Mini-review

Skin tumors and their viral origin

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Abstract

Cutaneous tumors have risk factors, including oncogenic viruses. In this paper, the most frequent viruses known to be related to skin tumors, the available diagnostic detection assays and possible prevention and therapy are presented. The clinical utility of this report is to raise awareness to the fact that some cancer-inducing viruses may be treated with targeted therapy and some other infections can be prevented by vaccination.

Keywords: *MCPyV; cutaneous HPV types; herpesviruses; skin cancer; virus-induced*

Introduction

The International Agency for Research on Cancer (IARC) estimated that 15-20% of cancers are associated with infectious agents [1]. Around 12% of cancers are causally linked to 7 viruses: Epstein-Barr virus (EBV), hepatitis B virus (HBV), human papillomavirus (HPV), human T-cell lymphotropic virus (HTLV), hepatitis C virus (HCV), Kaposi's sarcoma herpesvirus (KSHV), and Merkel cell polyomavirus (MCPyV) [2]. The above-mentioned viruses belong to *Polyomaviridae, Papillomaviridae, Herpesviridae, Hepadnaviridae, Flaviviridae* families and represent the research subject for many authors, mainly regarding their life-cycle into the host cell and the risk factors which lead to tumor transformation [3].

The recent IARC publication (September 2018) - the WHO Classification of Skin Tumors contains data regarding diagnostic criteria, pathological features, genetic and other associated molecular alterations, prognosis, and protective factors for each of the tumor types covered. Skin tumors have risk factors (e.g., sun susceptibility and/or exposure). The TNM classification of skin tumors includes certain types which are viral correlated, e.g., Merkel cell carcinoma of skin, skin carcinoma of the head and neck, and EBV-positive mucocutaneous ulcer [4].

GLOBOCAN rates Romania on 7th place in Central and Eastern Europe regarding incidence of all non-melanoma skin cancer and Kaposi sarcoma (male incidence 274.9 versus 81.5 female incidence, per 100 000 all ages). The percentage of melanoma cases in 2012, attributable to ultraviolet (UV) radiation exposure was 68.8 for men and 44.3 for women, all ages (30+ years) [5].

Oncogenic viruses and their potential role in skin cancer

Polyomaviruses: Recent sensitive molecular assays, like next generation sequencing, have led to the discovery of 10 human polyomaviruses (HPyVs): BKV, KIV, JCV, MCV, WUV, TSV, HPyV6, HPyV7, HPyV9, and SV40. Merkel cell carcinoma (MCC), produced by MCV (Merkel cell polyomavirus) is known as a rare skin tumor which can have an aggressive clinical evolution with an unfavorable prognosis. The incidence of this cancer has increased lately,

year by year in USA [6]. Recent studies had detected BKV DNA in 18.5% of patients with oral squamous cell carcinoma (OSCC) [7]. Also, increasing evidence links BKPyV to HIV-associated salivary gland disease [8].

Herpesviruses: Two members of the herpesvirus family, Epstein-Barr virus (EBV) and Kaposi's sarcoma herpes virus (KSHV) have been shown to be, at least partially, responsible for cancer in humans. EBV appears to be the causative agent for Burkitt lymphoma and is associated with other lymphoproliferative diseases such as Hodgkin lymphoma and nasopharyngeal carcinoma [3]. EBV/DNA was detected in oral squamous cell carcinoma in proportion of 16.66% [9], and other authors found EBV in 57.5%, HHV-1 in 7.5%, and CMV in 10% of patients [10].

