fungal FAS. To this aim, we performed a comprehensive sampling and evaluation of linker dynamics with several commonly used force fields. Structures of FAS in different stages of the reaction cycle indicate, that the linkers need to sample a broad range of both extended and collapsed configurations to not impede on ACP motility. We found, that the Charmm36m and amber99sb-disp forcefield performed best, allowing the linkers to sample a significantly broader range of configurations than other tested forcefields. Based on our initial results, we generated models of the fungal FAS, with the linker regions connecting the ACP to the core of the enzyme. Our model demonstrates the volume exclusion effect hypothesized to play a significant regulatory role in ACP dynamics. Ultimately this work lays the groundwork for future studies of FAS dynamics and function.

1634-Pos

Comprehensive virtual screening of 4.8k flavonoids reveals novel insights into the allosteric inhibition of SARS-CoV-2 M^{PRO}

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As of September 2021, there have been over 4.5 million deaths reported globally due to the COVID-19 pandemic. Developing effective treatments against the virus is a priority among the scientific community. This objective requires systematic narrowing of drug candidates, usually by virtual screening methods. SARS-CoV-2 main protease (M^{PRO}) is a common target for inhibition assays due to its high conservation among coronaviruses. M^{PRO} is an essential enzyme responsible for the catalytic cleavage of peptides necessary for viral replication and transcription. Since flavonoids show antiviral activity *in vitro*, several computational works have proposed them as potential M^{PRO} inhibitors. Nonetheless, there is reason to doubt certain results given the lack of consideration for flavonoid promiscuity or M^{PRO} plasticity, usage of short library sizes, absence of control molecules and/or limiting the methodology to only one target site.Here, we report a virtual screening and molecular dynamics study where dorsilurin E, euchrenone a11, sanggenol O and CHEMBL2171598 are proposed to inhibit M^{PRO} through different pathways. Remarkably, novel structural mechanisms were observed after sanggenol O and CHEMBL2171598 bound to experimentally proven allosteric sites. The former drastically affected the active site, while the latter triggered a hinge movement which has been previously reported for an inactive SARS-CoV M^{PRO} mutant. We propose a mechanism for the hinge movement, as it may be exploited in future works that try to trigger it with ligands. The use of a curated database of 4.8k flavonoids, combining two well-known docking software (AutoDock Vina and AutoDock4.2), 600ns molecular dynamics and MMPBSA methods, guaranteed an adequate analysis and robust interpretation. Flavonoids reported by the present article and the structural mechanisms related to them could be a starting point for designing new molecules to combat SARS-CoV-2.

1635-Pos

Hydrogen-deuterium exchange of plasma-derived von Willebrand factor reveals similar dynamics to isolated A1 domain and autoinhibitory module

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Von Willebrand factor (VWF) is a large multimeric, multidomain glycoprotein that circulates in the bloodstream and is essential for mediating platelet