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Recombinant lectins as pioneering anti-viral agents against COVID-19

Abstract

The primary target for vaccine design and anti-viral therapeutics for the deadly severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) is the coronavirus surface spike (S) glycoprotein. Like other enveloped viruses, S glycoproteins are masked by a dense sugar "coat" of host-derived glycans that mediate immune evasion by molecular mimicry through shielding the immunogenic surface proteins from host immune responses. Paradoxically, this same protective glycan shield can make these sugar-coated viruses vulnerable to immune attack by soluble lectins of the innate immune system that are still able to recognise these glycans as pathogen-associated molecular patterns (PAMPs) leading to complement activation. In reality, recombinant lectins that target virus-associated glycans have the potential to be used as anti-viral agents; and therefore, binding of recombinant lectins to viruses could represent a paradigm shift for viral infection therapy. Likewise, SARS-CoV-2- associated glycans can offer novel targets for recombinant lectins as innovative anti-SARSCoV-2 agents. Unfortunately, pharmacological hurdles currently constrain the entry of recombinant lectins into clinical trials but more vigorous research into potentially useful modifications of these agents can truly develop a new landscape of anti-viral lectin-based therapeutics.

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The biochemical basis of anti-viral lectins

Lectins are sugar-binding immunoglobulin-like proteins occurring in all types of organisms including animals, plants, bacteria, fungi and even viruses. The sugar receptor molecules of lectins are called glycans which collectively constitute the glycome formed by the most dominant and complex post-translational modification of proteins via glycosylation.[1] The lectin-glycan interaction ignites the lectin complement pathway (LP) of the innate immune system culminating in the formation of the $C_{5b\text{-}9}$ membrane attack complex (MAC) that efficiently results in target cell lysis. Complement activations also generates opsonins and thus contribute to phagocytosis.[2]

Glycans on the viral envelope often have a crucial role in enabling an efficient transmission of the pathogen and/or entry into its susceptible target cells. Moreover, the presence of glycans on the envelope of viruses, such as HIV and human hepatitis C (HCV) masks important immunogenic epitopes of the viral envelope and often protects the virus against recognition and eradication by neutralizing antibodies of the immune system. The anti-viral activity of lectins has dual mode of action. Lectins compromise the efficient entry of the virus into its susceptible target cells by interacting with the viral-envelope glycans[3] and also cause deletion of several N-linked glycans that constitute the protective glycan shield that lead to selection of weak virus variants.[4]

Not surprisingly, many natural lectins identified in bacteria, plants and marine algae have been reported to have anti-viral activity by inhibiting viral replication through interacting with viral envelope glycoproteins. Lectins are generally classified based on the glycan recognition of their carbohydrate recognition domains (CRDs), such as specificity for particular sugars (i.e. mannose, glucose, N-acetyl galactosamine etc.). The anti-viral lectins interact predominantly with high-mannose type N-glycans added as post translational modifications to the envelope proteins of viruses.[5] Therefore, virus-associated glycans were seriously envisaged as a therapeutic target for development of novel anti-viral lectins.

Recombinant lectins as anti-viral agents

The LP is a vital first-line host defense against infection and includes mannan-binding lectin (MBL), an endogenous C-type lectin of hepatic origin that promotes killing of a wide variety of pathogens through initiating of the LP via the MBL– MBL-associated serine protease (MASP) complexes. MBL deficiency is among the most common primary immunodeficiencies and is associated with recurrent infections and symptoms of poor immune complex clearance. Plasma-derived MBL has been used in reconstitution therapy but concerns over viral contamination and production capacity led to the production of recombinant MBL (rMBL).[6] rMBL has therapeutic potential as anti-viral agent through LP activation, opsonophagocytosis and direct spatial blocking of virus-receptor interactions and entry. In fact, lectins synthesized by recombinant DNA technology present several advantages in terms of the production and purification processes.[7] Recombinant MBL (rMBL) produced from transfected human cell line has also shown the same biological activity as plasma-derived MBL.[8] As MBLs exhibit a significant activity against human viruses (such as HIV), some of these have been cloned and expressed in E. coli.While HIV-1 uses several mechanisms to evade adaptive immune responses (e.g., "glycan shielding"), MBL is able to bind and neutralize diverse strains of HIV-1.[9] rMBL has therapeutic potential against Ebola virus infection as well. Unfortunately, due to its complex quaternary structure, rMBL is complicated and expensive to produce.[10]

