Molecular culprit behind virus-mediated chronic inflammation and cancers identified

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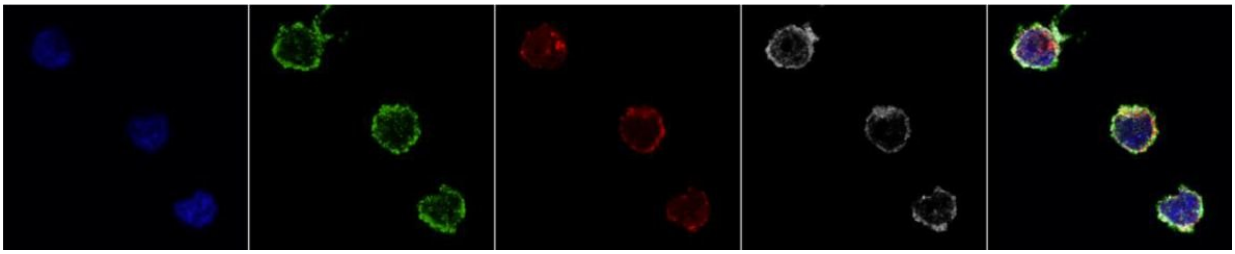

BC-3 cells were stained with DAPI, anti-vFLIP, anti-CADM1, and cholera toxin B conjugated with red fluorescence to detect GM-1 and subjected to confocal microscopy. Credit: Hunte R et al. (2018)

Within cells infected by Kaposi sarcoma herpesvirus (KSHV), the human protein CADM1 interacts with viral proteins to promote chronic inflammation, which plays a major role in the development of cancers caused by KSHV. Richard Hunte of the University of Miami, Florida, and colleagues present these new findings in *PLOS Pathogens*.

About 12 percent of all cancers are linked to viruses such as KSHV, which causes Kaposi's sarcoma, primary effusion lymphoma, and the lymphoma-like multicentric Castleman's disease. These cancers are associated with chronic inflammation caused by abnormal activation of the human protein NF-κB in KSHV-infected cells. However, the molecular mechanisms of NF-κB activation are poorly understood.

Hunte and colleagues had previously found that the human protein CADM1 might play a key role in NF-κB activation caused by a different cancer-associated virus known as HTLV-1. In the new study, they investigated whether CADM1 plays a similar role in KSHV-infected cells.

The research team infected primary human cells with KSHV and found that CADM1 levels in the cells increased significantly within hours of infection. Moreover, they identified CADM1 protein level is significantly high in KSHV-caused cancer cells. Then, they used artificial RNA molecules known as short hairpin RNA to suppress CADM1 production in KSHV-infected cells. This revealed that CADM1 is necessary for NF-κB activation in these cells.

Next, the researchers examined whether CADM1 interacts with the proteins vGPCR and vFLIP, which are encoded in the KSHV genome and have been linked to NF-κB activation in previous research. They found that CADM1 is indeed required for vGPCR and vFLIP-mediated NF-κB activation and showed that a particular stretch at one end of the CADM1 protein is essential for this process.

Further experiments showed that CADM1 production is required for KSHV-infected cells to survive. Taken together, these findings suggest that CADM1 plays a key role in the survival and growth of cancer cells associated with KSHV infection.

This is especially notable because CADM1 is known to play the opposite role in other cancers, suppressing the growth of melanoma, lung cancer, and other solid tumors. According to the authors, "targeting human protein CADM1 in viral-mediated cancers would be ultimate therapy against KSHV and HTLV-I associated malignancies."

More information: Hunte R, Alonso P, Thomas R, Bazile CA, Ramos

JC, van der Weyden L, et al. (2018) CADM1 is essential for KSHV-encoded vGPCR-and vFLIP-mediated chronic NF-κB activation. *PLoS Pathog* 14(4): e1006968. doi.org/10.1371/journal.ppat.1006968