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Microbes and their Participation in Selected Human Neoplastic Diseases

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Abstract

The progressing development of studies, particularly within genomics of pathogen-host interactions, allows to recognize better the causal link between the infection and the neoplastic disease. The data obtained till now point to a significant involvement of microbes and, in particular viruses in over 20% of human neoplastic diseases. Basing on the multi-year knowledge, World Health Organization (WHO) recognized the following viruses: Epstein-Barr virus (EBV), Kaposi's sarcoma-associated herpes virus (KSHV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodefiniciency virus-1 (HIV-1), human T-cell lymphotrophic virus-1 (HTLV-1), human papillomavirus type 16 (HPV-16) and a single bacterial pathogen, the *Helicobacter pylori* as "carcinogenic to humans". The above listed pathogens represent risk factors of specific neoplastic diseases, including Burkitt lymphoma (BL), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), nasopharyngeal carcinoma (NPC), Kaposi's sarcoma (KS), hepatocellular carcinoma (HCC), adult T-cell leukemia (ATL), cervical cancer (CC) and oropharyngeal cancer (OPC), nonmelanoma skin cancer (NMSC) and gastric cancer (GC). The causal link between the infections and development of the neoplastic diseases in humans, however, remains an open question. Nevertheless, the already obtained data promote novel investigative directions within the early diagnosis of neoplasia risk and prophylaxis as well as they allow to implement novel therapeutic strategies. Therefore, it is justified to present data related to involvement of microbes in etiopathogenesis of tumours.

Keywords: ***Microbes; Carcinogenesis; Oncoproteins; Pathogenesis; Human neoplastic diseases; Cancer research***

Introduction

Pathogenicity of microbes used to be manifested in humans by an acute morbid syndrome, usually terminated by vanishing clinical signs /symptoms and an elimination of the pathogen. Nevertheless, it is already well known that the course of infection may also be chronic, linked to a specific morbid syndrome, including those of an inflammatory-autoimmune character. In parallel, the increasingly well recognized pathogen-host relationships point to a significant, reaching involvement of specific microbes in over 20% of human neoplastic diseases [1], including annually over 14 million cases of cancer worldwide [2].

The microbes manifesting an oncogenic activity used to be capable of inducing chronic infections, which can lead to the complex process of oncogenesis. Microbes may promote this process by several mechanisms, mainly due to direct effects on signal transduction pathways in host cells, chronic inflammation and changes in host physiology [3,4].

Investigative data document that infective agents which participate in etiopathogenesis of human neoplastic diseases most frequently include viruses [5,6]. At present no doubts remain that viruses induce more rapidly and most directly genetic lesions in host target cells than those induced by other external factors. The knowledge accumulated through several decades of cancer research allowed for recognition by the World Health Organization (WHO) of certain viruses as "carcinogenic to humans" [1]. They include: Epstein-Barr virus (EBV), Kaposi's sarcoma-associated herpes virus (KSHV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodefiniciency virus-1 (HIV-1), human T-cell lymphotrophic virus-1 (HTLV-1), human papillomavirus type 16 (HPV-16). In addition, the only bacterial pathogen recognized by WHO as "carcinogenic to humans" involves *Helicobacter pylori* [1].

EBV

The discovery by Epstein et al. [7] of a new human herpesvirus (later termed the Epstein-Barr virus, EBV), identified in cells of Burkitt lymphoma, the tumour endemically manifested in African children, started studies on oncogenic properties of human viruses. Currently, EBV is classified within the *Lymphocrypto v*irus genus, composing the subfamily of Gamma herpesvirinae, belonging to the large family of Herpesviridae [8]. The virus manifests tropism to mainly lymphocytes B and epithelial cells; similarly to other herpesviruses it induces two types of infection: the lytic and the latent one [9]. However, in contrast to human alpha and beta herpesviruses, EBV codes for proteins linked to its latent infection, of which at least two belonged to the so called oncoproteins. They include: Epstein-Barr virus nuclear antigen (EBNA)-2, representing a transcription transactivator of key importance for immortalization of B lymphocytes and latent membrane protein (LMP)-1, representing an active tumour necrosis factor-alpha (TNF-α) receptor mimic, inducing neoplastic transformation of infected B lymphocytes [10,11]. Moreover, LMP-1 interacts with epithelial cells, stimulating their proliferation and inhibiting their terminal differentiation [12]. Involvement of EBV has already been well documented in non-immunocompromised persons in etiopathogenesis of tumours such as Burkitt lymphoma (BL) and Hodgkin lymphoma (HL), nasopharyngeal carcinoma (NPC), as well as in non-Hodgkin lymphoma (NHL). All the neoplastic diseases linked to EBV, result from its latent infection, determined by expression of specific viral latency-associated genes. Three types of EBV latency gene expression, with viral protein expression are being distinguished [13].

