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SARS-CoV-2 Spike Glycoprotein Binds Heparan Sulfate Chains and N-Glycans in Psoriatic Keratinocytes: A Hypothesis

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ABSTRACT

Psoriasis vulgaris, the most common form of psoriasis, is a chronic inflammatory skin disease that affects 2-3% of the worldwide population. It has been reported in patients with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) suggesting the percutaneous transmission of this infection which may cause the exacerbation of psoriasis. Interestingly, elevated expression of ACE2 receptor on differentiating keratinocytes and basal cell layer of the epidermis of patients with psoriasis and COVID-19 involving pro inflammatory cytokines such as IFN-γ and IL-17, has been reported; however little is known about the participation of other receptors expressed on the surface of psoriatic keratinocytes, in the SARS-CoV-2 infection. Here we hypothesize that, in the skin of patients with psoriasis who have been diagnosed with COVID-19, the interaction of the SARS-CoV-2 S glycoprotein with the HSPGs Synd-1 and CD44 through their HS side chains and N-linked glycan, and Gal-3 and Gal-8 through the N- glycans located on the ACE2, integrin-β_1, CD147, IFN-γR and IL-17A-R, would generate a Gal-glycan lattice at the surface of SARS-CoV-2 virus and psoriatic keratinocyte. Such Gal-glycan lattice in addition to influence keratinocyte proliferation and terminal differentiation, might induce conformational changes in the SARS-CoV-2 S glycoprotein facilitating the attachment and virus entry. We consider that future work will be required to understand the mechanisms regulating Gal-glycan lattice assembly during psoriatic keratinocyte and SARS-CoV-2 interaction as well as for the development of new inhibitors of virus attachment and internalization.

Keywords

ACE2, COVID-19, Galectin-glycan lattice, Psoriasis, Syndecan-1.

Abbreviations

ACE2: Angiotensin-converting enzyme 2; CHS: Chondroitin Sulfate; CRD: Carbohydrate-Recognition Domain; CTD: Carboxy Terminal Domain; Gal: Galectin; Gal-glycan: Galectin-glycan; GAGs: Glycosaminoglycans; HS: Heparan Sulfate; HSPG: Heparan Sulfate Proteoglycan; RBD: Receptor Binding Domain; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; Synd-1: Syndecan-1.

Introduction

Psoriasis vulgaris, the most common form of psoriasis, is a chronic inflammatory skin disease that affects 2-3% of the worldwide population and is associated with comorbidities such as hypertension, cardiovascular diseases, cancer, diabetes and obesity [1,2]. It is characterized by increased proliferation and altered terminal differentiation of keratinocytes as well as by pronounced infiltration of inflammatory cells, dilation and tortuosity of blood vessels [3]. Such disease has been reported in patients with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) suggesting the percutaneous transmission of this infection which may cause the exacerbation of psoriasis [4-7]. Several studies have proposed that the angiotensin-converting enzyme 2 (ACE2) is the principal receptor used by the SARS-CoV-2 virus for its entry into the host cell [8-11]. Interestingly, elevated expression of the ACE2 receptor in the keratinocytes' surface, especially in differentiating keratinocytes and basal cell layer of the epidermis, has indicated that the skin might be a potential target of SARS-CoV-2 infection [4,6,7]. Of note, increased levels of pro inflammatory cytokines such as gamma interferon (IFN-γ), interleukin-17A (IL-17A), IL-22, and tumor necrosis factor α (TNFα) in the skin of patients with psoriasis [2,4,7,12,13], have been shown to increase the ACE2 expression [4,7,14], enhancing the SARS-CoV-2 binding capacity and therefore increasing the risk of severe coronavirus disease 2019 (COVID-19) [4,7]. However, little is known about the binding of SARS-CoV-2 virus to the skin keratinocytes of patients with inflammatory skin diseases like psoriasis.

SARS-CoV-2 virus attachment and entrance

Recent studies have suggested that the SARS-CoV-2 virus enters into the host cell by clathrin-mediated endocytosis through the binding of its trimeric spike (S) glycoprotein to a cellular receptor which promotes virus attachment to the surface of host cells, membranes fusion and entry [8-11]. The ACE2, considered as the primary receptor for the SARS-CoV-2 entrance into the host cells, is a transmembrane glycoprotein that is widely expressed in various cell types, including skin keratinocytes [4,6,7,15]. Other receptors that are present in the host cell surface such as: the transmembrane protease serine-2 (TMPRS-2) that cleaves the S glycoprotein into two subunits (S1 and S2) [8,9], the glycoprotein integrin-β_1 [16-18], the transmembrane proteoglycans syndecan-1 (Synd-1) and CD44 [19-21], the transmembrane glycoprotein CD147 [22,23], the syalic acid residues located in the N-glycans [24,25], the IFN-γ receptor (IFN-γR), IL-17A receptor (IL-17AR), and TNF [4,7,26], could also interact with the SARS-CoV-2 S glycoprotein and mediate its entry. Nevertheless, the molecules implicated in the SARS-CoV-2 virus attachment and entrance into the host cells, particularly into the skin keratinocytes, still remains to be clarified.

