Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

behavior where the TCRαβ-pMHC bond lifetime increases under piconewton level force. We have recently found that load suppresses relative motion between Vα and Vβ variable domains that contain pMHC-binding complementarity determining region (CDR) loops. Suppression of Vα-Vβ motion thereby stabilizes the contacts between CDR loops and pMHC. The constant domains of TCRαβ allosterically control the interaction between the variable domains and pMHC via inter-domain contacts that promote mismatches unless stabilized by load. This mechanism was found using molecular dynamics (MD) simulation of the JM22 TCR complex with the HLA-A2 MHC molecule with a peptide from an influenza matrix protein. Here we test the mechanism for the case of A6 TCRαβ bound to HLA-A2 with a Tax peptide and its mutants that vary widely in equilibrium binding affinities. By performing all-atom MD simulations under piconewton-level forces of physiological magnitude, we analyze dynamics of interfacial contacts together with changes in the domain motion. The comparative analysis further elucidates the role of mechanical force for discriminating antigenic peptides by αβTCR.

1434-Pos

Unravelling Allosteric Cross-Talk between Co-Activator Peptide and Ligand Binding Site in Glucocorticoid Receptor

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Glucocorticoid receptor (GR) is a nuclear receptor that controls critical biological processes by regulating the transcription of specific genes. There is a known interconnection between the ligand and co-regulator binding sites of the GR ligand binding domain that is crucial for the functional differentiation of the downstream gene transcription. However, the molecular mechanisms underlying such an allosteric control remain elusive. The integration of molecular dynamics simulations, bioinformatic analysis and biophysical measurements led us to detect a network of dynamically interconnected evolutionary conserved residues that mediates the allosteric signal propagation between the co-regulator docking site and the ligand binding pocket. Co-regulator peptides alter the functionality of this network, explaining why the allosteric response depends on the peptide sequence. These findings provide useful insights for the comprehension of GR allosteric regulation that should help the design of novel drugs.

1435-Pos

The SARS-CoV-2 Spike Variant D614G Favors an Open Conformational State

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The COVID-19 global pandemic is an international health emergency. It is caused by the SARS-CoV-2 virus, which binds with its trimeric Spike protein to the ACE2 receptor in the human lung. Early in 2020, researchers observed the emergence of a single amino acid variant at residue 614 of the Spike trimer, in which the aspartic acid of the original ''D-form'' was replaced by a glycine in the emergent ''G-form.'' The G-form rapidly became the most dominant form, displaying heightened infectivity and transmissibility. To gain understanding of the molecular mechanisms underlying how a single amino acid shift could cause such a drastic change, we performed the first extensive all-atom simulations of the Spike trimer in explicit solvent in both the D-form and the G-form. For each form, we simulated the ''all down'' conformational state, which is not infection-capable, and the ''one up'' state, which is infection capable due to the ''blossoming'' outward of one of the three trimers. We show that a shift in the inter-protomer contacts likely leads to a shift in energetics that causes the G-form to have a heightened population of Spikes in the one up state. While there is no significant difference between the exposure of the ACE2 binding site when comparing the D- and G-forms, there is a difference when comparing the all down and one up states, so a heightened population in the one up state corresponds to higher infectivity. Overall, this work presents molecular-level understanding of the differences between the D- and G-forms that is of crucial importance for vaccine design and thus combating the COVID-19 pandemic.

1436-Pos

Molecular Dynamics Simulations Unravel the Mysteries of Hemoglobin Diseases

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Hemoglobin is the oxygen transport protein of our cardiovascular system. The tetrameric interfaces in hemoglobin regulate cooperative binding of oxygen to heme iron present in each hemoglobin subunit. Genetic mutations can cause hemoglobin misassembly or impaired hemoglobin stability diseases by altering inter-subunit interfaces or by disrupting heme binding in the subunits. We have performed atomic level molecular dynamics (MD) simulations (Samuel, P.P. and Case, D.A., 2020, *Biochemistry*) to examine heme disassociation pathways in both human adult and fetal hemoglobins. We have already determined experimentally (Samuel, P.P. et al, 2020, *Biophysical Journal*), using spectroscopy and small angle X-ray scattering methods, that heme disassociation causes the tetrameric hemoglobin to completely disassemble and unfold. Our MD simulations now reveal that hemichromes, which have been observed to accumulate in certain hemoglobin misassembly diseases, are on-pathway intermediates in folded hemoglobins before heme starts to disassociate. Hemichromes occur when both axial sites of ferric heme iron coordinate with amino acids. During the simulations, we also observed heme disassociation to be promoted by clinically relevant mutations that either introduce heme cavity packing deficiencies or disrupt hemichrome formation. Through our simulations, we further were able to determine that the initial stages of hemoglobin disassembly are prefaced by both α-helical structure loss surrounding the heme cavity and disruption of specific tetramer interface interactions. We are also currently implementing MD simulations in order to evaluate changes associated with cooperativity at the inter-subunit interactions level across the hemoglobin tetramer interfaces. Overall, using MD simulations, we have structurally characterized and evaluated critical atomic interactions and disassembly intermediates that are difficult to isolate and identify by conventional spectroscopy and X-ray crystallography methods. Eventually, this research will guide targeted therapy design for unstable hemoglobin genotypes.

1437-Pos

Dynamical Basis of Allosteric Activation for the *Plasmodium falciparum* Protein Kinase G

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The *Plasmodium falciparum* cGMP-dependent protein kinase (*Pf*PKG) is required for the progression of the *Plasmodiu*m's life cycle and is therefore a promising malaria drug target. *Pf*PKG includes four cGMP-binding domains (CBD-A to CBD-D). CBD-D plays the most crucial role in *Pf*PKG regulation. Hence, it is critical to understand how CBD-D is allosterically regulated by cGMP. Although the apo *versus* holo conformational changes of CBD-D have been reported, information on the intermediates of the activation pathway is currently lacking. Here, we employed molecular dynamics simulations to model four key states along the thermodynamic cycle for the cGMP-dependent activation of the *Pf*PKG CBD-D domain. The simulations were validated by NMR data and they revealed that the *Pf*PKG CBD-D activation pathway samples a compact intermediate in which the N- and C-terminal helices approach the central β-barrel. In addition, by comparing the cGMP-bound active and inactive states, the essential binding interactions that differentiate these states were identified. The identification of structural and dynamical features unique to the cGMP-bound inactive state provides a promising basis to design *Pf*PKG-selective allosteric inhibitors as a viable treatment for malaria.

1438-Pos

Multi-Scale Simulations and Neutron Scattering Experiments Reveal Dynamical Properties of the Bacterial Cytoplasm Near Cell-Death Temperature

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Life on Earth exhibits an amazing adaptive capacity to a vast range of temperatures. While the molecular mechanisms underlying such adaptability are not yet fully understood, it has been proposed that the cell-death temperature