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LETTER TO THE EDITOR

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SARS-COV-2 and infectivity: Possible increase in infectivity associated to integrin motif expression

To the Editor,

Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) represents the causal agent of a potentially fatal disease (coronavirus disease 2019) that is actually of great global public health concern.

SARS-COV-2 has diffused throughout the world surprisingly fast demonstrating a far greater infectivity than previously known human coronaviruses and it is also responsible for an unusual high variety of symptoms in affected patients.

Since viruses need to penetrate cells to replicate, one of their most important characteristics is the ability to interact with the cell membrane.

Different viruses utilize different approaches to penetrate into the cell, but they all use cell receptors through a method that mimics the receptor's ligand binding.

The virus transmission efficiency is directly correlated to the affinity of the virus to its cell membrane receptor. The presence of different receptors for the same virus on different cell types has been demonstrated, but even on the same cell, there can be different kind of receptors for the same virus.

It has been proposed that SARS-COV-2 has acquired the spike glycoprotein RGD (KGD in SARS-CoV)[1] integrin-binding site which is considered significant for the virus transmission efficiency. The sequence arginine-glycine-aspartic acid (RGD) was identified as a general integrin-binding motif, but individual integrins are also specific for particular protein ligands.

The most common of these motifs is the minimal peptide sequence for binding integrins, RGD, which is known for its role in virus infection via its ability to interact with over half of the more than 20 known integrins.[2,3] However, not all virus-integrin interactions are RGD-dependent. Non-RGD binding integrins have also been shown to effectively promote virus entry and infection. This type of virus-integrin binding is shown to facilitate adhesion, cytoskeleton rearrangement, integrin activation, and increased intracellular signaling.

The tripeptide LDI is also present in the spike glycoprotein SARS-COV-2.

SARS-CoV-2 554 TLEILDIT 633

SARS- CoV 540 TSEILDIS 619

BAT-Cov 563 TLEILDIT 642

Integrins are a family of cell surface receptors, formed through a noncovalent association of two type I transmembrane glycoproteins, the 18-α and 8-β subunits, which combine to form at least 24 different heterodimers to mediate the attachment of cells to the extracellular matrix as well to other cells. Integrins are widely expressed and every nucleated cell in the body owns a specific integrin signature.

Of note, the regulation of integrins is dynamic and quickly changes once cells are taken out of their normal environment. Integrins interaction with their extracellular ligands is tunable by microenvironment signals, such as chemokines and growth factors. It has been demonstrated that this kind of interaction is strictly correlated to the progression of many diseases such as tumors and chronic inflammatory disorders.

A few integrins are more restricted than others to certain cell lineages, but the expression is often developmentally regulated. Integrins were also found to be overexpressed on the surface of several inflamed tissues.[4] Besides the fibronectin binding motif RGD, other integrin-binding sites are specifically expressed in SARS-COV-2, and, particularly, a change from a LDV to a LDI motif is likely significant. The LDV/LDI switch in human immunodeficiency virus infection has been shown to play a key role in strain diffusion, contributing to high viral infectivity.[5]

We investigated the protein sequence of the human coronavirus and compared it to SARS and bat coronavirus to identify any eventual overexpression of other integrin-binding sites.

As expected, many integrin-binding motifs were conserved on the three sequences, but others were differently distributed. Interestingly, binding sequences of the SARS-COV-2 seems to be more similar to bat virus than SARS-Cov virus. Orf1ab polyprotein has many integrin-binding motifs implicated in cell adhesion with binding sites on Fibronectin, Tenascin_C, and VCAM. This polyprotein has RGD (KRGDK), LDI, LDV, LDG, LDS, LET, KTS, IDG homologous sequences LDV and IDA, LDA and IDS, all these serving as ligand binding sites for alpha/beta subfamilies of integrin.[3,6-8]

SARS-CoV-2 LIQPIGALDISASIVA 3034

SARS-CoV LVQPVGALDVSASVVA 3011

BAT-Cov LIQPIGALDISASIVA 3033

On the basis of these preliminary observations, we agree on the importance of focusing research studies on integrin-binding sites and their correlation with viral transmission efficiency. The interaction of integrins with their ligands or their expression in different tissues and cells may be considered as potential therapeutic targets. These class of therapeutic agents has already been developed for the treatment of oncologic and chronic inflammatory diseases making possible treatments readily available if proven effective. Of additional interest is the use of molecules able to interfere with cytokines production,[9] as these biomolecules are responsible for the modulation of integrin expression.[10-15]

Our conclusion is that further investigation into any possible links between integrin-binding peptides and their correlation with coronavirus infectivity and diffusion are needed, especially considering that their possible inhibition could be a potential therapeutic target for the SARS-COV-2 infection.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

IT, VM, and AM contributed equally to this paper. CFS contributed in sequence analysis.

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REFERENCES

1. Sigrist CJ, Bridge A, Le Mercier P. A potential role for integrins in host cell entry by SARS-CoV-2. *Antiviral Res*. 2020;177:104759.
2. Sigrist Hussein HAM, Walker LR, Abdel-Raouf UM, Desouky SA, Montasser AKM, Akula SM. Beyond RGD: virus interactions with integrins. *Arch Virol*. 2015;160:2669-2681.
3. Ruoslahti E. RGD and other recognition sequences for integrins. *Annu Rev Cell Dev*. 1996;12:697-715.
4. Adams JC, Ehrismann RC, Tucker RP. The evolution of tenascins and fibronectin. *Cell Adh Migr*. 2015;9(1-2):22-33.
5. Hait S, Soares EA, Sprinz E, Arthos J, Machado ES, Soares MA. Worldwide genetic features of HIV-1 Env a4b7 binding motif: the local dissemination impact of the LDI tripeptide. *J Acquir Immune Defic Syndr*. 2015;70(5):463-471.
6. Barczyk M, Carracedo S, Gullberg D. Integrins. *Cell Tissue Res*. 2010;339(1):269-280.
7. Takada Y, Ye X, Simon S. The integrins. *Genome Biol*. 2007;8(5):215.
8. Yokosaki Y, Matsuura N, Higashiyama S, et al. Identification of the Ligand Binding Site for the Integrin alpha9 beta1 in the third fibronectin type iii repeat of tenascin-C. *J Biol Chem*. 1998;273(19):11423-11428.
9. Hahn U. Charomers—interleukin-6 receptor specific aptamers for cellular internalization and targeted drug delivery. *Int J Mol Sci*. 2017;18(12):2641.
10. Shimaoka M, Springer TA. Therapeutic antagonists and conformational regulation of integrin function. *Nat Rev Drug Discov*. 2003;2:703-716.
11. Xiao T, Takagi J, Coller BS, Wang JH, Springer TA. Structural basis for allostery in integrins and binding to fibrinogen-mimetic therapeutics. *Nature*. 2004;432:59-67.
12. Pierschbacher MD, Ruoslahti E. Cell attachment activity of fibronectin can be duplicated by small synthetic fragments of the molecule. *Nature*. 1984;309:30-33.
13. O'Connor P. Natalizumab and the role of alpha 4-integrin antagonism in the treatment of multiple sclerosis. *Expert Opin Biol Ther*. 2007;7:123-136.
14. Huang XZ, Wu JF, Cass D, et al. Inactivation of the integrin beta 6 subunit gene reveals a role of epithelial integrins in regulating inflammation in the lung and skin. *J Cell Biol*. 1996;133:921-928.
15. Li H, Huang SY, Shi FH, Gu ZC, Zhang SG, Wei JF. $\alpha 4\beta 7$ integrin inhibitors: a patent review. *Expert Opin Ther Pat*. 2018;28(12):903-917.