Laboratory of Viral and Cellular Genetics

Receptors for retroviruses, retroviral vectors, endogenous retroviruses, integration and silencing of retroviruses

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Retroviruses interact with the host cells at multiple levels. They enter cells via specific receptors, integrate into the host genome, and use the cell transcription machinery to express their structural or enzymatically active proteins. Specific binding of retroviral envelope proteins to host cell receptors is the prerequisite for cell permissiveness to the infection. Retroviruses broaden their host range by mutations of the env gene, and vice versa, host cells develop resistance to retrovirus by mutations of genes encoding the specific receptors. We have described such an interesting semi-resistant phenotype in chicken line M and explained it by mutation of the receptor Tvb. Another defence mechanism used by the host cells is the inactivation of integrated invaders at the level of transcription via DNA methylation and modifications of adjacent histones. This was demonstrated in the case of HIV-1 latency, and inhibitors of DNA methyltransferases and histone deacetylases must be considered for HIV-1 eradication from the reservoir of long-lived, latently infected resting memory CD4$^+$ T cells. Another example of epigenetic regulation is represented by endogenous retroviruses in the human genome. Fusogenic envelope glycoproteins encoded by two copies of HERVs are strictly placenta-specific and their expression in other tissues must be prevented by DNA methylation and histone methylation. Epigenetic silencing is, however, an obstacle in using retroviruses as vectors for gene transfer and transgenesis. We have improved ASLV-based retroviral vectors by insertion of core element from CpG island between promoter and enhancer, which increases their resistance to transcriptional silencing and ensures long-term expression of transduced genes. Finally, we have identified two genomic copies of porcine endogenous retroviruses as a potential risk factor in xenotransplantation of pig organs and tissues.

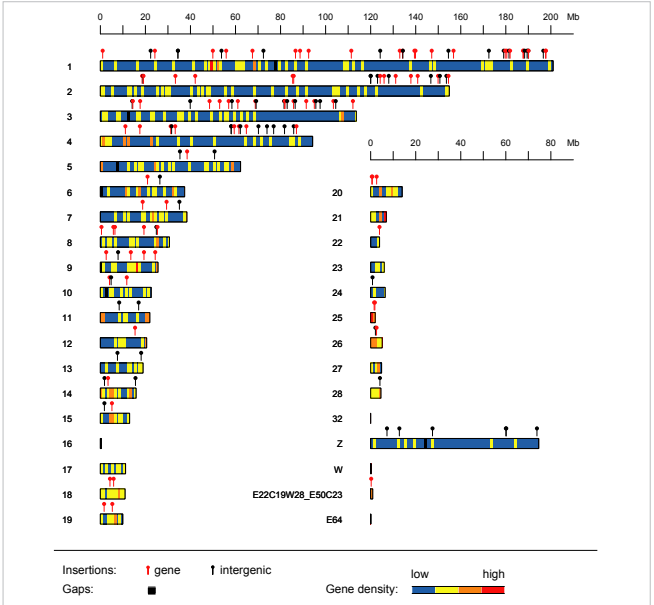

Fig. 1. Chromosomal locations of Rous sarcoma virus integrations in virus-induced chicken tumours. Integrations into and outside genes are shown as red and black lollipops, respectively.

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- GA CR, GA523/07/1282 – Characterization of the cellular receptor Tvc and its role in the pathogenesis of avian leukosis viruses subgroup C-induced diseases, 2007-2009, J. Geryk
- GA CR, GA204/07/1030 – Integration preference of retroviruses, 2007-2009, J. Plachý
- GA CR, GA523/07/1171 – L1 retrotransposon-based transgenic chicken models, 2007-2009, J. Hejnar
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- GA CR, GP204/08/P616 – The role of DNA methylation and histone modifications in the establishment and maintenance of HIV-1 latency, 2008-2010, J. Blažková
- GA CR, GA301/09/2031 – Fusogenic envelope glycoproteins of human endogenous retroviruses and their receptors, 2009-2011, J. Hejnar
- GA CR, GP301/09/P667 – Transcriptional silencing of retroviral vectors during their integration into the host genome, 2009-2011, F. Šenigl
- GA CR, GAP502/10/1651 – Characterization of new avian sarcoma and leukosis virus (ASLV) receptor alleles as revealed by the analysis of semiresistant cells, 2010-2012, J. Plachý

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