Human cytomegalovirus: A major regulator of IFN-g induced antimicrobial and immunoregulatory effects in human mesenchymal stem cells

W. Däubener\(^1\), S. Brockers\(^1\), K. Spekker\(^1\), R. Meisel\(^2\), R. Sorg\(^3\), S. Stuhlsatz\(^1\), S.K. Schmidt\(^1\), K. Heseler\(^1\)

\(^1\)Heinrich-Heine Universität, Medizinische Mikrobiologie und Krankenhaushygiene, Düsseldorf, Germany  
\(^2\)Heinrich-Heine-Universität, Clinic for PEdiatric Oncology, Hematology and Clinical Immunology, Düsseldorf, Germany  
\(^3\)Heinrich-Heine-University, Institute for Transplantation Diagnostics and Cell Therapeutics, Düsseldorf, Germany

Published on 23 Oct 2010

The IFN-\(\gamma\)-inducible enzyme indoleamine 2,3-dioxygenase (IDO) catalyzes the conversion of tryptophan to kynurenine. This enzyme is able to mediate antimicrobial functions which result in an inhibition of e.g. Toxoplasma gondii or Staphylococcus aureus. Furthermore, it is known that IDO-activity also leads to immunoregulatory effects, which inhibit T cell proliferation. Here, we analysed the influence of the human cytomegalovirus (hCMV) on IDO-mediated effects in human mesenchymal stem cells (MSC). This pathogen is known to be able to inhibit the IFN-\(\gamma\)-signalling pathway. As all herpes viruses hCMV has the characteristic ability to remain latent within the body over long periods. The infection or reactivation can be life threatening for patients, who are immunocompromised for example: patients with HIV, organ transplant recipients or neonates.

We recently detected that IFN-\(\gamma\)-stimulated human MSC mediate antibacterial, antiparasitical, antiviral and immunoregulatory effects in an IDO-dependent manner. The IDO-dependency of these effects was shown by the abrogation of antimicrobial effects by the supplementation of tryptophan or by the addition of the IDO-specific inhibitor 1-methyltryptophan.

Here, it is shown that an infection with hCMV reduces the IFN-\(\gamma\) induced IDO-activity in human MSC. This suppressive effect of hCMV can be explained by an inhibition of the IFN-\(\gamma\) signalling pathway. We observed that the inhibition of IDO-activity results from a dramatic reduction of IDO transcription and translation in infected cells. Consequently, these cells were no longer able to restrict bacterial and parasitic growth and, furthermore, these hCMV-infected cells lost their IDO-mediated immunosuppressive capacity. This coherence between virus infection and inhibition of IDO-induction still gains more importance in the case of organ or haematopoetic stem cell transplantation. From clinical observations it is known that after transplantations an active hCMV infection results in an increased risk of infection and in a higher risk of transplant rejection. Both effects could be explained by the observations...
of the hCMV-infection’s influence on IDO-activity in our *invitro* systems.