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JĀNIS OĻĢERTS ĒRENPREISS AND HIS SCHOOL OF CANCER RESEARCH: COMMEMORATING THE 90TH ANNIVERSARY

Jekaterina Ērenpreisa

Latvian Biomedicine Research and Study Centre, Rātsupītes 1k-1, Rīga, LV1067, LATVIA; katrina@biomed.lu.lv

Jānis Oļģerts Ērenpreiss (1929–1996) was a prominent Latvian cancer researcher and theoretician. Starting out as a student, he contributed to the embryonal theory of cancer, experimentally proving the differentiation and regenerative normalisation capabilities of tumour cells. His theoretical work, presented in its most complete form in his final monograph Current Concepts of Malignant Growth *(Zinātne Publ., Rīga, 1993), postulates that oncogenes are abnormally activated genes that are involved in gametogenesis and embryogenesis, and that carcinogenesis and senescence are mutually linked processes arising when the cell is exposed to stressful conditions. This article demonstrates how advancements in cancer research over the last decade have confirmed these core concepts, which were far ahead of their time, and how J. O. Ērenpreiss' legacy continues both under the guidance of the author and in foreign laboratories, expanding understanding of the nature of malignant tumours and the perspectives of cancer treatment.*

Key words: *cancer, embryological/gametogenesis theory, oncogenes, cellular senescence, tumour differentiation.*

INITIATION. EXPERIMENTS ON TUMOUR NORMALIZATION IN THE REGENERATIVE FIELD

In front of me is a laboratory notebook, yellowed from time, which was started to be filled in by the undergraduate student Jānis Oļģerts Ērenpreiss during the 5th year of his medical studies. The first protocol, dated from 19.08.1954, says: "A rat with a large Sa M465 was obtained from Moscow, Prof. L.A. Zilber's laboratory, where spindle-cell-shaped sarcoma was induced by applying dimethyl-benzanthracene. Using ether narcosis, the tumour was implanted in four two-month-old female rats". At the Histology Department of Rīga Medical Institute, lead by Prof. Konstantin S. Bogoyavlensky, J. O. Ērenpreiss (Fig. 1) started a complex experiment, operating on 104 animals over the course of two years. A ~3 mm bone piece was aseptically resected in the distal part of the tibia and a 1 mm^3 piece of Sa M465 was inserted into the bone defect. The goal was to see how the malignant sarcoma behaves in the morphogenic field of the regenerating bone. Observations and histological sampling were carried out for 23 days. In short, it was found that while in control animals the transplanted sarcoma was growing very aggressively and destroying soft tissues and bone, in the operated rats, during the second week post tibial resection, when the initial fibrous regeneration callus consolidating the bone defect was being replaced by the cartilaginous one before ossification, the invasive growth of the tumour was interrupted. Moreover, sarcoma cells underwent differentiation and participated along with the host tissue in the formation of regenerative cartilage tissue. The results were reported at the

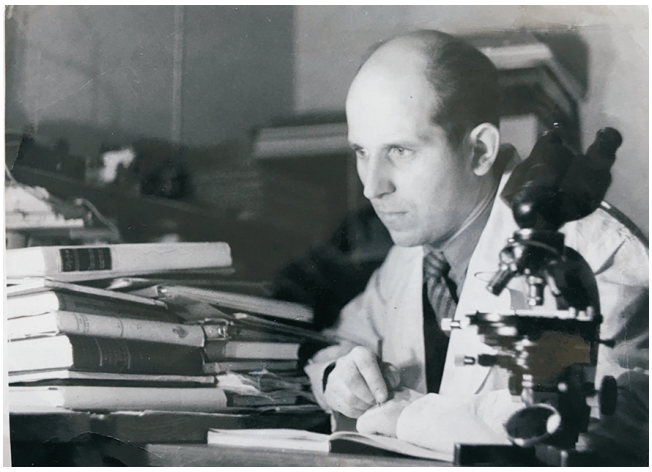

Fig. 1. Latvian oncologist Jānis Oļģerts Ērenpreiss in early 1970s.

