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MINI REVIEW

Oncomodulation by human cytomegalovirus: evidence becomes stronger

Martin Michaelis · Hans Wilhelm Doerr · Jindrich Cinatl Jr

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The human cytomegalovirus (HCMV), a ubiquitous herpes virus, establishes after (in healthy individuals typically subclinical) primary infection a lifelong persistence characterised by more or less frequent subclinical reactivations. It is an important pathogen in immunocompromised individuals and currently investigated for a plethora of different questions and aspects [1–25]. The (possible) relationship between HCMV and cancer has been discussed for decades [1]. Detection of viral DNA, mRNA and/or antigens in tumour tissues as well as seroepidemiologic evidence suggested a role of HCMV infection in several human malignancies. However, controversial clinical results from different groups had raised skepticism about a role of HCMV in cancer [1].

A major point of concern is that HCMV is not considered to be a tumour virus due to a lack of proven transformation potential in human cells. To explain the frequent presence of HCMV in tumour tissues, we proposed the concept of oncomodulation [26]. Oncomodulation means that HCMV may infect tumour cells and increase their malignancy. We postulated that tumour cells provide a genetic environment, characterised by disturbances in intracellular signalling pathways, transcription factors, and tumour suppressor proteins, that enables HCMV to exert its oncomodulatory potential while it cannot be manifested in normal cells (Fig. 1) [1].

Our experimental findings and those of others supported the concept of oncomodulation. Sub-cutaneous injection of long-term persistently HCMV-infected neuroblastoma cells resulted in enhanced tumour growth and metastasis formation compared to non-infected cells [26]. Subsequent in vivo findings by others supported the oncomodulatory effects of HCMV or murine cytomegalovirus proteins expressed in transformed cells [1].

HCMV-induced oncomodulation may result from the activity of virus regulatory proteins and noncoding RNAs which influence properties of tumour cells including cell proliferation, survival, invasion, immunogenicity, tumour angiogenesis, and chromosomal stability [1].

Although it is necessary to stress that no final conclusion about the (frequency of the) presence of HCMV in cancer cells and its effects on tumour biology can be drawn, recent pathological findings from different groups using highly sensitive techniques for virus detection indicated the presence of genome and antigens of HCMV in tumour cells (but not in adjacent normal tissue) of a great proportion of patients with malignancies, such as colon cancer, malignant glioma, prostatic carcinoma, and breast cancer [1, 27–30]. These observations indicated that HCMV causes low-grade infection in tumour cells probably sustained by persistent virus replication.

The establishment of low-grade infection by HCMV in tumour cells provides an explanation why HCMV was not detected in tumour cells by different other groups [1, 31–33]. These groups used pathological methods established for the detection of active HCMV replication, characterised by high HCMV titres and presence of high levels of HCMV proteins and HCMV genome that obviously fail to detect low-level replication. It might be helpful to exemplarily discuss pathological findings from glioma patients. Cobbs et al. [27] reported HCMV infection of tumour cells but not of surrounding normal brain tissue in a high percentage of gliomas. These findings were not confirmed by Lau et al. [31] or Polterman et al. [32], who both did not detect

M. Michaelis · H. W. Doerr · J. Cinatl Jr (✉)
Institut für Medizinische Virologie,
Klinikum der Johann Wolfgang Goethe-Universität,
Paul Ehrlich-Str. 40, 60596 Frankfurt am Main, Germany
e-mail: cinatl@em.uni-frankfurt.de

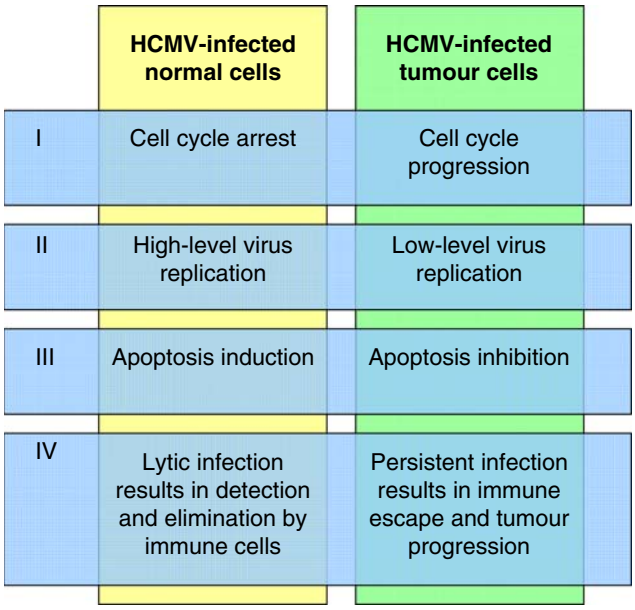

Fig. 1 Hallmarks of virus replication and cellular responses to HCMV infection in normal permissive and tumour cells. In normal permissive cells, HCMV infection induces cell-cycle arrest while infected tumour cells with disrupted regulatory pathways may progress through the cell-cycle (*I*). Normal arrested cells provide an intracellular environment conducive for high-level virus replication. Cycling tumour cells exert limited permissiveness for HCMV infection resulting in low-level virus replication (*II*). HCMV-induced antiapoptotic mechanisms in normal cells prolong virus replication but do not protect cells against death at late time points post infection when high virus titres are achieved. In tumour cells, virus-induced antiapoptotic mechanisms account for resistance to apoptosis induced by different stimuli (*III*). Death of normal permissive infected cells facilitates their detection and elimination by the immune system. HCMV may establish persistent infection in tumour cells and exert its oncomodulatory potential characterised by immune escape and tumour progression through activity of virus regulatory proteins and noncoding RNAs (*IV*)

HCMV-infected cancer cells. Sabatier et al. [33] found few infected cells only in a small fraction of tumours. Later, Mitchell et al., Scheurer et al., and the group of Söderberg-Nauclér, however, showed the presence of HCMV in gliomas by immunohistochemistry and/or in situ hybridisation [28–30]. Scheurer et al. [30] provided a very detailed discussion of the technical aspects that might be of relevance. Regarding immunohistochemistry, they pointed out that thickness of tumour sections, antibody dilution, and the deparaffinisation/post-fixation method may be critical to minimise false-negative results [30]. Crucial factors for in situ hybridisation may include the age of the tissue blocks used, the thickness of the tissue sections, the deparaffinisation procedure and the pre-treatment methods [30].

Low-grade HCMV infection of cancer cells appears to be sufficient to influence severity of cancer disease. Importantly, an inceased number of infected cancer cells correlated with more unfavourable outcome in glioma patients group [29]. In another report, the fraction of HCMV-infected tumours was higher (79%) than in lower grade tumours (48%) [30].

The (eventual) presence of HCMV in tumour cells may offer novel therapeutic options. In experimental models, treatment with the anti-HCMV drug ganciclovir reversed HCMV-induced chemoresistance in cancer cells [1]. Most recently, an HCMV-specific CD8+ T-cell response was induced in a glioblastoma patient after therapeutic vaccination with dendritic cells pulsed with autologous tumour lysate [34]. This finding supports that HCMV may be a potential immunotherapeutic target in HCMV-infected tumours.

In conclusion, the oncomodulatory role of HCMV still remains to be finally proven. However, based on recent clinical findings the authors feel that “evidence becomes stronger”. Therefore, a concentrated effort to clarify (1) if HCMV is present in (which?) tumours and (2) if HCMV exerts clinically relevant oncomodulatory effects and represents a (immuno)therapeutic target is highly warranted and justified, especially, since results may be rapidly transferable in improved therapeutic strategies.

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