BL used to be endemically manifested in equatorial Africa and New Guinea, the regions used to be affected also by *Plasmodium falciparum* malaria [14,15]. BL most frequently develops in children, manifested as a tumor in the jaw. EBV infection augments 3-fold to 52-fold the risk of endemic BL [2]. Currently, two infectious causal factors of the disease are recognized, including EBV and *P. falciparum* [15]. Infection with EBV presents type I latency, characterized by expression of a single protein, the EBNA-1. The studies indicate that EBNA-1 expression is critical for survival of BL cells [16]. Nevertheless, the protein demonstrates no growth-transforming function. In recent years the *in vitro* studies allowed to confirm involvement of *P. falciparum* in polyclonal B-cell activation, possibly promoting B-cell proliferation and BL [15].

In turn, latent infection of human epithelial cells may result in NPC, and also other epithelial cell tumours [12,17]. NPC is particularly common in areas of China and Southeast Asia. The disease most frequently develops in over 50 year-old males. At present, development of NPC is thought to be determined by a multistep process, initiated by three well defined and acting in common etiological factors: A genetic susceptibility (associated with a loss of heterozygosity-LOH, on chromosome regions of 3p/9p), environmental factors, especially the use of salted fish and preserved foods, and EBV [17]. Infection with the virus presents type II latency, characterized by expression of the oncogenic LMP-1 protein and, moreover, LMP-2 and EBNA-1

proteins. Nevertheless, recent data point to contribution of the recurrent EBV reactivation in the initiation and progression of NPC [18]. In the processes involvement of EBV lytic proteins is suggested, first of all the Immediate Early protein-Zta (inducing secretion of several inflammatory cytokines and angiogenic factor-VEGF) as well as some Early proteins, such as BHRF1 (representing homologue of human oncoprotein Bcl-2 with anti-apoptotic activity) and BCRF1 (a homologue of IL-10, representing an oncogenic cytokine) [18]. Currently, it is postulated that incidence of NPC is much higher in a few specific populations including natives of South China, Southeast Asia, the Arctic and the Middle East/North Africa due to the common genetic susceptibility to EBV chronic infection and NPC [19].

In EBV-positive HL also the above mentioned type of latency is observed [20]. EBV proteins and clonal viral DNA are present in Reed-Sternberg cells (large multinucleated cells of B-lymphocytes lineage) [21]. EBV-positive HL is manifested mainly in developing countries, much more frequently in children and older adults than in young persons.

NHL linked to EBV infection accounts for around 6% of cases in Europe [21,22]. This includes many distinct EBV-positive lymphomas originating from B cells or peripheral T-cells. EBV-infected tumor cells present LMP-1 expression and a variable expression of EBNA-2 (the cells used to manifest type 2 EBV latency). Moreover, potential role of EBV lytic infection is suggested in growth promotion of B cell lymphoma [23].

Investigations of recent years point to a potential involvement of EBV in etiopathogenesis of palatine tonsil carcinoma-PTC and tongue carcinoma-TC, and also of gastric carcinoma-GC [24-26]. EBV is detected in around 10% of GC, including over 90% of gastric lymphoepithelioma-like carcinomas. The latter tumours manifest a similar pathology to NPC-EBV positive tumours.

