Guest Editorial

Rous Sarcoma Virus Centennial in Folia Biologica

(Rous sarcoma virus / Folia Biologica)

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In 2011, 100 years had elapsed since the discovery of chicken Rous sarcoma virus, which became a principal tool for definition of oncogenes as well as for biological and molecular characterization of the retrovirus replication cycle, including reverse transcription of viral genomic RNA to DNA and its integration as a provirus. These discoveries facilitated HIV identification as a causative agent responsible for the AIDS epidemic.

For many years, Folia Biologica has been publishing internationally recognized articles covering essential topics of retrovirus research, in which I have also been personally involved. In this context I would like to remember some of our contributions that appeared in this journal.

In 1960 to 1961, I established rat tumour XC cells as the first mammalian tumour cell line carrying functional avian Rous sarcoma virus (RSV) genetic information and provided a set of controls demonstrating that RSV is responsible for tumour formation (Svoboda, 1961). Next, I provided evidence that XC cells behave as virogenic cells and do not contain or produce infectious virus, but the virus can be rescued after inoculation of intact cells in chickens (Svoboda, 1962). Together with my colleagues (Svoboda et al., 1963) we evaluated these and additional findings and came to the conclusion that the RSV genome is integrated as a provirus in the host cell and is rescuable by cell association enabling cell fusion. Our experimental arguments in favour of the provirus were recognized by H. Temin in his Nobel lecture as obtained independently of his study (Temin, 1976).

Furthermore, we substantiated our prediction by first data showing that if cell fusion is potentiated by Sendai virus, virus rescue is significantly enhanced (Svoboda et al., 1967). Two of the above-mentioned papers were selected by ISI as Citation Classics.

The impact of Peyton Rous discovery has been evaluated and discussed in relation to the main stream of Anglo-American research, not properly mentioning achievements of outside laboratories. In a following short article we present an extended view of the P. Rous discovery.

Several commemorative articles appeared in leading biomedical journals and a special international meeting, 'Centennial Retrovirus Meeting', was held in Prague on this occasion. I present the following comment on one of these article published by Weiss and Vogt (2011).

Comment on the impact of Peyton Rous virus discovery

In their well-written article about Peyton Rous achievements, Weiss and Vogt (2011) also touch a salient problem of tumour cell transplantation in relation to oncogenic virus detection. The original chicken sarcoma (No1) (Rous, 1910) was first passaged as tissue grafts in close-bred Plymouth Rock chicken, and only later, after several passages, the virus now called Rous sarcoma virus (Rous, 1911) was successfully isolated.

This non-canonical and original approach to the discovery of an oncogenic virus remained illustrious and inspiring for the next generation of tumour virologists and became a lasting challenge for new experiments. Peyton Rous was aware of the difficulty in interpreting his findings and provided the thoughtful inference "… it is quite possible that the failure to separate from these growths an agent causing them may be traceable to some interference with conditions under which this suppositious agent can exist alone or reproduce the growth in new hosts". What does such an interference preventing virus stability or growth stand for?

Weiss and Vogt (2011) raise the possibility that in the original sarcoma, cellular proto-oncogene *src* had been activated and later transduced by a retrovirus. Unfortunately, 100 years later there is no evidence for an *in vivo src* activation leading to tumour production in the absence of a retrovirus. Is it only due to the negligence of this problem, or is the *src* activation associated intimately with retrovirus replication? At least in the case of a prototypical cellular oncogene such data should be available.

From another point of view we may assume that the virus was present in the original No1 sarcoma, but suffered serious alterations that crippled its replication. According to our experience, fresh isolates of *src*-con-

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Abbreviation: RSV – Rous sarcoma virus.

taining virus PR2257 (Svoboda et al., 1985; Geryk et al., 1989) produced little of infectious virus. However, after passaging its titre rose ten times, which was accompanied by correction of the anomalous sequence in the vicinity of primer binding site and significant deletion of the last non-coding cellular *src* exon that became originally incorporated in its structure, followed by an increase in envelope gene structure representation (Yatsula et al., 1994)

Finally, we must take into account that tumour cell transplantation provides a several-day period during which cells are not rejected but ensure steady, even though low-amount virus production. Such a survival of grafted tumour cells was originally recorded by Rous in chicken transplanted with the sarcomas he studied (Rous, 1911). He also provided evidence that the allograft immunity differs from that against his virus (Rous, 1913). The same was observed by us in young rats in which the engrafted chicken tumours survived undamaged for several days, which was documented histologically by Svoboda and Grozdanovic (1959). In this way transplanted tumour cells keep in close contact with host cells, which could provide conditions for direct cell-to-cell transmission of even immature virus or virus equipped with the envelope not suited for efficient interactive cell receptors.

Thus, both prolonged virus shedding and unorthodox virus penetration might contribute to the increased efficiency of tumour grafts for triggering virus infection. One or both of these factors could have been responsible for successful transmission of the virus either to foreign avian species (Duran-Reynals, 1947) or to rats (Svet-Moldavsky, 1958; Svoboda, 1960).

There are available data documenting that association between virus-shedding and non-infected cells potentiate virus transmission via cell synapsis. In particular, the intracellular envelope domain triggers rearrangement in a normal cell associated with a retrovirus-infected cell, which facilitates retrovirus transfer from the former to the latter (rev. Sattentau, 2008; Mothes et al., 2010). Here, I would like to remind our first findings aiming at *in vitro* rat cell transformation. This goal was achieved by rat cell co-cultivation with RSV-infected chicken fibroblasts in the culture fluid where chicken fibroblasts were only short-lived. The possibility of cell-to-cell virus transmission involvement had been raised (Svoboda and Chýle, 1963). Thus, the Peyton Rous discovery is challenging us even at present.

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