Identification of potent HCMV-neutralizing antibodies targeting novel binding sites on the trimeric and pentameric surface complex.

M. Zehner[1,8], M. Alt[2], A. Ashurov[1], J. Goldsmith[3], K. Laib Sampaio[4], R. Spies[4], N. Weiler[4], D. Stoehr[4], C. Stegmann[5], M.S. Ercanoglu[1], L. Gieselmann[1], C. Kreer[1], S. Dähling[1], R. Lotfi[6], B.J. Ryckman[5], M. Koch, J.S. McLellan[3], A. Krawczyk[2], C. Sinzger[4], F. Klein[1]

[1] Institute of Virology, University Hospital Cologne, University of Cologne, Cologne, Germany
[2] Department of Infectious Diseases, University Hospital Essen, Essen, Germany.
[3] Department of Molecular Biosciences, University of Texas, Austin, TX, USA
[4] Institute for Virology, Ulm University Medical Center, Germany
[5] Division of Biological Sciences, University of Montana, Missoula, Montana, USA
[6] Institute for Transfusion Medicine, Ulm University Medical Center, 89081 Ulm, Germany
[7] Institute for Dental Research and Oral Musculoskeletal Biology and Center for Biochemistry, Faculty of Medicine and University Hospital Cologne, University of Cologne, Köln, Germany
[8] Contact address: matthias.zehner@uk-koeln.de

The human cytomegalovirus (HCMV) is a highly prevalent, host-adapted β-herpes virus with a seroprevalence of 56 to 94%. Thereby, HCMV can cause a variety of serious and fatal diseases of the fetus, newborns, and immunocompromised patients. So far, there is no approved HCMV vaccine, and treatment options are limited.

Monoclonal antibodies (mAbs) targeting HCMV gH/gL/gO (trimer) and gH/gL/pUL128/pUL130/pUL131A (pentamer) complexes are increasingly seen as a promising option for treatment and prevention of HCMV infections. In a previous study, 58 individuals with highly potent plasma neutralizing activity were identified among 9000 HCMV-seropositive donors. From four of these individuals we isolated 1,978 trimer or pentamer reactive B-cells and derived 299 mAbs, of which 157 mAbs were found to be strongly reactive for HCMV glycoproteins. The majority of these mAbs target the shared gH/gL-subunit, eight antibodies were found to be specific to the pUL128/pUL130/pUL131A-subunits of the pentamer and one antibody recognized the gO-subunit of the trimer. Moreover, competitive binding assays and crystal structure analysis highlight that the isolated mAbs cover a broad range of binding sites including seven so far not described target areas. In total, we identified 12 highly potent neutralizing antibodies (nAbs) blocking infection of fibroblasts (IC_{50} <100ng/mL) and 17 nAbs efficiently protecting endothelia and epithelia cells (IC_{50} <25ng/ml). Interestingly, the most promising antibody candidate potently neutralized eight laboratory strains as well as six different clinical isolates of HCMV and is superior to the phase 2 clinical trial antibody MCMV5322A. However, it did not compete with two main HCMV entry receptors for glycoprotein binding. This suggests that the neutralization activity occurs via a mechanism distinct from receptor antagonism.

Taken together, our findings show a complex composition of the humoral immune response against HCMV infection with the isolation of novel and potent neutralizing antibodies that are promising for the use as antiviral therapeutics. In particular, the combination of trimer and pentamer specific antibodies with strong neutralizing properties to different epitopes and neutralization mechanisms presents an effective approach for preventing and treating HCMV infection.