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·综 述·

新型冠状病毒的糖基化、糖受体识别及糖链抑制剂的发现

喻伟艳[1,2]，许跃强[2]，李建军[2]，李志敏[1]，王琪[3]，杜昱光[2]

1 江西农业大学 生物科学与工程学院，江西 南昌 330045
2 中国科学院过程工程研究所 生化工程国家重点实验室，北京 100190
3 大连医科大学附属第二医院 肺癌转化医学中心，辽宁 大连 116023

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摘 要：新型冠状病毒疫情 (COVID-19) 是 21 世纪截至目前人类面对的最为严重的公共卫生事件。疫苗、中和抗体以及小分子化合药物的出现有效预防和阻止了 COVID-19 的快速传播，而不断出现的病毒突变体却使这些疫苗及药物的效价降低，这对 COVID-19 的预防及治疗提出了新的挑战。新型冠状病毒 (SARS-CoV-2) 通常会先黏附于呼吸道表面的大分子糖链——硫酸乙酰肝素，进而与特异性受体人血管紧张素转化酶 2 (human angiotensin-converting enzyme 2, hACE2) 结合，从而实现对人体的侵入。SARS-CoV-2 的刺突 (spike, S) 蛋白是高度糖基化的，而糖基化对于 hACE2 与 S 蛋白的结合也有着重要影响，S 蛋白在宿主体内还会被一系列凝集素受体所结合，这意味着糖链在 SARS-CoV-2 的入侵及感染过程中有着重要的作用。基于 SARS-CoV-2 的糖基化及糖受体识别机制开发糖链抑制剂可能是预防或治疗新型冠状病毒感染的有效手段，相关研究发现海洋来源的硫酸化多糖、肝素分子及其他的一些糖类具有抗 SARS-CoV-2 的活性。本文系统阐述了新型冠状病毒的糖基化及其糖链在入侵、感染中的作用，并对抗 SARS-CoV-2 糖链抑制剂的发现和机制研究现状进行了总结，在此基础上还对糖类抗病毒药物的机遇与挑战进行了展望。

关键词：新型冠状病毒；糖基化；糖受体；糖链抑制剂

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Corresponding author: DU Yuguang. Tel: +86-10-82545039; E-mail: ygdu@ipe.ac.cn
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Glycosylation, glycan receptors recognition of SARS-CoV-2 and discoveries of glycan inhibitors against SARS-CoV-2

YU Weiyan[1,2], XU Yueqiang[2], LI Jianjun[2], LI Zhimin[1], WANG Qi[3], DU Yuguang[2]

1 School of Biological Sciences and Engineering, Jiangxi Agricultural University, Nanchang 330045, Jiangxi, China
2 State Key Laboratory of Biochemical Engineering, Institute of Processing and Engineering, Chinese Academy of Sciences, Beijing 100190, China
3 Lung Cancer Translational Medicine Center, The Second Affiliated Hospital of Dalian Medical University, Dalian 116023, Liaoning, China

Abstract: COVID-19 represents the most serious public health event in the past few decades of the 21st century. The development of vaccines, neutralizing antibodies, and small molecule chemical agents have effectively prevented the rapid spread of COVID-19. However, the continued emergence of SARS-CoV-2 variants have weakened the efficiency of these vaccines and antibodies, which brought new challenges for searching novel anti-SARS-CoV-2 drugs and methods. In the process of SARS-CoV-2 infection, the virus firstly attaches to heparan sulphate on the cell surface of respiratory tract, then specifically binds to hACE2. The S protein of SARS-CoV-2 is a highly glycosylated protein, and glycosylation is also important for the binding of hACE2 to S protein. Furthermore, the S protein is recognized by a series of lectin receptors in host cells. These finding implies that glycosylation plays important roles in the invasion and infection of SARS-CoV-2. Based on the glycosylation pattern and glycan recognition mechanisms of SARS-CoV-2, it is possible to develop glycan inhibitors against COVID-19. Recent studies have shown that sulfated polysaccharides originated from marine sources, heparin and some other glycans display anti-SARS-CoV-2 activity. This review summarized the function of glycosylation of SARS-CoV-2, discoveries of glycan inhibitors and the underpinning molecular mechanisms, which will provide guidelines to develop glycan-based new drugs against SARS-CoV-2.

Keywords: SARS-CoV-2; glycosylation; glycan receptor; glycan inhibitor

2020 年 1 月 30 日世界卫生组织宣布由 SARS-CoV-2 感染人类引发的新型冠状病毒肺炎为国际关注的突发公共卫生事件，并于 2020 年 3 月 11 日宣布该病为大流行病。新型冠状病毒 SARS-CoV-2 属于冠状病毒科的 β-冠状病毒属[1]，其与非典冠状病毒 SARS-CoV 和中东呼吸综合征相关病毒 MERS-CoV 是 3 种对人类生命最具威胁的冠状病毒[2]。SARS-CoV-2 传播力强，有较高的临床发病率，截至 2022 年 5 月底，全球已有超过 5 亿人感染，其中死亡人数超过 600 万 (WHO coronavirus (COVID-19) dashboard)。SARS-CoV-2 主要通过喷嚏和咳嗽从上呼吸道排出的飞沫传播，随后会黏附在鼻腔、口腔、眼睛以及呼吸道的黏膜表面[3-4]。SARS-CoV-2 会感染呼吸道上皮细胞，如肺中分泌纤毛黏液支气管上皮细胞和Ⅰ型肺细胞，以及胃肠道上皮细胞[5-6]。SARS-CoV-2 的刺突 (spike, S) 蛋白可以与宿主细胞膜表面的受体血管紧张素转化酶 2 (human angiotensin-converting enzyme 2, hACE2) 结合，再经 TMPRSS2 蛋白

