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Minireview

MINIREVIEW

Association of human papillomavirus infection and inflammation in cervical cancer

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One sentence summary: This review will summarize what is currently known in regard to the roles of human papillomavirus oncogenes in the occurrence of inflammation in cervical cancer and the effects of some other factors in cervical tissue.

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ABSTRACT

Human papillomavirus (HPV) associated cancers, and in particular cervical cancer, are considered to be directly stimulated by HPV oncogenes. Alternatively, these types of cancers could also be indirectly stimulated by HPV-induced chronic inflammations, which in turn are also caused by HPV oncogenes activity. Chronic inflammation is associated with repeated tissue injury and development of mutations in the vital tumor suppressor genes. Thus, it is important to understand that the persistent HPV infection and its associated chronic inflammation is responsible for the progression of HPV-induced cancers. HPV E5, E6 and E7 could upregulate the expression of cyclooxygenase (COX)-2 and prostaglandin (PG) E2 followed by the activation of the COX-PG pathway. This pathway is assumed to be the main cause of HPV-induced inflammation. Additionally, HPV oncogenes could have an impact on the upregulation of pro-inflammatory cytokines in HPV-positive patients. The upregulation of such cytokines accelerates the incidence of inflammation following HPV infection. Other factors such as microRNAs, which are involved in the inflammation pathways and aging, give rise to the increased level of pro-inflammatory cytokines and could also be responsible for the acceleration of HPV-induced inflammation and consequent cervical cancer. In this review, the exact roles of HPV oncogenes in the occurrence of inflammation in cervical tissue, and the effects of other factors in this event are evaluated.

Keywords: human papillomavirus; persistent infection; inflammation; cervical cancer

INTRODUCTION

According to the World Health Organization (WHO) report, cervical cancer is the fourth most common cancer among women, with approximately 570 000 new cases in 2018 (6.6% of all female cancer) (World Health Organization 2018). Furthermore, the incidence and fatality of this type of cancer is striking in East African and South Asian women (Arbyn *et al.* 2011). Cervical cancer cases, in these regions, are usually identified when the last stage of the disease is ongoing, because of the insufficient diagnosis methods and lack of equipment (Getahun *et al.* 2013; Catarino *et al.* 2015). There are some risk factors that are considered to be culprits for the induction of this type of cancer, such as gene polymorphisms (Pillai *et al.* 2002; Ni *et al.* 2011). However, the majority of cervical cancer cases are associated with persistent human papillomavirus (HPV) infections (Schiffman *et al.* 2007). HPV infection could also take part through the induction of some

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other types of cancers, including head and neck cancers, tonsillar carcinomas, penile cancer, etc. (Gross and Pfister 2004; Herberhold *et al.* 2017; Sarkar *et al.* 2017).

HPVs are the member of DNA viruses that are epitheliotropic and, based on its oncogenic ability, are divided into three groups: high-risk (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -68, -73, -82), probably high-risk (HPV-26, -53, -66) and low-risk (HPV-6, -11, -40, -42, -43, -44, -54, -61, -70, -72, -81) (Dueñas-González *et al.* 2005). High-risk HPVs, and particularly HPV-16 and HPV-18, are proven to be the main motive of cervical cancer (Bouvard *et al.* 2009). Among the well-known targets of HPV oncoproteins (E5, E6 and E7), including cellular tumor suppressors (pRB and p53) and epidermal growth factor receptors (EGFR) (Mathur *et al.* 2001; Kim *et al.* 2010; Tommasino 2014; Hemmat and Baghi 2018), some inflammation pathways are reported to be stimulated by this oncoprotein activity (Georgescu *et al.* 2018).

The relationship between inflammation pathway stimulation and induction of cancer has been considered for many years. Chronic inflammation, following tissue damage, could contribute to cell transformation and proliferation (Balkwill and Mantovani 2001). Cell proliferation, by itself, is not able to develop cancerous tumors. However, if this phenomenon is accompanied by an environment rich in inflammatory cells, DNA damage-inducing factors and growth factor activation, it could lead to an increased-risk of the neoplastic process taking place (Coussens and Werb 2002).

