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Review

The human papillomavirus (HPV)-related cancer biology: An overview

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ABSTRACT

Despite the novel diagnostic methods and therapies implemented in oncology, the number of patients that succumb by the cancer remains high globally. Currently studies point out that 20–25% of all human malignancies are related to micro-organism infections. Among these cancer-related pathogens, the human papillomavirus (HPV) has a prominent position, since the virus is responsible for about 30% of all infectious agent-related cancers. Thus, an amount of cancers could be avoided by means prophylactic and/or therapeutic measures. However, these measures required a holistic comprehension about HPV-related cancer biology. Based on this, this review aims to summarize the last evidences of HPV on cancer biology (from initiation to metastasis), focus on molecular and biochemical deregulations associated with viral infection, and discuss the viral etiology in different malignancies.

1. Infectious agent and cancer

Despite the novel diagnostic and therapeutic methods implemented in oncology, the cancer incidence have been grown, making the disease an important public health problem globally [1]. In 2012, 14.1 million of people were diagnosed with cancer and, 8.2 million dead due to the disease [2].

Theories aiming to describe the carcinogenesis have been proposed for centuries [3]. In this context, the identification of the intricate relation between virus and cancer was a landmark in the discoveries that led to the formulation of the modern cancer biology concepts [4].

Currently it is widely accepted that infectious agents are responsible for 20–25% of all cancer cases globally registered [4]. Among these agents, the virus stands out to be responsible for about 12% of all human cancers [5]. Among these viruses, the human papillomavirus (HPV) occupies a prominent position, being responsible for about 30% of all infectious agent-related cancers [6].

It is estimated that HPV causes 610,000 incident cancer cases [7] and 250,000 deaths every year [8]. According to the World Health Organization (WHO), 85% of these deaths occur in low- and middle-income countries (http://www.who.int/mediacentre/factsheets/fs380/en/). However, the HPV is not only a public health problem of developing countries, since the virus infects about 6.2 million of people in United States of America annually [9].

Based on the HPV impacts on oncology, this review aimed to summarize the most recent advances in HPV-related cancer biology, describing the viral action in each step of carcinogenesis, focus on metabolic deregulations induced by the viral oncoproteins. This review also discusses the HPV participation in different malignancies, including evidences of viral participation in different malignancies.

2. Basic aspects of human papillomavirus biology

2.1. Morphological and genetics aspects

The HPV belongs to *Papillomaviridae* family, one of the oldest viral family known [10], able to infect epithelial cells of the skin, oral and genital mucosa [11]. The HPV viral particles (virions) exhibit a conserved icosahedral morphology [11], with 50–55 nm of diameter [12,13] and a molecular weight of 5×10^6 Da [14]. HPV is evolutionarily conserved, presenting a divergence rate of 1% per 40,000–80,000 years [15,16]. The HPV has a circular double-strand

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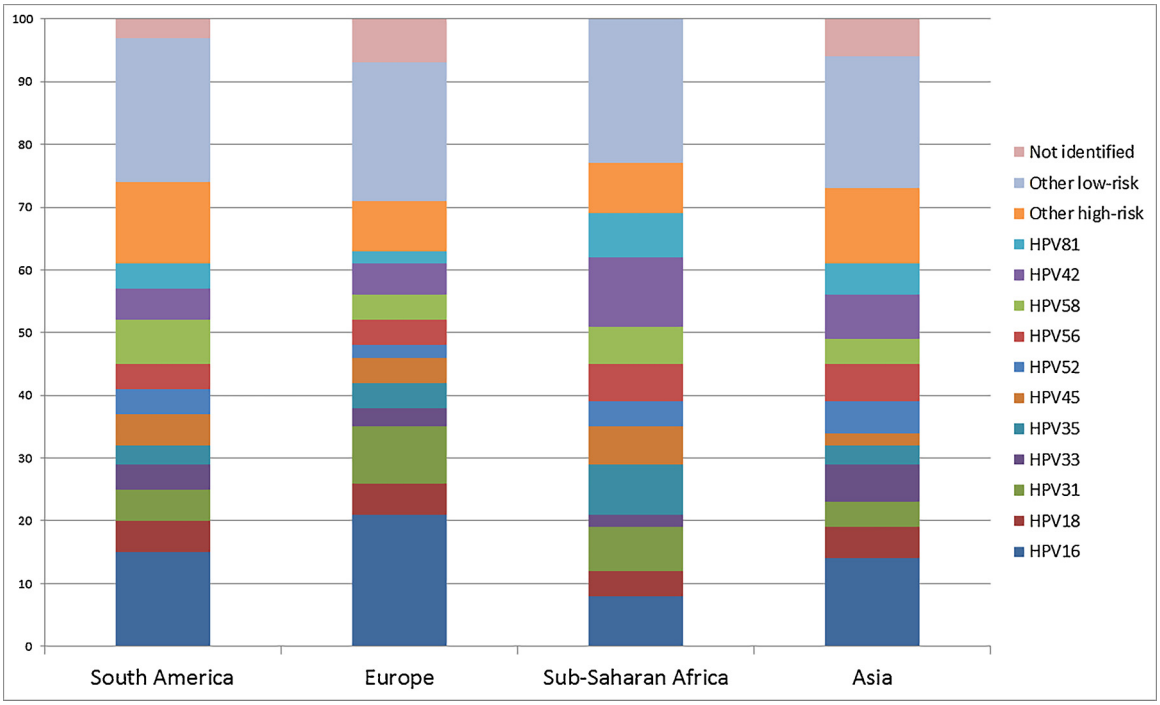

Fig. 1. Prevalence of the most common HPV types in different geographical areas. Adapted from Clifford et al. [25].

DNA, with approximately 8000 bp, which is associated with histone-like proteins [17].

The viral genome is divided into three regions: (1) early (E) region - containing the genes E1, E2, E4, E5, E6 and E7, which are associated with viral replication; (2) late (L) region, which encodes the major (L1) and minor (L2) capsid proteins; and (3) a non-coding region (NCR), also known as long control region (LCR), which is located between the L1 and E6 open reading frames (ORFs) [11]. Although not encoding, the LCR contains most of the regulatory elements involved in viral DNA replication and transcription, including the replication origin (*ori*) [11].

Nearly 280 papillomavirus types were already described in vertebrates [18]. More than 200 types infect human [18,19]. All HPVs can induce proliferative benign lesions [20]. However, 12 viral types are closely related with malignant neoplasms (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59). For this reason, the International Agency for Research on Cancer (IARC) classified these HPVs as high-risk (HR) [11]. Altogether, the HR-HPVs-16, 18, 31, 33, 45 and the low-risk (LR)-HPVs-6 and 11 comprise the most prevalent virus types [21–23]. Although the distribution of these HPVs change according to geographical area [24], as showed in Fig. 1, the HR-HPVs-16, 18, 31, 33 and 45 are responsible for 75% of all HPV-associated squamous cell carcinoma and 94% of all adenocarcinomas [22,24].

2.2. Proteins codified by late region (L1 and L2)

The L1 ORF codifies the major capsid protein (L1) [25], with 55 kDa [26]. The L1 ORF is also the most conserved genome sequence and, for this reason, it is used for phylogenetic classification of viral types and subtypes [27,28]. The L1 protein is crucial for the viral infection, since it promotes the virion binding to heparin sulfate receptors present in the basal membrane [25]. The L2 is a 64–78 kDa protein necessary for viral infection and assembly, facilitating the DNA packaging [29,30]. Considering that these proteins are exclusively related to the viral infection and assembly, they are lately expressed, can be detected in differentiated epithelium layers [31].

2.3. Proteins codified by early region (E1, E2 and E4)

The E1 and E2 ORFs codify the E1 and E2 proteins, which are essential for viral replication [32]. The E1 ORF is the second most conserved sequence among the papillomaviruses and codifies the E1 protein with 68 kDa [33,34]. The E1 protein has three functional domains: (1) N-terminal domain, that binds to motif region of Cdk2; (2) central domain, that binds to E2 protein, forming the E1-E2 complex and (3) C-terminal domain, that acts as an ATP-dependent helicase [30,35,36]. After the E1-E2 complex binding to viral *Ori* [34,37], the E1 protein forms a dihexameric complex [38], attracting topoisomerase I, DNA polymerase α and replication protein A (RPA), which are required for the viral replication [37]. The E1 protein also promotes DNA breaks in host chromatin, contributing to viral integration [37].

The E2 is a 48 kDa modular protein [39] that presents two domains: (1) C-terminal and (2) N-terminal transactivation domain [35]. The C-terminal domain binds to the Brd4 protein, which bromodomains interact with lysine residues of acetylated histones, resulting in chromatin remodeling by acting as a super-enhancer [40,41]. The E2-Brd4 complex binds to mitotic chromosomes, allowing the distribution of viral copies to daughter cells after cytokinesis [29,35].

The E2 acts as a transcriptional regulator of E6 and E7 ORFs [30,42–44]. When present in high levels, the E2 binds to 5′-ACCG(N)$_4$CGGT-3′ palindromic sequence present in E2 binding sites (E2BS) in LCR, including in the P97 promoter [42,45]. This action prevents the binding of RNA polymerase II to P97, repressing the E6 and E7 expression [30]. However, when in low levels, the E2 recruits transcription factors required to replication [40,41]. Thus, the E2 also regulates the number of viral copies [46]. The E2 is also an epigenetic regulator, being able to interact with p300/CBP-p/CAF complex, recognized as a global transcription activator [47], promoting the *TP53* hypo-acetylation and, therefore, reducing the p53 transcriptional activity [35].