Student Scientific Conference, on 20–22 April 1955, in Riga, at the Regeneration and Cell Growth Conference on 28–31 January 1958 in Moscow, and became the basis of the young scientist's MD PhD thesis "Influence of Bone Regeneration on the Growth and Differentiation of Sarcoma S465" which he defended in Rīga in 1959. J. O. Ērenpreiss also investigated with a similar approach how an epithelial tumour (Guerin carcinoma) behaved in the area of rat tibial fracture regeneration. He found that in the first phase, during the formation of the host granular connective tissue, the tumour formed its own stroma and unlimitedly proliferated, however, at the stage of cartilaginous callus, the stroma of carcinoma became involved in the formation of the cartilage, while the epithelial carcinoma cells, depleted from their stroma support, underwent degeneration (Fig. 2).

However, after the end of cartilagenesis, the callus became reinfiltrated by the tumour from outside. Several communications on both models were published (Erenpreiss, 1959; 1961; 1962). Unfortunately, due to the closed USSR borders at that time, the early report on this work appeared internationally only as a short communication "Tumour growth in the zone of bone regeneration" (Erenpreiss, 1964).

The idea that tumour growth is a biological process that depends on the embryonic nature of malignant cells, which hence possess morphogenic potency to differentiate and normalize, inspired Jānis O. Ērenpreiss throughout his entire life. The emergence of this concept in the head of the very young scientist can be explained by the deeply fundamental biological school of his tutor Prof. K. S. Bogoyavlensky and the genius intuition of his best scholar. J. O. Ērenpreiss was a microscopist trained to notice both the unexpectedly particular and generally new patterns in the heterogeneity of tumour cell specimens. These two methods obtained from his teacher — keeping to fundamental biological knowledge and applying this knowledge in creative microscopic observation ("Chance discovery favours only the prepared mind" – Louis Pasteur) — were transferred by J. O. Ērenpreiss to his pupils as well.

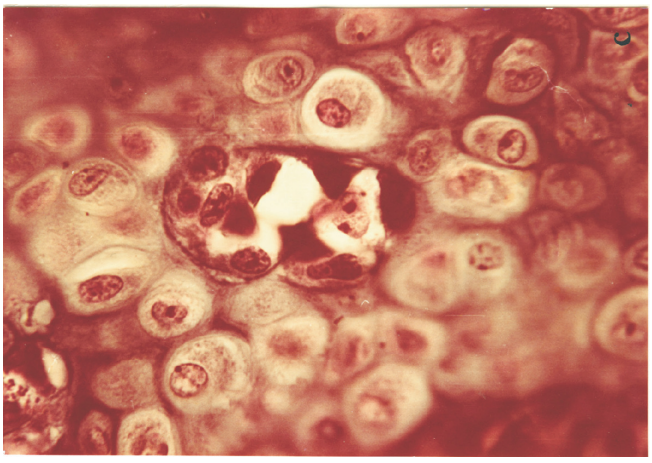

Fig. 2. Epithelial cells of Guerin carcinoma undergo degeneration in the cartilaginous callus of rat tibial fracture. Azan histological staining. Immersion. A copy of the original colour micro photo (Erenpreiss, 1962).

ESTABLISHMENT OF OWN LABORATORY. STUDIES OF THE NUCLEOPROTEINS AND CHROMATIN

The Laboratory of Cancer Cell Histochemistry established by J. O. Ērenpreiss in 1971 in the Latvian Institute of Experimental and Clinical Medicine later became the Laboratory of Cancer Cell Biology. His pupils were Rasma Krampe, Zinaida Frolenko, Alfrēds Miltiņš, Ruta Zirne, and Olga Demidenko. The present author, who led the lab after J. O. Ērenpreiss had passed away in 1996 at the age of 67, is also one of them. Methodically, J. O. Ērenpreiss began with the cytochemistry of nucleoproteins, a field of research introduced in Rīga by Prof. K. S. Bogoyavlensky. J. O. Ērenpreiss and his pupils studied and developed new cytochemical reactions for DNA, different categories of RNA, histones and other nuclear proteins. At that time, the impetus of the discovery of the DNA double-spiral by J. Watson and F. Crick, and soon after of the nucleotide code and the enthusiasm for that were enormous and also inspired J. O. Ērenpreiss. He was one of the first who began to deliver lectures on molecular biology at the University of Latvia, which occurred in 1967–1968. He applied his knowledge of nucleoproteins to the differentiation of tissues and wrote his first book. In 1963, in New York, his book (Erenpreis, 1963), translated by publishers from Russian into English, appeared (it still can be obtained on Amazon); the book became popular and was recommended to University students. The second dissertation of Jānis O. Ērenpreiss (*Dr. habilitus* of medicine) defended in 1967 was titled "The Cytochemistry of Nucleoproteins in Normal and Tumour Cells". At this time and during the next 15 years, most studies with his students concentrated on chromatin structure, among them the electron microscopy and cytochemistry of the cell nucleus and suprachromosomal organization; particularly in diagnostic reactions for tumour cells (Black-Spear reaction with ammoniacal silver and Roskin reaction with leucobase of methylene blue) we hoped to find a key to the tumour cell enigma (it turned out to be non-specific genome activation).