酶及 Furin 蛋白酶切割后与细胞膜融合进而实现入侵，病毒进入宿主体内后会释放遗传物质进一步复制和扩增。新型冠状病毒对人体的入侵会引起炎症因子风暴，并导致弥漫性肺泡损伤，最终引起肺水肿和呼吸衰竭。针对 SARS-CoV-2 的结合、蛋白酶加工、融合、内吞及复制等过程，全球的科学家及各大药厂研发了一系列的抗病毒药物，包括老药新用的瑞德西韦、法匹拉韦等，而新开发的靶向病毒 RNA 合成的莫纳匹拉韦和 3CL 蛋白酶抑制剂帕罗维德目前已逐步在全球上市。国内也有普克鲁胺、阿兹夫定、VV116、DC402234、SHEN26 等多个抗新冠小分子药物进入临床试验[7]。中医药在预防及治疗新型冠状病毒肺炎中也占据着重要的地位，连花清瘟颗粒、香霍喷雾剂及基于四性五味的中药新处方等在新型冠状病毒肺炎的治疗中得到了应用[8-11]，此外，中和抗体和疫苗也是对抗新冠病毒的有力武器。目前，全球已有超过 300 种新冠候选疫苗，198 种新冠疫苗处于临床前研究阶段，156 种进入临床试验，11 种获得世界卫生组织紧急使用授权，其中包括灭活疫苗 (BBIBP-CorV、PiCoVacc 等)、重组蛋白质疫苗 (ZF2001 等)、mRNA 疫苗 (mRNA-1273、BNT162 mRNA 等) 和腺病毒疫苗 (Ad5-nCoV 等)。这些疫苗在全球的大规模接种有效预防了新型冠状病毒的感染及减轻感染引起的症状。在抗体药物方面，包括礼来、阿斯利康、葛兰素史克、再生元等在内的全球各大药企及国内的创新药企已开发一系列产品进入临床试验或得到紧急授权使用，但部分抗体对 Omicron 突变株无效[7,12]。中国腾盛博药研发的新冠病毒中和抗体联合药物安巴韦单抗/罗米司韦单抗注射液 (BRII-196/BRII-198) 于 2021 年 12 月 8 日获得国家药品监督管理局的紧急审批，并进入国家卫健委于 2022 年 3 月 15 日发布的《新型冠状病毒肺炎诊疗方案》[7]。虽然疫苗及药物的出现有效降低了 SARS-CoV-2 的传播和感染，但是随着新型冠状病毒变异株的不断出现，如 Alpha 突变株 (B.1.1.7)、Beta 突变株 (B.1.351)、Gamma 突变株 (P.1)、Kappa 突变株 (B.1.671.1)、Delta 突变株 (B.1.617.2) 及 Omicron (B.1.1.529) 等，这些疫苗及药物对新型冠状病毒“群防”的效果却不尽如人意。特别是对于感染力更强的 Omicron 突变株，人们以 SARS-CoV-2 武汉株为模本开发的抗体药物及疫苗已出现了效价的大幅下滑[12-14]。面对这种情况，寻找新的预防和治疗手段迫在眉睫。

我们注意到，新型冠病毒的 S 蛋白是一个高度糖基化的蛋白，而在其对宿主细胞受体的识别、结合及入侵过程中，糖识别机制发挥了重要的作用，这也为抗 SARS-CoV-2 糖类药物的开发提供了契机。因此，本文将从新冠病毒的糖基化、糖链介导的入侵机制及抗新型冠状病毒糖类药物开发及机制研究几个方面阐述糖链与新型冠状病毒的关系，旨在为开发抗冠状病毒糖类药物提供参考依据。

1 SARS-CoV-2 的糖基化修饰

SARS-CoV-2 属于包膜病毒，具有约 30 kb 的正义单链 RNA 基因组，可转录多达 29 种蛋白质，其中主要的 4 种结构蛋白包括刺突糖蛋白、包膜 (envelope, E) 蛋白、膜 (membrane, M) 蛋白和核衣壳 (nucleocapsid, N) 蛋白[15](图 1)。

1.1 新型冠状病毒 S 蛋白的糖基化

S 蛋白是一种高度糖基化的跨膜蛋白，以三聚体形式存在，由两个亚基组成：S1 亚基包含 N 端域 (N-terminal domain, NTD)、受体结合域 (receptor binding domain, RBD) 和其他几个结构域，S2 亚基介导病毒-细胞膜融合[16-17]。其中受体结合域 RBD 负责与 hACE2 受体结合，

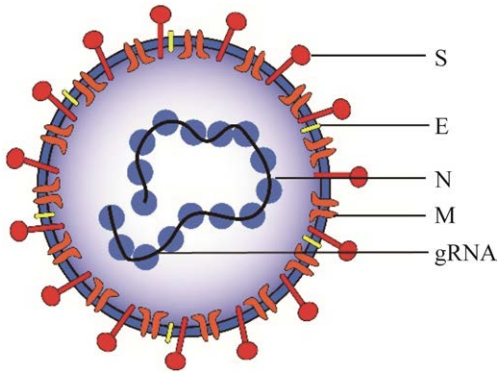

图 1 新型冠状病毒的结构
Figure 1 Structure model of SARS-CoV-2.