The E4 ORF codifies a protein family produced by splicing followed by post-translational modifications [48]. The E4 protein is expressed in suprabasal and granular epithelium layers [49], being the most expressed viral protein [50,51]. The E4 interacts with keratin-associated amyloid fibers [51], leading to cell fragility, contributing to virion

release [48].

2.4. Oncoproteins codified by early region (E5, E6 and E7)

The E5 is a 9.4 (HPV-16) and 8.3 kDa (HPV-18) hydrophobic transmembrane protein [52] with two cysteine residues in the C-terminal region that confer stability for the homodimer (E5-E5) [44,53]. The E5 oncoprotein has a prominent participation on cancer progression, which is related to the mitogenic activity.

The E5 oncoprotein can interact with the 16-kDa component of vacuolar proton-ATPase, increasing the endosomal pH from 5.9 to 6.9 [54–57]. This action inhibits the degradation of epidermal growth factor (EGF) receptor in endosomal compartments after ligand-stimulated endocytosis, increasing the number of receptors recycled back to the cell membrane [55,56]. Thus, the HPV E5 oncoprotein acts sinergically with the EGF, leading to cell proliferation. However, the effects of E5 oncoprotein are not limited to the cell membrane. The E5 is also located to the Golgi apparatus (GA) and endoplasmic reticulum [54,58].

The E5 interaction with GA causes the retention of major histocompatibility class I (HLA) complexes and avoids their transport to the cell surface [58]. Thus, the E5 oncoprotein is also involved with the immune evasion and, therefore, viral infection persistence. The HPV-16 E5 oncoprotein also inhibits the hydrogen peroxide-induced apoptosis in cervical cancer through the Bax ubiquitination, contributing with the cancer progression [59].

Recently, Wetherill et al. [60] described a novel function for HPV-16 E5 as an oligomeric channel-forming protein. Thus, the E5 oncoprotein was proposed to be classified as a viroporin, a channel protein able to modulate ion homeostasis, trafficking, virion production and viral genome entry [60–62]. In addition, using human keratinocytes (HaCaT) transfected with the HPV-16 E5 ORF, Oelze et al. [63] showed a strong correlation between E5 expression and dephosphorylation of connexin 43, the major gap junctional protein. This result suggests that the E5 oncoprotein can affect the intercellular communication [63], contributing to epithelial-mesenchymal transition (EMT).

The HPV E6 is a small oncoprotein with 151–158 amino acids [64,65], without enzymatic activity [66]. The E6 oncoprotein is characterized by the presence of a class I PDZ domain (PSD-95/Dlg/ZO-1), located in the C-terminal, and four conserved motifs (Cys-X-X-Cys) [67–70]. The PDZ domain is found in HR-HPVs and can interact with different proteins [70], promoting the loss of cell polarity [11] and intercellular communication [70].

The E6 oncoprotein has a central role on cell immortalization [71], once it induces the transcriptional activation of human telomerase reverse transcriptase (*hTERT*) gene [11]. The E6 oncoprotein promotes the expression of *NKX2-1*, leading to the up-regulation of *FOXM1* in HPV-associated head and neck carcinomas [72]. This action results in cyclin B1, D1 and cdc25 overexpression [72]. The E6 also promotes the *NOTCH* downregulation [73]. Altogether, these actions lead to the proliferation of keratinocytes. The *FOXM1* up-regulation also promotes β-catenin nuclear translocation, contributing with the EMT and, therefore, tumor metastasis [72].

Currently studies have shown that the both HPV [74] and bovine papillomavirus type 1 (BPV-1) E6 oncoprotein is related to energetic metabolism deregulation [75,76]. Considering the relevance of these alterations for the carcinogenesis, the E6-related metabolic deregulations will be discussed in the Section 3.4.

However, the most studied action of E6 oncoprotein is its capability to reduce the levels of p53, tumor suppressor protein encoded by the *TP53* gene (17p13.1) which is activated in response to DNA damages [77,78]. This occurs due to the E6 oncoprotein capability to form a ternary complex with E6AP ubiquitin ligase and p53 (E6-E6AP-p53) [66,79–82]. This action promotes the p53 degradation [13,21,79,83]. Additionaly, the HPV-5 and 8 E6 oncoproteins interact with the CBP/p300 complex [84–86], causing the *TP53* downregulation by epigenetic mechanisms [87]. Furthermore, the E6 oncoprotein can interact with XRCC1 and O^6-methylguanosine-DNA-methyltransferase proteins, which are recruited during the single-strand DNA break (SSB) repair [35], leading to cytogenetic damages [35] and neosis [88]. Altogether, these actions lead to genetics instability, increasing the mutational and entropic status, contributing to cancer initiation [44,75,88].

Studies also show that the E6 oncoprotein can bind to interferon regulatory factor 3 (IRF-3), a transcriptional factor that promotes the IFN-α and β expression, resulting in the downregulation of interferon β (INF- β), preventing the viral recognition [82,89]. Combined, these actions suggest that the E6 oncoprotein is necessary and sufficient to promote the carcinogenesis.

The E7 is a small oncoprotein, with 127 amino acids [90] able to bind to LXCXE conserved motif of pRb tumor suppressor protein [13,46,91], resulting in pRb phosphorylation and in the consecutive E2F transcriptional factor nuclear translocation [20,21,92]. In the nucleus, the E2F factor recruits different chromatin modifiers, including histone deacetylases (HDAC), that promotes the E2F-responsive gene expression, including cyclin A, E [11,46], D1, D2 and D3 [20], leading to cell proliferation [32,93]. Current studies have also demonstrated that the E7 oncoprotein induces DNA breaks (clastogenesis) [94–96], at the same time that increases the *Sirt1* deacetylase expression levels, reducing the levels of histone γ-H2 AX [96], a protein that participates of DSB repair [97,98]. Thus, the E7 oncoprotein acts synergically with E6 oncoprotein inducing cell mutations and genomic instability.

According to Cardeal et al. [99], the co-expression of E6 and E7 oncoproteins promote the downregulation of reversion inducing cysteine-rich protein with Kazal motif (RECK) [100] and tissue inhibitor of metalloproteinase (TIMP-1 to 4) [101]. The RECK and TIMP downregulation results in extracellular matrix remodeling, cooperating to cancer progression and metastasis. The E6 and E7 oncoproteins also promote immune-evasion through the Toll-like receptor (TLR) downregulation, which is responsible for the virus recognition and activation of phagocytes [13,89]. Besides, the HPV induces the interleukin 10 (IL-10) production, pleiotropic cytokine produced by myeloid cells and lymphocytes that lead to IL-2, IL-12, interferon gamma (IFN-γ), tumor necrosis factor alfa (TNF-α) inhibition and MHC-I downregulation [102–104]. Combined, these actions facilitate the HPV infection and persistence.

2.5. HPV infection pathway

Mucosa and skin are the most common sites of infection for different microorganisms [105], including papillomaviruses [46,106]. The HPV infection occurs through the tissue lesions, which are necessary to guarantee the virus access to basal keratinocytes [83]. Once these cells have been reached, the L1 protein binds to heparin sulfate proteoglycan (HSPGs) [106,107], promoting a conformational change in the viral capsid [25]. Although recognized as an important binding site, the HSPG is not unique, since studies show that the L1 protein can also bind to different integrins, such as α6 (CD49f), 332 (laminin 5) [108] and α6β4 integrin [109].

The conformational changes in capsid expose the N-terminal region of L2 protein [25], which is cleaved by the furine [25,110], a protein with proteolytic activity, able to interact with different growth factors, cell and viral receptors [111]. This action is necessary to promote a second conformational change in viral capsid that allow the virus binding to cell receptors, including α6β4 integrin [25,110]. Next, the virus is internalized in vacuolar structures by clathrin or caveolin-mediated endocytosis mechanisms [112]. When lysosomes bind to these endocytic vesicles forming the phagolysosomes, occurs a reduction in pH, leading to the viral capsid disassembling and, therefore, the viral genome release [112].