SARS-CoV-2 S glycoprotein monomer structure

The SARS-CoV-2 S glycoprotein is a large class I viral fusion transmembrane protein that assembles into homotrimer on the virus surface and is synthetized as a single 1273 aminoacid polypeptide chain. Structural evidences have shown that each monomer of SARS-CoV-2 S glycoprotein is glycosylated with host-derived glycans at 24 N-linked glycosylation sites and at least three or four O-linked glycosylation sites [8-11,27-30]. Each monomer also comprises two functional subunits or domains, S1 and S2 subunits [8-11,27]. The S1 subunit enclose a receptor binding domain (RBD) which seems to be responsible for initial virus attachment to the host cell [8-11,27-30]. RBD has a conserved RGD (Arg-Gly-Asp) tripeptide motif close to the ACE2 binding site which mediates the virus attachment through of integrins [8,16,17] and furthermore, at least two O-glycosylation sites, exhibiting considerable levels of fucosylation and N-acetyl galactosylation (GalNAc) [28]. Interestingly, emerging data indicates that the S glycoprotein monomer contains glycosaminoglycans (GAGs)-binding motifs, suggesting that SARS-CoV-2 may enter by interaction of its S glycoprotein with the GAGs present in the host cell surface, particularly heparan sulfate (HS) and chondroitin sulfate (CHS) chains [19,31-35].

Nevertheless, whether certain GAGs and N-linked glycans might also be active players in COVID-19 progression, is a question that needs to be answered.

Glycans, glycosaminoglycans and galectins

Glycans are oligosaccharides chain complexes located on the cell surface, considered crucial in the cell-cell communication and cell-extracellular matrix (ECM) interaction [36,37]. Glycans appear organized as functional linear sulfated polysaccharides called GAGs and associated to glycoproteins as N-glycans and O-glycans residues [38,39].

GAGs are covalently linked to serine residues of a core protein as proteoglycans (PGs) through the GAG-protein linkage region tetrasaccharide (xylose, galactose, glucuronic acid, N-Acetyl-glucosamine), followed by repeating disaccharide units formed by alternating linked GlcA and GlcNAc [40,41], being the PGs most common the syndecan (Synd) family and CD44 [40,42]. In particular, Synd-1 ectodomain contains three extracellular sites for HS attachment and two for CHS [42,43]. In addition to HS and CHS, these HSPGs can contain N-and O-linked glycans. Importantly, studies have reported that several viruses utilize the HS chains of HSPGs that are expressed in the host cell surface, as binding receptors to promote its internalization [16,19,41].

As for N-linked glycans, they are composed of sialic acid, galactose, GlcNAc, and mannose (Man), while the O-linked glycans are composed of fucose, galactose, N-acetylgalactosamine, (GalNAc), and GlcNAc [37-39]. Interestingly, N-linked glycans can have an indirect effect on virus-host cell interaction with the participation of the galectins (Gals) [44-46]. Gals are a sub-family of lectins that are characterized by an affinity for glycans containing β-galactoside and that are defined by the presence of one or two carbohydrate recognition domains (CRDs) [44-46]. In general, Gals regulate several physiological and pathological processes, including viral infections, particularly Gal-3 and Gal-8 [47,48].

Gal-3 is the only chimera type Gal that has affinity by disaccharides containing β-galactose and GlcNAc present in N- and O-linked glycans. This protein consists of a CRD that binds to specific N- and O-glycan ligands and an N-terminal domain which facilitates its pentamerization and generation of Gal-glycan lattices on the cell surface and into the extracellular milieu regulating several cellular processes [45,46,49]. Gal-8 is a tandem-repeat type Gal that possesses two CRDs, connected by a linker peptide. This Gal has a particular affinity by certain O-sulfated and sialylated glycans attributed to its N-terminal domain [50,51]. Like Gal-3, Gal-8 binds the N- and/or O-linked glycans residues of integrin-β_1 and CD44, which are also recognized as binding partners of both Gals that regulate cell adhesion, spreading, migration, differentiation, and apoptosis [52,53].

