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Cytomegalovirus infection in brain tumors
A potential new target for therapy?

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Emerging evidence demonstrate a high prevalence of cytomegalovirus (CMV) proteins and nucleic acids in different tumors. CMV is confined to tumor cells and non-cancer cells in close proximity to tumors are consistently virus negative. CMV confers both oncogenic and oncomodulatory mechanisms, and may therefore provide a novel target in cancer treatment.

Emerging evidence demonstrate a frequent presence of human cytomegalovirus (CMV) proteins and nucleic acids in brain tumors in both adults (glioblastoma) and children (medulloblastoma).[1,2] Other more common cancer forms such as breast cancer, colon and prostate cancer as well as salivary gland mucoepidermoid carcinomas are also frequently virus positive, with a prevalence approaching 90–100%.[3-5] CMV proteins are expressed only in tumor cells, while non-tumor cells surrounding the tumor are CMV negative. CMV proteins confer both oncogenic and oncomodulatory mechanisms; they control cell cycle progression by interacting with p53, Rb and cyclins, activates oncogenic signaling pathways (PI3K/Akt, Erk, Wnt and NFκB), inhibit cellular differentiation, induce chromosomal damage, affect epigenetic mechanisms, induce DNA damage and inhibit DNA repair mechanisms, induce oncogene expression and telomerase activity, induce inflammation and at the same time avoid recognition by the immune system.[4,6] Furthermore, CMV encoded proteins inhibit apoptosis through interactions with key proteins in the extrinsic and intrinsic apoptotic signaling cascade, and can induce drug resistance to chemotherapeutic agents, which may impair the efficiency of cancer therapy[4] (**Fig. 1**).

Although CMV proteins may both trigger oncogenesis and confer oncomodulatory functions, it is under debate if the virus truly plays a role in tumorigenesis and tumor progression. Glioblastoma patients have a very dismal prognosis with a mean survival of 12–14 mon. We recently found that a low grade CMV infection in glioblastomas was associated with longer time to tumor progression and improved survival.[7] These observations imply that CMV may be involved in tumor progression rather than representing an epiphenomenon in these tumors. However, regardless of its role in the development of a tumor, the presence of CMV in tumor cells but not in normal cells surrounding the tumor, makes it a potential new and novel therapeutic target. We recently demonstrated that 92% of primary medulloblastoma tumors are positive for CMV proteins; viral DNA and RNA were detected in primary tumors and in medulloblastoma cell lines.[2] The expression of CMV proteins varied over time in medulloblastoma cell lines, and was highly induced by xenografting in nude mice. Established human medulloblastoma xenografts were positive for CMV immediately early (IE) and late proteins; two viral proteins that are expressed during different phases of CMV replication, but infectious virus were not obtained from primary tumors or xenografts.[2] These observations imply that CMV behaves differently in tumor cells compared with an acute infection that often results in virus-induced lysis of infected cells. Instead viral proteins exhibiting oncogenic and oncomodularatory functions may act to aggravate tumor growth and disease progression.

Earlier studies have demonstrated that CMV induces the expression of cyclooxygenase-2 (COX-2). COX-2 inhibitors are efficient anti-CMV drugs, as virus replication appear to depend on the synthesis of prostaglandin E 2 (PGE_2).[6] Several cancer types including those that are frequently CMV positive often demonstrate high levels of COX-2; in some of these tumors high levels of COX-2 expression correlates with poor patient outcome.[6] COX-2 inhibitors are under evaluation as additional treatment options for several cancer forms, and a recent study demonstrates up to 70% reduced incidence of colon cancer in individuals receiving long-term aspirin treatment.[8] It is possible that CMV contributes to induced COX-2 levels in certain tumors and that COX-2 inhibitors interfere with viral effects in CMV positive tumors. Interestingly, we found that only CMV positive medulloblastoma cells in culture expressed COX-2, and CMV proteins and COX-2 were also co-expressed in medulloblastoma tumors in patients.[2] Nude mice carrying human medulloblastoma xenografts treated with either celecoxib or the anti-CMV drug valganciclovir demonstrated approximately 40% inhibition of tumor growth in vivo whereas combined celecoxib and valganciclovir treatment resulted in 72% reduced