However, the HPV is not able to self-replicate, since the virus does not express polymerases. For this reason, during the amplification process, the early proteins (E) interact with the host cell, inducing the S

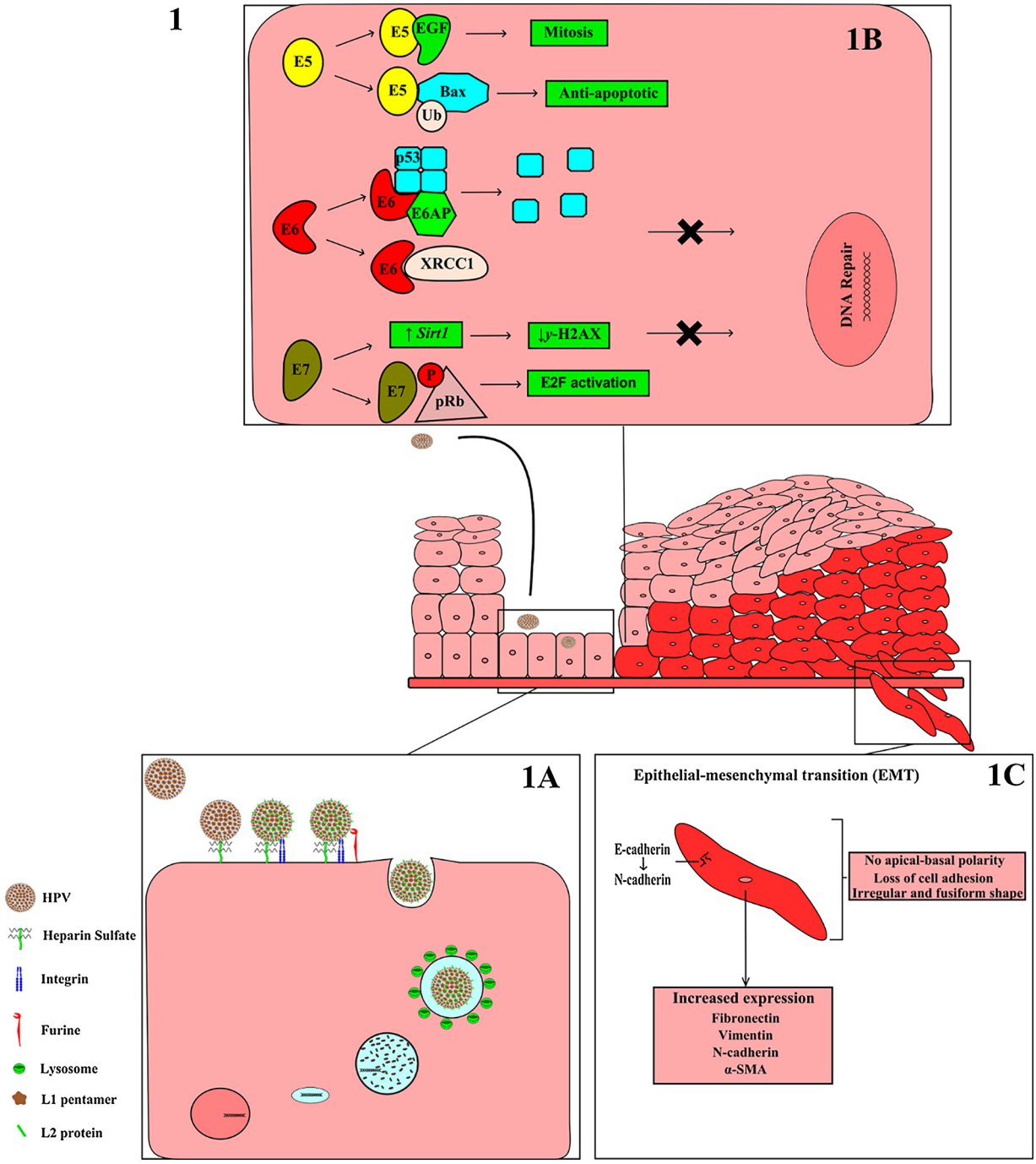

Fig. 2. Schematic models showing the HPV infection and the viral pathology. 1 A) The HPV infects micro-injured epithelial tissues. The micro-injury exposes the heparin sulfate proteoglycans present in basal lamina. HPV binds to these proteoglycans, resulting in a first conformational chance in capsid. The furin cleaves the N-terminal region of L2 protein, leading to a second conformational chance in the viral capsid. Next, the virus bind to integrin present in basal keratinocytes membrane. The virus is internalized through endocytosis, which is mediated by clathrin or caveolin. The vesicles containing the HPV particle is fused to lysosomes, which acid content promotes chemical changes in capsid proteins, resulting in viral disassembling. Into the cell, HPV expresses its early genes, that induce the S phase entry, which is mandatory to guarantee the DNA polymerase supply for viral replication. 1B) Among these proteins are the E5, E6 and E7 oncoproteins. The E5 binds to EGF, conferring a mitogenic stimulation at the same time that confers an anti-apoptotic stimulus through the Bax ubiquitination. The E6 oncoprotein cooperates with this anti-apoptotic stimulus through the p53 ubiquitination, at the same time that binds to XRCC1. This actions increase the mutational status, leading to genomic instability. The E7 oncoprotein cooperates to genomic instability, reducing the levels of histone γ-H2 AX, which is involved in the DSB repair. The E7 also promotes the pRb phosphorylation, contributing to cell proliferation. 1C) Viral infection persistence increase the genomic instability, can lead to cancer initiation. Following cancer initiation, the viral oncoproteins promotes metabolic deregulation, leading to EMT, increasing the expression of mesenchymal markers.

phase entry as obtaining mechanism of DNA polymerases [46]. However, this proliferative action can lead to DNA replication stress [113] and, as consequence, numerical and structural chromosome instability [114,115], that can drive the cancer initiation.

Viral assembly is verified in most differentiated epithelium layers [116]. Virion release occurs through the differentiated cell degeneration [25,116,117], leading to koilocytes formation [32,118–121]. The term koilocyte comes from Greek *koillos* (cavity) [32]. This term was introduced by Koss and Durfee in 1956 to refer to cytopathic alteration characterized by a prominent halo and pycnotic nucleus [32].

Table 1
Evidences of HPV presence in unusualinfection sites, suggesting vertical transmission.

Peripheral blood mononuclear cells (PBMCs)					
	Diagnostic method	Primer	Viral type(s)	Country	Reference
Peripheral blood	PCR followed by DNA sequencing	FAP59/FAP64	HPV-16, 18, 27, 32, 70, 97, 102, 12, 15, 47, 48, 65, HPV-FA31 and HPV-FA55	Australia	Chen et al. [360]
	PCR and Southern blot	Specific	HPV-6, 11, 16 and 18	Taiwan	Pao et al. [361]
	PCR followed by DNA sequencing	Specific	HPV-16	USA	Bodaghi et al. [362]

Circulating tumor cells in peripheral blood					
	Diagnostic method		Viral type(s)	Country	Reference
Peripheral blood	RT-PCR	Specific	HPV-16 and 18	Slovak Republic	Weissmann et al. [363]
	RT-PCR	Specific	HPV-16	Taiwan	Pao et al. [364]
	Nested PCR	Specific	HPV-16 and 18	Taiwan	Chiou et al. [282]
	qRT-PCR	Specific	HPV-16, 18 and 52	Taiwan	Ho et al. [365]
	Nested PCR	Specific	HPV-16 and 18	South Africa	Kay et al. [366]
	RT-PCR	Specific	HPV-16 and 18	Taiwan	Pao et al. [364]

Semen, placenta, umbilical cord and breast milk					
	Diagnostic method		Viral type(s)	Country	Reference
Perinatal transmission	FISH for HPV-16 E6 and L1	–	HPV-16	Italy	Foresta et al. [367]
	Nested PCR and Southern blot	Specific	High-risk HPVs	Finland	Rintala et al. [368]
	PCR	MY09/MY11	Not detailed	Canada	Olatunbosun et al. [369]
	Array-based HPV detection	Specific	HPV-6, 16, 18, 31, 35, 51, 52, 54, 58, 61, 62, 66, 72, 81 and 84	France	Kaspersen et al. [134]
	PCR and in situ hybridization	GP05/GP06 MY09/MY11	HPV-6, 16, 39 and 83	Finland	Sarkola et al. [131]
	PCR-RFLP	CPIIG	HPV-18, 31, 33 and 35	Mexico	Uribarren-Berrueta et al. [370]
	PCR followed by DNA sequencing	GP05/GP06 MY09/MY11	HPV-16 and 18	Brazil	Teixeira et al. [132]
	PCR followed by DNA sequencing	Specific	HPV-16	Finland	Sarkola et al. [130]
	qRT-PCR	GP5/GP6	HPV-16, 18, 31, 33, 35, 39, 45, 52, 56 and 68	Greece	Mammas et al. [371]
	PCR	GP5/GP6 PGMY	HPV-16	Australia	Glenn et al. [372]
	PCR	Specific	HPV-8, 9, 15, 17, 18, 20-24, 36, 38, 92, 93	Italy	Cazzaniga et al. [373]
	PCR followed by DNA sequencing	GP05/GP06 MY09/MY11	HPV-16 and 62	Belgium	Weyn et al. [374]

Newborn and infants				
Diagnostic method		Viral type(s)	Country	Reference
PCR using GG HPV Genotyping Chip	Specific	HPV 6, 11, 16, 18, 26, 30–35, 39, 40, 42–45, 51–56, 58, 59, 61, 62, 66–70, 72, 73, 81–84, 90, and 91	Korea	Lee et al. [375]
PCR followed by DNA sequencing	Specific	HPV-51 and 61	USA	Smith et al. [376]
PCR followed by DNA sequencing and hybridization	GP05/GP06 MY09/MY11	HPV-16, 18, 31, 33, 51 and 61	USA	Smith et al. [129]
PCR and Southern blot	MY09/MY11	HPV-6, 11, 16 and 18	Finland	Puranen et al. [377]
PCR and Southern blot	MY09/MY11	HPV-16 and 18	Italy	Tenti et al. [378]
PCR	MY09/MY11	HPV-16	India	Bandyopadhyay et al. [379]

Koilocytosis is discussed as a pathognomonic marker of PVs infection [122,123]. The koilocyte formation is attributed to E5 and E6 oncoprotein, although the vacuolization mechanism remains unclear up to date [122,124]. However, study suggests that the cytoplasmic vacuolization contributes to keratinocyte fragility, facilitating the virion release [122]. Thus, koilocytes are cells destined to apoptosis [122], which is a consequence of macromolecules synthesis inhibition [125]. A schematic model of HPV infection is shown in Fig. 2.