Cutaneous beta papilloma viruses' types: The beta HPV types (HPV 5, 8, 9, 12, 14, 15, 17, 19, 20, 21, 22, 23, 24, 25, 36, 37, 38, 47, 49, 75, 76, 80, 92, 93, and 96) are originally isolated in non-melanoma skin cancer (NMSC) of individuals with a rare genetic disorder called *Epidermodysplasia Verruciformis.* Immunosuppressed organ transplant recipients have a 50-100-fold increased risk of developing NMSC compared to the general population. DNA from several beta HPV types were detected in skin cancers in immunosuppressed patients. The antibodies titer against some beta HPV types was observed to be higher in patients with cutaneous SCC in comparison with controls. Only E6 and E7 of a few beta HPV types immortalize primary keratinocytes: HPV 37, 38, 49, 76, but not HPV 14, 24, 36, 100, 120 and 122. The role in carcinogenesis was demonstrated by beta HPV 38, 49 which inactivates pRb and p53 functions; HPV 49 E6 and E7 shares some proteins with HPV 16 and E7; HPV 16 and HPV 49 induce p16INK4a accumulation. Transforming activities of HPV 8, 38 and HPV 49 were demonstrated in an *in vivo* model. Beta HPV may contribute to the initiation but not the maintenance of SCC, being one co-factor that could enhance the carcinogenetic potential of UV damage [11].

Molecular assays used for detection of oncogenic viruses

Oncogenic viruses are not detected by routine tests in local laboratories. Nowadays there are many commercially available detections kits. In order to be clinically efficient, one should know which assay to choose for detection of these viruses in tumor samples. The lab assays should fulfill some criteria (e.g., sensitivity, specificity, positive and negative predictive values) to be able then to confirm the diagnosis and to optimize therapy, if possible. Keywords/terms for searching scientific literature on PubMed regarding oncogenic viruses' involvement in skin tumors: „polyomaviruses/cutaneous HPV types/ herpesviruses AND skin tumors" for the last 5 years, retrieved 192 articles for polyomaviruses, 41 for cutaneous HPV types and 7 for herpesviruses, which is suggestive of the huge involvement of MCPyV in skin carcinogenesis. Table 1 lists the majority of the assay used in 2017-2018 for MCPyV as molecular assays, based on different types of PCR and a few of the immunohistochemistry assays. For HPV cutaneous types we identified studies performed in very well-known research centers (e.g. IARC, France; DKFZ, Germany) equipped for this high level of research. Table 2 lists the cutaneous HPV types detected in associations with skin cancers.

Inclusion criteria for skin cancer-inducing viruses

Inclusion criteria for viruses inducing skin cancer are established after evaluating the type of study (cohort or case-control), quality of the analyzed studies, temporal effects, use of biomarkers in epidemiological studies, criteria for causality and studies of cancer in experimental animals. Also important are the toxicokinetic data, information regarding mechanisms of carcinogenesis, functional changes at the cellular and molecular level [27].

Table 1. Laboratory assays used for MCPyV in skin tumors [12–21]

AUTHOR, YEAR OF PUBLICATION	COUNTRY	ASSAY	CONCLUSIONS
Murakami I, 2018	Japan	Quantitative PCR for MCPyV-DNA, proteomics, immunohistochemistry IL-17	MCPyV was established as a causal agent in tested tumors
Konstatinell A, 2018	Norway	MicroRNAs	MicroRNAs was considered as a biomarker for the diagnosis, progression and prognosis, and treatment of MCC
Kervarrec T, 2018	France	Multiplex genotyping assay	Half of the combined MCC cases were positive for MCPyV
Vandeven N, 2018	Washington USA	Whole-exome sequence data	Stronger underlying immunity against MCC contributes to primary lesion elimination and improved survival
Li L, 2018	Texax, SUA	Immunohistochemistry in a fine needle aspirate	The tumor cells were positive with pan cytokeratin AE1/AE3, CK20, CD56, synaptophysin, chromogranin, and MCPyV
Álvarez-Argüelles ME, 2017	Spain	Quantitative Real-Time-PCR (qRT-PCR) in FFPE MCC	The amplification techniques are easily applied and suitable for detecting the presence of MCPyV
Kuromi T, 2017	Japan	Immunohistochemistry for hedgehog signaling (SHH, IHH, PTCH1, SMO, GLI1, GLI2, Polymerase chain reaction and sequence analysis for SHH and GLI1 exons	Expression of SHH and GLI1 may be useful prognostic markers of MCC
Wang L, 2017	Michigan, SUA	RNAscope, an RNA *in situ* hybridization (ISH) assay for detection of RNA transcripts in tissues qPCR for comparison	A strong correlation between qPCR copy number and RNA-ISH product score RNA-ISH is comparably sensitive to qPCR for detection of MCPyV and allows for correlation with tissue morphology.
Arvia R, 2017	Italy	qPCR and ddPCR for MCPyV detection and quantification in FFPE tissue samples.	The ddPCR represents a better method for detection of MCPyV in FFPE biopsies
Harms KL, 2017	Michigan, USA	Next-generation sequencing	Next-generation sequencing analysis of chromosomal copy number changes and mutations is useful in distinguishing multiple primary MCCs

