LABORATORY OF

VIRAL AND CELLULAR GENETICS

Retrovirus, entry receptor, epigenetics, somatic hypermutation, endogenous retrovirus

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Our scientific interests cover the entire field of molecular interactions between retroviruses and their hosts. The retrovirus replication cycle starts by specific binding of retroviral envelope proteins to host cell receptors. After entering host cells, retroviruses integrate into the host chromosomes and use the cell transcription and proteosynthesis machineries to express retroviral proteins and propagate their own progeny. At multiple levels, cellular restriction factors regulate retroviral replication.

Retroviruses broaden their host range by mutations of the env gene, and we identified particular env mutations that activate the receptor-independent virus-cell fusion capacity and could be efficient in retroviral host range extension and cross-species transmission[1]. Vice versa, host cells develop resistance to retroviruses by mutations of genes encoding the specific receptors. We studied the natural polymorphisms in Na+/H+ exchanger (NHE1) in galliform species susceptible or resistant to avian leukosis virus subgroup J (ALV-J), an important pathogen of domestic poultry. Based on this knowledge, we introduced specific mutation of NHE1 into the chicken genome using the CRISPR/Cas9 technology and created an ALV-J-resistant chicken line[2].

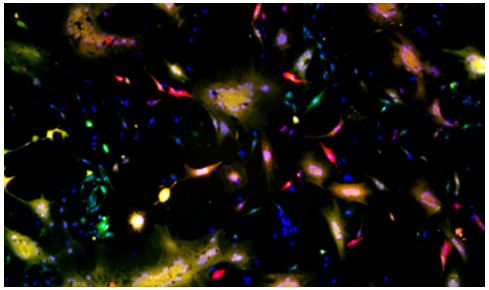

Figure 1. Cell-to-cell fusion induced by human endogenous retrovirus-encoded envelope glycoprotein, syncytin-1, and its receptor, hASCT2. Cells expressing syncytin-1 are marked by red fluorescence (dsRed), hASCT2-positive cells by green fluorescence (GFP). Cell nuclei are stained by Hoechst 33342 (blue). Multinuclear syncytia appear yellow by merging the red and green fluorescence.

An efficient defence mechanism used by the host cells is inactivation of the integrated invaders at the level of transcription via DNA methylation and modifications of adjacent histones. We used the epigenomic approach to retrovirus integration and revealed that transcriptionally active proviruses are preferentially localized close to the transcription starts of targeted genes or in enhancer regions[3]. The epigenomic expertise was used in designing the retroviral vector-based screen of somatic hypermutation (SHM) mistargeting outside the immunoglobulin genes. Our findings showed that topologically associated domains (TAD) of chromatin delineate susceptibility to SHM and that insertion of a strong Ig SHM-targeting element into a cold TAD renders it hot[4].

The last but not least topic in our laboratory are endogenous retroviruses. We described the loss of epigenetic control and the possible role of active DNA demethylation in aberrant expression of endogenous retrovirus HERVWE1 in germ line cancer[5]. By systematic screening of newly published mammalian genomes for endogenous retrovirus copies, we detected the first endogenous deltaretrovirus in the genome of Miniopterus bats[6]. This molecular fossil elucidates the deep evolutionary history of deltaretroviruses.

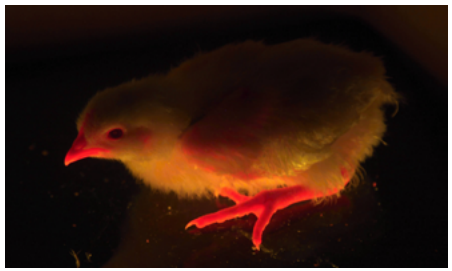

Figure 2. Freshly hatched mCherry-positive chicken. The mCherry reporter gene was introduced into the chicken genome by transposon-driven integration and orthotopic transplantation of primordial germinal cells. This is to document the efficiency of our transgenesis technology used in generation of ALV-J-resistant chicken line by the CRISPR/Cas9 editing.

Selected publications:

1. Lounková A*, Kosla J, Přikryl D, Štafl K, Kučerová D, Svoboda J (2017) Retroviral host range extension is coupled with Env-activating mutations resulting in receptor-independent entry. *Proc Natl Acad Sci USA*, **114**:5148-5157.
2. Koslová A, Trefil P, Mucksová J, Reinišová M, Plachý J, Kalina J, Kučerová D, Geryk J, Krchlíková V, Lejčková B, Hejnar J* (2020) Precise CRISPR/Cas9 editing of the NHE1 gene renders chickens resistant to the J subgroup of avian leukosis virus. *Proc Natl Acad Sci USA*, **117**:2108-2112.
3. Šenigl F, Miklík D, Auxt M, Hejnar J* (2017) Accumulation of long-term transcriptionally active integrated retroviral vectors in active promoters and enhancers. *Nucleic Acids Res*, **45**:12752-12765.
4. Šenigl F*, Maman Y, Dinesh RK, Alinikula J, Seth RB, Pecnová L, Omer AD, Rao SSP, Weisz D, Buerstedde JM, Aiden EL, Casellas R, Hejnar J, Schatz DG* (2019) Topologically associated domains delineate susceptibility to somatic hypermutation. *Cell Rep*, **29**:3902-3915.
5. Benešová M, Trejbalová K, Kovářová D, Vernerová Z, Hron T, Kučerová D, Hejnar J* (2017) DNA hypomethylation and aberrant expression of the human endogenous retrovirus ERVWE1/syncytin-1 in seminomas. *Retrovirology*, **14**:e20.
6. Farkašová H, Hron T, Pačes J, Hulva P, Benda P, Gifford RJ, Elleder D* (2017) Discovery of an endogenous Deltaretrovirus in the genome of long-fingered bats (Chiroptera: Miniopteridae). *Proc Natl Acad Sci USA*, **114**:3145-3150.

In the picture: 1. Karafiát Vít | 2. Kaňka Jakub | 3. Plachý Jiří | 4. Štafl Kryštof | 5. Miklík Dalibor | 6. Elleder Daniel | 7. Geryk Josef | 8. Trávníček Martin | 9. Pečenka Vladimír | 10. Stepanets Volodymyr | 11. Hejnar Jiří | 12. Matoušková Magda | 13. Krchlíková Veronika 14. Trejbalová Kateřina | 15. Slavková Martina | 16. Reinišová Markéta | 17. Hron Tomáš | 18. Gáliková Eliška | 19. Kučerová Dana | 20. Pecnová Ľubomíra