Although discussed as a sexually transmitted disease, evidences suggest that the HPV can be vertically transmitted, since viral DNA sequences were identified in the oral cavity of newborns [126–128], breast milk [129], amniotic liquid, placenta, umbilical blood [130,131] and in spermatozoa [132,133]. In this sense, studies have shown that HPV can affect the spermatozoa motility, can be discussed as cause of infertility [134,135]. Moreover, the HPV-16 E6 and E7 oncoprotein can cause genome damages in trophoblastic cells and lead to spontaneous abortion [109]. Evidences of HPV infection in non-usual sites suggesting viral vertical transmission are summarized in Table 1.

According to Gillison et al. [81], children of women with genital warts during pregnancy have a high risk to develop laryngeal papillomas, reinforcing the HPV vertical transmission. Respiratory papillomas are commonly associated with HPV-16 and 11, affecting 4 in each 100,000 children up to four year-old [81]. However, 5% of HPV-16-associated respiratory papillomas can progress to cancer [81]. In addition, studies based on bovine papillomavirus (BPV), which is recognized as useful model to study the HPV biology, have been described the productive infection in bovine placenta [136], lymphocytes [137,138] and cell lines derived from primary cultures of papilloma, fibropapilloma and esophageal carcinoma [139]. Altogether, these data suggest the need to review the paradigm of papillomavirus replication biology.

About 90% of HPV-infected patients present an innate and humoral immune-mediated viral clearance within few months after viral infection [14,22,140,141]. During the wart regression process, occurs an infiltration of CD4+, CD8+ lymphocytes and macrophages, as well as an increase of pro-inflammatory cytokines, resulting in a production of

neutralizing antibodies [22,141]. However, this does not prevent the reinfection by the same HPV type, neither to other viral types. Furthermore, in 10% of patients, the HPV can persist, increasing the risk to cancer, which is verified in about 1% of all patients infected [14,140].

3. HPV: from mutation to metastasis

The cancer biology recognizes that the oncogenic process has a Darwinian evolutionary dynamic [142], in which is verified a plethora of alterations that characterize the natural history of disease [143]. According to the stochastic model introduced by the Germany surgeon and oncologist Karl-Heinrich Bauer in 1928 [144], carcinogenesis can be defined as a multiple step process that comes from a clonal evolution of somatic cells, governed by gradual and heritable changes in neoplastic subpopulation and a selective pressure that promotes the proliferation of phenotypes better adapted to the tumor microenvironment [145]. These steps comprise cancer initiation, promotion, progression and metastasis [146–148]. This section summarizes the HPV action in each step of carcinogenesis, from mutation to metastasis.

3.1. HPV and cancer initiation

Cancer initiation is an irreversible process, resulted from the normal cell exposure to a physical, chemical and/or biological agents (mutagen) able to promote genetic damages (mutation), leading to genomic instability [147,149–153]. This process is characterized by the increase in cell plasticity and entropic status, resulting in clonal expansion of mutated cells [154].

Normal human cells present a spontaneous mutational rate of 1.4×10^{-10} bases/division attributed to replication process errors [155]. Under normal conditions, these mutations are repaired by different mechanisms. However, with the aging, these mechanisms become less efficient, contributing to increase the mutational rate and entropic status can lead to cancer initiation. For this reason, with the population aging, as consequence of medical advances, it is expected an increase in cancer cases in next decades.

The mutations can affect intragenic or intergenic regions of both non-coding and coding DNA sequences. Considering that each amino acid is encoded by a triplet of nucleotides and that different triplets can codify the same amino acid, changes in one nucleotide does not always change the amino acid. Thus, silent mutations are verified when mutated triplets add the same amino acid. By the opposite, non-silent mutations in critical genes involved in the control of cell proliferation such as proto-oncogenes and/or tumor suppressor genes confer adaptive advantages to mutated sub-clones. Generally, the proto-oncogene activation is dependent on only single allele mutation, when the tumor suppressor gene inactivation is dependent on two allele mutations or the loss of heterozygosity [156].

The SSBs and DSBs are recognized as an important source of mutation [157–160]. These breaks can be repaired by two different mechanisms: homologous recombination (HR) or non-homologous end joining (NHEJ) [157]. The DSBs are preferable repaired by NHEJ [158]. In this process, the Ku70 and Ku80 proteins active the catalytic subunit of DNA-dependent kinase protein (DNA-PK), that stabilizes the DNA end regions, which are linked by DNA ligase, can lead to frameshift mutations [158,161,162]. In attempt to reduce the endogenous mutagenesis introduced by NHEJ, the DNA-PK activation can promote the p53 phosphorylation, resulting in p21 activation, which acts as cell proliferation repressor [158,163]. Considering that p53 is recruited in response to DNA damages, it is not surprising that p53 is downregulated by mutagens, including HPV.

Thus, the HPV oncoproteins (E5, E6 and E7) promote the cell proliferation by different means. The E5 inhibits the EGFR degradation, acting with EGF, stimulating the cell proliferation [55,56], at the same time that leads to the ubiquitination of Bax, conferring an anti-apoptotic action [59]. The E6 forms a ternary complex E6-E6AP-p53, which drives the p53 to degradation in proteasome 26S [66,79–82]. The E6 can also interact with XRCC1 and O^6-methylguanosine-DNA-methyltransferase proteins, making difficult the repair of SSBs [35]. The E7 promotes the pRb phosphorylation and activation of E2F-responsive genes such as A, E [11,46], D1, D2 and D3, promoting an additional mitogenic stimulation [20]. However, the hyperproliferative action of these oncoproteins can lead to DNA replication fork stress and clastogenesis, resulting in genomic instability [44,75,88].

3.2. Genomic instability and HPV integration in host chromatin

The first study describing the HPV integration in human genome was carried out in 1987, when it was reported the virus integration between *KLF5* and *KLF12* genes in SiHa cells [164]. Currently, 417 HPV breakpoints affecting 389 genes were already identified using polymerase chain reaction (PCR), sequencing of host-viral DNA or RNA junctions [164]. In a current study using whole-genome sequencing (WGS), Hu et al. [164] identified 3666 HPV integration breakpoints, showing a large possibility of virus integration to host genome. Other study, using a dataset of 279 head and neck squamous cell carcinomas (HNSCC), reported the HPV integration in 103 samples, in which 56 (54%) showed an integration in a known gene [165].

Although the breakpoints are distributed through the whole genome, the fragile sites are most susceptible to viral integration, suggesting that the integration is a nonrandom event [164,166,167]. Furthermore, microhomologous sequence between the human and HPV genome was enriched near integration breakpoints, indicating that the fusion between viral and human DNA may have occurred by microhomology-mediated DNA repair pathway [164]. However, it still remains unclear if the fragile sites are the target of viral integration merely because of their innate instability or if the integration into these sites specifically contributes to carcinogenesis [166]. Although this question remains unsolved, the viral integration is recognized as an important event to carcinogenesis, once it can affect the DNA methylation patterns and gene expression [165].

As discussed on Section 3.1, the genetic damages induced by HPV oncoproteins occur early in pre-neoplastic lesions, when the virus genome still persists in an episomal state [168,169]. Integration seems to be a direct consequence of chromosomal instability induced by the E5, E6 and E7 oncoproteins, as previous described on section 3.1. Although the viral integration in host genome is not part of the normal viral life cycle, it is an important molecular event in the progression of pre-neoplastic lesion to invasive carcinoma [168,169].

Several studies suggest that the integration-dependent disruption of HR-HPV E2 gene function is important to achieve neoplastic transformation [170], since the E2 repress the E6 and E7 expression [168]. This hypothesis is based on experiment carried out with cervical cancers cells bearing integrated HPV genomes, and assumed to be applicable to the normal HPV replication cycle, in which the viral genomes are episomal [171]. However, these results were observed from the ectopic expression of BPV-1 E2 gene (E2TA) in HeLa cells, but not with the E2TR, a BPV-2 E2 variant that lacks the N-terminal transactivation domain [172]. Moreover, using two isogenic cell lines, W12 (containing episomal HPV-16 genomes) and S12 (derived from W12 and containing HPV DNA as integrated copies), Bechtold et al. [171] showed that E2 promoted a strong repression of E6 and E7 transcription in S12 cells, but no effect on the transcription of these genes was observed in W12 cells. These results were attributed to the chromatin structure in the region of E6 and E7 promoter (P97), which is very different in these two cell lines [171]. In addition, only 62% of all carcinoma samples displayed integrated HPV genomes [170]. For these reasons, although Vinokurova et al. [170] had confirmed that there is an increasing frequency of integrated viral genome in more advanced pre-neoplastic lesions, the authors suggest that the viral integration is a direct consequence of the degree of chromosomal instability induced by the oncoproteins.

The recurrent patterns of focal genomic instability adjacent to sites of HPV integration, verified in cancer samples from different tissues led Akagi et al. [173] to hypothesize a possible looping model to explain these patterns of genomic instability. According to the viral biology, the HPV depends on the DNA polymerases and transcription factors expressed by the host cell for the viral replication, which can occur either bi-directionally or as a rolling cycle [168]. During the rolling cycle replication, transient loops composed of HPV integrants and adjacent chromosomal sequences are formed to facilitate the viral replication [168]. In this context, the subsequent repair of linear structures consisting of virus-host concatemers would lead to chromosomal amplifications and rearrangements, including breakpoints [168].