Hypothesis

We hypothesize that, in the skin of patients with psoriasis who have been diagnosed with COVID-19, the interaction of the SARS-CoV-2 S glycoprotein with the HSPGs Synd-1 and CD44 through their HS side chains and N-linked glycan, and Gal-3 and Gal-8 through the N-glycans located on the ACE2, integrin-β_1, CD147, IFN-γR and IL-17A-R, in the presence of certain pro inflammatory cytokines, would generate a Gal-glycan lattice at the surface of SARS-CoV-2 virus and psoriatic keratinocyte. This supramolecular structure in addition to influence the psoriatic keratinocyte proliferation and terminal differentiation, might also induce conformational changes in the SARS-CoV-2 S glycoprotein facilitating the attachment and entry of the virus.

The SARS-CoV-2 S glycoprotein and Synd-1, CD44, CD147, integrin-β_1, IFN-γR, IL-17A-R, Gal-3 and Gal-8 in psoriatic keratinocytes

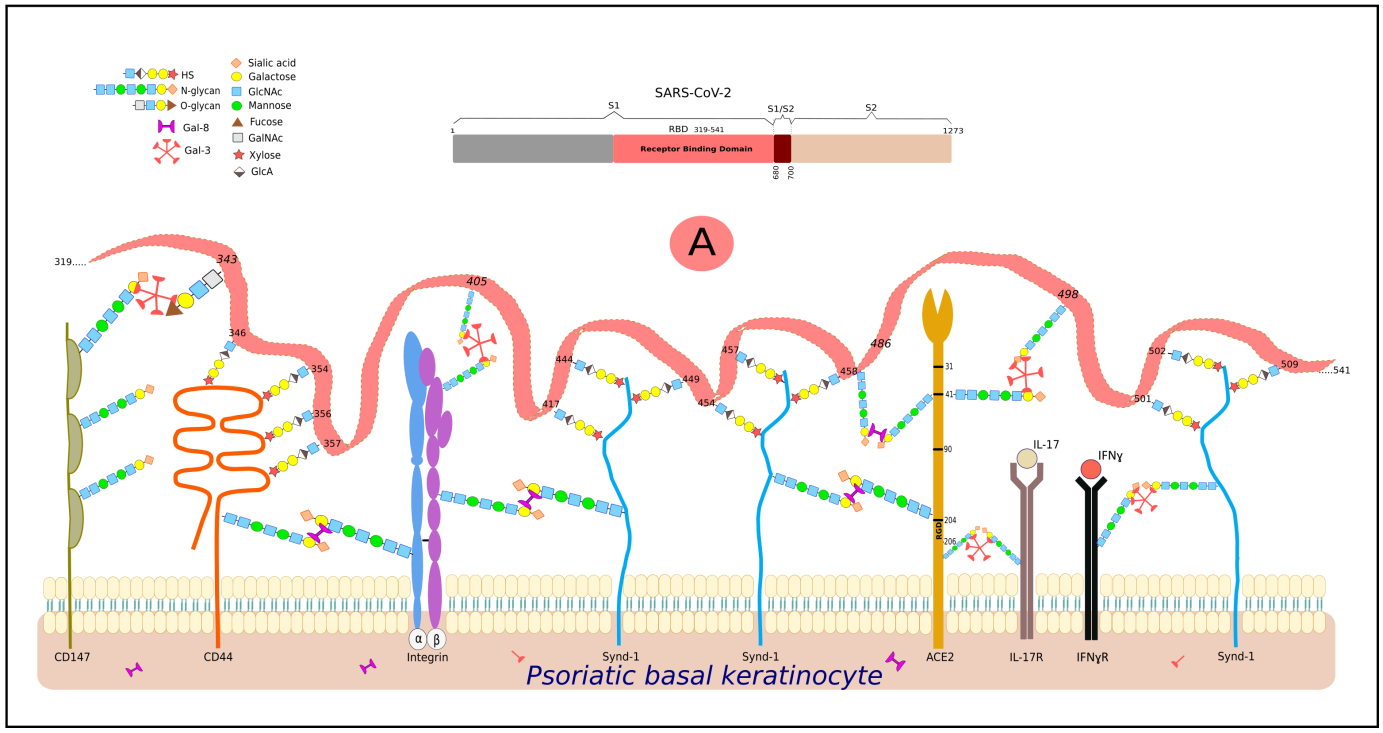
Although an elevated expression of the ACE2 receptor on differentiating keratinocytes and basal cell layer of the epidermis of patients with psoriasis and COVID-19, involving pro inflammatory cytokines such as IFN-γ and IL-17 has been reported [4,6,7], little is known about the involvement in the SARS-CoV-2 infection of other receptors expressed in the surface of psoriatic keratinocytes. For instance, PGs containing both HS and CHS side chains such as Synd-1 and CD44, and glycoproteins containing N-linked Glycans, including CD147 and integrin-β_1.