ONCOGENES: CREATIVE SYNTHESIS OF THE ONCOGENIC AND EMBRYOLOGICAL THEORY OF CANCER

The biomedical science was becoming more and more molecular, and around 1973, the time for the first oncogene discovery had arrived. Under its influence, J. O. Ērenpreiss, like many others, believed, although for a short time, that a specific mutant cancer gene would be found. But the list of oncogenes was growing and growing and the hope for the reductionistic variant of the somatic mutation theory of cancer was shrinking. J. O. Ērenpreiss was one of the first who perceived this, whereas many were doomed to disappointment only after the cancer genome sequencing projects of the 21st century failed to confirm this theory (Weinberg, 2014) and the whole oncology school did not recover from this illusion till now (Bizzarri, 2018).

However, as the great Niels Bohr said: "The opposite of a great truth is another truth." J. O. Ērenpreiss locked himself away in the lab and library and worked tirelessly in the pre-internet era, gathering and digesting a huge amount of literature on oncogenes. He systematised this literature, and showed that most oncogenes are also key development genes that participate in normal gametogenesis and embryogenesis, and hence their role in cancer can be deduced as inappropriate constitutive activation, which shifts normal somatic cells to an epigenetic state similar to that of an embryo. Importantly, it does not occur randomly (as the somatic gene mutation theory presumes), but as a pre-programmed response to adverse (stressful) intrinsic and extrinsic conditions. Thus, he managed to conform and join genetics with epigenetics, returning to the notion of the embryonal character of cancer and thus contributed to the embryonal cancer theory. In its initial form, this theory was proposed by the prominent pathologists of the 19th century. In the 20th century, the experiments with transplanting carcinoma nucleus in the enucleated ovum to reveal its ability to prime normal embryo development and the opposite approach — ectopically transplanting a normal embryo, which then converted into a tumour (teratocarcinoma), confirmed this theory (for more details see Bignold, 2006). The analysis performed by J. O. Ērenpreiss led him to favour the gametogenic variant of the embryonal theory of cancer (later he appraised the parthenogenetic variant of Vinnitsky (1993). In 1987, J. O. Ērenpreiss published a monograph in Russian (Erenpreiss, 1987) and about ten articles among them (Erenpreiss, 1983; 1990a; 1990b) on his theory, and finally in 1993, a monograph in English (Erenpreiss, 1993) summarised his studies. Before his passing away, J. O. Ērenpreiss had started to prepare "Part B: From Cancer to a Normal Cell". In his archive dated 12 July 1996, I found prepared 28 pictures with legends from his first scientific work on the normalisation of sarcoma in the rat bone regeneration field. His sudden death interrupted this work. Were he alive now, he would have witnessed the article by Hu *et al*. (2017), who reported that the transient hypertrophic cartilage of bone fracture activates at the chondro-osseous border (the place where he found the involvement of sarcoma cells in the morphogenesis) the expression of the embryonic pluripotency transcription factors (Oct4, NANOG and SOX2), indispensable for fracture healing [12], thus molecularly explaining his results.

Jānis Oļģerts Ērenpreiss was awarded the status of a Professor and a full member of the Latvian Academy of Sciences. A list of publications written by J. O. Ērenpreiss himself until 1995 includes 141 items. Among them there are five monographs on carcinogenesis, special thematic issues, journal articles, and conference abstracts. He achieved much in science and teaching, but still, his life was short. Twenty-three years have passed since that time. I wish to further expand on the contribution of Jānis O. Ērenpreiss to the theory of carcinogenesis in the light of the developments and current state in cancer research.