(FFPE: Formalin fixed paraffin embedded)

Table 2. Cutaneous HPV types detected in skin cancers by different assays [22–26]

AUTHOR, YEAR OF PUBLICATION	COUNTRY	ASSAY	HPV types involved in skin cancers
Viarisio D, 2018	Germany	Mouse model that expresses beta HPV38 E6 and E7 whole-exome sequencing	Beta HPV type (e.g., HPV 38) act only at an initial stage of carcinogenesis
Faust H, 2016	Sweden	IgG to pseudovirions	16 different HPV types (3, 5, 6, 11, 15, 16, 18, 31, 32, 33, 38, 45, 52, 58, 68, and 76)
Arroyo Mühr LS, 2015	Sweden	Whole genome amplified DNA	HPV197
Shterzer N, 2014	Israel	Vaccinogenic abilities in primary human keratinocytes (PHKs)	HPV types 10, 49 and 38,
Bzhalava D, 2014	Sweden	Metagenomic deep sequencing	396 different HPV types in human skin

In order to label a virus as causal factor in tumorigenesis, objective criteria of diagnosis are necessary. For example, to conclude that an MCV is the etiological factor in a FFPE tumor samples, it is necessary to get a very high signal by MagPix detection, in comparison with controls (unpublished personal data). The reason for this is that polyomaviruses can be part of normal flora and only the simple detection of DNA is not enough to establish the diagnosis. For HPV HNC driven cases there are also criteria for establishing diagnosis (some authors have published an algorithm of diagnosis which included three biomarkers - DNA, RNA, p16INK4a of HPV [28], while others used only the last two biomarkers) [29, 30]. In some fresh skin and HNC tumors we have detected by multiplex genotyping the DNA of some polyoma and herpesviruses (EBV, HH7, HH8, MCV – unpublished personal data), but for the moment we cannot conclude that these viruses are causally-related with the analyzed tumors. Further on, this paper is referring to other tumors which could be oncogenic viruses related, e.g. malignant melanoma, sarcoma, other soft tissues tumors.

Melanoma of skin is mentioned by GLOBOCAN with a 5-year prevalence of 18 in adult Romanian men and 20 in women, occupying the last place of the first 20

European countries (after countries like Germany, with a male incidence of 342, UK - 274, France - 187, Sweden – 61) [5]. This report raises the question of whether the official data regarding this type of cancer is correctly performed in our country, or maybe there are different risk factors for this cancer. WHO mentions that the main risk factors for malignant melanoma are the skin type, the number of nevi, and exposure to solar UV [31].

We sought to review the scientific literature to see if there are publications which detected oncogenic viruses in malignant melanoma (MM). From 26 studies identified in PubMed using the key words "polyomaviruses malignant melanoma", one paper published the results of testing samples of primary malignant melanoma for polyomaviruses. Ramqvist T et al tested 57 MM samples by sensitive assay Luminex multiplex genotyping for 10 HPyVs and none of these DNA viruses were detected. The authors concluded that these viruses don't have any role in development of this kind of tumor [32]. Interestingly, a few other articles detected polyomaviruses in induced cutaneous squamous cell carcinoma in patients with MM after therapy with BRAF inhibitors (e.g., vemurafenib) [33-35]. Regarding cutaneous HPV types and herpesviruses, the PubMed search did not find any study that detected

these viruses being involved in development of MM.

