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The role of viruses in the cancerogenesis

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ABSTRACT

It is estimated that seven key viruses such as Hepatitis B virus (HBV), Hepatitis C virus (HCV), Human T-lymphotropic virus (HTLV), Human papilloma viruses (HPV), Kaposi's sarcoma-associated herpes-virus (KSHV), Epstein-Barr virus (EBV) and Merkel cell polyomavirus (MCV), are responsible for about 11% of cancers all over the world. Viruses however are not only associated with cancerogenesis process. Scientific researches from recent years emphasize the possible use of the microorganisms as antitumor therapy. Oncoviruses, also defined as tumor viruses cause cancers whereas oncolytic viruses infect the host's cancer cells leading to destruction of tumor and due to that they are described as cancer killing viruses. It offers the potential application of viral infections to the cancer therapy.

Key words: cancers, cancerogensis, viruses.

Early days

A number of findings published within the past few years have confirmed pathogens' involvement in the aetiology of a significant share of human malignant cancers. According to 2008 data, 2 million out of 12.7 million newly diagnosed carcinomas worldwide are estimated to be associated with infectious factors, of which 1.9 million are assumed to be caused by four pathogens: Hepatitis B and Hepatitis C viruses, Human Papilloma Virus (HPV), and *Helicobacter pylori* [1]. The role of viruses and bacteria in carcinogenesis is becoming more and more apparent and can be the basis for actions aimed at limiting cancer prevalence, having eliminated carcinogenic pathogens by vaccination or eradication. This type of phenomena has been observed after Hepatitis B immunization was applied population-wide [2]. Effective primary prophylaxis was made possible after over 150 years of combined efforts of biologists, chemists, and physicians who have been searching for evidence in laboratory and epidemiological studies. A lecture by Domenico Antonio Rigoni-Sterna, held in 1824 in Verona, was the first documented suggestion of viral origins of the cancer. In his medical practice, Rigoni-Sterna learned that endometrial cancer was significantly more common in married women than in nuns. However, there were no methods available at that time to differentiate the results into cervical cancer and endometrial cancer, which makes it difficult to objectively evaluate these findings [3].

In 1882, Charles Chamberland, a French biologist, and Louis Pasteur developed a porcelain filter that could be used to remove micro-organisms from a solution. Many believe the year 1882 was the birth date of virology. The Chamberland-Pasteur filter could be used to obtain a filtrate which apparently contained no living microorganisms [3].

However, a decade later, Dmitry Ivanovsky, a Russian scientist, studied a plant disease called mosaic disease in tobacco. The results indicated that the filtrate contained some invisible, unquantifiable pathogenic microorganisms, which the scientist believed were toxins produced by bacteria [4]. Ivanovsky did not dissem-

inate his findings as, apparently, he was oblivious to their true significance.

Another scientist, Martinus Beijerinck, also investigated the mosaic disease and repeated the experiment in 1898 without having any knowledge of Ivanovsky's work. He named the infectious microbes, *contagium vivum fluidum*, and discovered that, unlike *contagium fixum,* they could not be extracted from water with any filters at hand. Beijerinck was the first to discover that *contagium vivum fluidum* can only be formed in the presence of living cells and became the first person in modern era biology to use the word 'virus' [4].

Virions – the virus particles

In early 20th century, with significant technical progress and improvements made to the filters, more and more sophisticated methods were developed to isolate the still elusive particles – virions. First experiments on animals were performed after a much clearer filtrate was successfully obtained. Two veterinary physicians, Vilhelm Ellerman and Olaf Bang, working at the University of Copenhagen, demonstrated the way leukaemia, or more specifically erythroblastosis, could be transmitted to healthy chickens by injecting them with a cell-free filtrate obtained from tissue. These experiments paved way for Peyton Rous to perform more research. In his work, Peyton Rous focused on investigating the biology of solid tumours in animals. He believed environmental factors to be the key to their origin. In his break-through publication entitled *Transmission of a Malignant New Growth by Means of a Cell-Free Filtrate* published in 1912 in *The Journal of Experimental Medicine*, Rous demonstrated that, when using sub-cellular filters, chicken sarcoma could be similarly transmitted [5]. Rous' studies were initially considered interesting, though entirely unreliable. Nevertheless, the scientist was awarded the Nobel Prize in 1966. A record time of 55 years had to pass from the first discovery until the results were fully recognised by the scientific community, proving the ground-breaking nature of the experiments performed, pointing to the viral aetiology of cancers. Despite much scepticism, some new papers on the alleged infectious origin of cancers were published at the end of the first decade of the 20th century [6].