而在 S1 和 S2 之间有一个 PRRA 序列基序，该序列包含一个 Furin 蛋白酶裂解位点，该位点对于病毒进入人体细胞至关重要[18]。研究显示，宿主细胞表面丝氨酸蛋白酶 TMPRSS2 参与许多冠状病毒包括 SARS-CoV-2 的质膜融合[19-21]，而溶酶体组织蛋白酶通常参与内体膜的融合过程[22]。冠状病毒的 S 蛋白对于病毒颗粒与宿主受体的相互作用至关重要，如 SARS-CoV 与血管紧张素转换酶 2 (ACE2)[19,23]、MERS-CoV 与二肽基肽酶 4 (DPP4)[24]以及 HCoV-229E 与氨肽酶 N (APN) 结合[25]。

S 蛋白具有广泛的糖基化，其单体含有 22 个 N-糖基化位点和 17 个 O-糖基化位点[26-27]，其糖基化位点的分布如图 2 所示。S 蛋白表面覆盖着大量的糖链，这些糖链的存在可以避免宿主免疫系统对病毒的识别，从而逃避免疫系统的杀伤。值得注意的是，不论从哺乳动物细胞还是从昆虫系统表达所得的 S 蛋白，以及从 SARS-CoV-2 中提取的 S 蛋白，22 个 N-糖基化位点始终存在，而 S 蛋白在不同宿主表达系统中获得的 O-糖基化修饰存在差异[28]，这意味着 O-糖基化修饰可能使新型冠状病毒 S 蛋白在结构上具有更高的灵活性。

S 蛋白融合前以亚稳态构象存在，这种状态称为“向下” (down) 构象；当 S1 亚基与宿主细胞受体结合时，蛋白结构进行重排，暴露出与受体结合的关键因素，这种状态称为“向上” (up) 构象。受体结合后，三聚体不稳定，导致 S1 亚基脱落，S2 亚基转变为稳定的融合后构象，介导病毒膜与宿主细胞膜融合[29]。有研究发现，当 S 蛋白处于“向下”构象时，受体结合位点可被近端糖基化位点 (N165、N243 或 N343) 隐蔽，从而保护关键氨基酸残基和其他表位不受细胞和抗体的识别。这几个糖基化位点对于 S 蛋白处于“打开”还是“关闭”状态非常重要，也直接影响了对 hACE2 的结合[30]。

1.2 新型冠状病毒其他蛋白的糖基化

有证据表明，除 S 蛋白，E、M 蛋白的表达也具有 N-糖基化修饰[31]。SARS-CoV-2 的 N 蛋白与甘露糖结合相关丝氨酸蛋白酶 2 (MASP-2) 结合，该酶是 MBL 补体激活途径中的关键酶，异常结合会导致补体激活和加重肺损伤[32]。N 蛋白还与 11 种人类趋化因子高度结合，可导致白细胞的趋化作用被抑制[33]。E 蛋白则通过糖链识别结合 TLR2 受体，引起炎症细胞因子的释放，如肿瘤坏死因子 (tumor necrosis factor α, TNF-α) 和干扰素 γ (interferon gamma, INF-γ)[34]。

1.3 病毒糖基化修饰的生理功能及意义

与其他病原体相比，大部分病毒自身不能进行糖基化修饰，病毒在细胞内复制过程中，可利用宿主的糖基化系统对自身蛋白进行修饰。病毒的糖基化通常具有以下功能[35]：第一，有助于糖蛋白的折叠和运输，进而完成病毒组装。第二，糖基化有利于病毒的释放。第三，病毒可以通过脱落或分泌糖蛋白误导免疫反应进行免疫逃避。这些分泌的糖蛋白类似于“替身”，可以结合中和抗体或引起非中和抗体的产生。如埃博拉病毒分泌的 sGP 糖蛋白[36]及呼