KSHV

Another lymphotropic *Gamma herpes virus* involves Kaposi's sarcoma-associated herpesvirus (KSHV) identified by Chang et al. [27] in 1994, currently included into *Rhadinovirus* genus [8]. KSHV causes Kaposi's sarcoma (KS) in endothelial cells as well as primary effusion lymphoma, involving B cells. KS represents a rare neoplastic disease, identified in early 1980s together with the globally spreading HIV as the most common AIDS-related cancer-AIDS-KS (developing in over 35% patients with AIDS) [28]. The disease remains strongly linked to HIV-1 infection (an epidemiological study shows that the risk for KS manifestation increases 20-fold in HIV-infected patients) and it manifests by multifocal cutaneous lesions, forming papules, patches, plaques or nodules and tumours [29]. In AIDS-KS development of the lesions is frequently aggressive, tumours may develop in all internal organs [30]. In histology of KS tumors proliferating cells of endothelial lineage dominate, called the spindle cells and presence of neovascular spaces can be noted [31]. KSHV is characterized by tendency for multiple cell type infections, including B cells, monocytes/macrophages, fibroblasts, epithelial, endothelial cells and smooth muscles. In the genome of the virus 14 unique, so called pirate genes were identified, representing homologues of human genes, characteristically manifesting an oncogenic potential [32,33]. Most of them have been well described; they code proteins making latent infection possible, mainly in endothelial cells, and presence of some of them is detected also during lytic replication. In oncogenesis of the virus particular role is played by the latency-associated nuclear antigen (LANA), the expression of which is observed during latency and lytic replication. LANA represents a large and multifunctional protein, exerting a dramatic effect in latently infected cells, it interacts with many cellular proteins, in which it inactivates the p53 and pRB tumour suppressor pathways [34,35]. The protein is

important for maintenance of KSHV latency, cells survival and it may promote their neoplastic transformation. In its influence on cells, cooperation with LANA is shown mainly by KSHV latent proteins of oncogenic potential: vCYC, representing a viral homologue of cellular cyclin D (inducing cell cycle) and vFLIP, forming FLICE (now called caspase 8) inhibitory protein (manifesting the capacity of NFκB activation and promoting cell survival) [35]. LANA can be detected in all spindle cells and, therefore, it is regarded to provide a marker of the cells [36,37].

HBV and HCV

HBV and HCV are specifically hepatotropic viruses. Hepatocellular carcinoma (HCC) belongs to the most frequently manifested tumours all over the world and its etiopathogenesis is linked to, first of all, chronic infection with HBV or HCV.

Hepatitis B virus (HBV) was demonstrated for the first time by electron microscopy in 1970 and described as a Dane particle [38]. It represents a prototypic virus of Hepadnaviridae family, classified within the Orthohepadnavirus genus [8]. The structure of HBV genome contains the smallest viral gene, gene coding for the small X protein (HBx), manifesting oncogenic properties [39]. HBx is required for efficient infection and replication of the virus and it can be detected in both the cytoplasm and cell nucleus of infected hepatocytes. Data of recent years indicate that HBx not only promotes viral replication and chronic transformation of HBV infection but it may also induce proliferation of hepatocytes, playing role in development of HCC [40]. HBV is known to manifest an insignificant pathogenicity while type of morbid lesions determines type and intensity of immune response. In parallel, role of T cytotoxic lymphocytes (CTL) has already been well documented in elimination of infected hepatocytes. Inadequate and uncontrolled response of CTL to HBV infection releases chronic liver pathology (the inflammatory infiltrate is dominated by CTLs) [41]. Immunological destruction of infected hepatocytes linked to their partial killing stimulates regenerative activity of hepatic tissue, which as a sequel may lead to HCC. The sequence of events is as follows: the induced by HBV dynamically developing chronic necrotic/inflammatory process promotes regenerative activity of hepatic parenchyma with its reconstruction and formation of regenerative tophi, or liver cirrhosis. The process is accompanied by markedly increased mitogenesis and intensified "cell turnover", linked to genetic instability and mutagenesis, resulting in genetic instability and mutagenesis, which lead to neoplastic transformation of hepatocytes and HCC. Due to the dominance of the indirect hepatic damage associated with the chronic HBV infection the above presented multi-stage oncogenetic profile used to be defined as homogenous [42]. Nevertheless, at present cooperation is accepted of a direct interaction of HBV and HBx in particular in neoplastic transformation of hepatocytes [43]. It is estimated that oncogenic potential of HBV is high, 100-fold times increasing the risk of HCC development.