Rous resumed his studies on chicken sarcoma in the 1920s and confirmed the initial results. First studies on mammals were conducted in the 1930s. American virologist, Richard Edwin Shope, who later identified the influenza virus and created the first effective vaccine, was the pioneer of studies on mammals. He discovered that rodents infected with the papilloma virus, now known as the Shope papilloma virus, developed a specific type of cancer, a keratinous tumour growing exophytically on the animal's head [7]. The theory of "particle-free pathogens" was abandoned after the mosaic disease virus was first crystallized in the 1930s by an American chemist, Wendell Meredith Stanley, working at the University of California, Berkley. Stanley, who later won the Nobel Prize, discovered that viruses were composed of nucleic acids and thus proved them-to be made up of particles [6, 7].

Isolation of the murine leukaemia virus (MuLV) and polyomavirus, both evidently associated with carcinogenesis, was another important contribution to virology in the early 20th century. Both discoveries were made by Ludwik Gross, a Cracow-born virologist working in the USA [8].

Viral carcinogenesis in humans

Works by Michael Anthony Epstein and his assistant, Yvonne Barr, marked the most important step towards investigating the role of viruses in carcinogenesis. In collaboration with Bert Achong, expert in the field of newly invented electron microscopy, the scientists analysed preparations from Uganda sent by Denis Burkitt, a surgeon. By combining epidemiological data and endogenous cancer sites, thesis was formulated and evidence of viral carcinogenesis provided [9]. During his work at the American Health Institute in the 1960s, Baruch Samuel Blumberg isolated viruses causing hepatitis in humans. These were Hepatitis A and Hepatitis B viruses. Despite numerous indications of their role in carcinogenesis, epidemiological evidence was brought up only 20 years later. In the1980s, Bernard Poiesz and Francis Ruscetti studied retroviruses at the Robert Gallo Laboratory and discovered the Human T-lymphotropic virus, etiologically related to T-cell leukemia/lymphoma [10]. The isolation of human papilloma virus, strains 16 and 18, still remains one of the most important discoveries in clinical terms. It was accomplished by a team led by Harald zur Hausen, who won the Nobel Prize in 2008. Human papilloma virus strains 16 and 18 cause 70% of all cases of cervical cancer, which can be prevented by effective immunization. In many interviews, professor Harald zur Hausen argued that the vaccine could have been developed as early as in the 1980s, however, no pharmaceutical companies decided to take up production since the financial forecasts were unsatisfactory [11]. In 1987, Michael Houghton and David W. Bradley independently identified a virus which was formerly known as the Non-A, Non-B Hepatitis virus.

The Hepatitis C virus is one of the most common infectious factors which leads to the development of hepatic cancer. In the 1990s, a married couple of scientists, Patrick Moore and Yuan Chang used the Representational Difference Analysis (RDA) to isolate Kaposi's sarcoma-associated herpesvirus (KSHV), classified as Human Herpes Virus 8 (HHV-8). In the first years of the 21st century, they developed a new virus isolation method, the so-called Digital Transcriptome Subtraction (DTS). It was used to prove that the Merkel cell carcinoma was associated with the polyomavirus [13].

In recent years, the relationship between viral infections and carcinoma has been discussed in the context of eliminating cancer cells by infecting them with viruses. For example, infection with human cytomegalovirus may affect cancer in a process called oncomodulation, which favours the growth of more malignant cell clones [14]. Oncomodulation has been investigated by several research centres, and the results obtained can reasonably be expected to contribute to the development of new therapeutic interventions [15, 16].

Oncolytic viruses open up new possibilities in developing new cancer treatment options [17]. It was demonstrated that some viruses preferentially infect and kill cancer cells. Therapies based on this type of viruses could be used if the cancer fails to respond to traditional chemotherapeutics [18]. Oncolytic viruses were in the spotlight after cases of cancer regression following natural infection or immunization have been observed. Oncolytic viruses preferentially attack cancer cells, penetrate them using cell receptors, use molecular pathomechanisms associated with malignant transformation, and block interferon-mediated anti-viral response. Viral replication in the cancer cell leads to its destruction and regression. In light of these observations, cancer cell infections with oncolytic viruses are now examined for their potential use in cancer treatment [19].

Summary

It is estimated that the seven key viruses: Hepatitis B and Hepatitis C viruses, Human T-lymphotropic Virus, Human Papilloma Virus (HPV), Kaposi's sarcoma-associated herpesvirus (KSHV), Epstein-Barr Virus, and Polyomavirus associated with Merkel cell carcinoma [20] are responsible for 11% of all cases of cancer worldwide. In recent years, potential opportunities to use viral infections in the development of new cancer treatment options were investigated [18]. Oncovirus, synonymously called a 'tumour virus', is a virus that can cause cancer, whereas an oncolytic virus preferentially infects the host's cancer cells and lyses them, causing tumour destruction, and is thus referred to as a 'cancer killing virus'. Viruses which have been associated with cancer so far,may become a promising therapeutic tool as the mechanisms of their functioning in the host's cells are more closely investigated.

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