Consequences of viral DNA integration on the host cell:

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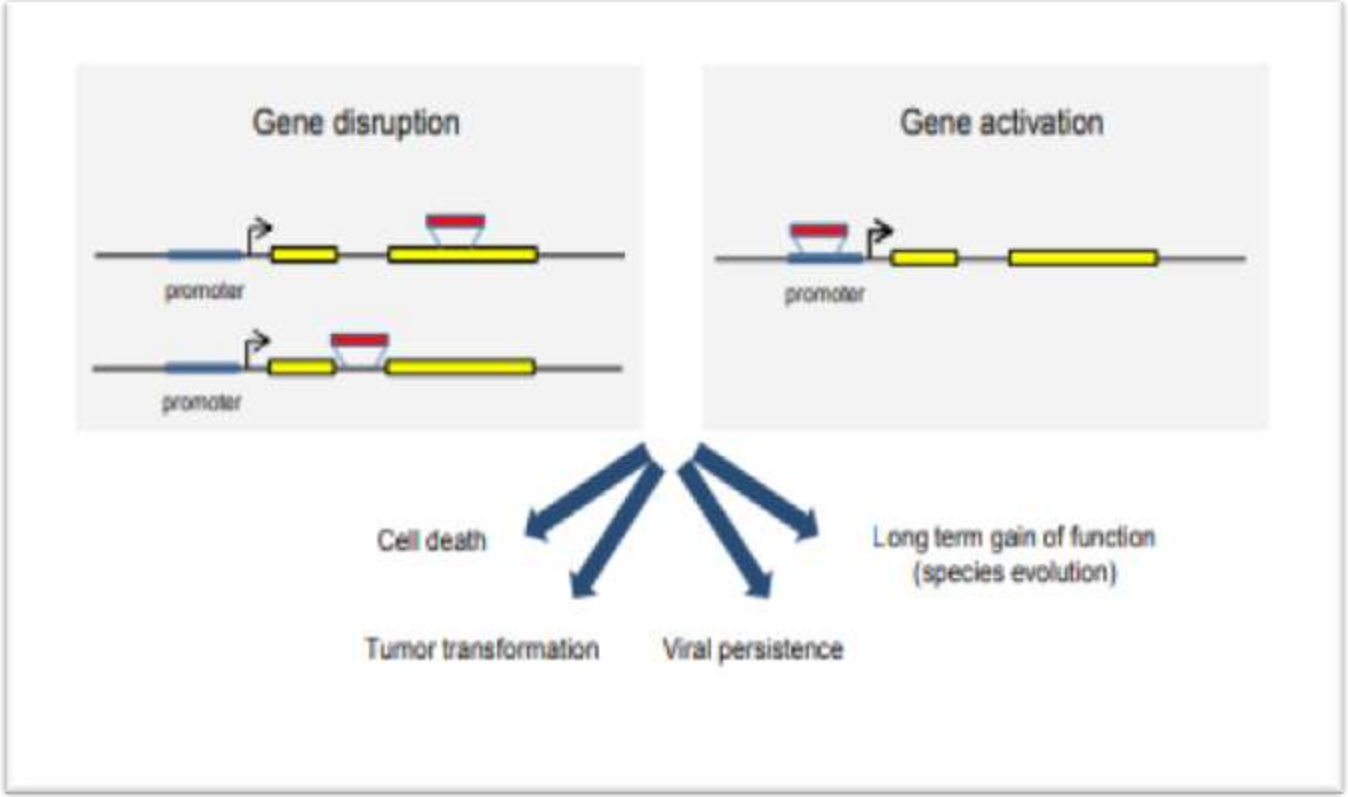
Consequences of viral DNA integration on the host cell:

- The site of the viral integration event can have multiple consequences for the host, as well as for the virus itself. Indeed, viral integration can lead to cell death or proliferation as a result of insertional mutagenesis.
- However, integration can also lead to consequences for the virus, i.e. active production or transcriptional silencing, a process also called latency that is key to establish viral persistence.
- Finally, integration in the germline can contribute shaping the host genome and participate in species evolution. Each of these effects will be further discussed next:

• Cell death:

- Apoptosis is a general mechanism involved in cell homeostasis regulation eliminating aberrant cells, with altered physiological parameters as well as a compromised genome integrity.
- Upon viral invasion, the presence of a linear double-stranded DNA is sensed by the host DNA repair machinery as a DNA break, which will lead to cell apoptosis unless successfully repaired.
- Following the same concept, if the cell is invaded by multiple viral particles, thus multiple DNA genomes, it is likely that the DNA repair machinery will be overwhelmed, and will thus fail in repairing all the DNA molecules, thereby resulting in cell death. Similarly, if too many viral genomes integrate successfully, the integrity of the host genome itself may be compromised, also leading to cell death.

- In addition, viral integration will eventually lead to gene expression deregulation that may induce cell apoptosis. For instance, it has been reported that integration of HBV in SERCA-1 gene resulted in gene disruption and in the expression of a chimeric non functional protein HBVx/SERCA-1 (Figure 4).
- This chimeric protein lost calcium and ATP binding domains, thereby strongly disturbing the reticulum endoplasmic calcium homeostasis and inducing apoptosis.



• Tumorigenesis:

- Many viruses have been characterized based on their ability to induce cellular transformation and thus tumors. However, two mechanisms of virus-induced cellular transformation should be distinguished.
- The first one leads to a rapid tumorigenesis process and is exemplified by oncoviruses, i.e. viruses coding for a viral oncogene and thus directly responsible for the cellular proliferation, such as some retroviruses (MMTV, MLV, RSV, HTLV) and DNA viruses (HPV, EBV, HBV, Ad).

- The second mechanism, which is directly related to viral integration, is called insertional mutagenesis.
- In this case, tumorigenesis is a slow process directly related to the viral integration site, which disturbs the cell homeostasis. Indeed, viral integration alters and modulates the expression of cellular nearby genes.
- A first scenario is the result of gene disruption by the viral integration event. If the disrupted gene is a tumor suppressor gene for example, this may ultimately lead to cellular transformation.
- Second, viral integration occurring close to cellular oncogenes may result in viral promoter-induced overexpression of the oncogene.

• Viral persistence:

- Many viruses can exist in a latent state, thus establishing a persistent infection. During this phase, viruses are transcriptionally silent, either completely or partially, allowing them to escape immune surveillance and establish viral reservoirs.
- Viral reservoirs represent a major obstacle for therapeutic strategies and virus eradication. A well-known example is illustrated by HIV-1, which can persist in resting memory CD4+ T cells.

• Species evolution:

- The integrating virus can be persistent not only at the level of the cell but also at the level of the organism. Indeed, viral integrationmay have a significant impact on the organism and its progeny if the virus succeeds in infecting the germ line.
- Retroviruses are the only viral group that has remnants in the form of integrated endogenous elements (ERV for Endogenous Retrovirus), accumulating over time in the human genome, and reaching to date approximately 8% of the total genome.

Thank You!