Viral Impact on Long-term Kidney Graft Function

Ilkka Helanterä, MD, PhD[a,b], Adrian Egli, MD, PhD[c,d], Petri Koskinen, MD, PhD[b], Irmeli Lautenschlager, MD, PhD[a,e], Hans H. Hirsch, MD, MS[c,f,*]

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In the past 2 decades, novel potent immunosuppressive regimens have helped to significantly reduce graft lost caused by acute rejection from 30% to 15% across HLA- and ABO-mismatches. However, in the same time period, infectious complications have steadily increased.[1] Viral infections 6 months after transplant have significantly increased from 10% to 30%.[2,3] Immunosuppression unspecifically blocks the function of immune effectors including those needed to control microbes and their infectious complications.[4] In addition, virus replication may trigger long-term effects through inflammation with cytokine release and induction of fibrosis.[5,6] These factors may contribute to reduced graft function and survival. In kidney transplant recipients, early cytomegalovirus (CMV) reactivation has been associated with reduced graft function in the following years.[6]

Reactivation of latent virus infection and uncontrolled viral replication following transplantation is common, especially in the classic high-risk situation of transplanting

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I.H. and A.E. equally contributed to this article.

[a] Transplant Unit Research Laboratory, Transplantation and Liver Surgery Clinic, Helsinki University Hospital, and University of Helsinki, Meilahti, PL 340, Helsinki, FI-00029 HUS, Finland
[b] Department of Medicine, Division of Nephrology, Helsinki University Hospital, and University of Helsinki, PL 263, Helsinki, FI-00029 HUS, Finland
[c] Department of Biomedicine, Transplantation Virology, Institute for Medical Microbiology, University of Basel, Petersplatz 10, CH-4003 Basel, Switzerland
[d] Department of Medicine, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland
[e] Department of Virology, Helsinki University Hospital, and University of Helsinki, PL 400, Helsinki, FI-00029 HUS, Finland
[f] Department of Internal Medicine, Infectious diseases and Hospital Epidemiology, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland
* Corresponding author. Department of Biomedicine, Transplantation Virology, Institute for Medical Microbiology, University of Basel, Petersplatz 10, CH-4003 Basel, Switzerland.
E-mail address: Hans.Hirsch@unibas.ch

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the graft of a seropositive donor (D+) into a seronegative recipient (R−). Despite receiving (val)ganciclovir prophylaxis, 40% of CMV D+R− patients seroconvert within the first 6 months after solid-organ transplantation (SOT).[7] For polyomavirus BK (BKV), low-level BK viruria of less than 5 log10 genome equivalents (geq)/mL is found in 5% to 10% of immunocompetent healthy blood donors, but high-level BKV viruria of more than 7 log10 geq/mL is observed in up to 60% of urine samples from SOT recipients.[8–12] On the one hand, the procedure of transplantation is associated with stress signals resulting from brain death, ischemia, inflammatory mediators, catecholamines, and drugs. Intracellular transduction may activate transcription factor sites shared by host and virus genes such as NFkB, AP1, glucocorticoid regulatory elements that among others stimulate virus reactivation and replication.[11,13,14]

On the other hand, virus replication is kept in check by virus-specific cellular immune surveillance mediating deletion of infected cells in immunocompetent individuals.[4,15–20] Current immunosuppressive protocols unspecifically reduce the quality (function) and quantity (frequency) of the virus-specific immune response. Accordingly, CMV-specific T cells are low or absent early after transplantation when CMV replication is observed.[16,20–24] Calcineurin inhibitors interfering with signal 1 of T-cell activation cause a dose-dependent decrease of interferon gamma (IFNγ) releasing BKV- and CMV-specific T cells, whereas antiproliferative drugs such as mycophenolic acid leave IFN production unaffected, but interfere with antigen-specific T-cell expansion.[25,26] Particularly in the first 3 months after transplant, when immunosuppression is more intense, BKV-specific killing function is inhibited.[27,28] Thus, immunosuppression interferes with the quality and quantity of virus-specific immune effectors thereby disturbing the balance of virus replication and control (**Fig. 1**).

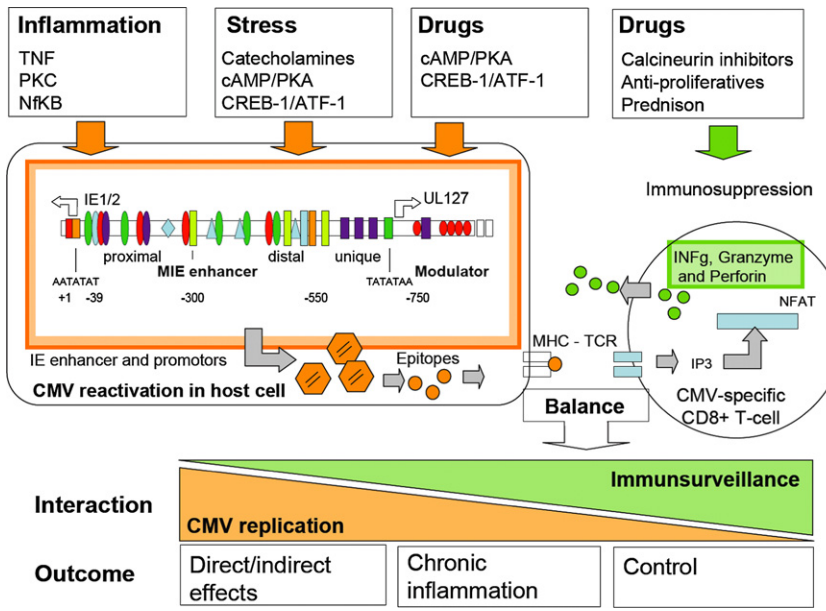

Fig. 1. Reactivation and control of virus. The binding of stress factors leading to an intracellular reactivation of CMV is shown. In parallel, CMV-specific T cells controlling the amount of virus epitope expressing host cells are suppressed by drugs. The balance between replication and control defines the patient's outcome.