SARS-CoV-2: Why ACE2 isn't the whole story for infection

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For years, the angiotensin-converting enzyme 2 (ACE2) receptor has been widely accepted as the primary docking site for SARS-CoV-2, initiating cell attachment and subsequent entry. This understanding has shaped much of the therapeutic and vaccine development against COVID-19. But new research challenges this foundational premise, suggesting a different, earlier point of viral engagement.

A study published in eLife posits that heparan sulfate (HS) clusters are the true initial mediators of SARS-CoV-2 attachment and endocytosis, with ACE2 playing a role only later in the viral life cycle.1 This revised entry paradigm could redirect anti-COVID-19 strategies, focusing on HS interactions as a key therapeutic target.

KEY TAKEAWAYS

- The Pivot: Heparan sulfate (HS) clusters, not ACE2, are the primary docking sites for SARS-CoV-2 attachment and endocytosis, with ACE2 acting downstream for viral genome expression.
- The Data: Blocking HS binding with pixantrone strongly inhibited SARS-CoV-2 Omicron JN.1 attachment and infection in human airway cells.1
- The Action: Clinicians should consider the implications of HS as a primary viral attachment point, potentially opening avenues for novel antiviral therapies targeting HS interactions.

The prevailing model of SARS-CoV-2 cellular entry has long centered on the virus's spike protein binding to the ACE2 receptor on host cells. This interaction was thought to initiate the entire infection process, from surface attachment to cytosolic entry and replication. This model, while influential, has always had certain inconsistencies, particularly regarding the broad tropism of SARS-CoV-2 across various cell types, some of which express low levels of ACE2. The new research, detailed in a paper by Han, Wang, and Li, directly challenges this established view, proposing a more complex, multi-step entry mechanism where ACE2 is a secondary player.1

Han and colleagues employed advanced light microscopy techniques, specifically nanoscopy, to achieve unprecedented resolution, allowing them to visualize individual virions and host cell receptors.1 This high-resolution approach was critical for dissecting the intricate molecular interactions occurring at the cell surface during viral attachment. The investigators focused on human airway cells, a clinically relevant model for SARS-CoV-2 infection, and utilized the authentic SARS-CoV-2 Omicron JN.1 subvariant, ensuring the relevance of their findings to current circulating strains. The study's methodology allowed for direct observation of viral particles interacting with specific cell surface molecules, moving beyond inferential evidence to direct visualization.1

Revisiting the Entry Mechanism

The central finding of the study is that heparan sulfate (HS), a linear polysaccharide found on the surface of virtually all mammalian cells, mediates SARS-CoV-2 cell-surface attachment and subsequent endocytosis.1 This contradicts the long-held belief that ACE2 is the sole or primary mediator of initial attachment. The investigators observed that ACE2's role is relegated to a downstream function, specifically enabling viral genome expression after the virus has already entered the cell via HS-mediated endocytosis. This reordering of events fundamentally alters our understanding of the initial stages of SARS-CoV-2 infection.

The researchers found that SARS-CoV-2 does not bind to single HS molecules, which would typically result in weak electrostatic interactions with viral surface proteins. Instead, the virus targets and binds to clusters of HS molecules.1 These clusters are substantial, comprising approximately 6 to 137 HS molecules, and project significantly from the plasma membrane, extending 60 to 410 nm above the cell surface. These tall, HS-rich structures are not ubiquitous but are present at a density of about one per 6 μm^2, acting as highly specific docking sites for viral attachment. The sheer number of HS molecules within these clusters likely provides a strong, multivalent binding platform, overcoming the weak electrostatic forces of individual HS interactions.1

The study's use of nanoscopy allowed for direct visualization of these clusters and their interaction with viral particles. This level of detail was previously unattainable with conventional microscopy, which could not resolve individual virions or the precise spatial arrangement of receptors. The ability to see these interactions directly provides compelling evidence for the proposed mechanism, moving it beyond theoretical models. The investigators also noted that these HS clusters appear to be dynamic structures, potentially forming or reorganizing in response to cellular signals or viral presence, although the precise regulatory mechanisms were not fully elucidated in this particular study.1

Therapeutic Implications and Validation

The identification of HS clusters as primary docking sites opens a new therapeutic avenue. If HS binding is critical for initial attachment and entry, then blocking this interaction could prevent infection. To test this hypothesis, Han and colleagues used pixantrone, a clinically used HS-binding agent.1 Pixantrone is an anthracenedione derivative, typically employed in oncology for its DNA-intercalating properties, but it also possesses strong HS-binding capabilities. The choice of a clinically approved agent is significant, as it suggests a more direct path to repurposing if the mechanism proves robust.