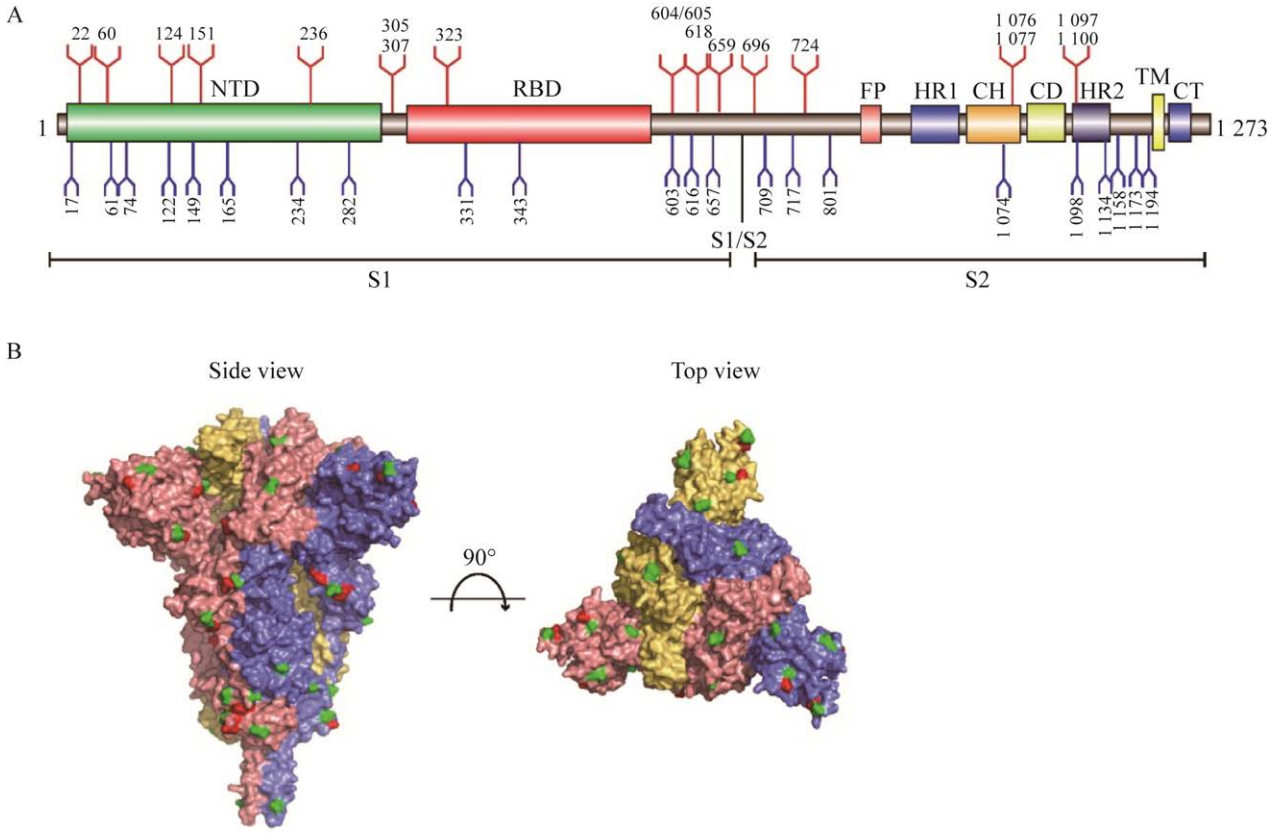

图 2　新型冠状病毒 S 蛋白的糖基化位点分布

Figure 2　Distribution of the glycosylation sites in S protein of SARS-CoV-2. (A) Distribution of glycosylation sites in S protein. The lower branch with blue indicates N-glycosites and the upper branch with red indicates O-glycosites; NTD: N-terminal structural domain; RBD: receptor binding domain; FP: fusion peptide; HR1: heptad repeat 1; HR2: heptad repeat 2; CH: central helix; CD: connector domain; TM: transmembrane structural domain; CT: cell tail. (B) Structural simulation of glycosylated S proteins (PDB: 6XR8[29]). Pink indicates S protein A chain, purple indicates S protein B chain, yellow indicates S protein C chain, red dots indicates O-glycosylation sites, green dots indicates N-glycosylation sites.

吸道合胞病毒分泌的 G 糖蛋白[37]。第四，病毒表面糖链可以遮蔽抗原表位，逃避免疫系统的识别。第五，病毒表面糖链可被宿主体内的糖受体识别，便于病毒在体内的运输及感染宿主。第六，病毒表面糖链本身还可作为抗原表位。

对于新型冠状病毒来说，糖基化不仅影响自身的折叠及结构稳定，而且对于其入侵、识别及免疫逃避都非常重要，相关的研究还在不断深入中。

2　糖链介导的新型冠状病毒入侵

2.1　SARS-CoV-2 对宿主细胞表面糖胺聚糖的结合

研究表明，SARS-CoV-2 通过 S 蛋白的 RBD 与 hACE2 结合从而进入宿主细胞[19,38] (图 3A)。通过对 SARS-CoV-2 S 蛋白序列分析，与 SARS-CoV 相比，该病毒已进化出潜在的糖胺聚糖 (glycosaminoglycan, GAG) 结合域[39-40]。GAG 是一个线性硫酸多糖家族，几乎存在于所有哺

乳动物细胞表面，通常包括硫酸乙酰肝素(heparan sulfate, HS)、硫酸软骨素 (chondroitin sulfate, CS)、透明质酸 (hyaluronic acid, HA)、硫酸皮肤素 (dermatan sulfate, DS) 和硫酸角质素 (keratan sulfate, KS)，这些多糖已被证明可促进多种病毒附着[41-42]。SARS-CoV-2 与宿主细胞表面的硫酸乙酰肝素结合可促进 S 蛋白的 RBD 与 hACE2 的结合。在这种相互作用下，S 蛋白结构由“向下”构象变为“向上”构象，使其更易与宿主受体结合[43-44] (图 3B)。此外，硫酸乙酰肝素的分子多样性在支持病毒进入、运输和复制过程中起着重要作用，而这些过程跨越了病毒生命周期的大多数细胞过程[45]。

