Large Isoform of Mammalian Relative of DnaJ is a Major Determinant of Human Susceptibility to HIV-1 Infection

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Individual differences in susceptibility to human immunodeficiency virus type 1 (HIV-1) infection have been of interest for decades. We aimed to determine the contribution of large isoform of Mammalian DnaJ (MRJ-L), a HIV-1 Vpr-interacting cellular protein, to this natural variation. Expression levels of MRJ were assayed in different types of cell and cell lines. Two groups of HIV-1 infected subjects together with uninfected controls were recruited to determine levels of MRJ in their monocyte-derived macrophages. Demographic data, sex behaviors, and HIV-1 infection status were analyzed using Bayesian logistic regression to identify risk factors for HIV-1 infection. Expression of MRJ-L in monocyte-derived macrophages was significantly higher in HIV-infected individuals (n=31) than their uninfected counterparts (n=27) (p=0.009). Fifty male homosexual subjects were further recruited to examine the association between MRJ-L levels and occurrence of HIV infection. Among them, 20/50 developed HIV-1 infection. Bayesian multiple logistic regression revealed that playing a receptive role and levels of MRJ-L in macrophages were two risk factors for HIV-1 infection. Subjects with medium MRJ-L levels had a 7.6 fold increased risk and subjects with high MRJ-L levels had a 41.5 fold increased risk for HIV-1 infection, which was comparable to playing a receptive role (43.9 fold). A 1% rise in MRJ-L expression was associated with a 1.13 fold (95% CrI 1.06–1.29) increase in odds of contracting HIV-1 infection. Ex vivo experiments revealed that MRJ-L facilitated Vpr-dependent nuclear localization of virus. Infection of macrophages is a critical step in HIV-1 transmission, because macrophage-tropic strains are responsible for infecting naïve individuals. MRJ-L is a critical factor in this process; hence, subjects with higher macrophage MRJ-L levels are more vulnerable to HIV-1 infection.

Similar effects of MRJ-L on viral replication have been observed in human cytomegalovirus and HIV-2. This suggests that MRJ pathway is commonly exploited by various viruses for nuclear trafficking of viral proteins. Intervention strategy aiming to disturb MRJ-L may be a safe and effective way for many viral infections and worth pursuing in the future.