Cancerous cervical cells represent a deteriorated and hyperactivated induction of inflammation pathways (Balkwill and Mantovani 2001; Balkwill and Coussens 2004) and considering that HPV infections are the main cause of cervical cancer, in the current review, we consider the exact roles of HPV-induced inflammation in the progression of cervical cancer. We also evaluate the functions of HPV-associated proteins within this process in detail.

HPV ONCOGENICITY

Among the early proteins, which are encoded in the HPV genome, E5, E6 and E7 are best known as HPV-associated oncoproteins. These proteins could exert their effects on different stages of cellular division and its associated signaling pathways (Schiffman *et al.* 2007) (Fig. 1). High risk (HR) HPV E6 is a short protein that contains zinc finger domains and PDZ-binding motifs, by which E6 is able to put on its efficacies through cell transformation (Kiyono *et al.* 1997; Lee, Weiss and Javier 1997). HR HPV E6 acts through three different means: degradation, interaction and disruption (Wallace and Galloway 2015). One of the most important tumor suppressors, p53, has been proven to be the main target for E6. Furthermore, in this suppression, E6 should interact with another protein called E6-associated protein (E6AP). Generally, HR HPV E6 interferes in the degradation of p53, telomerase activation, immortalization of the infected-cell, microRNAs regulation, genome destabilization, G protein signaling, disturbance of the innate immune system, debilitation of cellular apoptotic signaling and changing in cell adhesion, polarity and differentiation (Wallace and Galloway 2015). As with E6, HR HPV E7 proteins are also functionally correlated with the induction of cellular transformation. The principal target of E7 is reported to be another important cellular tumor suppressor, retinoblastoma protein (pRb) (Dyson *et al.* 1989). The consequence of this disruption, in the interaction of pRB and E2F (a transcription factor), leads to the maintenance of S-phase capability in the differentiated epithelium (Hwang *et al.* 2002). Additionally, it had been reported that E7 could abolish the E2F6 capacity to behave as a transcription suppressor (McLaughlin-Drubin, Huh and Munger 2008). Recently, some studies have depicted that PTPN14, another important tumor suppressor, is targeted by HPV E7 protein. This suppressive interaction can facilitate the HPV life cycle as well as the progression of malignancies (White, Munger and Howley 2016; Szalmás *et al.* 2017; Hatterschide *et al.* 2019; Yun *et al.* 2019). In general, HR HPV E7 is involved in the cellular transformation procedure by association with, pRB degradation and maintenance of S-phase capability, interferon signaling pathways, chromosomal destabilization and abnormality, cellular metabolism, epigenetic modification, interference with microRNAs regulation and regulation of cellular growth factors (Mittal and Banks 2017). E6 and E7 not only participate in cell transformation by their direct effects suppressors but also by providing an inflammatory microenvironment around the HPV-infected cell (Iuliano *et al.* 2018). HR HPV E5 proteins, as another type of the HPV oncoproteins, play a key role in cellular transformation; particularly by intervention in the EGFR signaling pathway (Genther Williams *et al.* 2005). Overall, E5 could contribute to the HPV oncogenicity by disturbance in the degradation of EGFR, induction of angiogenesis in cancerous cells, providing proper resistance to cellular apoptosis and immune evasion (Kim *et al.* 2010). Similarly to E6 and E7, E5 has also been shown to correlate with the induction of inflammation pathways (Kim *et al.* 2009).

RELATION OF INFECTION-INDUCED INFLAMMATION AND CANCER

Inflammation as the accelerator for cancer development

Correlation of inflammation and cancer poses an important issue in the detection of tumor origins and has been researched for several years (Coussens and Werb 2002; Proctor *et al.* 2010). It has been proven that cancerous cells could release several cytokines and chemokines, by which diverse types of leukocytes migrate to the tumor location, including neutrophils, macrophages, lymphocytes, mast cells and dendritic cells. These immune cells occur after the secretion of cytokines, reactive oxygen species (ROS) and cell death-associated mediators (such as tumor necrosis factor-alpha (TNF-α)), interferons, and interleukins (Wahl and Kleinman 1998; Kuper, Adami and Trichopoulos 2000). Tumor-associated macrophages (TAMs) constitute a pivotal ingredient of inflammation and are brought to the neoplastic sites, and based on their functions, neoplasm could have two different fates: survival or degeneration. If TAMs get activated by interleukin (IL)-2, IL-12 and interferons, they could take part in the killing of neoplastic cells. On the other hand, they could potentiate cancer development by the production of angiogenesis-associated growth factors (Brigati *et al.* 2002; Schoppmann *et al.* 2002; Tsung *et al.* 2002).

