A tricky tumor virus

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Epstein-Barr virus (EBV) is a human-pathogenic virus which belongs to the herpes virus family. Almost every adult carries EBV inside. With an infestation rate of more than 90 %, EBV is one of the most successful human viruses. Its viral genome consists of double-stranded DNA, and it is one of the few known viruses which cause cancer in humans under certain circumstances. EBV-associated cancers include lymphomas (cancer of the lymph nodes), nasopharyngeal carcinoma and gastric cancer.

A protein encoded by the virus, the latent membrane protein 1 (LMP1), is required for the uncontrolled proliferation of EBV-infected cells and, thus, the formation of cancer. Arnd Kieser and his team are studying the molecular mode of action of this EBV protein. LMP1 is a membrane-bound oncoprotein that binds certain signal molecules of its host cell and thereby critically contributes to the oncogenic transformation of the cells.

One of these signal proteins is the factor TRADD. TRADD stands for TNF-receptor 1-associated death domain protein. The scientists used TRADD knockout cell lines which they had established by removing the TRADD gene from the genome of human B-cells in order to demonstrate that TRADD is an essential factor for LMP1 function.

They found that in the absence of TRADD, LMP1 can no longer activate a cellular communication (also called: signal transduction) pathway which is crucial for cell transformation. However, TRADD's normal function within the cell includes the induction of programmed cell death

which would be fatal for the virus. In fact, the scientists made the surprising observation that TRADD can no longer induce apoptosis if it is activated by the viral protein LMP1.

How does Epstein-Barr virus manage to switch off the apoptosis function of TRADD? Kieser and his colleagues discovered that the LMP1 protein possesses a unique TRADD binding domain which dictates an unusual TRADD interaction and prevents TRADD from transmitting cell death signals. Thus, LMP1 masks the apoptotic activity of TRADD. This viral TRADD-binding domain consists of the 16 carboxyterminal amino acids of the LMP1 protein and can be transplanted to cellular receptor proteins where it shows the same effects.

Hence, Epstein-Barr virus has found a unique molecular way to extinguish an undesired property of a cellular protein in order to adapt this protein to its own needs. This finding might also be the basis for a new therapeutic approach. Arnd Kieser explains: “Since the specific structure of the LMP1-TRADD interaction is most likely restricted to EBV-infected cells, it might serve as a target structure to develop specific inhibitors which interrupt the transforming signal cascade of the LMP1 oncogene.”

Source: National Research Center for Environment and Health