THE EMBRYONAL CANCER THEORY OF JĀNIS OĻĢERTS ĒRENPREISS IN VIEW OF THE CURRENT DEVELOPMENTS

Below I shall cite the most essential notions of J. O. Ērenpreiss' views from his last book. I aim to briefly demonstrate the development of his and relative ideas in our and some other selected work from all over the world, which appeared in the last ten years. This essentially new material is given in italics.

Jānis Oļģerts Ērenpreiss (JOE): "The oncogenes can be classified as immortalising, and promoting neoplastic transformation. Immortalising oncogenes (the most prominent among them — *c-myc*) determine the inability to undergo terminal differentiation and the promotability". *It is essential to note that we and others have added the polyploidy of cancer cells as an important component of the embryo-gametogenic carcinogenesis and associated it with c-myc. The cells with hyper-activated c-myc uncouple from the normal cell cycle regulation and undergo polyploidisation which is linked to reprogramming by inducing the key genes of the embryonal pluripotency, POU5F1 (OCT4A), NANOG, SOX2* (Salmina *et al*., 2010; Vazquez-Martin *et al*., 2016*).* JOE: "The leucine zipper domain of *myc* forms a stable heterodimer with the protein products of *fos* and *jun* forming the activator protein AP-1". *Polyploid tumour cells also activate adaptive stress-response cassette (c-myc-AP-1), this gene module favours the repair of DNA damage and proliferative survival in adverse conditions* (Vazquez-Martin *et al*., 2016). *Moreover, the activation of AP-1 is associated with the early cancer genome change, a prerequisite for the differentiation induction in the breast cancer cell* (Saeki *et al*., 2009; Tsuchiya *et al*., 2016; Salmina *et al*., in preparation). JOE: "The immortalising oncogenes are engaged in *ras* gene activation. The *ras* oncogene completes the neoplastic transformation of an initiated (immortal) cell and triggers the differentiation process. True tumours arise as a result of the activity of the complementary pair *myc-ras.*" (Fig. 3).

In turn, our collaborative bioinformatics studies revealed that polyploidy as such activates the cancer gene ontology module, in particular, the gene cluster of the c-myc-H-ras axis (Vazquez-Martin *et al*., 2016). A multinuclear polyploid cancer cell possesses the molecular signature and phenotypic features of the germ and early embryo (Erenpreisa

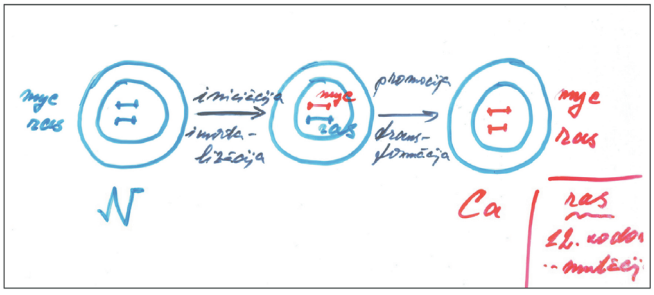

Fig. 3. The lecture slide by Jānis Oļģerts Ērenpreiss with his hand-drawn scheme of carcinogenesis showing the role of a complementary pair of the important oncogenes, *c-myc* and *ras*.