2.2 hACE2 的糖基化

hACE2 有 7 个 N-糖基化和 1 个 O-糖基化位点[47]，其中 N90、N322 和 N546 会促进 S 蛋

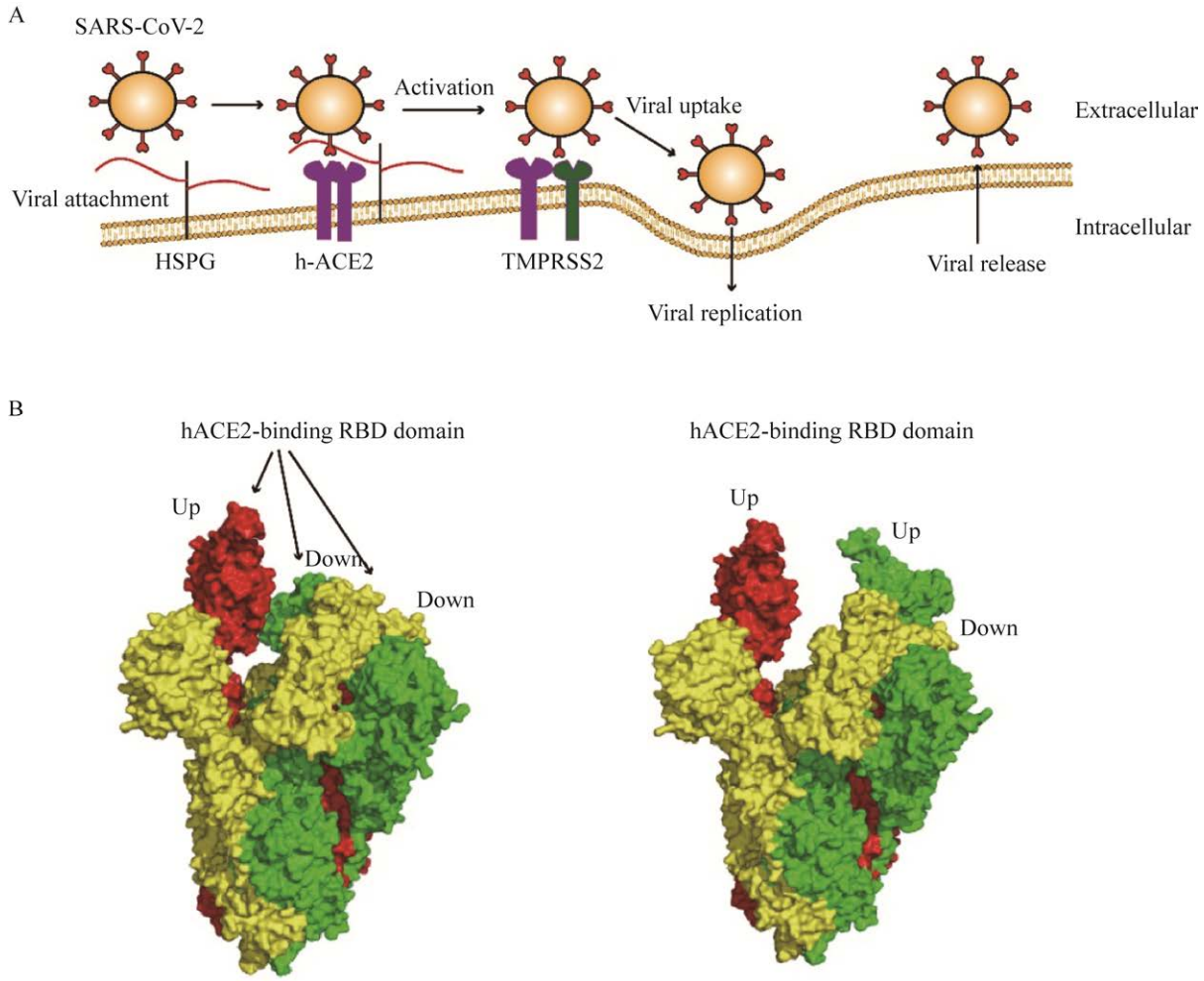

图 3 SARS-CoV-2 感染宿主的过程及 S 蛋白的构象变化[46]

Figure 3 The process of SARS-CoV-2 infection and conformation change of S protein. (A) SARS-CoV-2 infection processes through cell surface HSPG. HSPG: acetyl heparan sulfate proteoglycan; hACE2: human angiotensin-converting enzyme 2; TMPRSS2: transmembrane serine protease. (B) Structure conformation simulation of SARS-CoV-2 (one RBD-up conformation, PBD: 7EB3[46]; two RBD-up conformation, PBD: 7EB5[46]).

白与 hACE2 的结合[48]。此外，在人类基因组中发现 hACE2 会存在单核苷酸多态性 (single nucleotide polymorphisms, SNPs)，其改变可能会影响 hACE2 的糖基化以及对病毒 S 蛋白的亲和力[49]。之前报道，hACE2 在各种类型细胞中表达，如心脏、肾脏和睾丸的内皮细胞和肺泡上皮细胞[50-51]。最近研究发现，hACE2 在肺、肝脏、皮肤和肠道内皮细胞表达水平相对较低以及在肺组织中检测不到，仅在肺泡上皮 II 型、基底细胞和杯状细胞亚群上表达[52–55]。

虽然 SARS-CoV-2 通过 hACE2 受体进入细胞的机制已明确，但该病毒在不表达或低表达 hACE2 的细胞中也被检测出，以及在病毒引起的“过度免疫激活”的免疫系统中依旧生存，这似乎表明还存在其他作用机制。

2.3 宿主免疫系统凝集素受体对 SARS-CoV-2 的识别

病毒侵入宿主细胞，一方面可由进入受体介导，通过内吞和融合等多种机制进入细胞；另一方面，细胞表面的聚糖和凝集素可作为黏附受体与病毒结合，介导病毒的入侵。宿主免疫系统有一类进化保守的糖蛋白——凝集素，能够结合不同的糖链表位，并以糖链依赖的形式启动先天性免疫反应[56]。细胞表面的凝集素可作为进入受体直接介导病毒的入侵，也可作为黏附分子，以转染的方式加强进入受体 (ACE2) 介导的传播[57-58]。SARS-CoV 的 8 个糖基化位点与受体 DC-SIGN、L-SIGN 发生相互作用，其中有 6 个糖基化位点在 SARS-CoV-2 中是保守的[59-60]。同样，S 蛋白糖链表型的鉴定结果中，包含一些凝集素的配体，这似乎暗示 SARS-CoV-2 可能具有类似的相互作用。

新型冠状病毒 RBD 的 N331 和 N343 位点上的 N-糖链可以特异性结合巨噬细胞半乳糖凝集素 (macrophage galactose-type lectin, MGL)、人半乳糖凝集素 galectin-3/7/8、Siglec-10 和 DC-SIGN[61]。而 S 蛋白的 NTD 及 CTD 结构域与 C 型凝集素 DC-SIGN、L-SIGN、LSECtin、ASGR1 及 CLEC10A 等受体结合[62]。此外，S 蛋白上 Thr323/Ser325 的 O-糖链在 MGL 与 SARS-CoV-2 的结合中发挥重要作用[60,63]。

在缺乏 hACE2 的内皮细胞中，L-SIGN 和 DC-SIGN 可作为进入受体介导病毒的感染。L-SIGN 可以与 hACE2 相互作用，形成异二聚体，说明 L-SIGN 可以通过依赖 hACE2 及不依赖 hACE2 两种方式介导 SARS-CoV-2 的感染。而 S 蛋白与 DC-SIGN 的结合依赖于糖链[60]，去除 L-SIGN 的 N92 位的 N-糖链，L-SIGN 和 S 蛋白的结合更紧密[64]。这说明在 hACE2 低表达的细胞中，凝集素可能是 SARS-CoV-2 感染细胞的协同受体。