Genomic instability is commonly verified in cancer cells, which exhibits genetic rearrangements and gene amplification. However, cells genetically unstable are susceptible to apoptosis. To avoid the cell death, the HPV developed anti-apoptotic strategies. The E6-mediated p53 [13,21,79,83] and E5-mediated Bax ubiquitination [59] are examples of these anti-apoptotic mechanisms. Other strategy is the viral integration within the promoter region of *TERT* (5q15) or next to 3q26 *locus* with consequent gain of the human telomerase gene *TERC* [164,174]. The genome integration in these *loci* leads to the gain of telomeric function, resulting in cell immortalization [174]. This event allows the expansion of transformed sub-clones, leading to cancer development.

3.3. HPV-associated genomic instability and cancer stem-cell (CSC) development

Stem-cells represent a reduced cell subpopulation that occupies different niches in normal tissue [175–178], being characterized by their capability to self-renewal and produce differentiated cells through asymmetric division [176,179], which is crucial for the stem-cell subpopulation maintenance in the tissue [180]. Based on these data, some authors proposed that the cancer initiation is dependent on mutation in adult stem-cells, leading to cancer stem-cell (CSC) formation [176,181].

However, studies showed that the genomic instability can repress genes associated with cell differentiation, resulting in CSC formation [176,182–186]. CSCs express Polycomb group genes (PcG) that repress reversibly transcription factors required for cell differentiation [187]. Among these genes is the *BMI1*, which leads to CSC proliferation by the inhibition of *CDKN2A* transcription factor, which codified the cyclin inhibitors INK4A (p16) and ARF (p14) [188]. These cells also express biomarkers responsible for the maintenance of stem-cell phenotype, including *NANOG*, *OCT-3/4*, *SOX-2, WNT, PTEN* and *SSH* [176,182,189]. The activation of *WNT* pathway, for example, leads to β-catenin nuclear translocation, resulting in aberrant expression of *c-Myc* and cyclin D1 [188]. Considering that β-catenin nuclear translocation is an event verified during the epithelial-mesenchymal transition (EMT), discussed on Section 3.6, currently studies have shown that the stem-cell phenotype acquisition is as a consequence of genetic and epigenetic alterations verified during the EMT [182,190,191]. Thus, the dedifferentiation of specialized normal cell to CSC can be considered as part of the natural cancer history.

Clinically, the CSCs represent the main challenge to be surpassed [192], since these cells express anti-apoptotic and drug resistance genes [188,191]. When in HPV-free normal cells, the DNA damages promoted by chemotherapeutics lead to p53-dependent apoptosis [193], in CSCs the p53 and p21 induce the DNA repair, reducing the therapy efficacy [193]. The p53 not only contributes to stem-cell resistance to apoptosis, but also has a key-role in stem-cell phenotype maintenance [194]. This occurs because the loss of p53 increases the inosine-5′-monophosphate dehydrogenase (IMPDH) expression, leading to asymmetric division [194]. In this sense, the genomic instability induced by the HPV oncoproteins can repress genes associated with cell differentiation, resulting in the CSC development. In addition, the E6-mediated p53 ubiquitination can facilitate the asymmetric division and, therefore, maintaining the subpopulation of CSC into the tumor.

3.4. Metabolic deregulation following cancer initiation associated with HPV

The expansion of transformed sub-clones following cancer initiation requires metabolic alterations to provide the energy supply to cell replication [195,196]. Carbohydrates are the main cell energy source [197]. Under normal conditions, cells convert glucose to pyruvate through glycolysis [197]. Under aerobic conditions, pyruvate is converted to acetyl-CoA, which is directed to mitochondria, where participates of the tricarboxylic acid cycle [71]. During this process, flavine and adenine (FADH) and nicotine and adenine dinucleotides ($NADH_2$) donate electrons to protein complex of electron transporter chain, generating a proton-motor force which is necessary to ATP production [75,198]. This force results in a mitochondrial membrane potential ($\Delta\Psi m$), which maintenance is crucial for the cell survival [75]. The loss of $\Delta\Psi m$ leads to the transitory permeable pore (TPPs) opening [75]. TPPs are K^+, Ca^{2+} and Mg^{2+}-responsive channels that allow the passage of substances with up to 1.5 KDa [199]. However, TPPs opening results in apoptogenic factors release, such as cytochrome c, which can bind to activator of protease factor 1 (Apaf-1), activating caspase 9 [200], resulting in ATP synthesis inhibition [201].

If in one hand the oxidative metabolism results in the production of 32 ATP moles, by the other side it produces reactive oxygen species (ROS), including: superoxide anion, hydrogen peroxide, hydroxyl peroxide, singlet oxygen, peroxyl radical, aldoxyl, lipid hydroperoxide, peroxinitrite and ozone [202–206]. The mechanisms of ROS production involve different pathways that end with the partial oxygen reduction, as revised by Araldi et al. [75] and de-Sá-Júnior et al. [198].

Although widely discussed as toxic, currently data have shown that ROS can act in different cell signaling process [198,207]. This because the hydrogen peroxide produced by complex III of electron transporter chain can be converted to hydrogen peroxide by the isoform 1 of superoxide dismutase (SOD1) [71]. When in the cytosol, hydrogen peroxide acts as a second messenger, inducing the oxidation of cysteine residues present in proteins [75]. This action promotes allosteric alteration, changing the protein function, and can lead to cell proliferation and/or immunomodulation [204,206,208].

ROS are important activators of Toll-like receptors (TLRs), including TLR1, TLR2 and TLR4, that participate of the immune response [206]. For this reason, in attempt to evade the immune system, cells infected by HPV promote the TLR4 downregulation [13,89,209]. In addition, it is not surprising that the pathogens causing persistent infections such as HPV had developed mechanism to promote cell metabolism deregulations as an additional mechanism of immune evasion.

In this sense, studies have been shown that HPV E6 and E6* (a splicing isoform of HPV-16 E6) [74,210,211] and BPV-1 E6 oncoproteins increase the ROS production [76] through the downregulation of SOD2 and GPx anti-oxidant enzymes [212]. The chronical oxidative stress promoted by E6 oncoprotein can lead to nucleotide oxidation and, therefore, genetic damages, including DSBs [213], which are commonly observed in cells infected by HPV [109] or BPV [76,214–216]. However, the repair of oxidize nucleotides by base excision can result in SSBs [217]. These DNA breaks can lead to chromosomal instability, contributing with the viral integration to host chromatin, as well as cancer initiation [210,213].

The DNA damages induced by ROS can activate the p53 [218,219]. The p53 has a central role in the energetic metabolism regulation, since the tumor suppressor protein promotes the degradation of several proteins involved in glycolysis, such as PGAM and GLUT [219]. Thus, the E6-mediated p53 ubiquitination drive the cell metabolism to glycolysis, contributing with the “Warburg effect” [220]. This effect is verified during the cancer progression, when is verified the hypoxia-inducible factor 1 alfa (HIF-1α) overexpression as a consequence of the reduction of oxygen partial pressure into tumor micro-environment [221,222]. However, even after the restoration of oxygen supply due to

the angiogenesis, cancer cells maintain the glycolic metabolism in a process known as aerobic glycolysis [198,223,224].

Despite the data, the ROS action following cancer initiation remains little explored, especially in viral oncogenesis. Thus, most investments and efforts in field are required, especially because the genetic and metabolic deregulations that drive the carcinogenesis occur slowly and gradually in a time of 10–30 years after the initial HPV infection. In this sense, this time may be considered an opportunity to implement novel therapies, including the use of anti-oxidant agents, in order to avoid the cancer development.

3.5. HPV and cancer progression

The genomic instability is necessary, but not sufficient to promote the carcinogenesis [150,225]. Although the genetic alterations increase the fitness of initiated cell, contributing with the growth of genetically unstable sub-clones [150,226], secondary changes in cell metabolism are required to guarantee the energetic supply for cancer development [195,227]. Thus, while the cancer initiation is dependent on mutations, the cancer promotion and progression are dependent on metabolic deregulations [147,228,229]. For this reason, Francis Peyton Rous (1879–1970) defined the cancer progression as a "process in which tumor goes from bad to worse" [230].

Normal cells present a mitotic lifespan (MLS) and next, enter in senescence and death [231]. However, in function of the increase in telomerase activity, which is verified in more than 85% human cancers [155], cancer cells do not present a MLS [231]. Due to the lack of cell cycle control, attributed to the deregulations in tumor suppressor genes or proto-oncogenes and the exposure to secondary stimulus that induces mitosis, cancer cells exhibit a special type of cell division known as neosis. This process is characterized by the hyperproliferation of cells with: (1) DNA damages; (2) loss of checkpoint control; (3) genomic instability; (4) errors introduced by homologous recombination (HR) or non-homologous end-joining (NHEJ) repair and (5) endoreduplication [88,231].

Currently it is clear that HPV oncoproteins not only contribute with cancer initiation, but also cancer promotion and progression. Although each oncoprotein (E5, E6 and E7) has a singular action in carcinogenesis, they act driving the cancer progression. In this context, the E5 oncoprotein acts in synergism with EGF, conferring a secondary stimulus to cell proliferation [55,56], at the same time that prevents the apoptosis through the ubiquitination of Bax pro-apoptotic protein [59]. The E6 oncoprotein leads to cell immortalization inducing the transcriptional activation of *hTERT* [11]. The E6 also confer a mitogenic stimulation through the *FOXM1* up-regulation [72] and can promote both the p53 ubiquitination [13,21,79,83] and epigenetic down-regulation [84–86]. The E7 oncoprotein induces the cell proliferation through the pRb phosphorylation [20,21,92].

