VIRAL TUMORIGENESIS

Viral hijacking

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URLs
CCR1
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=1230
US28

VEGF
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=7422

Despite its association with tumours and unlike other DNA viruses, human cytomegalovirus (HCMV) does not transform cells, so how it exerts its oncogenic potential has been unclear. Martine Smit and colleagues now show that *US28*, an HCMV gene that encodes a G-protein-coupled receptor, is important for initiating angiogenesis in transformed cells.

The US28 receptor is a homologue of the human chemokine receptor CCR1 but, unlike its cellular counterpart, it signals in a constitutively active manner and has previously been shown to activate pathways that lead to cell proliferation and migration.

HCMV might use US28 to hijack several signalling networks within infected cells. In fact, this viral receptor displays promiscuous G-protein coupling that causes the constitutive activation of different G proteins and potentiates the signalling of other cellular chemokine receptors.

Smit and colleagues found that when US28 is stably expressed in NIH-3T3 cells, the cells have an increased growth rate that results, at least in part, from the increased expression of cyclin D1. The US28-expressing cells also form foci *in vitro*, and after 5 days the cells express high levels of vascular endothelial growth factor (VEGF) compared with cells that express a mutant US28 that is unable to bind G proteins. To further dissect the pathway activated by US28, the authors investigated the downstream signalling pathways and found that US28 signals through both Gαq and Gβγ protein subunits and two different MAPKs (mitogen activated protein kinases) to stimulate downstream transcription factors, which ultimately lead to *VEGF* promoter activation. Consistent with this, NIH-3T3 cells that expressed US28 formed highly vascularized, VEGF-expressing tumours 2 weeks after inoculation into nude mice. This indicates that VEGF-mediated angiogenesis is responsible for at least some of the oncogenic properties of US28.

To verify these findings the authors used an HCMV strain that does not express US28 to infect a glioblastoma cell line. This strain failed to induce *VEGF* promoter activation, unlike the wild-type virus.

Interestingly, the expression of US28 in non-tumorigenic cells can also induce apoptosis. So, it seems that the cellular context determines whether *US28* functions as an oncogene and a pro-angiogenic factor. The authors conclude that US28 might be a potential target for the treatment of early-stage HCMV-related proliferative diseases.

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ORIGINAL RESEARCH PAPER Maussang, D. *et al.* Human cytomegalovirus-encoded chemokine receptor US28 promotes tumorigenesis. *Proc. Natl Acad. Sci. USA* **103**, 13068–13073 (2006)