表 1 展示了最近研究报道的细胞表面与 SARS-CoV-2 结合的凝集素受体，从表中看出，这些受体大部分位于免疫细胞表面，这似乎表明病毒通过与受体结合参与了免疫调节，从而说明在免疫系统过度活化的患者体内，病毒依旧生存的可能原因之一。

3 抗病毒糖链抑制剂的作用机制

如上所述，新型冠状病毒可利用糖链对宿主细胞侵染和逃避免疫反应，但是，糖类抗病毒的效果也是显而易见的[66-69]，糖链可以通过多种作用机制作用于病毒，其潜在的抗病毒靶点及作用机制见图 4。

3.1 糖链对病毒的直接杀伤

一方面，大多数多糖携带电荷，可与病毒表面直接作用并改变病毒结构导致病毒失去感染力或直接杀伤病毒。例如角叉菜胶可与疱疹病毒 (herpes simplex virus, HSV) 发生不可逆结合导致病毒粒子失活使其无法感染，从而有效

表 1 细胞表面与 SARS-CoV-2 结合的凝集素受体

Table 1 Lectin receptors binding to SARS-CoV-2 on the cell surface

Receptors	Organ	Cell types	Glycan ligand	References
DC-SIGN	Lung	Dendritic cells	High mannose and fucosylated glycans	[57-58,60,63-64]
L-SIGN	Lung	Lung endothelial cells, type Ⅱ alveoli cells	High mannose and complex N-glycans	[57-58,60,64]
MGL	Lung Upper respiratory tract	Dendritic cells and macrophage	Gal and GalNAc terminated glycans, complex N-glycans	[58,60,63-64]
MR	Lung Upper respiratory tract	Dendritic cells and macrophage	High mannose N-glycans	[60]
Langerin	Marrow	Langerhans cells	High mannose and sulfated glycans	[58]
Siglec-1	Lung	Myeloid cells, macrophage	GM1	[57,65]
Siglec-3/9/10	Marrow	Monocytes, macrophage, neutrophil, DCs, NK cells, T-lymphocytes, B-lymphocytes, eosinophilic granulocyte	Fucosylated or sulfated α2,3-sialic acid, α2,6-sialic acid	[63]

减少病毒的增殖[70]。另一方面糖类疫苗佐剂也相继问世，并且显示出抗病毒效果，如壳聚糖、岩藻酸盐、透明质酸和 β-葡聚糖已被用作抗病毒疫苗佐剂[71]。

3.2 糖链可阻断病毒对宿主细胞的黏附及膜融合

病毒可以通过表面糖链来遮蔽关键氨基酸位点，根据病毒表面糖链的结构和特点“投其所好”，在宿主细胞表面预先加入特定糖链保护剂，使糖链与宿主受体结合，隐藏宿主细胞可被病毒识别与结合的位点，此方法即通过添加外源糖链竞争性抑制病毒与受体的结合。

3.3 糖链可抑制病毒在细胞中的复制

病毒遗传物质进入细胞后，利用宿主细胞的遗传及表达系统，进行复制和完成生物大分子的合成，最后装配和释放子代病毒。多糖可以干扰病毒复制过程中相关酶的活性从而影响病毒复制[72]。黄芪多糖 APS 在体外以剂量依赖性方式抑制禽类传染性支气管炎病毒 IBV 的复制[73]，灰树花多糖 GFP1 可以抑制肠道病毒 71 (EV71) RNA 基因组的合成[74]。多种亚氨基糖衍生物也具有抑制感染性病毒粒子释放和减少感染细胞数量的功能[75]，来自乳酸菌的 EPS26a 可以完全抑制人腺病毒 5 (HAdV-5) 的形成和释放[76]。

3.4 糖链可以调节宿主免疫功能进而抵抗病毒

病毒可通过糖链和宿主免疫细胞结合，同理，可通过外源糖类调节免疫系统，从而提高机体抗病毒效力或缓解病毒带来的伤害。多糖可与免疫细胞表面的特异性受体结合，从而激活受体介导的免疫反应。如 Toll 样受体 (TLR2、TLR4) 是多糖激活免疫反应的主要受体，激活后的受体通过接头蛋白 My D88 将信号传递出去，最后激活 NK-κB 或 AP-1，引起炎症细胞因子的释放[77]。不同来源的多糖已被证明可以调节巨噬细胞的活性[78-82]。甘露聚糖可以和巨噬细胞表面的 MR 受体结合，从而增强吞噬作用和促炎症因子释放[83]。1,3-β-D-葡聚糖 (GOS) 与巨噬细胞表面 CR3 和 TLR2 结