Cancer promotion is characterized by the clonal expansion of metabolic deregulated and morphological changed cells [149,150,198]. The clonal expansion of cells without genetic damages leads to benign neoplasm formation, such as papillomas (warts) and polyps, whereas the expansion of genetically unstable cells lead to malignant neoplasm [150]. Thus, the oncogenic process promotes the growth of different sub-clones, each one with different genetic, epigenetic and metabolic status, resulting in a highly heterogeneous microenvironment [153,198].

On the one hand, the cancer cells are sympatrically originated, on the other hand, the proliferation of a determinate sub-clone can lead to extinction of its ancestral in a process known as clonal sweep [142,153]. However, considering that the competition is the main adaptive force into the tumor microenvironment, different sub-clones can evolve in parallel in a process known as branched evolution, increasing the heterogeneity [153,230] and disorganization of normal tissue architecture [232,233]. The sub-clone competition can also lead to adaptation, including the activation of aerobic glycolysis and invasion, contributing to epithelial-mesenchymal transition (EMT) and metastasis [142,234].

3.6. HPV and metastasis

The acquisition of invasive and migratory phenotype verified during metastasis requires metabolic, genetic and morphological alterations. These changes characterize a reprogramming biological process known as EMT [203,204,235–238]. The EMT was first verified by Frank Lillie in 1908 and later described by Dr. Elizabeth Hay at Harvard University, using 3D culture from corneal epithelium cells [239–241].

Considering the Darwinian dynamics of natural cancer history, the EMT can be discussed as a consequence of metazoan cell plasticity [241,242], being a result of different sub-clones competition that comprise the tumor microenvironment [145,146].

Epithelial cell cancers (carcinomas) comprises 90% of all malignancies [233,243]. Epithelial cells are characterized by apical-basal polarity and intercellular adhesion [236,244]. By the opposite, mesenchymal cells do not present apical-basal polarity, neither cell adhesion, being morphologically irregular and fusiform [204,244], conferring a scaffold for epithelium [245]. However, under determined conditions, epithelial cells can acquire reversibly a mesenchymal phenotype (EMT). This process is verified during: (1) gastrulation, in which EMT originates the mesoderm, responsible for the muscle, bone and connective tissue formations; (2) neural crest delamination, resulting in glial and neural cell, adrenal gland tissue and pigmented epidermal cell formation [204,246–248]. In adult life, although crucial for tissue regeneration [246], the unappropriated EMT activation can result in critical homeostasis disturbs, affecting the epithelium integrity, contributing to cancer [203,243,245].

The cell polarity maintenance is fundamental to ensure the tissue homeostasis [249]. For this reason, the loss of apical-basal polarity is recognized as the main characteristic of EMT [249]. Although the loss of polarity could be regulated by different mechanisms, the genetic switch of E- to N-cadherin has been pointed out as the main genetic event of EMT [237,241,244,247,249,250].

The E-cadherin is a transmembrane glycoprotein [244], constitutively expressed, that mediates calcium-dependent homophilic interaction with immunoglobulin domains, forming adhesive bridges [241,251,252]. The E-cadherin connects to actin through α, β and γ-catenin present in cytoplasm [241,252]. These interactions are responsible for the cytoskeleton organization, controlling the apical-basal polarity [251]. The E-cadherin also participates of desmosome formation [241] and gap junctions, conferring intercellular adhesion [251,253]. The E-cadherin expression levels can be also regulated by epigenetic mechanisms, including: CpG islands hyper methylation [241], histone deacetylation and repressor interaction with the E-box present close to the E-cadherin promoter [237,254].

The E-cadherin repressor and/or cytoplasmic sequester results in the β-catenin nuclear translocation [252]. When in the nucleus, the β-catenin acts as an activator of *TWIST, SNAIL* (*SNAIL1*) and *SLUG* (*SNAIL2*) genes [252]. These genes codify nuclear transcription factors with C-terminal zinc-fingers able to bind to E-box region upstream of E-cadherin gene, resulting in the glycoprotein repression [204] and, therefore, the acquisition of fibroblastoid morphology acquisition [251]. The loss of intercellular adhesion leads to asymmetric division [255], contributing to CSCs formation [238,243,245].

The EMT is also characterized by the increase in mesenchymal protein expression, such as fibronectin, vimentin, N-cadherin and α-SMA [203,250,256]. In addition, cancer-associated fibroblasts (CAFs) express plasminogen activator, metalloproteinases (MMP-2, 3 and 9), growth factors and cytokines that contribute with basal lamina extracellular matrix degradation, facilitating the loss of tissue architecture and cell migration [251].

The EMT can be stimulated by different pleiotropic signs [236], including oncogenic virus such as HPV [3]. However, metabolic

alterations have been discussed as the main trigger for EMT [75,257,258]. In this sense, studies have been shown that the HPV-16 E6* oncoprotein has a pro-oxidant action [74,210]. Similar results were described in study involving the BPV-1 E6 oncoprotein [76]. Moreover, both BPV E6 [88] and HPV E6/E7 oncoprotein can lead to cytogenic damages [114,115], resulting in genomic instability, which can result in the CSC development.

The CSC development has been discussed as a consequence of EMT, which promotes a reversible epithelial genes repression, resulting in a mesenchymal phenotype acquisition [75]. However, the lack of attention given to primary cell cultures derived from HPV-associated neoplasms justify the restrict number of studies about HPV and EMT. The studies describing the viral role in EMT are generally based on cell lines.

Using non-small cell lung cancer (NSCLC) transiently transfected with HPV-16 E6 and E7 plasmid, Zhang et al. [259] demonstrated that these oncoproteins overexpression cause the downregulation of mRNA and protein levels of epithelial markers (E-cadherin and ZO-1) and promote the up-regulation of N-cadherin and vimentin (mesenchymal markers). The authors also showed that HPV-16 E6 promotes the STAT3 activation [259]. The STAT3 activation was also described in cell line derived from bovine esophageal carcinoma co-infected by BPV-1, 2 and 4, suggesting that the STAT3 phosphorilation is a consequence of oxidative stress induced by E6 oncoprotein [76]. Interestling, Araldi et al. [182] verified that BPV-infected cells from bovine fibropapilloma and esophageal carcinoma exhibit morphological alterations, including the loss of cell polarity, and increase the expression levels of *Oct-3/4*, suggesting that the EMT onset in pre-neoplastic lesions (fibropapillomas). The use of primary culture cells brings a novel opportunity to study the papillomavirus action in metastasis, allowing to discovery novel therapeutic targets for HPV-related cancers.

4. Malignances associated to HPV

4.1. Cervical and anogenital cancer

The HPV is associated with both pre-malignant and malignant lesion, including the cervical [140,260,261], anogenital (vulvar, vaginal, penile, anal) head and neck (oral, tonsillar, pharyngeal and laryngeal), breast and esophageal carcinomas [23,81,141,262].

Cervical cancer is the third most common malignancy and the fourth cause of death in women globally [99,263,264], affecting women 25–30 years old [140]. According to Torre et al. [264], in 2012 was verified 527,600 new cases and 265,700 deaths by the disease worldwide. Only in 28 States that comprise the European Union (EU), are verified 34,000 new cases and 13,000 deaths by cervical cancer annually [265]. According to the World Health Organization (WHO), it is expected about 27 million of new cases of cervical cancer and 17 million of deaths by the disease in 2030 [266]. The disease presents an high incidence in Sub-Saharan Africa, Eastern European, and Latin America [262], reinforcing the correlation between the cancer incidence and developing countries [9]. Epidemiological studies show the HPV presence in 99% of cervical cancers [260], making the virus the main etiological factor of cervical carcinoma.

The disease has a long development time, which can reach 10–30 years, beginning with a pre-malignant lesion, within an average time of 3–5 years [141]. For this reason, the natural history of the disease can be changed along its course. Thus, the reduction of cervical cancer-associated metastasis verified in last decade can be attributed to the therapeutic advances and the early HPV screening [267].

The HPV is sexually transmitted during the intercourse [262], infecting cells of squamocolumnar junction, which comprise a transformation zone in which is verified the columnar epithelium transformation to squamous epithelium [11,140]. Approximately 80% of sexually active women get a HPV infection during their lifetime [11]. In about 90% of infected women, it is verified a viral clearance. However, in 10% of infected women, the viral infection can persist, inducing E5, E6 and E7-mediated mutations that, according to the stochastic model, can lead to cancer initiation, which is verified in 1% of infected women, in which occurs the virus integration.

Considering that cancer is a multifactorial disease, others environmental factors contribute to increase the genomic instability. For this reason, studies show that smoking, alcohol consumption, long-term contraceptive hormone use (for more than five years) and co-infection by other oncogenic viruses, such as human immunodeficient virus (HIV) increase the risk of cervical carcinoma [140,268,269].

The HPV is also detected in 40–85% of all anal, penile, vaginal and vulvar carcinomas [263]. Among the different virus types described, the HPV-16 and 18 are present in 65.6% and 5.1%, respectively, of all HPV-associated anal carcinomas [270]. In this scene, the cervical infection can act as a HPV reservoir for anogenital infection, as well as the anogenital infection can act as viral reservoir for cervical infection [140].

