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Endothelial growth factor receptor (EGFR) is likely to be a cellular receptor for elephant endotheliotropic herpesvirus (EEHV)

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Elephant endotheliotropic herpesvirus (EEHV) is one of the most virulent and highly fatal viral infections affecting Asian elephants (Elephas maximus) worldwide. EEHV is an enveloped, double-stranded DNA virus that belongs to the genus Proboscivirus. Most EEHV-infected cases are predominantly associated with lesion, edema and hemorrhaging in the internal organs. Based on genetic distinctions, EEHVs have been classified into 8 genotypes that include EEHV1A, EEHV1B and EEHV2-7, for which the clinical characteristics differ among EEHV genotypes. Currently, in vitro isolation of EEHV through the use of various cells has been tested intensively, but the results have remained unsuccessful in recognizing EEHV as one of the most challenging viruses for detection and eradication. To date, despite pathogenesis underlying the EEHV-hemorrhagic disease (EEHV-HD) has been proposed, the cellular receptors that EEHV might use to infect target cells remained to be determined. It is known that beteherpesviruses, including human cytomegalovirus (HCMV), have a broad range of cell tropism for virus infection. The broad range of target cell types indicate that the virus uses several cellular receptors for cell entry. There have been shown that platelet derived growth factor receptor (PDGF) is among the most important cellular receptors for HCMV. Since EEHV is targeted several cell types similar to that of HCMV and it also shared several similarity resembling that of betaherpesviruses, it is interesting to know whether PDGF involves in the infection and entry of EEHV. In the present study, we then aimed to investigate the potential cellular receptor for EEHV infection in Asian elephants. Formalin-fixed paraffine embedded (FFPE) samples of EEHV-HD and elephants died due to non-EEHV infected cases were obtained and included in the study. FFPE samples of the heart, spleen, lungs, liver, kidney, intestine and tongue were subjected to determine for the presence of the PDGF, EEHV glycoprotein B (EEHV-gB) and EEHV-DNA polymerase (EEHV-DNApol) proteins by an immunohistochemistry and double immunofluorescence, compared to the negative controls. The results indicated that co-localizations of PDGF and EEHV-gB or EEHV-DNApol antigens were shown to be observed in the monocytes/macrophages and epithelia of the EEHV-HD cases. Since EEHV-DNApol protein was shown to be the replicative marker of EEHV in the infected cells, the double immunostaining of PDGF and DNApol could likely indicative the role of this molecule in processes of EEHV infection. Furthermore, the results also demonstrated that not all EEHV immunolabelling positive cells were positive for the PDGF immunostaining. These findings suggested that other cellular receptors in elephant cells may also play a role in EEHV infection and entry. To the best of our knowledge, this is the first study to demonstrate the potential candidate cellular receptor for EEHV infection in vivo. Further studies are required to fulfill the pathomechanisms of EEHV-HD in Asian elephants.