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.

information (i.e. inhibitor-bound and substrate-bound structures) becomes available for PLpro, we now have insights into optimizing various inhibitors using structure-based drug design as well as starting to develop a broad-spectrum papain-like protease inhibitor.

930-Pos

Computational investigation of glycosaminoglycan cofactors in SARS-CoV-2 infection dynamics

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COVID-19, caused by the SARS-CoV-2 virus, continues to cause widespread disruption to all aspects of society. The SARS-CoV-2 virion is studded by trimeric spike proteins that play the predominant role in initiating viral invasion by binding to human angiotensin-converting enzyme 2 (hACE2). However, contact between SARS-CoV-2 and hACE2 is merely half of the invasion story, ignoring the complexity of other necessary infection cofactors on the mammalian cell surface. All cell surfaces are surrounded by a glycocalyx composed of various glycoconjugates, including glycoproteins, glycosphingolipids, and proteoglycans. Many pathogens exploit these glycoconjugates as attachment factors and receptors for infection, including influenza, herpes simplex, human immunodeficiency virus, and coronaviruses (SARS-CoV and MERS). Heparan sulfate is a long, negatively charged, linear polysaccharide and a component of particular interest in the glycocalyx. Esko and coworkers have shown that spike protein binds to cell surface HS and hACE2 in a cooperative manner, and furthermore that heparan sulfate is required for host-cell invasion by SARS-CoV-2. Using extensive ensemble-based docking simulations to incorporate protein and glycan motions, we elucidated important clues regarding how heparan sulfate and other glycocalyx components bind the spike glycoprotein during the SARS-CoV-2 host-cell invasion. We identified 7 novel heparan sulfate-spike binding sites and validated 7 literature-proposed binding sites. Through use of a ‘‘binding site importance score,’’ we posited which sites are most likely to be required for anchoring to cellular heparan sulfate for ultimate initiation of cell invasion. Because we incorporated both protein and glycan flexibility in our analysis, we were able to elucidate two key mechanistic hypotheses: (1) GAGs are likely to bind in multiple compensatory modes to accommodate changes in spike conformation, and (2) the spike’s glycans compete with GAGs for certain binding sites on the spike’s surface yet stabilize other GAG-spike interactions.

931-Pos

Dimethyl sulfoxide (DMSO) affects activity of SARS-CoV-2 main protease

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The SARS-CoV-2 main protease (re) is necessary for viral replication and is therefore the subject of intense inhibitor development efforts. We find that this enzyme is active at very high concentrations of dimethyl sulfoxide (DMSO), a common co-solvent for inhibitor candidates. The enzyme has enhanced activity with increasing DMSO, reaching a maximum at 33%. The impact of this additive has a profound effect on activity assays: in water/DMSO solutions, modest inhibitors appear to be inactive, while poor inhibitors appear to act as agonists. Molecular dynamics simulations suggest DMSO does not binding to a specific site, but rather changes the conformation of the enzyme, particularly near the active site and at the C-terminus. However, experiments indicate that it remains in the dimer form rather than dissociating even at concentrations where it is inactive.

932-Pos

Probing key interactions between SARS-CoV-2 spike and heparan sulfate

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The COVID-19 pandemic, caused by the SARS-CoV-2 virus, continues to cause widespread devastation to the global community. The SARS-CoV-2 virion is studded by ~30 trimeric spike proteins, which themselves play the predominant role in initiating viral invasion by binding to human angiotensin-converting enzyme 2 (hACE2). However, this simple model of spike and hACE2 binding is merely half of the story. All cell surfaces are surrounded by a dense sugary matrix, called the glycocalyx, which is composed of various types of glycoconjugates, including N-linked and O-linked glycoproteins, glycosphingolipids, and proteoglycans. Many pathogens exploit these glycoconjugates as attachment factors and receptors for infection, including, but not limited to, coronaviruses. Heparan sulfate (HS) – a long, negatively charged, linear polysaccharide – is a vital proteoglycan in glycocalyx that is known to play a co-factorial role for many viruses. In our current work, via extensive ensemble-based docking simulations to incorporate protein and glycan motions, we have elucidated important clues as to how heparan sulfate and other glycocalyx components bind the spike glycoprotein during the SARS-CoV-2 host-cell invasion. We identified 7 novel heparan sulfate-spike binding sites and validated 7 literature proposed binding sites. Additionally, through use of a ‘‘binding site importance score,’’ we have posited which sites are most likely to be required for anchoring to cellular heparan sulfate for ultimate initiation of cell invasion. Finally, since we incorporated both protein and glycan flexibility in our analysis, we were able to elucidate two key mechanistic hypotheses: (1) GAGs are likely to bind in multiple compensatory modes to accommodate changes in spike conformation, and (2) the spike’s glycans compete with GAGs for certain binding sites on the spike’s surface yet stabilize other GAG-spike interactions.

933-Pos

Developing inhibitors of the SARS-CoV-2 main protease

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SARS-CoV-2 is the causative virus of the global pandemic disease COVID-19, causing a significant public health burden. With the continued spread of SARS-CoV-2 comes an urgent need for drugs to treat those infected. The main protease (M^{pro}, also known as 3CL) of SARS-CoV-2 is a validated drug target. We created a pipeline to computationally screen molecules on a variety of M^{pro} pockets and pocket sizes, identified with enhanced sampling molecular dynamics simulations before carrying the putative hits forward to in vitro and in vivo assays for hit validation and optimization. This work advances drug discovery and provides leads for further drug optimization towards the SARS-CoV-2 M^{pro}.