Although the anal cancer is considered a rare, representing 3% of all gastrointestinal tract neoplasms, the disease incidence has grown 2% per year since 1970, being related to sexual behavior, being closely related to HIV-infected patients [140,270–272]. In Brazil, for example, it was verified an increase in 116% of anal cancer incidence among 1998 and 2007 [271]. The disease is most frequent in women and homosexual men, that are 15 fold most susceptible to the HPV-associated anal carcinoma [273,274]. The HPV is responsible for 88% of all anal cancers, with the majority caused by HPV-16 and 18 [272]. Approximately 80% of anal cancers arise from de anal canal [272], fact that reinforces the relationship between the virus infection and sexual transmission. In this sense, the presence of anal fissures and fistulas facilitate the viral infection [140], that in accordance to the viral biology requires micro-injuries for the virus access epithelial cells of the basal layer.

In general, chemo radiotherapy with 5-fluorouacil (5-FU) and infusion with mitomycin or cisplatin has been established as the standard-of-care regimen for no metastatic anal cancer [272].

The virus is also related to penile intraepithelial neoplasm (PIN), a pre-carcinogenic lesion similar to cervical intraepithelial neoplasm (CIN) [140], and penile carcinoma [21]. Penile cancer rate varies greatly by ethnicity and country. Brazil has the highest rates of penile cancer in the world (about 8/100,000). Unlike as cervical cancer, which occurs at an average age (45 years), the penile cancer is verified in older aged (> 60 years) [275].

4.2. Head and neck squamous cell carcinoma

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer type, representing 6% of all cases and counting for an about 650,000 new cancer cases and 350,000 deaths worldwide every year [276,277]. The HNSCCS comprise a set of cancers that affect tonsils, oropharynx, oral cavity and larynx [276]. The tobacco and alcohol consumption is responsible for 75% of HNSCCs, especially in patients with genetic polymorphism in enzymes that metabolize tobacco and alcohol, when 25% of cases are associated with HPV infection [276]. As verified in other HPV-associated malignancies, the HPV-16 is the most prevalent virus type detected in viral-related HNSCCs [278].

The HPV is detected in 72% of all oropharyngeal carcinomas of individuals who do not smoke, drink or are not immunosuppressed [276]. Besides, the HPV prevalence in oropharyngeal carcinoma increased from 16% to 72% among 1980–2000 [81]. Although the tobacco consumption had declined from 51.9 to 19.0% among men and from 33.0 to 17.3% among women among 1965–2011 [278], epidemiological data from America, Europe, Asia and Oceania points out that the rate of oropharyngeal carcinoma is increasing annually [81]. Although this growth has been attributed to sexual behavior changes and synergic consumption of tobacco and alcohol [81,278,279], considering

the last evidence of productive viral infection in peripheral blood, as well as the hematologic role as virus carrier [134,137,280,281], we cannot disregard the hematologic and vertical transmission as responsible for the high oropharyngeal cancer incidence verified in last two decades.

HPV-related HNSCC represents a subset of head and neck cancers, with unique epidemiology, clinical and molecular characteristics [282], but with favorable prognosis [283]. In general, the HPV-related HNSCC occurs primarily in the oropharynx and arise from the lymphoid tissues of the palatine and lingual tonsils [278]. Individuals with HPV-HNSCC have a better response to treatment, which can involve surgery, radiotherapy and chemotherapy [278]. Although the hypoxia verified during cancer progression reduces the radiosensitivity, Lassen et al. [277] showed that HPV-HNSC-related hypoxia does not reduce the radiotherapy efficacy. Various classes of chemotherapies, including platinum compounds, antimetabolites and taxanes have shown single-agent activity against HPV-HNSC [276]. For this reason, the cisplatin is regarded as a standard agent in combination with radiotherapy [276]. Drugs that have epidermal growth factor receptor (EGFR) as a target, such as Cetuximab, combined to radiotherapy have also shown an effective result, especially for platinum-resistant recurrent or metastatic HNSCC [284,285]. Similar results were also verified with the use of Nivolumab [286].

4.3. Esophageal carcinoma

Esophageal carcinoma (EC) is the eight human malignancy most frequent globally [287,288] and the third most common gastrointestinal cancer [289]. In 2012, it was verified 45,800 new cases and 400,200 deaths by the EC [264]. According to the *Instituto Nacional de Câncer* (INCA), Brazil registered 7636 EC-associated deaths in 2011 and 10,780 new cases of the disease in 2014 [266,290]. These data are alarming, since the EC has a high mortality rate [291], which is 25% superior to the cervical cancer [292]. According to the National Institute of Health (NIH), only 18.4% of patients diagnosed with the disease among 2006–2012 survived for more than five years [293]. For this reason, the EC was included in this review.

Among the clinical signs of EC are: progressive dysphagia, weight loss, odynophagia, anorexia, fever and retrosternal pain [289,294]. The disease diagnosis requires upper digestive endoscopy followed by biopsy [289,294]. However, unfortunately, the diagnostic is generally performed very late after the onset of dysphagia, leading a worse prognostic [289]. According to epidemiological data, only 10% of patients present a survival more than five years [289].

The EC has a variable incidence according to the geographical area [287,295–298]. Among the countries that comprise the high risk for the disease are: China, Singapura, Iran, Sweden, South Africa and Brazil [291,295,297,299]. Due to the high incidence of EC in Central Asia, this area was known as Asian Esophageal Cancer Belt [18,298]. Although the reason for this geographical incidence variation remains unclear [295,298], it is suggested that environmental factors could be associated with EC etiopathogenesis [18].

The tobacco and alcohol consumption are recognized as the main risk factors for EC [291,294,295,300]. However, due to social and cultural questions, the tobacco and alcohol consumption do not justify the high incidence of EC in Asian Esophageal Cancer Belt [298]. Thus, other factors have been associated with EC, including: deficiency of vitamins (A, B and C), the hot food intake, low consumption of vegetables and fruits [291,294,295] and gastric reflux of acid secretion [294]. The gastric reflux leads to the Barrett's metaplasia, characterized by the replacement of normal mucosa of distal esophagus by specialized columnar epithelium [294]. Additionally, currently studies also pointed out the etiological role of infectious agent in EC, such as: cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex and HPV [18,295].

The association between HPV infection and CE was first proposed by Syrjänen (1982). The Harrison's Principles of Internal Medicine, in its 18th edition, already consider the HPV etiopathological action in EC [292]. Currently, the HPV is recognized as the main risk factor for EC in individuals that do not consume tobacco or alcohol [288]. Moreover, studies also demonstrated the association between HPV and Barrett's metaplasia and esophageal adenocarcinoma [302].

Although the association between HPV infection and the cervical pre-malignant lesion is known since 1970 decade [295], the recognition of viral etiological role on EC was marked by data *a priori* controversial [303]. On the one hand, studies showed the HPV protein expression by immunohistochemistry [304–306] and viral DNA sequences by chromogenic *in situ* hybridization in EC samples [307–309], on the other hand, serological studies contested these results [291,300,310]. However, nowadays, it is known that these controversial data obtained from serological studies were associated with methodological problems attributed to the sensitivity of this method, as well as the quality of antibodies employed [295,297,303]. This because, the antibodies used were directed against capsid proteins (L1 and/or L2) of HPV-16 and 18 [300,310]. However, the HPV has an abortive infection in carcinomas in function of viral integration to the host genome [18], leading to the loss of open reading frame L1 and L2, which difficult the immunodetection of these proteins through the use of anti-L1 or anti-L2 antibodies.

Not only serological studies showed divergent results, but also molecular analysis, using PCR as an diagnostic method, showed a low prevalence of HPV DNA sequences in samples of EC from Australia [287,311]. Although at a first sight these data could reinforce the results obtained from serological analysis, Australia is not considered a high-risk area for HPV-associated EC. Moreover, we cannot forget that as all malignancies, the EC is a multifactorial disease and, therefore, other environmental agents can contribute to carcinogenesis. Furthermore, as previously described, the absence of a gold standard primer for HPV diagnostic represents a challenge to identify the viral infection [28,303,312,313], once the prevalent virus types are variable according to the geographical area. Despite these data, evidences of HPV in EC etiopathogenesis have accumulated along these years, as showed in Table 2.

On the one hand, the high-risk HPV association with EC still remains in discussion despite the evidences collected over the last decades

Table 2
HPV DNA sequences identified in esophageal carcinoma.

