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Blocking SARS-CoV-2 and host cell interactions using peptide-based drugs

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Before entering the cell through its spike (S) protein, the virus SARS-CoV-2 interacts with the human angiotensin-converting enzyme-2 (ACE-2) receptor which serves as an entry point for the virus. This receptor is found in the lungs, kidneys and gastrointestinal cells which are known to show tropism (the ability of a virus to infect different types of cells) for the virus. The S protein has protease cleavage sites and two subunits S1 and S2. The S1 site is responsible for binding to the ACE-2 receptor and the S2 site is responsible for carrying out the processes that enable the viral and host cell membranes to fuse. This viral-host cell interaction step is very important for viral infection.

Recent studies have shown that the receptors and receptor-binding domains (RBD) of the host cell and virus, respectively, are good targets for inhibition by engineered proteins, peptides or small molecules. Drug discovery and manufacturing could hence use this approach to stop the infection by the virus at the early stages. Additionally, coupling this strategy with other drugs and therapies that treat the symptoms of the disease could show good results. Further, the S protein of SARS-CoV-2 has its N-terminal on the surface outside the virus and its RBD is recognised by the polar residues on the ACE-2 receptor. The S1 subunit has amino acid residues that provide for receptor specificity and these residues have been sequenced. The S2 domain has fusion peptides, namely heptad (HRP) 1 and 2 domains, which come together during the interaction with the ACE-2 receptor. This interaction aids in the conformational change to expose a hydrophobic α-helix interface. The fusion peptide domain is also inserted into the host membrane to help in the fusion of the two membranes.

Quite evidently, the RBD recognition machinery and the membrane fusion process depend on peptide domains which can be mimicked by decoy-engineered peptides to stop recognition and fusion. Recent studies involving HRP-derived peptides as inhibitory proteins show the prevention of membrane fusion. Xia et al. studied derivatives of HRP-2 peptides and additionally showed their inhibitory capabilities. They also engineered HRP-1 and HRP-2 peptides, which they called 2019-nCoV-HR1P (aa924–965) and 2019-nCoV-HR2P (aa1168–1203), respectively. The study reported that HRP-2 peptide along with a known pan-CoV fusion inhibitor, EK1 peptide, showed inhibition activity against SARS-CoV-2 pseudovirus infection. Peptide-based drugs have a short half-life in vivo but it increases when conjugated with lipids. Xia et al. also addressed the modification of EK1 through its linkage to cholesterol. Therefore EK1C4 was developed and is now the leading preclinical therapeutic inhibitor against SARS-CoV-2. Peptide-based drugs target these highly conserved regions of the virus, thus lowering the chances of drug resistance development. Along with many other advantages, this strategy of using proteins or peptides to block viral infections aids in improving the field of drug development using peptide-based drugs.

Keywords: SARS-CoV-2, Drug design, Proteins, Peptides, Molecule inhibitors, Viral-host cell interactions

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