Hepatitis C virus (HCV) represents the first in history of microbiology virus detected not by traditional methods but using techniques of molecular biology. Its genome was identified for the first time by Choo et al. [44]; its first infectious clone was obtained in 1997 [45,46]. The new era of HCV studies began in 2005, when a system was described of culturing infectious virus particles in human hepatoma line [47]. HCV is classified within a large family of Flaviviridae, and it represent the genus of Hepacivirus [8]. Nucleocapsid of the virus contains core protein (pC), which together with HCV-coded nonstructural proteins (NS3, NS4A i NS4B and NS5A) forms the replication complex RNA (RdRp) [48]. Protein pC is indicated to carry the potential of disturbing intracellular communication, transcription control and it promotes transformation of hepatocytes. In turn, NS3-NS5A form in cells a membranous web, in which HCV RNA replication occurs. Recent data indicate that NS, and NS5A in particular, are associated with chromosomal instability and mitotic cell cycle dysregulation [49]. Replication of HCV is a

dynamic one; in chronically infected patient production of virions yields approximately 1012 particles per day. In parallel it is accepted that pC recruits a membrane-associated replication complex through its interaction with NS, the effect of which includes induction of chronic liver inflammation with accompanying fibrosis. This multi-stage process is linked to production of reactive oxygen species (ROS), DNA damage, endoplasmic reticulum stress, finally resulting in neoplastic transformation of hepatocytes [42]. Nevertheless, HCV is not directly cytopathic, and therefore in pathogenesis of chronic infection with the virus indirect mechanisms play also role, associated with an inadequate immune response [50]. The above presented profile of oncogenesis is defined, therefore, as a heterogenous one. It is estimated that infection with HCV augments 20-fold the risk of developing HCC. Recently also the relationship is indicated between chronic HCV infection and B cell NHL. The HCV lymphotropism is already well known; the major envelope protein of HCV (HCV-E2) manifests the capacity of binding with high affinity the CD81 receptor, the presence of which has been demonstrated not only on hepatocytes but also in various cell types, including B lymphocytes. It has been suggested that due to the chronic HCV infection, with mediation of HCV-E2 attached to CD81, chronic stimulation and polyclonal proliferation of B lymphocytes may take place, with the resulting development of HCV-associated B cell NHL [51,52]. Chronic HCV infection is estimated to increase the risk of NHL by 2.5 fold [53].

HIV-1 and HTLV-1

They represent human T lymphotropic viruses, classified within the large family of Retroviridae [8]. Only two genera of the family, Lentivirus (with the most known representatives of HIV-1 and HIV-2) and Deltaretrovirus (represented by HTLV-1 and HTLV-2) manifest a documented significance for human pathology. Both genera manifest the ability to induce persistent asymptomatic infections and show oncogenic properties.

Human immunodefiniciency virus type 1 (HIV-1) as the causative agent of the acquired immune deficiency syndrome (AIDS) was identified for the first time by Barré-Sinoussi et al. [54,55]. In the course of over 32 years of studies on HIV/AIDS, pathogenesis of the infections was recognized in its wide scope [56]. Currently, it is accepted that HIV-1 not only induces AIDS, but also represents a serious risk factor of certain neoplastic diseases, most frequently KS (with cooperation of KSHV) and the heterogenous group of NHL, originating mainly from B cells [57,58]. The etiopathogenic link between KSHV and KS has already been well established, as presented above. Nevertheless, the most important co-factor in development of the disease involves HIV-1 infection, even if the direct role of the virus as the main determinant of KS remains to be clarified. Data of recent years indicate that participation of virus-encoded Tat protein in stimulation of growth of KS spindle cells is possible KS [59]. HIV-1 Tat represents a nuclear protein and it form an extremely potent transcription transactivator, not only required in productive phase of HIV infection but also playing a significant role in activation of cellular genes. Studies of recent years demonstrated that Tat may be released from infected cells and may induce growth of KS cells [60]. It is known that the cytopathic effect of HIV results in a drastic reduction in lymphocytes T CD4 (persons infected with HIV loose annually 60 × 106/l lymphocytes T CD4), which correlates with development of immunosuppresion and AIDS. Therefore, it is speculated that the HIV-1 induced immunodeficiency is also accompanied by an inadequate B-cell control by T lymphocytes, which may result in polyclonal proliferation of B cells and NHL. A significant role in the process may be played by p17 matrix protein (MA) of HIV, mainly due to its direct action on peripheral blood mononuclear cells and stimulated production of proinflammatory cytokines (IL-1, IL-6, TNF-α, INF-γ) [61]. HIV-1 is thought to augment 100 to 10000 fold, 10 to 3000 fold the risk of manifestation of KS with co-infection with KSHV, 10 to 300 fold the risk of NHL with co-infection EBV or KSHV and 4 to 38 fold the risk of HL with co-infection with EBV [2].