Kaposi sarcoma in adults is the most frequent in Italy and Spain. Romania is not among the first 20 countries in Europe regarding the prevalence of this cancer. Still, Romania can be found on the 7th place in Central and Eastern Europe, after Russian Federation, Hungary, Poland, but with no mentioned values for incidence and prevalence [5].

First time detected in Kaposi sarcomas associated with AIDS, this virus was coined Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8) [27].

KSHV is known to be involved in Kaposi sarcoma (supported by 22 cohort studies and 80 case–control studies – all showing broadly consistent evidence of an association between KSHV infection and Kaposi sarcoma), primary effusion lymphoma, multicentric Castleman disease, multiple myeloma [27]. HHV-8 is frequently associated with immunosuppression no matter the cause (iatrogenic, viral or age-related) [36]. This feature explains the presence of this virus post-transplant (e.g., heart and kidney transplantation) [37, 38].

Following the same model used for MM, we searched PubMed for oncogenic viruses' involvement in sarcoma; there was a double viral infection presence of Beta papillomavirus in Kaposi sarcoma lesions [39]. Other interesting associations were detected between MCC and Langerhans cell sarcoma tissues [40] and during treatment with superpotent topical steroids and methotrexate for bullous pemphigoid [41].

Soft tissue tumors: regarding oncogenic viruses' involvement in soft tissues tumors, EBV is mentioned as primary Epstein-Barr virus-positive large B-cell lymphoma mainly affecting the lumina of the aorta [42], and bilateral psoas muscle lymphoma [43]. Also, HHV-8 was detected on multiple, erythematous to purple tumors, located on areas of post-mastectomy lymphedema [44]. EBV-associated tumors are recognized by IARC to be involved in Lymphoepithelioma-like carcinoma with > 80% positivity [27].

Therapy and available prevention of these viruses-induced tumors

The classical therapy of skin tumors is surgical radical excision, followed by radio- and chemotherapy.

The main prevention method of tumor induced viruses is by vaccination [45]. The example of HPV vaccine is illustrative. From the bivalent HPV vaccine in 2014 the Food and Drug Administration (FDA) approved the 9 vHPV which prevent infections with HPV types 16/18/31/33/45/52/58, as well as genital warts related to HPV types 6 and 11 [46]. Moreover, therapeutic HPV vaccines are in discussion [47]. There are studies about future vaccines which could prevent skin cancers induced by HPV cutaneous types [48, 49]. Another novel cancer therapy recently revealed that Oncolytic Viruses (OV) have a peculiar replication life cycle, by replicating only in cancer cells and not in healthy tissue. In addition to this direct oncolytic activity, OVs have a double effect, leading to the appearance of antibodies against the virus itself and also against the cancer tissue. These OVs can use both DNA and RNA viruses and require much care regarding monitoring the efficiency of this therapy [50, 51]. Even though there is no known oncogenic virus involvement in MM, there is an interesting therapy with the help of a herpesvirus, a DNA virus harboring the capacity to establish lifelong latent-recurrent infections. Recently, patients with melanoma that were not resected surgically were treated with Talimogene laherparepvec (T-VEC). T-VEC contains an oncolytic herpesvirus type 1 which is known to produce granulocyte macrophage colony-stimulating factor (GM-CSF) during its intratumoral replication [52–54].

Recent studies published data which support the anti-PD-L1 antibody - Avelumab's approval in the United States and European Union and use as a standard-of-care treatment for metastatic MCC [55, 56]. Detecting the virus presence in a tumor could optimize targeted therapy, such as RB1 tumor-suppressor or NVP-BEZ235, a dual PI3K/mTOR inhibitor [57, 58].

Conclusion

The clinical utility of this mini-review is to emphasize that certain tumors are virus-induced. Diagnosing these tumors requires reliable criteria for involving viruses as etiologic agents through sensitive molecular biology assays. Further research is needed in order to find specific therapy (e.g., oncolytic viruses, gene targeted therapy, therapeutic vaccination) or oncologic prevention by classical vaccines.

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