## Oncomodulatory properties of the human cytomegalovirus-encoded receptors US28 and UL33

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# summary

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In this thesis, we describe the role of in signal transduction and oncomodulation of two G protein coupled receptor proteins (GPCRs), encoded by the human cytomegalovirus (HCMV). The vGPCRs US28 and UL33 were shown to activate several signal transduction pathways that might be involved in the development of glioblastoma, an HCMV-linked pathology.

**Chapter 2** describes how US28 induces upregulation of COX-2 expression via the inflammation-related transcriptional regulator NF-κB. Furthermore, involvement of COX-2 in tumor formation is exemplified. In **Chapter 3** we show that US28 constitutively activates β-catenin dependent transcription through the Rho-Rho kinase (ROCK) pathway, instead of the classical Wnt/Frizzled signaling pathway. Additionally, HCMV-infected cells also display activation of β-catenin signaling through US28. This might be of relevance for (colon) cancer and glioblastoma development as well as other HCMV-associated pathologies. **Chapter 4** focuses on the HCMV-encoded receptor UL33. We show that UL33, like US28, may act as an oncomodulator, rewiring several cellular signaling pathways. UL33 promotes tumor formation in a xenograft model and is detected in glioblastoma. Hence, UL33 might also play a role in proliferative diseases. Finally, in **Chapter 5,** we

describe a role of US28 in epigenetic regulation through hypomethylation of the promoter of the cell cycle progression gene cyclin D1.

Taken together, our data shed new light on the mechanisms that might be involved in oncomodulatory properties of the vGPCRs US28 and UL33, and might lead to new strategies to target HCMV-associated pathologies such as glioblastoma and colon cancer.