Human T-cell lymphotrophic virus type 1 (HTLV-1) was identified for the first time by Gallo's group [62] as the first human retrovirus. The virus is endemically manifested, mainly in South-Western Japan, the Caribbean Island, Central and West Africa and South America; it is etiopathogenically linked to adult T-cell leukemia (ATL). HTLV-1 preferentially infects CD4 T cells. The non-structural viral protein Tax, produced by region HTLV-1-pX is thought to play a central role in the proliferation of HTLV-1-infected cells and in development of ATL cells with multilobulated nuclei, so-called flower cells [63]. Tax is a major target of cytotoxic T lymphocytes (CTL) in HTLV-1-infected carriers, the effect of which might involve their rapid elimination [64,65]. Therefore, cellular immune response probably remains of critical importance for the control of HTLV-1 infection. Data of recent years sufficiently document the key role of Tax in immortalization/transformation of HTLV-1-infected T cells [66]. HTLV-1 exists as a provirus in the host cells and most of the infected cells have a single copy of the provirus. Percent of provirus-positive cells determines the number of infected cells (which represents the provirus load). In HTLV-1-infected persons, the provirus load ranges from less than 0.01% to more than 50%. At present it is accepted that a high provirus load provides a risk factor of ATL development [63]. About 2% to 5% of HTLV-1 of carriers develop ATL after a long latent period [2].

HPV

Human papillomaviruses (HPV) were demonstrated for the first time in an electron microscope by Dunn and Ogilvie [67] and described as genital wart viral particles. In 1976 Gissmann and zur Hausen [68] demonstrated HPV DNA genetic heterogenecity. First reports on HPV sequences in human tumours were published in 1982 [69-72]. HPV has a strict tissue tropism for epithelial cells. At present over 120 different HPV types are distinguished (denoted by individual sequential numbers of identification), the types which manifest lower than 90% homology of L1 of viral DNA coding capsid protein L1 [73]. HPV are classified within a distinct large family of Papillomaviridae belonging to five genera, of which two are most important from the medical point of view: *Alpha papilloma virus* and *Beta papilloma virus* [8].

Within the genus of *Alpha papilloma virus* over 30 HPV types were identified, defined collectively as "genital-mucosal" types. Epidemiological studies allowed to distinguish among them three groups of HPV types. Group 1 encompasses HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 , 59 carrying high-risk of cervical cancer (CC), and the risk liked to infection with HPV-16 infection is thought to be much higher than that linked to the other high-risk HPV types [16,74]. In sexually active individuals preferring oral sex the infection with, first of all, HPV-16 may involve oral mucosa. It is estimated that HPV-16 is in at least 60% of cases the etiopathogenic factor of oropharyngeal cancer (OPC). The Group 2 includes HPV-68, defined as "probably carcinogenic to humans" (Group 2A) and HPV types (26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85 and 97) defined as "possibly carcinogenic" (Group 2B). Moreover, the latter group ("possibly carcinogenic") encompasses also HPV-5 and HPV-8 of the *Beta papilloma virus* genus. Group 3 includes HPV types (6, 11) "not classifiable as to its carcinogenicity to humans" [1]. The genus of *Beta papilloma virus* genus encompasses at least 20 HPV types which infect non-genital skin. The HPV types are associated with skin warts (Benign papillomas) and other types, first of all HPV-5 and HPV-8, which induce development of nonmelanoma skin cancer (NMSC) in patients with epidermodysplasia verruciformis (EV). Data of recent years indicate that HPV-5 and HPV-8 may also be linked to NMSC in persons not carrying EV [75]. However, in such cases the exposure to sun is thought to represent the predominant risk factor [76]. The early HPV genes coding for two small proteins, E6 and E7, have already been well documented to represent complementarily acting oncoproteins [77,78]. The proteins probably activate cellular genes necessary for viral DNA replication in differentiating cells, which supports productive phase of HPV infection. The interaction of E6 and E7 may result in immortalization/transformation of cells and in development of the tumour. It is speculated

