Human Cytomegalovirus Infection Enhances NK Cell Activity In Vitro

Astrid Tschan-Plessl, Martin Stern, Laurent Schmied, Christelle Retière, Hans H Hirsch, Christian Garzoni, Christian Van Delden, Katia Boggian, Nicolas J Mueller, Christoph Berger, Jean Villard, Oriol Manuel, Pascal Meylan & Grzegorz Terszowski

BACKGROUND
Occurring frequently after solid organ and hematopoietic stem cell transplantation, cytomegalovirus (CMV) replication remains a relevant cause of mortality and morbidity in affected patients. Despite these adverse effects, an increased alloreactivity of natural killer (NK) cells after CMV infection has been assumed, but the underlying physiopathological mechanisms have remained elusive.

METHODS
We used serial analyses of NK cells before and after CMV infection in kidney transplant recipients as an in vivo model for CMV primary infection to explore the imprint of CMV infection using every patient as their own control: We analyzed NK cell phenotype and function in 47 CMV seronegative recipients of CMV seropositive kidney grafts, who developed CMV primary infection posttransplant. Seronegative recipients of seronegative kidney grafts served as controls.

RESULTS
We observed a significant increase of NKG2C expressing NK cells after CMV infection (mean increase, 17.5%; 95% confidence interval [95% CI], 10.2-24.9, P < 0.001), whereas cluster of differentiation (CD)57 expressing cells decreased (mean decrease, 14.1%; 95% CI, 8.0-20.2; P < 0.001). Analysis of killer immunoglobulin-like receptor (KIR) expression showed an increase of cells expressing KIR2DL1 as their only inhibitory KIR in patients carrying the cognate ligand HLA-C2 (mean increase, 10.0%; 95% CI, 1.7-18.3; P = 0.018). In C2-negative individuals, KIR2DL1 expression decreased (mean decrease, 3.9%; 95% CI, 1.6-6.2; P = 0.001). As for activating KIR, there was no conclusive change pattern. Most importantly, we observed a significantly higher NK cell degranulation and IFNγ production in response to different target cells (target K562, CD107a: mean increase, 9.9%; 95% CI, 4.8-15.0; P < 0.001; IFNγ: mean increase, 6.6%; 95% CI, 1.6-11.1; P < 0.001; target MRC-5, CD107a: mean increase, 6.9%; 95% CI, 0.7-13.1; P = 0.03; IFNγ: mean increase, 4.8%; 95% CI, 1.7-7.8; P = 0.002).
CONCLUSIONS
We report evidence for an increased function of NK cells induced by CMV infection. This increased in vitro functionality was seen in NKG2C-positive and NKG2C-negative subsets, arguing for an NKG2C independent mechanism of action.