Chiara Stefani et al., Madridge J Cancer Stud Res. 2019
http://dx.doi.org/10.18689/2640-5180.a4.008

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5th International Conference on
Oncology & Virology

July 25-26, 2019 Rome, Italy

Study of HLA-C Binding Stability in HIV-1 Infection and in Cognitive Disorders

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MHC-I is an heterotrimeric complex composed by HLA-C/β_2-microglobulin/peptide. The different HLA-C variants can be grouped into stable and unstable clusters based on their binding stability to β_2-microglobulin. The presence of unstable HLA-C molecules increases β_2-microglobulin release. It is known that patients affected by AIDS Dementia Complex (ADC), a very severe neurological condition of HIV-1 infection, present high level of β_2-microglobulin in the cerebrospinal fluid. We observed a higher frequency of unstable HLA-C alleles in ADC patients. We demonstrated that, upon HIV-1 infection, HLA-C molecules associate with HIV-1 virions, increasing viral infectivity. In addition, HIV-1 virions produced in the presence of unstable HLA-C variants are more infectious.We aimed to evaluate how each HLA-C variant affects the ADC onset in HIV-1 infected patients. To assess the contribution of each HLA-C variant in the modulation of HIV-1 infection, CRISPR/Cas9 was used to generate 293T HLA-$C^{-/-}$ packaging cells. The different HLA-C alleles were transfected in 293T HLA-$C^{-/-}$ cells, to develop different cell lines expressing a specific HLA-C allotype. The different cell lines will be used to produce HIV-1 pseudotyped viruses to be tested in infectivity assays conducted on TZm-bl cells. Furthermore, to assign stability score to each HLA-C variant, based on their dissociation rate from β_2-microglobulin, each HLA-C expressing cell line will be treated with an acid wash, to study the kinetic of β_2-microglobulin dissociation from HLA-C. These analyses will be fundamental to clarify the relationship between HLA-C binding stability, HIV-1 infection progression and the development of HIV-1 related neurocognitive diseases.