The results were unequivocal: pixantrone strongly inhibited the SARS-CoV-2 Omicron JN.1 subvariant from attaching to and infecting human airway cells.1 This inhibition was dose-dependent and highly effective, providing strong validation for the HS-mediated entry paradigm. The fact that pixantrone, an existing drug, could disrupt this process suggests immediate translational potential. This finding is particularly relevant for the Omicron JN.1 subvariant, which has demonstrated significant immune evasion and transmissibility, making effective new antiviral strategies highly desirable. The inhibition of both attachment and subsequent infection indicates that targeting HS effectively prevents the entire viral entry cascade.1

The implications extend beyond SARS-CoV-2. Many other viruses are known to bind HS, though HS has typically been considered merely an attachment regulator, facilitating binding to a primary receptor.1 If the revised entry paradigm holds true for other viruses, then HS clusters could represent a broadly applicable anti-viral strategy. This could include viruses like herpes simplex virus, human papillomavirus, and respiratory syncytial virus, all of which utilize HS for initial cell surface interactions. The study posits that the mechanism observed for SARS-CoV-2, where HS clusters mediate

endocytosis and ACE2 acts downstream, may be a general principle for a wider array of viral pathogens. This broad applicability would significantly amplify the impact of these findings.

The Role of ACE2 Re-evaluated

The study does not entirely dismiss ACE2 but redefines its function. Instead of being the initial attachment receptor, ACE2 appears to be essential for subsequent steps, specifically viral genome expression, which is vital for the virus to replicate.1 This suggests a sequential process: HS clusters facilitate the initial physical attachment and internalization of the virus into endosomes, and only then does ACE2 become involved, likely in the uncoating or release of the viral genome into the host cell cytoplasm. This two-step model provides a clearer understanding of viral entry, integrating both HS and ACE2 into a coherent, albeit revised, pathway.

The precise molecular interactions between the virus, HS clusters, and ACE2, particularly within the endosomal compartment, warrant further investigation. Understanding how ACE2 facilitates genome expression downstream of HS-mediated endocytosis could reveal additional therapeutic targets. For instance, drugs that interfere with the endosomal processing or the ACE2-dependent uncoating step could complement HS-targeting agents. This revised model also explains why some cells with low ACE2 expression can still be infected, as long as they possess sufficient HS clusters.1

The open-label design of the pixantrone experiment is an obvious caveat, as is typical for initial mechanistic studies. While the inhibition was strong and visually confirmed, a blinded, controlled study would provide further clinical-grade evidence. The study was also conducted in vitro using human airway cells. While highly relevant, the complexity of the human respiratory tract in vivo, with its diverse cell types, mucus layers, and immune responses, presents a more challenging environment. Whether pixantrone or other HS-binding agents can achieve similar efficacy and safety profiles in living organisms remains to be seen. The concentration of pixantrone required for inhibition in the study also needs careful consideration for systemic administration, given its existing toxicity profile as a chemotherapeutic agent.1 For clinicians managing infectious diseases, a comprehensive resource like the Oxford Handbook of Infectious Diseases and Microbiology can be invaluable for understanding the broader context of viral pathogenesis and treatment.

The study did not explore the potential for viral escape mutations that might alter HS binding. Given the rapid evolution of SARS-CoV-2, this is a critical consideration for any long-term therapeutic strategy. If HS binding is a highly conserved mechanism across viral variants, then targeting it could offer a more durable antiviral approach compared to therapies that target rapidly evolving spike protein regions. But if mutations can reduce HS affinity, then resistance could emerge. Future research should investigate the structural basis of HS cluster binding and its conservation across different SARS-CoV-2 variants and potentially other HS-binding viruses.1

> **CLINICAL IMPLICATIONS**
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> This research fundamentally reorients our understanding of SARS-CoV-2 entry, moving heparan sulfate clusters to the forefront of initial viral attachment. For clinicians, this means that therapies targeting ACE2, while still relevant for downstream viral processes, may have missed the earliest, most critical point of intervention. The focus should now broaden to include agents that disrupt HS interactions.
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> The finding that pixantrone, an existing drug, effectively blocks SARS-CoV-2 attachment is particularly compelling. While its current use in oncology presents challenges for repurposing as a widespread antiviral,

> the principle is established. Pharmaceutical companies should now prioritize the development of novel, safer HS-binding agents specifically designed for antiviral prophylaxis or early treatment.
> This revised paradigm also has implications for patient care beyond COVID-19. If HS clusters are indeed common docking sites for a range of viruses, then a single class of HS-targeting antivirals could offer broad-spectrum protection. This would be a significant advancement, potentially simplifying treatment algorithms and reducing the burden of multiple viral infections, especially in vulnerable populations.
> The challenge now lies in translating these mechanistic insights into clinically viable treatments. The efficacy of HS-targeting agents in human trials, their safety profiles, and their potential for combination therapy with existing antivirals will need rigorous evaluation. The field needs to move quickly from nanoscopy to clinical pharmacology.

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