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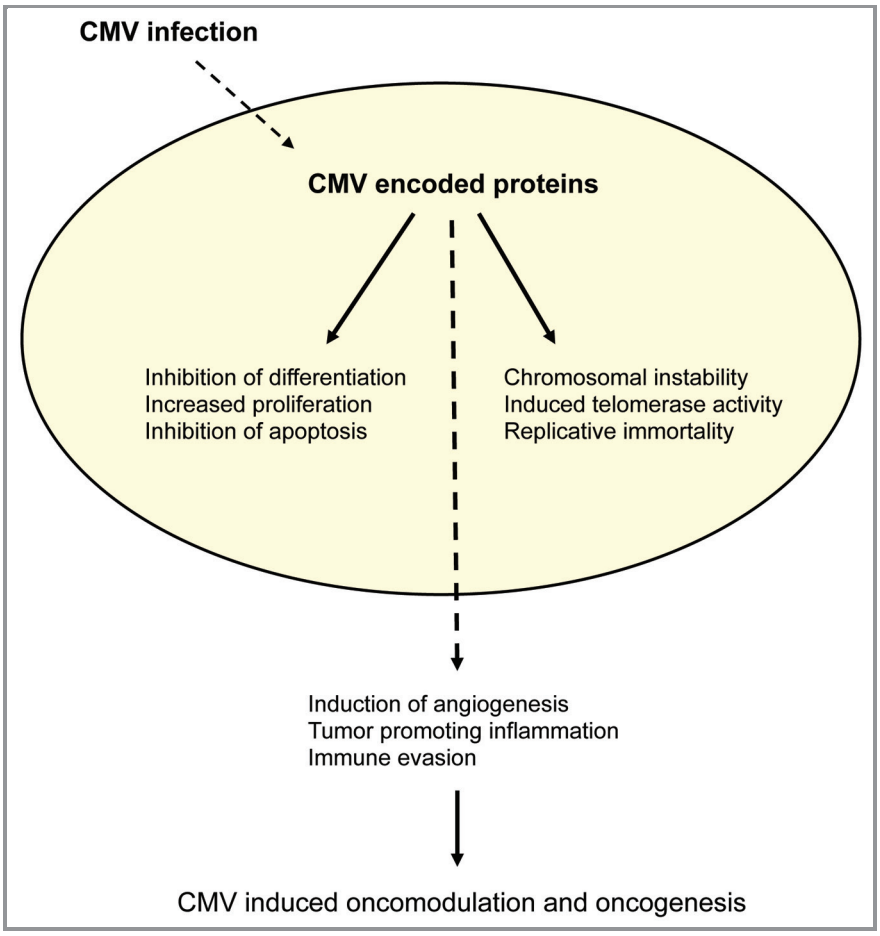

Figure 1. CMV encodes proteins that have important functions on tumor cell growth and the tumor microenvironment.

tumor growth without the use of chemotherapy.[2] Importantly, no significant effects were observed on the growth of CMV negative tumor cells or xenografts treated with ganciclovir/valganciclovir.[2] The expression of CMV late proteins was reduced by about 80% in CMV positive xenografts. In a recent study of a salivary gland tumor model, small molecule inhibitors of the COX/Amphiregulin/EGFR/Erk pathways also attenuated CMV induced pathogenesis.[9] These observations imply that interfering with CMV in CMV positive tumors may provide a new therapeutic option for patients carrying such tumors. Further studies need to evaluate which chemotherapy that is most suitable to combine with celecoxib and valganciclovir in patients. Importantly, we propose that this therapeutic strategy is further evaluated as an additional treatment option also for other CMV positive tumors than medulloblastoma.

Recently, we have evaluated the effect of valganciclovir in glioblastoma patients[(unpublished data)]. The drug was well tolerated in patients receiving combined chemotherapy and radiotherapy and indicates an unexpectedly high survival in patients undergoing radical surgery and receiving long-term treatment with valganciclovir in combination with chemotherapy and radiation. However, the study was small including only 42 patients, and therefore well-powered studies have to further evaluate the efficacy of valganciclovir in glioblastoma patients. Several small immunotherapy trials are also ongoing to evaluate whether enhanced CMV specific immunity improve the survival of glioblastoma patients. The described studies should encourage for further investigations on this topic; the role of CMV needs to be further evaluated in tumor biology and medical and immunotherapeutic strategies targeting CMV should be further evaluated for potentially improved outcome of patients carrying CMV positive tumors.

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