Correspondence

Possible role of neuropilins in dermatological manifestations of SARS-CoV-2 infection

Dear Editor,

The respiratory route is considered as the primary transmission modality for SARS-CoV-2 infection.[1] SARS-CoV-2 can enter host cells binding the angiotensin-converting enzyme 2 (ACE2). However, ACE2 expression pattern does not match SARS-CoV-2 tissue tropism.[2] It is possible that co-factors are needed for virus-host cell interactions in cells with low ACE2 expression. Neuropilins (NRPs) are cell surface receptors for various ligands, including vascular endothelial growth factor (VEGF).[3] Two isoforms, NRP-1 and NRP-2, display ~44% sequence identity. NRP1 acts mainly as a co-receptor in different cell types, such as neurons and endothelial cells; it is involved in axon control, regulation of cell proliferation, and angiogenesis.[3] SARS-CoV-2 uses the spike (S) protein for cell attachment and entry. Cleavage of S by the host protease furin generates two polypeptides, S1 and S2, and a sequence on S1 is capable to bind NRPs. Very interestingly, the expression patterns of ACE2 and NRPs in human lung tissue and olfactory epithelium have been compared: ACE2 was detected at very low levels, while NRP1 and NRP2 were richly expressed.[2] In addition, autopsies on COVID-19 patients revealed SARS-CoV-2-infected cells including olfactory neuronal cells covering the nasal cavity positive for NRP1.[2] Thus, SARS-CoV-2 may potentially enter cells using NRP1 as co-receptor or as a unique receptor if viral loads are high.[2] Several viruses capable of inducing dermatological disorders use NRPs as entry factors, such as Epstein-Barr virus (EBV), human cytomegalovirus (HCMV), and human T-lymphotropic virus-1 (HTLV-1). To date, no studies have investigated the role of NRPs at cutaneous level in COVID-19 patients, even if dermatological manifestations are a well-known sign of SARS-CoV-2 infection. Indeed, NP1 is highly expressed in keratinocytes.[3] It is involved in the inhibition of keratinocytes' migration and in the suppression of UV-induced keratinocytes' apoptosis.[3] NRP1 also regulates angiogenesis and initiates proliferation of keratinocytes in psoriatic skin. Keratinocytes and endothelial cells express both VEGF receptors (VEGF-Rs) and NRPs, which are able to enhance VEGF's effects. Keratinocytes-derived VEGF acts not only on the endothelial cells of the dermis but also on the same keratinocytes, in an autocrine stimulation manner. Of note, VEGF-A levels in COVID-19 patients correlated positively with disease severity and acute respiratory distress syndrome (ARDS) development.[4] Thus, we hypothesize not only that NRPs may constitute receptors or co-receptors used by SARS-CoV-2 to enter keratinocytes but also the existence of a pathophysiological loop between VEGF-Rs and NRPs expressed by cutaneous endothelial cells and keratinocytes, contributing to the onset of skin lesions in COVID-19 patients. Interestingly, an upregulation of NRP1 and NRP2 in lung tissue from COVID-19 subjects has been detected.[5] If a similar upregulation also occurred in the skin, could a different level of keratinocytes' NRPs expression explain why some individuals show skin manifestations and others do not? We do not know.

Ours are only hypotheses, but we believe they could be useful to direct researchers' investigations toward the clarification of the pathogenetic mechanisms of a disease not yet fully understood, which still claims victims all over the world.

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Telogen effluvium in the new SARS-CoV-2 era

Dear Editor,

SARS-CoV-2 infection is well known to produce various dermatologic manifestations, including affection of skin and hair.[1] Telogen effluvium (TE) is one of the most common forms of hair loss, especially in women.[2] It is a nonscarring alopecia