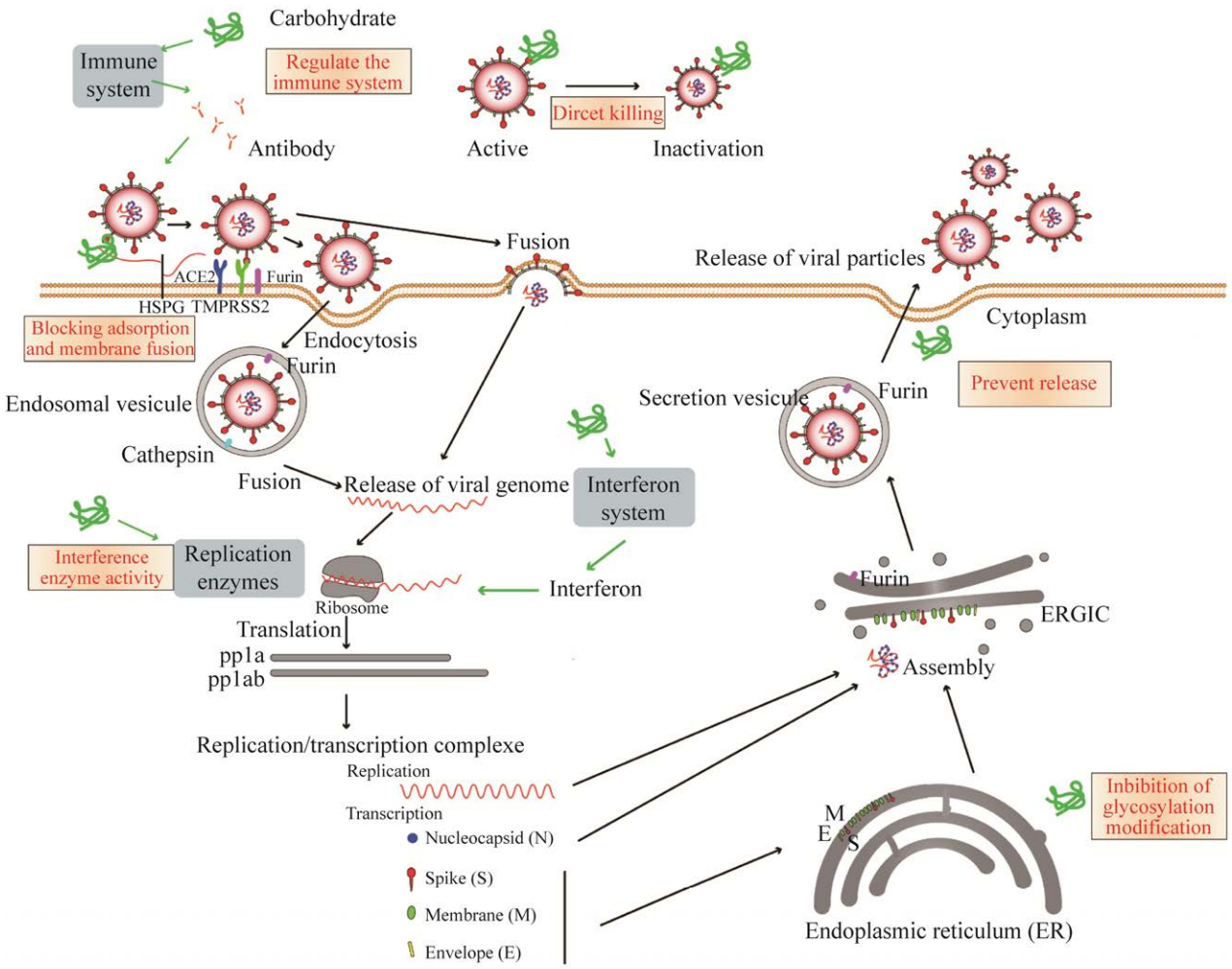

图 4　抗病毒糖链化合物的靶点及作用机制

Figure 4　Multi-targets of antiviral glycans and the underpinning molecular mechanisms.

合，激活 MAPK 和 NF-κB 通路，增强内吞作用和杀菌能力[84]。Dectin-1 受体可与 β-D-葡聚糖结合，通过免疫受体酪氨酸激活基序(immunoreceptor tyrosine-based activation motif, ITAM)，激活下游 MAPK 信号通路[85]；此外海带多糖也可以结合 Dectin-1，参与免疫调节作用[86]。

对于新型冠状病毒给机体带来的“细胞因子风暴”，似乎更需要激活免疫抑制通路，减少炎症反应对机体的伤害[87]。目前已有多种免疫调节剂在临床上减轻了过度炎症，但带来效果的同时也带来了巨大的风险，如抗 IL-6 受体抗体 Sarilumab 不仅没有改善临床结果和死亡率，反而引起了严重的并发症[88]。因此，需要开发有效的免疫调节剂，在不损害宿主免疫保护的情况下抑制炎症。

多糖还可以通过控制促炎症因子的产生和调节氧化还原的平衡，从而调节免疫抑制反应。板蓝根多糖在抗流感病毒中，可诱导 TLR-3 的蛋白表达，通过抑制 TLR-3 信号通路的激活来削弱流感病毒诱导的促炎因子的上调[89]。紫菜多糖不仅抑制由内毒素 (lipopolysaccharide,

LPS) 诱导的小鼠骨髓来源树突状细胞 (bone marrow-derived dendritic cell, BMDC) 和脾脏树突状细胞中共刺激分子的表达，还可抑制促细胞炎症因子的产生以及小鼠中 Th1 和 Tc1 细胞的分化[90]。其他糖类也显示出抑制促炎因子 (TNF-α、IL-1β、IL-6 和 IL-8) 的产生[91–93]。硫酸化多糖可提高细胞过氧化氢酶 (catalase, CAT) 和超氧化物歧化酶 (super oxide dismutase, SOD) 的水平[94]，防止脂质过氧化引起的组织损伤[95]，减少细胞内活性氧 (reactive oxygen species, ROS) 的产生并保护细胞免受 ROS 损伤[96]。从葡萄酒中分离的甘露聚糖样多糖可抑制内毒素刺激的细胞炎症因子和一氧化氮的生成[97]。此外，岩藻多糖和硫酸化鼠李糖可以干扰或抑制 EGFR 通路，从而防止病毒感染引起的肺过度纤维化反应[98–100]。

