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identify changes in interfaces associated with linker substitutions and surface mutations while single-molecule FRET probes the exchange rates between conformational states. The effects linker mutations within the PDZ12 tandem provide insights into linkers' energetics and functional implications in modulating supertertiary structure and potential regulatory functions in complex intermolecular interactions.

196-Pos
A structure-function approach to elucidate the molecular mechanism of the telomere C-strand fill-in process
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Telomeres are repetitive DNA sequences decorated with telomere-specific proteins at the ends of linear chromosomes in eukaryotic cells. The regulation of human telomere length is essential for maintaining genome stability and cellular lifespan, and its dysregulation causes premature aging and cancer. The heterotrimeric CTC1-STN1-TEN1 (CST) protein complex is vital for the timely termination of telomere elongation by telomerase. CST is also required to recruit DNA polymerase ζ-prime (pol ζ-prime) to the newly synthesized telomeric G-overhang ssDNA to convert the telomeric ssDNA to dsDNA (known as C-strand fill-in). Due to the lack of biochemical and structural knowledge on CST-pol ζ-prime, it is unknown how the complementary C-strand at telomeric G-overhang is synthesized by CST-pol ζ-prime machine. To answer this question, we combine biochemical and cryo-electron microscopy (cryo-EM) methods to investigate the molecular mechanisms of human Pol ζ-prime recruitment to telomeres and its activity stimulation by CST. We show recombinant CST directly interacts with Pol ζ-prime, and a single-stranded telomeric DNA is not needed to form the co-complex. We also used cryo-EM single-particle analysis to solve a catalytic state of Pol ζ-prime engaged to a DNA/RNA molecule.

197-Pos
Differential interactions between human ACE2 and spike RBD of SARS-CoV-2 variants of concern
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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the current coronavirus disease 2019 (COVID-19) pandemic. It is known that the receptor-binding domain (RBD) of the spike protein of SARS-CoV-2 interacts with the human angiotensin-converting enzyme 2 (ACE2) receptor, initiating the entry of SARS-CoV-2. Since its emergence, a variety of SARS-CoV-2 variants have been identified, and the variants showing high infectivity and possessing potential diagnostic impact are classified as the variants of concern (VOC) and the variants of interest (VOI) by the US CDC. This work characterizes distinctive binding interactions between ACE2 and RBD of all current VOC (Alpha, Beta, Gamma, and Delta) and two VOI (Epsilon and Kappa) employing both all-atom steered molecular dynamics (SMD) simulations and microscale thermophoresis (MST) experiments. We report that the RBD of the Alpha (N501Y) variant requires the highest amount of forces to be detached from ACE2 due to the N501Y mutation in addition to the role of N900-glycan, followed by Beta/Gamma (K417N/T, E484K, and N501Y) or Delta (L452R and T478K) variant. The RBD of the Epsilon (L452R) variant is relatively easily detached from ACE2 compared to other variants. Our SMD simulations and MST experiments reveal what makes each variant more contagious in terms of RBD and ACE2 interactions. This study provides valuable information that distinguishes important features of all variants in terms of RBD-ACE2 interactions and sheds a light on developing new drugs to inhibit SARS-CoV-2 entry effectively.

198-Pos
Higher-order structure analysis of high concentration monoclonal antibody by circular dichroism (CD) and infrared (IR) spectroscopy
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Antibody therapeutics have been dramatically expanding their market over the past decade and become one of the major biotherapeutics proteins. Circular dichroism (CD) spectroscopy is an easy and robust method to analyze the higher-order structure (HOS) of antibodies. It is used to check the HOS comparability/homogeneity before and after a change in the manufacturing process as specified in ICH-Q7E, and to compare the HOS between innovators and biosimilars as described in FDA, EMA and other guidelines. In addition, CD spectroscopy is a well-known technique to estimate the protein secondary structure. While CD measurement of protein is often performed with relatively low concentration up to about 10 to 5 mg/mL, most of the antibody therapeutics are formulated and prescribed with concentrations of 10 mg/mL or higher. In the case of pre-filled syringe-type dosage form, which has become increasingly popular in recent years, the concentration can be above 100 mg/mL. It is known that proteins behave differently at high concentrations in comparison to dilute conditions, and there is a need to evaluate the HOS of antibody therapeutics at their prescribed concentration. In this study, we developed a method to study IgG with high concentration using far-UV and near-UV CD spectroscopy. A combination of the latest CD spectrometer J-1500 and the BeStSel algorithm [Beta Structure Selection, provided by Department of Biochemistry, Institute of Biology, Eötvös Loránd University] enabled the analysis of the secondary structure of antibodies at concentrations of 10 mg/mL or higher with high accuracy. The results of the secondary structure analysis were consistent with the ones obtained by FT-IR. Furthermore, we surprisingly succeeded in measuring near-UV CD spectrum of above 100 mg/mL IgG to obtain the tertiary structure information.