



**Karolinska
Institutet**

Institutionen för medicin

The Role of Human Cytomegalovirus Infection in Cancer

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska
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av

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ABSTRACT

Cancer is a major cause of morbidity and mortality worldwide. It is thought that up to 20% of cancers are caused by infectious agents, and an oncogenic role of several viruses has been established for certain tumours. Increasing evidence implies that human cytomegalovirus (HCMV) infection is associated with a number of malignancies. Several studies have suggested different mechanisms by which HCMV could modulate the tumour environment and dysregulate several key pathways relevant in tumour development and progression. However, the role of HCMV in cancer has remained highly controversial. The studies in this thesis investigated the possible role of HCMV in certain types of cancers. Additionally, they addressed the question of whether HCMV targeted therapy could be used as a treatment option for cancer patients.

In **study I**, we found that HCMV proteins were abundantly expressed in all breast cancer specimens examined and in 94% of sentinel lymph node specimens with metastases. HCMV infections were mostly confined to the neoplastic cells, while some inflammatory cells were also HCMV positive in 60% of lymph nodes without metastases.

In **study II**, we investigated brain metastases and paired primary tissue samples of breast and colon cancer patients for HCMV proteins and nucleic acids. Interestingly, HCMV proteins were abundantly expressed in the majority (98.7%) of brain metastases and paired primary breast and colorectal cancer specimens. Patients with high grade HCMV infection tended to have shorter time to tumour progression and shorter survival, both after primary tumour diagnosis, as well as after establishment of brain metastases.

In **study III**, we found that the majority of primary medulloblastomas and medulloblastoma cell lines were infected with HCMV. HCMV infection induced expression of cyclooxygenase-2 (COX-2) activity and prostaglandin-E2 (PGE2) production in vitro. Additionally, expression of HCMV proteins and COX-2 were strongly correlated in primary tumours as well as in medulloblastoma xenografts. Targeting viral replication using an anti-viral drug and a COX-2 inhibitor prevented HCMV replication in vitro, inhibited PGE2 production and reduced medulloblastoma tumour cell growth both in vitro and in vivo.

In **study IV**, we discovered a novel genetic variant of HCMV, which lacks a gene segment in a regulatory gene. This viral strain was frequently detected in cancers of different origins and was associated with non-productive infection and expression of splice variant immediate early proteins. In contrast, this variant was less frequently detected in healthy donors, and in patients with HCMV viremia or myocardial infarction. We isolated this variant from 3 out of 110 clinical isolates. Thus, our results demonstrate a high prevalence of this novel genetic variant of HCMV in cancer patients; this virus variant may be tumour promoting virus for cancers of different origin. Understanding molecular pathways modulated by this virus is therefore highly necessary to further understand the behaviour of this unique HCMV variant, and its possible role in cancer development or progression.