综上所述，糖类作为抗病毒药物的潜力是不可否认的，且同一种糖具有多种抗病毒机制，这可能暗示其具有广谱抗病毒的潜能，表 2 为不同多糖的抗病毒活性研究总结。

表 2　不同多糖的抗病毒活性研究

Table 2　Activities and mechanisms of anti-viral polysaccharides

Types	Virus	Possible mechanisms	References
Polysaccharide extract from *Laminaria japonica*	RSV	Inhibit RSV replication and induce IFN-α secretion	[101]
Fucoidan	IAV	Target viral neuraminidase and cellular EGFR pathway	[98]
Sulphated polysaccharides from *Enteromorpha compressa*	HSV	Inhibit virus replication	[102]
Polysaccharide from *Laminaria japonic*	EV71	Inhibit viral proliferation, suppress viral-induced apoptosis, induce IFN-β expression	[103]
Iota-carrageenan	VZV	Inhibit viral proliferation	[104]
EPS 26a from Lactic Acid Bacteria	HAdV-5	Inhibit viral particles formation and release	[76]
Fucoidan from *Sargassum henslowianum*	HSV-2	Inhibit viral attachment	[105]

4　抗新型冠状病毒糖链抑制剂的开发现状

截至目前，研究者已发现部分糖链具有抗 SARS-CoV-2 的功能，其中以硫酸化多糖及肝素类寡糖为主。

岩藻多糖、未降解肝素及三聚体肝素分子 (Tris-HP) 可以有效抑制 SARS-CoV-2 的感染[106]，而硫酸化的海参多糖 SCSP、褐藻多糖和卡拉胶也具有抗病毒活性[107]。对海带多糖中抗 SARS-CoV-2 的活性结构单元进行鉴定，发现葡萄糖醛酸甘露寡糖 (glucuronomannan) 和硫酸化半乳糖岩藻多糖 (sulfated galactofucan) 是主要的抗病毒成分[108]。硫酸化海参多糖中抗 SARS-CoV-2 的活性结构单元也得到了鉴定[109]。进一步的研究发现昆布多糖可以靶向 3CLpro 从而抑制 SARS-CoV-2 的感染[110]。

宿主细胞表面的硫酸乙酰肝素作为辅助受体 (co-receptors) 可以与新型冠状病毒的 S 蛋白结合，从而协助病毒入侵[43]。而外源性硫酸乙酰肝素可通过竞争性抑制阻止或延缓黄病毒、疱疹病毒、流感病毒、HIV 及冠状病毒的入侵。相关报道显示肝素及硫酸乙酰肝素可抑制 SARS-CoV-2 的入侵，且其抑制活性与肝素分子的长度及硫酸化程度相关[39,43,111]。

此外，细菌的 LPS[63,112]、白桦茸多糖[113]也展现出与新型冠状病毒 S 蛋白良好的结合力，这同样意味着自然界中存在更多的糖链化

合物具有开发成为糖链药物的潜力。

5 总结与展望

由于迫切需要针对 SARS-CoV-2 的抗病毒药物，许多研究人员将重点放在重新利用现有药物上，利用体外高通量筛选已批准的药物，发现一些潜在的抗病毒分子，这些分子在新型冠状病毒患者的临床治疗上仍有待检测[114-115]。

新型冠状病毒目前还在持续变异，这可能导致疫苗或抗体药物无效。此外，非中和抗体带来的抗体依赖的病毒感染增强效应(antibody-dependent enhancement, ADE)，对疫苗及中和抗体的研发也是一大挑战，所以应对未来的新变种病毒，亟需研发安全、有效的广谱抗病毒疫苗和药物。

糖类物质具有生物相容性、安全性、低成本、低毒性等特点，且众多研究表示糖类具有抗病毒效果。但作为自然界结构最为复杂的生物大分子，糖链抗病毒的机制还在不断挖掘中，一种多糖可以抵抗多种病毒，开发针对 SARS-CoV-2 的糖类药物是具有前景的，未来需要从以下几个方面入手。

第一，加强对抗病毒功能糖链的筛选。目前已有许多关于抗病毒的糖类制品。硫酸化多糖 SPMG 已在中国进入Ⅱ期临床试验，它是第一种具有成为抗艾滋病药物潜力的多糖。阳离子改性壳聚糖 (N-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride hydrophobically-modified derivative, HM-HTCC) 是冠状病毒 HCoV-NL 的有效抑制剂[116]。Iota-角叉菜胶鼻喷雾剂可以减少由鼻病毒、冠状病毒和流感病毒等引起的普通感冒的持续时间[117-118]。根据已有的抗病毒糖链类型及结构特征，结合我国丰富的糖资源，可预见会有更多抗病毒功能糖链被发现。

第二，深入开展抗病毒功能糖链结构的解析工作。众所周知，糖类独特的结构和生物活性相关，分子量、组成、官能团和结构构象都可能影响其生物活性，提取和纯化方法也会影响糖类的生物活性[119-120]。糖链结构的复杂性和异质性使得多糖的提取和纯化异常繁琐，而通过化学合成的方法来制备均一化糖链也充满挑战，因此也阻碍了糖类药物开发。功能糖链结构的解析将有助于明确活性结构单元，以便进一步大规模生产及运行作用机理的相关研究。

第三，明确糖类药物的抗病毒机制。由于从自然界获得的糖链特别是多糖往往结构不均一，由此导致糖类抗病毒机制不唯一，也导致药物的选择性不强，难以获得高效专一的糖类药物。如亚氨基糖尚未在临床上被批准用于抗病毒适应症，在治疗病毒感染所需的浓度下，该药物存在一个脱靶效应，该药会阻碍宿主肠道葡萄糖苷酶活性，导致腹泻和腹痛[121]。阐明作用机制是当前抗病毒药物研发面临的巨大挑战。

新型冠状病毒利用宿主细胞糖基化系统完成自身蛋白的糖基化，一方面有助于其蛋白的稳定与运输，另一方面携带宿主细胞的表位糖链，可以使其躲避免疫防御，并且可能参与调节免疫系统从而对宿主产生巨大威胁。糖基化赋予了 SARS-CoV-2 更强的适应性，我们也可以采取“以糖攻糖”的策略，筛选和开发更多的糖类药物对抗病毒。

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