Review of PhD thesis by David Přikryl

entitled

Retroviral variants and their relationship to nonpermissive cells

PhD thesis by David Přikryl was prepared in the Laboratory of Viral and Cellular Genetics, Institute of Molecular Genetics of the ASCR under supervision of RNDr. Jiří Hejnar, CSc. The PhD thesis is focused on three major areas of retrovirus research: (i) identification of a receptor for the emerging ALV-K subgroup, (ii) the host range of ALV-C (RSV), and (iii) the involvement of MAV-2.2 in the mechanism of viral osteopetrosis.

In the first part, David Přikryl investigated whether a new group of ALV, denoted ALV-K, represents a new subgroup of ALV and explored this recent example of env-receptor co-evolution. He identified a receptor of ALV-K that proved to be Tva, the receptor known to be used also by ALV-A. However, since the K subgroup differs from the A subgroup by its host range and inhibition by the soluble form of Tva, the results suggest that the two subgroups use different epitopes of the Tva receptor. This work was published in the Journal of Virology with the name of David Přikryl as the first author. Then in the model of a hamster cell line H20 derived from Rous sarcoma virus-induced tumors, he investigated RSV provirus from the point of view of env-receptor evolution. He found that the extended host range, permitting to infect hamster cells, correlates with the ability of the envelope glycoprotein to acquire activated prefusion state prematurely, without interaction with the receptor. This work was published in PNAS with the name of David Přikryl as the third author. Finally, David Přikryl studied the cause and mechanism of virus-induced osteopetrosis. He compared the genome of a highly osteopetrotic strain, MAV-2.O, with non-osteopetrotic strains and showed that its envelope glycoprotein gene is important in osteopetrosis induction. In addition, he analyzed virus stability and its ability to enter the cells lacking its Tvb receptor.

The thesis is classically organized to – Preface, Acknowledgement, Abstract, Introduction, Aims, Materials and methods, Results, Conclusions, Discussion, Involvement of student in the publication, and References. The thesis successfully synthesizes heterogeneous subjects to unique study on retroviral variants and their relationship to nonpermissive cells, namely interactions of retrovirus envelopes with their cellular receptors. It contains well written literature overview. Appropriate size, without unnecessary redundancies is another

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positive value of the thesis. The presented PhD thesis is a clear example of contribution of the renowned laboratory to retrovirus research

David Přikryl could clarify or discuss during defense of his thesis the following points:

1. The term innate, intrinsic or natural immunity is not even once used throughout the manuscript. Can the restriction factors described in the thesis be divided into inducible (by the virus infection) and constitutive ones? What is the role of envelope in cell signaling?
2. Innate immune responses in ALV-J infected chickens are well documented. https://doi.org/10.3389/fmicb.2016.00786. Do you think that PRR, specifically TLR signaling could play a role in post-entry restriction or stimulation? Could IL-6 be induced by MAV-2.O infection and could it be involved in the development of osteopetrosis.
3. It would be helpful to show a scheme how the virus-driven down-regulation of Hyal-2 results in stronger signaling from RON, which in turn activates both PI3k/Akt and Ras/Raf/MEK/MAPK signaling pathways.
4. Does the receptor interference influence geographical distribution of ALV subgroups in vivo?
5. What is a relative efficiency of cell entry of hamster cell-adapted and non-adapted RSV in permissive system? Just a note – In the first part of thesis, the virus is referred as ALV-C, while in the second one as RSV-C.

In conclusion, the thesis of Mgr. David Přikryl perfectly fulfills requirements demanded for the level of dissertation work. David Přikryl is the first author of one paper published in the Journal of Virology and collaborating author of paper published in the Proc. Natl. Acad. Sci. USA. I heartily recommend submitted work for defense, and depending on the outcome of defense procedure for approval of doctor degree.

Prague, January 30, 2021 Prof. RNDr. Ivan Hirsch, CSc

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