On the other hand, recombinant chimeric lectins (RCLs) consisting of MBL and L-ficolin exhibit superior protective potency and cost-effectiveness over rMBLs. The hemagglutinin (HA) of influenza A virus (IAV) plays a major role in influenza virus entry but bears high-mannose-type N-glycans that are susceptible to host lectins as well as to RCLs. RCLs demonstrated potent inhibition of IAV and have surpassed rMBL for several anti-viral activities, including inhibition of hemagglutination, viral aggregation, virus-mediated hemagglutination and neuraminidase activities.[11] As anti-IAV, RCLs have also showed significantly higher dose-dependent activation of the LP than that of rMBLs. All RCLs can activate the LP without MASP despite that RCLs are more efficient in associating with MASP-2 than rMBLs. Due to their preferential reduced association with MASP-1 (mediator of coagulation-like activity), the RCL-mediated coagulation-like enzyme activities are diminished compared with rMBL. This is a significant advantage for RCLs as therapeutic agents since infectious diseases can cause coagulation disorders.[12]

rMBLs and RCLs are not the only available anti-viral recombinant lectins. For example, the engineered Pseudomonas taiwanensis lectin (PTL) bind high-mannose glycans on the HA protein of the influenza virus, thereby inhibiting the entry of viral particles.[13] BanLec (an engineered plant lectin isolated from the fruit of bananas) is another recombinant lectin with anti-viral activity against HIV, HCV, and influenza virus, all of which have high-mannose-type N-glycans on their surfaces. Because BanLec exhibited a strong T-cell mitogenic response, a recombinant H84T mutant was generated to reduce mitogenicity while preserving the virucidal activity.[14] The H84T BanLec is highly efficacious against pandemic, epidemic, and avian influenza in vitro and against lethal influenza virus infection in vivo when administered intranasally, yet its safety and efficacy via other clinically important routes of administration remain to be determined.[15]

Recombinant lectins as anti-SARS-CoV-2 agents

The encouraging results of recombinant lectins as potent inhibitors of enveloped viruses should be replicated against the SARS-CoV-2, an enveloped single-stranded positive RNA virus. Like other coronaviruses, the SARS-CoV-2 genome encodes S glycoproteins, which play essential roles in virus attachment, fusion and entry into the host cell. On coronavirus envelope, S glycoproteins form trimers (the distinguishing big spikes) that are the main target of neutralizing antibodies upon infection.[16] Unfortunately, studies using recovered SARS and COVID-19 patients' sera show limited cross-neutralization, suggesting that recovery from one infection might not protect against the other.[17] Interestingly, the SARS-CoV-2 S proteins are heavily glycosylated by heterogeneous N-linked glycans projecting from the S trimer surface which play an important role in protein folding and host immune evasion (modulate accessibility to host proteases and neutralizing antibodies) as a glycan shield. The SARS-CoV-2 S sequence encodes up to 22 N-linked glycan sequons per protomer.[18] Among viral genotypes, glycosylation sites are found highly conserved.[19] 20 out of 22 SARS-CoV-2 S N-linked glycosylation sequons are conserved in SARS-CoV S.[20] In a similar way to IAV where specific N-linked glycans on HA have been shown to be essential for the elicitation of broadly neutralizing antibodies, it was found that a highly conserved epitope in the domain B of subunit S1 (S^B) that comprises the N343 glycan is immunogenic and mount potent neutralizing antibodies.[21,22] S^B is the receptor-binding domain (RBD) of the S glycoprotein that binds to the angiotensin converting enzyme 2 (ACE2) (the functional receptor for SARS-CoV-2) with high affinity, which possibly contributed to the current rapid transmission of SARS-CoV-2 in humans.[23] The envelope membrane M protein (a glycoprotein with 1 N-linked glycan at position 4) is the main structural component of the virion that mediates assembly and budding of viral particles and could be another target for recombinant lectins.[24] In conclusion, targeted recombinant lectins against SARS-CoV-2-associated glycans would conceivably be efficient anti- SARS-CoV-2 therapy that can be generated through the current state-of-the-art lectin engineering technologies.

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None.

Conflicts of interest

The authors declare no conflicts of interest.

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