We believe that in addition to the ACE2, the SARS-CoV-2 S glycoprotein may also bind other receptors located in the psoriatic keratinocytes surface; particularly, HSPGs such as Synd-1 and CD44, and glycoproteins including CD147 and integrin-β_1. Consistent with this, previous studies have suggested that Synd-1 and CD44, which have been involved in the pathogenesis of psoriasis [54,55], might interact with the SARS-CoV-2 S glycoprotein acting as additional binding receptors to retain the virus close to the host cell surface, allowing its interaction with other receptor molecules and promoting the internalization process [16,19]. Of significance, the interaction of HS with the RBD of the S1 subunit of the SARS-CoV-2 S glycoprotein producing a conformational change in the SARS-CoV-2 S glycoprotein structure that facilitates ACE2 binding and virus internalization, has been proposed [31,32]. Similarly, studies have shown that HS interacts, not only with the GAG-binding motif within RBD of the S1 subunit and at S2 proteolytic cleavage site of the S2 subunit, but also with the GAG-binding motif at the S1/S2 junction of each monomer of the trimeric SARS-CoV-2 S glycoprotein when the RBD displays an open conformation [33]. Remarkably, emerging evidence *in vitro* and *in vivo* have indicated that overexpression of some members of the syndecan family, particularly Synd-1, significantly increases the cellular SARS-CoV-2 attachment and internalization, suggesting an important contribution of these HSPGs to the cellular entry of SARS-CoV-2, and have held it as a new therapeutic target against COVID-19 infection [34,35].

With respect to CD147, a glycoprotein that has three N-glycosylation sites and interacts with CD44 and integrin-β_1 [23,56], previous studies have shown an elevated CD147 expression in the basal layer of the epidermis of human psoriatic skin lesions [57]. Moreover, recent studies in SARS-CoV-2 identified CD147 as a novel receptor of S glycoprotein, suggesting that the CD147 and S glycoprotein interaction facilitates the virus internalization [22,23]. Other proteins that would be participating in the binding of SARS-CoV-2 S glycoprotein to skin keratinocytes of patients with psoriasis would be Gal-3 and Gal-8, considering that Gal-3, an important mediator of viral adhesion [58], interacts with the N-Glycans of CD147 and integrin-β_1 [51], and that this Gal also binds the N-Glycans of IFN-γ [59]. Moreover, considering that Gal-8, a Gal that binds to CD44 and integrin-β_1 [53], is upregulated by IL-17A in psoriasis [60]. Also of significance, the formation of heterodimers by Gal-8 and pentamers by Gal-3 which can bind and cross-link specific glycoconjugates generating webs, known as Gal-glycan lattices at the cell surface and in the extracellular space has been shown [45,46,49]. Importantly, such Gal-glycan lattices regulate viral infections [47,48]. Therefore, we believe that during the SARS-CoV-2 S glycoprotein-psoriatic keratinocyte interaction and in the presence of certain pro inflammatory cytokines, the HSPGs Synd-1 and CD44, through their HS side chains and N-linked glycan and Gal-3 and Gal-8, through the N-linked Glycans located on the ACE2, integrin-β_1, CD147, IFN-γR and IL-17A-R, would generate a Gal-glycan lattice at the surface of SARS-CoV-2 virus and psoriatic keratinocyte (Figure 1A, B). Such Gal-glycan lattice in addition to influence keratinocyte proliferation and terminal differentiation, also might induce conformational changes in the SARS-CoV-2 S glycoprotein facilitating the attachment and entry of the virus.

Future directions

In this article we highlight the important role of HSPGs and Gal-glycan lattices facilitating the attachment and internalization of the SARS-CoV-2 virus during its interaction with the psoriatic keratinocyte. In this regard, modulation of such interaction by using heparan sulfate mimetics, antibodies, and specific inhibitors of heparan sulfate biosynthesis as well as of antagonists and truncate forms of galectins, would signify a therapeutic strategy to prevent virus entry into the host cells, decreasing the SARS-CoV-2 virus infectivity.



