

A Probable Role for Zonula Occludens-1, a Tight Junction Protein, in the Pathogenesis of Human Lung Cytomegalovirus Infection

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To the Editor,

Tight Junctions (TJs) are areas where adjacent cell membranes join together to form an almost impermeable barrier to fluid. They hold cells together and serve both as protective and functional barriers. The integrity of the tight junction is crucial to restrict the dissemination of microorganisms [1]. Thus, it is conceivable that microbes may target tight junctions during their life cycle. Using Immuno Histo Chemistry (IHC) applied on formalin-fixed, paraffin tissue sections [2]; we have investigated the possible involvement of Zonula Occludens-1 (ZO-1), a 225 kDa tight junction protein, in several different viral infections.

A total of 9 different viruses were studied, comprising 4 paramyxoviruses (Nipah virus (NiV), Measles Virus (MeV), Canine Distemper Virus (CDV) and Tioman virus (TioPV)), 3 herpesviruses, (Herpes Simplex-1 (HSV-1), Human Cytomegalovirus (HCMV) and Epstein-Barr Virus (EBV)), 1 flavivirus (dengue virus, DenV) and 1 picornavirus (enterovirus-71, EV-71). The source of infected tissues/cell for each virus was as followed: NiV (human brain), MeV (human brain), CDV (dog brain), TioPV (mouse brain), HSV-1 (human skin biopsy), HCMV (human lung, colon), EBV (Raji cells),

DenV (mouse brain) and EV-71 (mouse brain). Five micron thick paraffin sections were dewaxed and subjected to IHC following proteinase k and/or microwave to unmask the antigens. Anti-ZO-1 antibody or the respective antibodies to specifically detect viral antigens were used as the primary antibody. The immunoreactivity was revealed by DAB as chromogen.

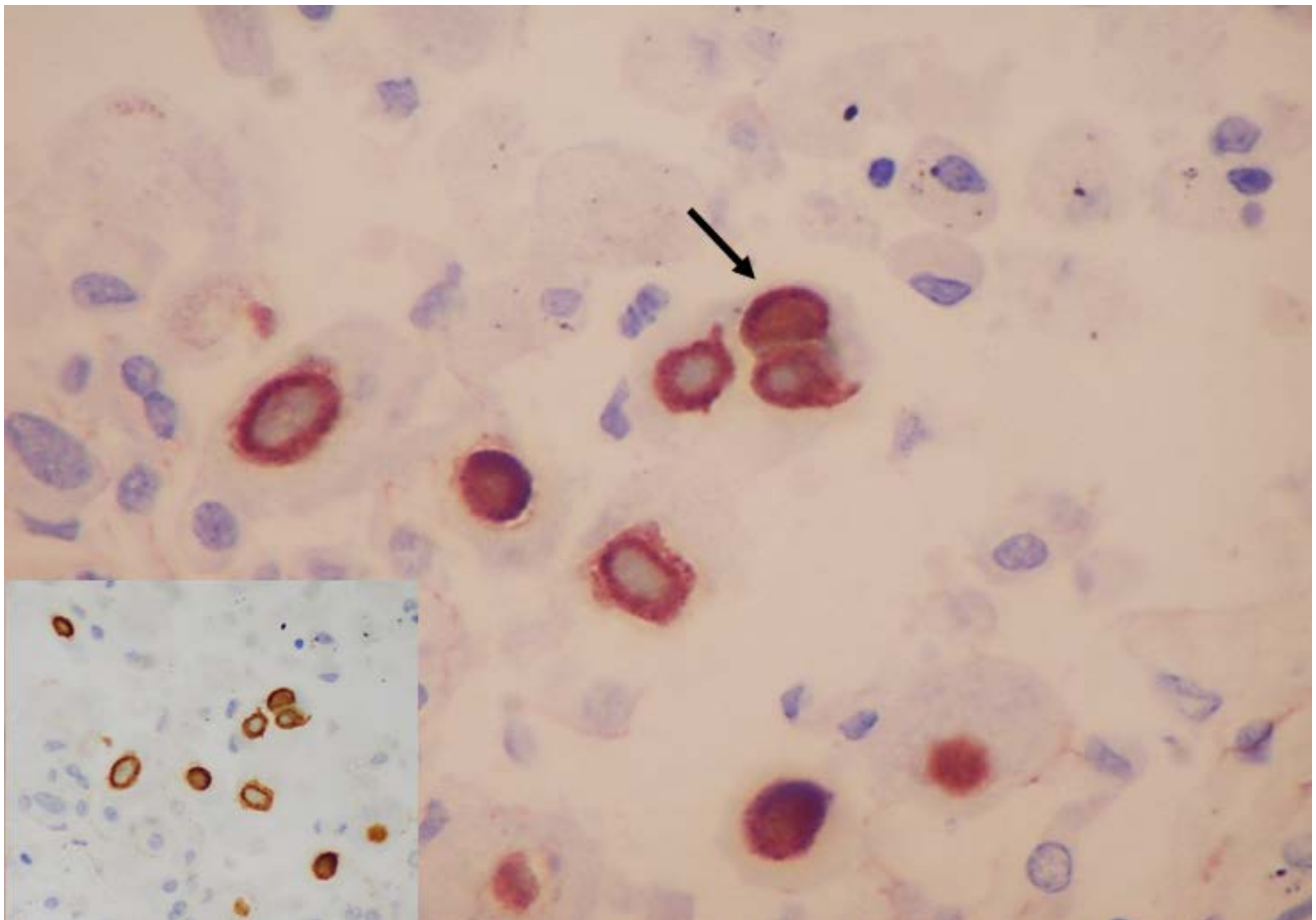
The ZO-1 immunostaining revealed strong, continuous vascular endothelial staining in TioPV-, CDV- and DenV-infected tissues. A more diffuse ZO-1 staining pattern was observed in HSV-1 and EBV infections (unpublished observations). Only subtle immunostaining was noted in MeV-infected human brain, whereas no positive staining was observed in NiV infection, possibly due to severe tight junction disruption. Nuclear accumulation of ZO-1 was observed predominantly in "Owl's eye" viral inclusions, a hallmark of HCMV infection (Figure 1), and appeared to co-localize with HCMV viral antigens in the infected lung tissue (Figure 1, inset). Interestingly, similar ZO-1 nuclear immunostaining was not observed in HCMV-infected colon tissue, where only the endothelial staining pattern of ZO-1 was detected.

Many pathogens are known to exploit TJs for their advantages [1]. We demonstrated here not all viral infections involved the disassembly of ZO-1. Our study also revealed a possible intimate relationship between ZO-1 and HCMV infection in lung. To the best of our knowledge, this is the first in vivo evidence of co-localization of HCMV antigens and ZO-1 in

“Owl’s eye” nuclear viral inclusions. We postulate that ZO-1 might play an active role in the formation of HCMV nuclear

inclusions. Further study is warranted to dissect the role of ZO-1 in the pathogenesis of HCMV pneumonitis.

Figure 1: Zonula occludens-1 (ZO-1) immunostaining in “Owl’s eyes” cell (arrow), the hallmark of HCMV infection in a pneumonitis patient. Inset, HCMV antigens immunostaining. Obj. x400.



References

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