LABORATORY OF

VIRAL AND CELLULAR GENETICS

Retroviruses, endogenous retroviruses, receptors for retrovirus entry, restriction factors, antivirus innate immunity, gene editing in chicken, syncytins, epigenetic suppression of retroviruses, chicken genetics and genomics

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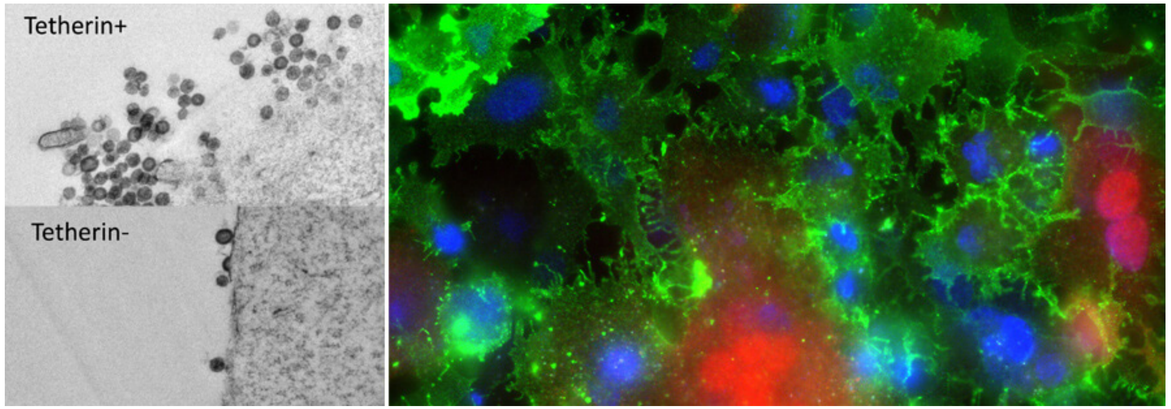
Replication of retroviruses in host cells is a result of the interplay between the virus and multiple cellular factors, either the virus dependence factors necessary for subsequent steps of the replication cycle or restriction factors that block virus replication and contribute to the innate antiviral immunity. The major focus of our group are receptors for retroviruses that specifically attach the virus and assist in virus entry. Avian leukosis virus (ALV), an important pathogen in the domestic chicken, diversified into several subgroups differing in their receptor usage. This creates an opportunity to study the virus-host coevolution and accommodation of the virus to a new host. As a practical outcome of this research, we pioneer the techniques of CRISPR/Cas9 genome editing of the chicken (together with partners from commercial sphere) and manipulate the genes for ALV receptors with the aim to obtain virus-resistant chicken lines (1, 2). Physiological functions of ALV receptors are another domain of our interest (3).

Working with avian retroviruses, we also need a strong background in the genetics and genomics of birds, particularly the chicken. Our analyses of the GC-rich parts of the chicken genome led to the discovery of several genes formerly considered to have been lost in the lineage of galliform birds (TNF-a, BST-2, PTX3, EPO, EPOR, etc). In combination with CRISPR/Cas9 gene editing either in cell lines or in vivo, we are now able to test the biological activities of these genes and compare them with functions in other vertebrates. For example, chicken BST-2/Tetherin exerts antiviral activity against ALV (4, Fig. 1) and potentially against other enveloped viruses (avian flu, avian coronaviruses, etc.). Factors of innate immunity will be of particular interest in the future.

We are also interested in endogenous retroviruses in the genome of vertebrates, which are the signs of ancient infections. Previously, we identified endogenous lentiviruses and deltaretroviruses in various mammalian lineages – the oldest HIV- and HTLV-related molecular fossils. Endogenous retroviruses adopt unexpected functions like syncytin-1, which is inevitable for cell-to-cell fusion in human placenta (Fig. 2). We focus on the interaction of syncytin-1 with its specific receptor (hASCT2 amino acid transporter) and cell-to-cell fusion (5), which occurs physiologically in the placenta and aberrantly in germline tumours.



Left: Retrovirus particles are retained in clusters on the cell surface in the presence of tetherin (top), whereas individual particles bud and are released from the host cell (bottom). Right: Chicken cells artificially fused into multinuclear syncythia by ectopic expression of human ASCT2 and syncytin-1. Green colour, ASCT2 fused with AcGFP; red colour, cells co-expressing syncytin-1 and dsRed; blue colour, cell nuclei stained with DAPI.

Selected publications:

1. Koslová A, Trefil P, Mucksová J, Reinišová M, Plachý J, Kalina J, Kučerová D, Geryk J, Krchlíková V, Lejčková B, Hejnar J*: Precise CRISPR/Cas9 editing of the NHE1 gene renders chickens resistant to the J subgroup of avian leukosis virus. Proc Natl Acad Sci USA 2020 117(4):2108-2112.
2. Koslová A, Trefil P, Mucksová J, Krchlíková V, Plachý J, Krijt J, Reinišová M, Kučerová D, Geryk J, Kalina J, Šenigl F, Elleder D, Kožich V, Hejnar J*: Knock-out of retrovirus receptor gene tva in the chicken confers resistance to avian leukosis virus subgroups A and K and affects cobalamin (vitamin B12)-dependent level of methylmalonic acid. Viruses 2021 13(12):2504.
3. Krchlíková V, Mikešová J, Geryk J, Bařinka C, Nexo E, Fedosov SN, Kosla J, Kučerová D, Reinišová M, Hejnar J, Elleder D*: The avian retroviral receptor Tva mediates the uptake of transcobalamin bound vitamin B12 (cobalamin). J Virol 2021 95(8):e02136-20.
4. Krchlíková V, Fábryová H, Hron T, Young JM, Koslová A, Hejnar J, Strebel K, Elleder D*: Antiviral activity and adaptive evolution of avian tetherins. J Virol 2020 94(12):e00416-20.
5. Štafl K, Trávníček M, Kučerová D, Pecnová Ľ, Krchlíková V, Gáliková E, Stepanets V, Hejnar J, Trejbalová K*: Heterologous avian system for quantitative analysis of Syncytin-1 interaction with ASCT2 receptor. Retrovirology 2021 18(1):15.