特集3　第50回日本ウイルス学会学術集会イブニングシンポジウム
「ウイルス遺伝子操作技術の進展と応用」

2．Pathogenesis of Ebola Virus Infection in Nonhuman Primates

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Previous vaccine and drug intervention strategies in rodents have, with few exceptions, failed to predict protection of nonhuman primates against infection with Ebola virus（EBOV）. This may be due to the fact that the disease pathology of EBOV in rodents is somewhat different than that reported in human and nonhuman primate infection. The requirements for proof of protection in nonhuman primates by vaccines and/or various chemotherapeutic regimens intended for use in humans, demands that the pathogenesis of the disease and correlates of immunity be understood in nonhuman primates. Insight into the mechanism（s）of pathogenesis came from recent studies in nonhuman primates, where we showed that EBOV infects cells of the mononuclear phagocyte system（MPS）, resulting in apoptosis of bystander lymphocytes.

To further elucidate the pathologic changes that occur in the development of EBOV hemorrhagic fever, and follow the course of infection of the MPS cells, we analyzed sera and tissues collected during a serial study of experimentally-infected nonhuman primates. Results show that dendritic cells and macrophages are early and sustained cellular targets of EBOV in cynomolgus macaques. Increased numbers of apoptotic lymphocytes, primarily NK cells, were detected in peripheral blood at day 3 postinfection, and a significant decrease in the NK cell population was evident by day 4 . RNA analysis of peripheral blood leukocytes showed multiple gene expression patterns；most notable were changes in apoptosis-associated signaling molecules. Increased levels of interferon（IFN）-α, IFN-β, interleukin（IL）-6, IL-18, MIP-1α, and MIP-1β protein were observed in sera of all EBOV-infected monkeys by day 4 , indicating the occurrence of a strong proinflammatory response. Endothelial cells, which have been reported to be primary targets of EBOV, were not infected until the very latest stages of disease（days 5 and 6 ）. We saw evidence of disseminated intravascular coagulation（DIC）by day 4 , and the DIC preceded endothelial cell infection. Increased tissue factor transcripts were detected by day 3 in peripheral blood leukocytes, while fibrin deposits were readily seen in lymphoid tissues by day 4 .

Together, these findings suggest that infection of monocytes/macrophages may trigger cascades of events critical to both the development of hematological abnormalities and immunosuppression that characterizes EBOV infection of primates.

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