Evidences	Country	Reference
HPV-6, 11, 16 and 18 DNA sequences	China	Chang et al. [380]
HPV-16 and 18 DNA sequences	Japan	Thoh et al. [381]
	Portugal	Fidalfo et al. [382]
HPV-6, 11, 16, 18 and 30 DNA sequences	China	Chang et al. [308]
	Portugal	Vieira et al. [303]
HPV-16 (serological method)	China	Han et al. [292]
HPV-6, 11, 16, 18, 31 and 33 DNA sequences	China and USA	Suzuk et al. [383]
HPV-6, 16 and 33 DNA sequences	China	Lavergne and De Villiers [304]
TP53 gene polymorphism increase the HPV-associated esophageal carcinoma risk	Japan and China	Kawaguchi et al. [384]
	Brazil	Herbster et al. [289]
	China	Chang et al. [385]
		Chang et al. [386]
HPV-16 DNA sequence	China	Li et al. [387]
HPV-16 DNA sequence	Sweden	Dreilich et al. [388]
HPV-16 and 18 DNA sequence	China	Yao et al. [389]
LMP7/TAP2 gene polymorfism increases the risk for HPV-associated esophageal carcinoma	China	Cao et al. [390]
HPV-16, 18, 26 and 57 DNA sequences	China and USA	Wang et al. [391]
Koilocytes presence	Oslo	Bjørge et al. [297]
		Syrjänen [395]

(Table 2) [311], on the other hand, it is clear that bovine papillomavirus (BPV) persistent infection can lead to upper digestive cancer, including EC [18,29,303,314,315]. Although the papillomaviruses are recognized as specie-specific viruses [18], the BPV represents an exception, being able to infect different species, including buffaloes [316,317], giraffes [318,319], yaks [320,321] and horses [322–324]. Furthermore, among the different viruses that comprise the *Papillomaviridae* family, only HPV and BPV can induce malignancies. For this reason, evolutionary studies suggest that BPV comes from animal domestication, that leads to HPV transmission to bovine [325]. Thus, the virus co-evolved with its host [30]. Although there is not report to BPV infection in humans, a study performed in Germany showed that veterinarian exposed to bovine contact presented common warts [326]. The presence of common warts was also reported in butchers' hands. However, these lesions were attributed to HPV-7 infection, the viral type also related to lung cancer [327]. Another study, performed in Asian Esophageal Cancer Belt, also verified a statistic association between human EC and ruminant contact, once due to sociocultural question, children with less than three years have direct contact with bovines [298]. Furthermore, it is verified a high milk consumption in Central Asia [298]. In this sense, our group verified the BPV DNA sequences in milk [315], as well as demonstrated the viral capsid thermoresistance by optic dichroism [328]. These data suggest that BPV can survive to pasteurization process, requiring new studies about the possible viral transmission for humans.

4.4. Ophthalmologic and breast cancer

Although less discussed by the literature, the HPV is related to ophthalmologic malignancies, including squamous tumor of conjunctiva and lacrimal sac [329] and retinoblastoma in children with three years-old or more [330], reinforcing the vertical transmission.

According to Torre et al. [264], breast and cervical cancer are responsible for 60% of all malignancies. In 2012, it was registered 1.7 million new cases of breast cancer and 521,900 deaths worldwide [264]. Over the last decade, breast cancer incidence rate has increased by around 20% worldwide [331]. The disease can be attributed to different factors, such as weight gain after 18 years, overweight and obesity, use of menopause hormone therapy (MHT), sedentary lifestyle, use of oral contraceptive and reproductive and hormonal factors [264]. The high incidence of breast cancer around the world has woken the interest in a viral etiology of the disease [332]. However, since 1992 evidences have suggested the HPV participation on breast cancer [333–336] Nevertheless, there are still disputes about the virus association with the disease [337], HPV DNA sequences were identified in: invasive breast cancer from Austria [338], Australia [333], Mexico [339], Syria [340], China [341], Pakistan [332] and India [342]. Moreover, HPV DNA sequences were also identified in benign breast tumors, reinforcing the HPV etiological role on breast neoplasms [343].

Among the different HPV types known, the HPV-16 is the most prevalent viral type identified [338,342–346], followed by HPV-18 [332,333,342], HPV-31, 32, 33 [340,341], HPV-58, 59, 73 and 82 [344]. Meta-analysis based on the literature supported that HPV infection increases the risk for breast cancer [337]. A systematic review based on 29 studies and 211 samples showed that HPV is present in 13.4% of breast cancer in Europe and 42.9% in North America and Australia [347]. The HPV can arise the breast by two pathways: by hand from female perineum to breast [333] or through the bloodstream [338].

5. Economic impacts of HPV: from vaccination to cancer treatment

The HPV has direct impacts on public health, resulting in economic hazard due to the costs with viral diagnostic, immunization and treatment [102,262]. In the USA, for example, the HPV-associated diseases demand a cost of US$ 6.6 billion/year [102]. Denmark, in turns, expenses € 7.6 million/year with anal cancer treatment [263].

The early diagnosis remains considered as the best politics to reduce the cancer mortality rates [348,349]. These diagnostic methods can vary from simple techniques with low-cost, as Papanicolau's test and ultrasonography (US) to expensive, such as Positron Emission Tomography (PET-SCAN). Thus, economic crisis has a direct impact on health, especially in oncology, which therapeutic methods are expensive. In 2012, for example, Greek reduced the health investments in 23.7%, Spain in 14% and Brazil, 32% in 2015 [348].

The immunization is considered one of the most important medical interventions [350]. Immunization reduces the infectious agent transmission and dissemination, increasing the life quality and longevity [350]. Undoubtedly, vaccines against HPV are mandatory to prevent cancers associated with the virus [336].

Two prophylactic vaccines against HPV are available in the market since 2006 [263]: (1) Cervarix, produced by Glaxo-Smith Klein (GSK) and (2) Gardasil, produced by Merck [22,26]. These vaccines are based on virus-like particles (VLPs) of the L1 structural protein [351]. Cervarix is a bivalent vaccine, able to confer protection against HPV-16 and 18, employing L1 VLPs produced in Baculovirus in *Thricoplusia ni* insect cells, using aluminum hydrophosphate as adjuvant [26,141]. Gardasil can confer protection against two high-risk HPV types (HPV-16 and 18) and two low-risk (HPV-6 and 11), associated with genital warts. This vaccine is composed by L1 VLPs, produced *Saccharomyces cerevisiae*, employing A lipid 3-O-diacilete-44-monophosphoryl (ASO4) as adjuvant [26,141]. Three doses of quadrivalent vaccine are recommended at intervals of 0, 2 and 6 months [352]. Both bivalent and quadrivalent vaccines have a prevention effectiveness of 95.8% against HPV-16 and 18, and 78.6% against anal intraepithelial neoplasms (AIN) associated with these virus types [273]. Both vaccines are considered safe and well tolerated [26]. For these reasons, more than 30 countries, including Brazil, adopted immunization programs against HPV based on these vaccines [18]. Besides these, a new nine-valent vaccine (HPV-6, 11, 16, 18, 31, 33, 45, 52 and 58), also based on HPV L1 VLPs, was developed by Merck, Gardasil®9. According to the Phase III study, Gardasil®9 was able to prevent 97% of high-grade pre-cancer lesions, showing an immune response better than those generated by quadrivalent vaccine [353].

Australia was the first country to adopt the vaccination against HPV. Between 2007 and 2009, the country vaccinated over half of its young women aged 12–26 years [352], observing a reduction in 70% of HPV-6, 11, 16 and 18 infection incidence [26]. Similar results were also verified in Denmark, Finland and Sweden [26].

Considering that HPV-16 L1 has 83% of homology with HPV-31 L1 and, the HPV-18 L1 has 88% of homology with HPV-45 L1, both vaccines (Cervarix and Gardasil) present cross-neutralization, being able to protect against the high-risk HPV-31 and 45 [22]. However, available vaccines are not able to protect against all HPV types, since there are more than 200 virus types described. Moreover, these vaccines have a high cost of production. Thus, it is necessary to invest in novel multivalent vaccines, with less production cost. In this sense, vaccines based on recombinant protein expressed in *Escherichia coli* have demonstrated a useful alternative, because they have a less production cost, at the same time that do not require the L1 VLPs, being more stable [26,354].

Studies have demonstrated that early proteins (E6 and E7) show a therapeutic action, whether later proteins (L1 and L2), a prophylactic action [355]. Vaccines based on E6 and E7 have been also discussed against HPV [356–358]. However, in a current study based on BPV-1 E6 recombinant oncoprotein, Araldi et al. [88] demonstrated that this oncoprotein can induce clastogenesis and neosis *per se*. This data emphasizes the necessity of *in silico* analysis of E6 and E7 oncoproteins, aiming to obtain novel constructions most antigenic and less mutagenic.

6. Conclusion

Despite the recent advances in HPV biology, pathology and vaccinology, the number of HPV-related incident cancer remains growing globally. Among the advances already achieved, undoubtedly, the comprehension of metabolic deregulation induced by HPV oncorpoteins represents one of the most relevant impacts in oncology field, have been the subjected of discussion on "3rd ICGEB Workshop on HPV and associated malignancies: biology, prevention and therapy" (Brazil, from 2nd to 5th September 2017). This because, the oxidative stress participates of all steps of carcinogenesis, increasing both the entropic status and genomic instability, that trigger the cancer development. However, considering that carcinogenesis is a multiple step process, which involves genetic, cytological and metabolic changes that occurs in years, the time between HPV infection and cancer development, which could reach 10 to 30 years, emerges as a target for novel therapies in attempt to avoid the cancer development. In this context, therapies based on anti-oxidant drugs should be better exploited as alterative to reduce the oxidative stress promoted by HPV E6 oncoprotein, avoiding the cancer initiation. Moreover, therapeutic vaccines based on E6/E7 DNA or recombinant protein are mandatory to treat the patients already infected by the virus. In addition, most investments in prophylactic vaccines based on L1/L2 and novel formulations with adjuvants are also crucial to increase the coverage and reduce the cost with production. In this context, the use of VLPs or capsomers from *E. coli* emerge as a plausible alternative [359]. Finally, increase the investments in public health that aim the early diagnosis and to identify biomarkers expressed exclusively in HPV-related CSCs and EMT process are crucial to detect pre-malignant and malignant neoplasms, respectively, before that cancer cells spreads to distant organs.

Conflict of interest

The authors declare that is no conflict of interest in this publication.

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