新学術領域研究「脳構築における発生時計と場の連携」共催

形態形成セミナー

Virus-targeted CRISPR/Cas9 intervention for congenital cytomegalovirus infection -associated brain deficits

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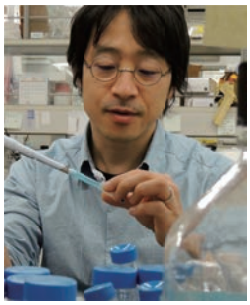

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11月15日（木）17:30 ～

慶應義塾大学信濃町キャンパス　総合医科学研究棟３階　会議室３

Congenital cytomegalovirus (CMV) infection is a significant health problem worldwide, frequently resulting in permanent neurological disabilities and psychiatric dysfunctions, such as microcephaly and intellectual disability. Nevertheless, there are currently no effective treatments, nor vaccines against CMV. Thus, it is awaited to establish good animal models. Here, we establish a novel mouse model to study congenital CMV infection. We first demonstrate the CMV-encoded immediate early 1 (IE1) specifically interferes with a host cellular cascade involving DISC1 and promyelocytic leukemia (PML). Although being a novel mechanism to CMV, this is analogous to the virus-host interaction mechanism in human papilloma virus (HPV) infection which leads to the oncogenic transformation in the host cell. By using this novel mouse model, we show that the interference of DISC1-PML cascade by a specific exogenous viral protein IE1 leads to deficits in neural progenitor proliferation and resultant deficits in behaviors. To look for a novel therapeutic strategy, we paid attention to non-homologous sequences of viral IE1 protein from any host proteins. Thus, we utilized the CRISPR/Cas9 system, and now show that a specific knockout of viral IE1 by CRISPR/Cas9 in utero rescues the CMV-induced brain deficits. Our findings provide insight into a novel cell autonomous mechanism in the pathology of congenital CMV infection, and a direction towards ameliorating the pathology using a virus-targeted CRISPR/Cas9 strategy. This novel therapeutic strategy against infectious agents will be widely applicable to other viruses and pathogens beyond CMV.

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