and Cragg, 2007; Erenpreisa *et al*., 2014; Niu *et al*., 2017; Chen *et al*., 2018) and even as a single one is able to initiate tumour growth *in vivo* (Weihua *et al*., 2011). JOE: "Promotability (induced by a mutant or otherwise constitutively activated *ras* oncogene) may be defined as the ability to undergo neoplastic transformation. *ras*–oncogene, which completes neoplastic transformation in the immortal cell triggers the differentiation process." This is a very important point of JOE's theoretical work because differentiation is associated with cellular senescence. Moreover, J. O. Ērenpreiss had calculated from the literature sources that the species-specific life span (SSL) and cellular life-span (Hayflick's limit) correlate with the shortest latency (ShL) period of tumour induction (as established in the experiments with chemical cancerogenesis). For different animals (rat, rabbit, hen, horse, human, Galapagos turtle, etc), ShL/SSL=1/20. From this important regularity, J. O. Ērenpreiss concluded that SSL, Hayflick's limit, and ShL are determined by the same programme. JOE: "Thus, it is likely that the molecular mechanism shared by both ageing and neoplastic transformation can be viewed as belonging to the evolutionary (programmed – JeE) process." Therefore, it is notable that oncogenic H-ras, typically mutated in the Val 12 position, turned out as a model for induction of cellular senescence in normal (not immortalised) human fibroblasts and that this model of cellular senescence has been used in this century in multiple studies. It remains to be added that in concordance with the concept of JOE on the causal link between cancer and senescence, our laboratory (partly in collaboration with the lab of Prof. Mark S. Cragg in the UK) revealed bi-potential transient cell senescence, which is heterogeneously and competitively coupled in the same cells, with stemness markers being a prerequisite for cancer cell survival after anticancer drugs. The important epigenetic molecular mechanism that depends on activation by tumour suppressor TP53 of the OCT4 alternative splicing, restricting both embryonal stemness and terminal senescence until DNA damage repair, has been identified and three articles and a book chapter have been published on this mechanism (Jackson *et al*., 2013; Huna *et al*., 2015; Erenpreisa *et al*., 2017; Baryshev *et al*., 2018), and two PhD theses defended (Jackson, 2013; Huna, 2015). Comparing the similarities between germ and cancer cells, J. O. Ērenpreiss postulated: "All of the basic traits inherent in cancer cells are displayed in gametes, and vice versa. Nothing but cell fetalisation occurs during cancerogenesis and cancer cell possesses no other properties but foetal." This seems to be an extreme view. However, our recent in silico study of the karyotypes of nearly 3000 cancer patients from the Mitelman database revealed interesting triploid XXY karyotypes that present further evidence in favour of the gametogenic theory of cancer (Vainshelbaum *et al*., 2019; Salmina *et al*., 2019). In line with the embryonal/gametogenesis theory of cancer, Liu C. *et al*. (2018) using $TP53^{-/-}$ mice showed that abnormal oogenesis induced by p53 deficiency and then spontaneous parthenogenetic activation endows tumours with imitated embryonic development, life cycle, and therapeutic resistance.

CONCLUSION AND PERSPECTIVES

Jānis Oļģerts Ērenpreiss passionately and faithfully developed the embryonal cancer theory throughout his entire scientific career, mostly going against the mainstream of the reductionistic cancer research schools of his time. His general ideas turned out to be much ahead of their time and are bearing fruit now, particularly in the work of the next generation of his school. The differentiation of cancer cells by the morphogenetic factors (embryonal inducers) experimentally attempted by J. O. Ērenpreiss 65 years ago at the student bench currently seems to be one of the promising perspectives in causal cancer treatment (Erenpreisa *et al*., 2014; Liu *et al*., 2018; Chen *et al*., 2019).

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JĀNIS OĻĢERTS ĒRENPREISS UN VIŅA VĒŽA PĒTĪJUMU SKOLA: ATCEROTIES 90. GADADIENU

Jānis Oļģerts Ērenpreiss (1929–1996) bija izcils Latvijas vēža pētnieks – teorētiķis. Kopš studenta gadiem viņš piekopa un attīstīja embrionālu vēža teoriju, eksperimentāli pierādot, ka vēža šūnas spēj diferencēties un normalizēties reģeneratīvā laukā. Savā teorijā, kas vispilnīgāk tika izklāstīta viņa pēdējā monogrāfijā *Current Concepts of Malignant Growth* (Zinātne, Rīga, 1993), viņš sistematizēja materiālu par to, ka onkogēni ir nenormāli aktivēti šūnas gēni, kas atbild par gametoģenēzi un embrioģenēzi, un ka kanceroģenēze un novecošanās ir savstarpēji saistīti procesi, kas rodas, šūnām adaptējoties stresa apstākļos. Rakstā arī parādīts, ka šīs pamatidejas, kas gāja savam laikam pa priekšu, vēža pētniecības gaitā pēdējos desmit gadu laikā apstiprinājās un tika attīstītas J. O. Ērenpreisa skolas darbos, šī raksta autores vadībā, kā arī cituviet pasaulē, veidojot gan izpratni par ļaundabīgo audzēju dabu, gan perspektīvu to ārstēšanai.