that a difference between the "high risk" and "low risk" HPV types is determined by structure of their genomes. E6 and E7 "high risk" HPV become preferentially expressed, because they take advantage of a single promoter. In turn, in "low risk" HPV the proteins are expressed from two independent promoters.

Helicobacter pylori

H. pylori represent a bacterial pathogen, the direct relationship of which with chronic gastritis and development of ulcerative disease in stomach and duodenum was demonstrated for the first time by Marshall and Warren [79]. At present, the species of *H. pylori* is classified within the family of Helicobacteraceae and it represents the only bacterial pathogen recognized by WHO as a risk factor for development of gastric cancer (GC) in humans [1]. Carcinogenicity of *H. pylori* is associated mainly with activity of cytotoxin-associated gene A, the product of which is the oncoprotein CagA [80]. It has already been well documented that due to contact with gastric epithelium CagA undergoes translocation to cell interior, with participation of a syringe-like structure, representing a secretory apparatus of the fourth type, T4SS (fourth type of transport system). The translocated CagA in host cells interacts with multiple proteins engaged in various signaling pathways, which results in alterations in epithelial cell cytoskeleton and a deranged expression of genes coding for transcription factors [81]. In addition, epithelial cells are activated to secrete IL-8, and an intense inflammatory process develops, accompanied by dysregulated growth of epithelial cells, which may result in their neoplastic transformation [82]. At present the risk of developing gastric cancer is known to increase with duration of *H. pylori* infection. The progressive damage to gastric mucosa may develop gradually, which is reflected by definition of *H. pylori* as a slow bacterial pathogen [83]. In parallel, analysis of cagA gene expression in strains isolated from patients with gastric cancer demonstrated hyperexpression of the gene [84]. In progression of gastric pathology and *H. pylori*-linked carcinogenesis hypervirulent strains play a significant role.

Conclusions

Epidemiological, clinical and molecular studies supplied proofs for recognizing EBV, KSHV, HBV, HCV, HIV-1, HTLV-1, HPV and the single bacterial pathogen of *H. pylori*, as human carcinogens. It has been well documented that the above listed pathogens, except HCV and HIV-1, contain oncogenes, usually encode proteins, which may effectively induce transformation and immortalization of permissive human cells. Most commonly targets for viral oncoproteins are p53 and retinoblastoma (pRb) tumour suppressor proteins. In turn, the produced by *H. pyl*ori oncoprotein-CagA affects several cellular proteins, which control cell growth. HCV and HIV-1 lack viral oncogenes. However, the core protein of HCV (pC) and its nonstructural proteins (particularly NS5A) may trigger DNA damage, mitotic cell cycle dysregulation and, as a sequel they may promote transformation of hepatocytes. In turn, HIV-1 does not directly induce oncogenic transformation, even if specific viral proteins (Tat and p17) may stimulate polyclonal proliferation of lymphocytes B and may promote the carcinogenic effects of other agents. Therefore, infection of humans with the presented above pathogens creates high risk of development of certain neoplastic diseases. However, it is possible to significantly restrict manifestation of the diseases, first by introduction of new vaccines and their global application, aimed at developing a populational barrier against infections with the above listed pathogens and second: development of early diagnoses of the infections and their early treatment, leading to elimination of the pathogen from the body (for example due to use of direct acting antivirals-DAAs).

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