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Health & Medicine

Editorial on the Research Topic

Immune Control of JC Virus Infection and Immune Failure during Progressive Multifocal Leukoencephalopathy

From a scientific point of view, JCV is one of the most fascinating human viruses. This old, rustic, small, and stable DNA virus has cohabited with humans over the course of evolution (1), silently replicating in kidney epithelial cells and spreading from person to person through urine. Billions of people are infected worldwide, making JCV one of the most successful human viruses. Most remarkably, all this viral activity occurs with no detectable symptoms: even the primary infection appears to be clinically silent. JCV can elicit specific antibodies but its replication in the kidney does not appear to trigger effector T-cell responses (2), which appear more important than antibodies for controlling human polyomaviruses (Durali et al.). JCV replication in the kidneys thus appears to be perfectly tolerated by the human immune system, possibly as a result of long-term co-evolution driven by mutual benefit. However, contrasting with this idyllic picture of pacific and fruitful cohabitation with a discrete neighbor, JCV can on rare occasions become a merciless killer that targets the human central nervous system with lytic infection of glial cells, causing a rapidly fatal demyelinating disease called progressive multifocal leukoencephalopathy (PML). PML occurs almost exclusively in individuals with severe and prolonged immunosuppression that affects T-cells. PML, once a medical curiosity, entered the hall of infamy first during the AIDS pandemic and then as a major adverse effect of potent new immunosuppressive biologics such as

natalizumab. AIDS, hematological malignancies, and natalizumab now account for more than 90% of all PML cases (3).

JCV infection is far from being fully understood, but several outstanding issues are addressed in a series of exciting papers published in this research topic.

Neurovirulent JCV strains that infect the brain are thought to arise from non-pathogenic “ archetypal” viruses that replicate in the kidney, through a process of rearrangement (deletion–duplication) in the non-coding control region of the viral genome, as well as through mutations of the capsid protein VP1. From an evolutionary point of view, one might wonder why such a successful virus has this neurovirulent potential, which does nothing to promote its spread through the population, which is the driving force behind viral adaptation. JCV transmission may occur *via* the oral route (4 – 6). It is conceivable that this neurovirulence is a left-over property from an ancient period in which JCV transmission occurred mainly through brain-eating cannibalism, which appears to have been widespread within and between the different human subspecies that coexisted throughout prehistory (7 – 9). Even more speculatively, a predominantly neurotropic form might have co-evolved with *Homo-sapiens* to become the contemporary pacific archetypal virus. Other intriguing questions include whether or not other humanoid subspecies such as Neanderthals were susceptible to JCV and PML and, if so, whether this virus played a role in the extinction of these *Homo-sapiens* competitors.

Where and when neurotropic JCV variants are generated, and how they reach the brain, are controversial topics. One conventional view is that neurotropic viruses emerge after prolonged immunosuppression, then spread to the brain with the help of B-cells (Durali et al.). However, JCV has been detected in the brains of healthy individuals (10). JCV might, therefore, infect the brain of immunocompetent individuals but would remain under tight immunological control. As suggested by Frost and Lukacher , this control could involve brain-resident memory T-cells, which rely on help from the periphery, provided by re-circulating CD4-T-cells (Krzysiek et al.). This may explain why prolonged treatment with immunosuppressive antibodies such as natalizumab, which block T-cell trafficking, favor PML. JCV infection would thus represent a model of tissue-dependent immune tolerance, being tolerated in the kidney but under tight control in the brain. Frost and Lukacher stress that experimental models of polyomavirus CNS infection are urgently needed to understand the immunological mechanisms underlying PML.

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