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Key Mechanism for the Proliferation of Epstein-Barr Virus Discovered

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Scientists of Helmholtz Zentrum München have elucidated a crucial mechanism in the lytic cycle of Epstein-Barr virus. A team of researchers led by Professor Wolfgang Hammerschmidt identified the function of a protein which plays a critical role in the proliferation of the virus. The Epstein-Barr virus can induce cancer. The findings, published in the current issue of the renowned journal *PNAS*, represent a major step forward in understanding tumor development.

The Epstein-Barr virus (EBV), a virus of the herpes family, has two distinct life phases: After infecting a cell it first goes into a resting phase. Under certain circumstances the virus can become active - and then induces tumor growth or promotes its synthesis in the cell. Especially in patients with weakened immune systems, EBV can cause its host cells to divide uncontrollably - causing a tumor to develop.

The causes for the transition of EBV from the quiescent phase to an active mode - particularly with respect to the responsible factors and to how the molecular mechanisms function - have until now remained elusive. With their findings, the scientists at Helmholtz Zentrum München have discovered how the virus terminates latency and activates its synthesis in the infected cells.

Professor Wolfgang Hammerschmidt, head of the Department of Gene Vectors at Helmholtz Zentrum München, explained: "We have now identified the crucial function of the viral BZLF1 protein: It activates the genes of EBV, which are essential for the proliferation of virus particles

." About 70 different genes are switched off during the latent phase because certain DNA segments are chemically modified: Some DNA building blocks carry methyl groups. They are a kind of stop signal for the cell apparatus, so that these genes cannot be converted into protein.

“BZLF1 can detect these methylation patterns in the DNA,” said Markus Kalla, lead author of the study. With its DNA binding domain, the protein binds directly to the methylated DNA sequence. A second domain of BZLF1 is responsible for the reactivation of the gene. “Such a mechanism was not known before,” Wolfgang Hammerschmidt said. Previous research assumed that the methyl groups had to be removed from the DNA building blocks before the transcription factors could bind to the regulatory DNA sequence and thus activate the gene.

The researchers’ findings indicate that BZLF1 avoids this hurdle. Accordingly, BZLF1 appears to be essential for establishing and maintaining latency, but also for escaping from it.

During viral synthesis a large number of new particles are usually formed within the cell. To achieve this, viruses use large portions of the cell apparatus, in particular specific proteins and factors. After progeny synthesis the new viruses are released - researchers speak of a lytic cycle. The disadvantage: the viruses thus attract the attention of the immune system, which then fights against the pathogen and destroys the cell supporting viral synthesis.

However, the Epstein-Barr virus uses another strategy. Instead of putting all of its energy into immediate synthesis of progeny in the infected cell, it goes into a resting phase following the infection and thus prevents a reaction of the immune system. The virus infects cells of the immune system - the so-called B cells - first inserting its DNA into their cell nucleus. Whereas most viruses immediately start their lytic proliferation cycle and thus use the cell apparatus to replicate the DNA and to

generate important structural proteins from the genes, EBV drives transformation of merely a few genes from the cell into proteins. These so-called latent genes are important for the quiescent phase: They see to it that the DNA of the Epstein-Barr virus remains stable in the cell nucleus while the cell itself proliferates. This seemingly peaceful co-existence ends when the virus goes into the lytic phase or induces tumor growth.

These findings published in PNAS by Wolfgang Hammerschmidt and his colleagues constitute an important step for a better understanding of the role of EBV in tumor growth.

More information: Kalla, M, Schmeinck, A, Bergbauer, M, Pich, D, Hammerschmidt, W: AP-1 homolog BZLF1 of Epstein-Barr virus has two essential functions dependent on the epigenetic state of the viral genome. *PNAS* - Online Publication (DOI 10.1073/pnas.0911948107)

Provided by Helmholtz Zentrum Muenchen