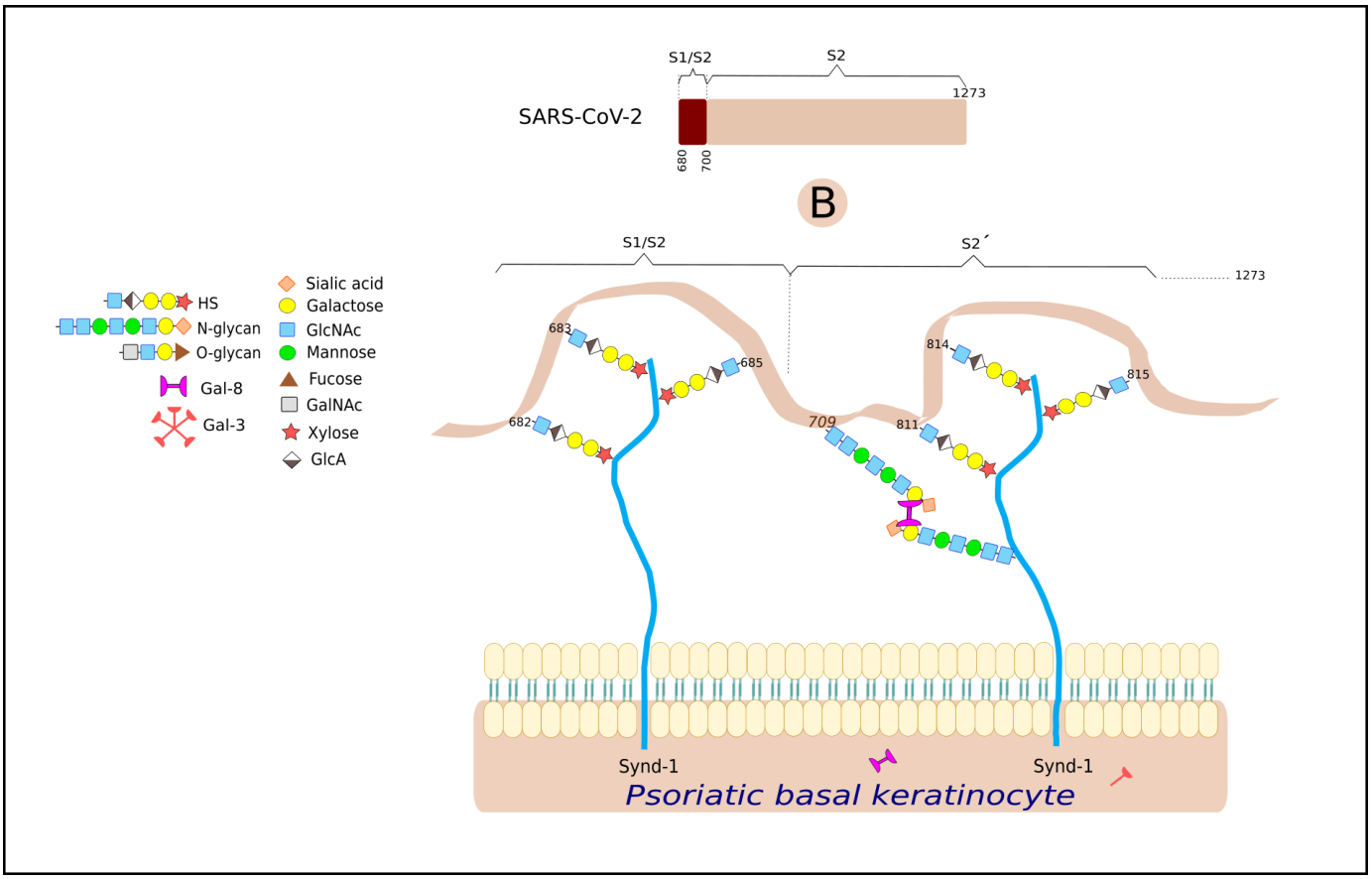


Figure 1A,B: Schematic representation of the full-length of SARS-CoV-2 spike (S) glycoprotein (aa1-aa1273), showing the S1 and S2 domains, the receptor binding domain (RBD) (aa319-aa341), the proteolytic cleavage site (S1/S2), and the S2 proteolytic site.

"A" and "B" show Gal-3 and Gal-8 forming a Gal-glycan lattice on the SARS-CoV-2 virus and psoriatic keratinocyte through the HS side chains and the N-linked glycan that are located on CD44 and Synd-1, and the N- and O-linked glycan residues that are located on CD147, integrin-β1, ACE2, IL-17A-R and IFN-γ. The small numbers indicate the contact site of HS chains and the big numbers, the site of N-linked glycan residues on S glycoprotein.

Conclusions

Finally, we consider that future work will be required to understand the mechanisms regulating Gal-glycan lattice assembly during psoriatic keratinocyte and SARS-CoV-2 interaction as well as for the development of new inhibitors of virus attachment and internalization.

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