The causative feature of inflammation in cancer progression is manipulated by two different origins, exterior agents-induced inflammation (such as infection) and interior agent-induced inflammation (such as genetic mutations) (Mantovani *et al.* 2008). It has been demonstrated that numerous malignancies emanate from chronic inflammation, which has been the consequence of infection (exterior) (Kuper, Adami and Trichopoulos 2000; Shacter and Weitzman 2002). However, the relationship between the inflammation and inducing of cancer is thoroughly accepted, the exact molecular mechanisms mediating this relationship have not been completely illuminated yet.

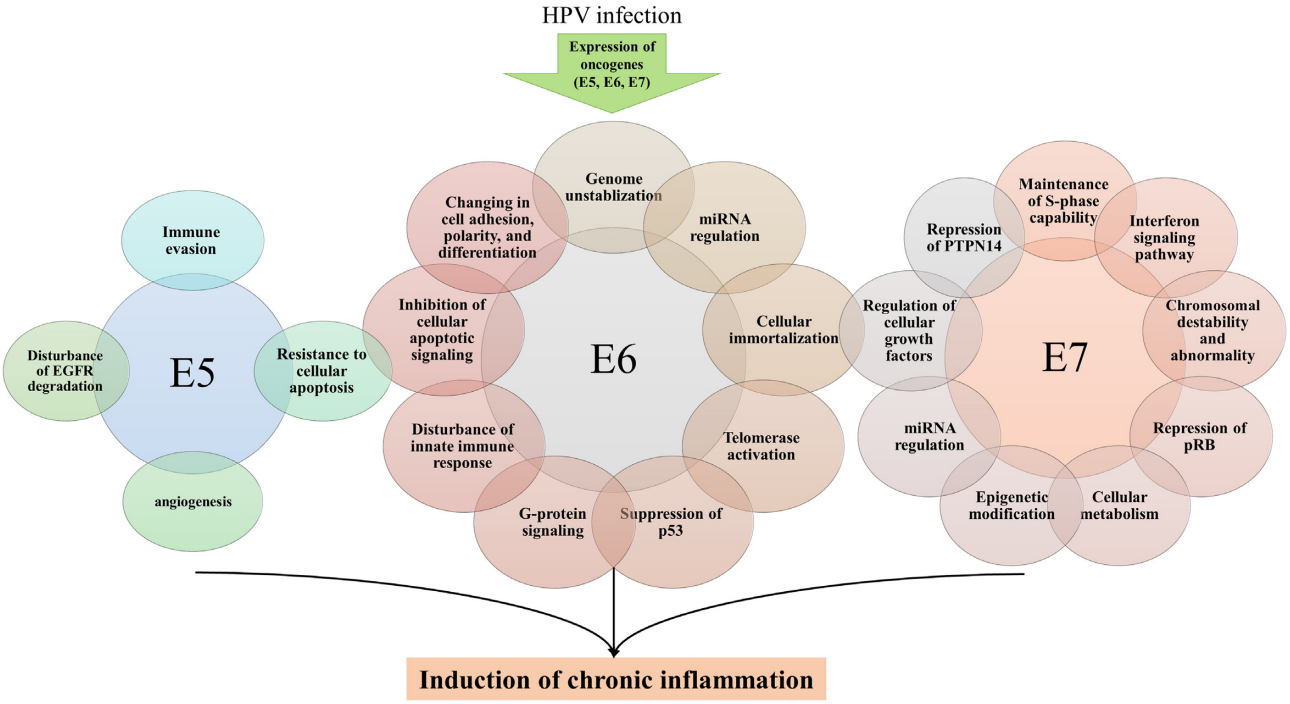

Figure 1. The roles of HPV oncogenes in carcinogenicity.

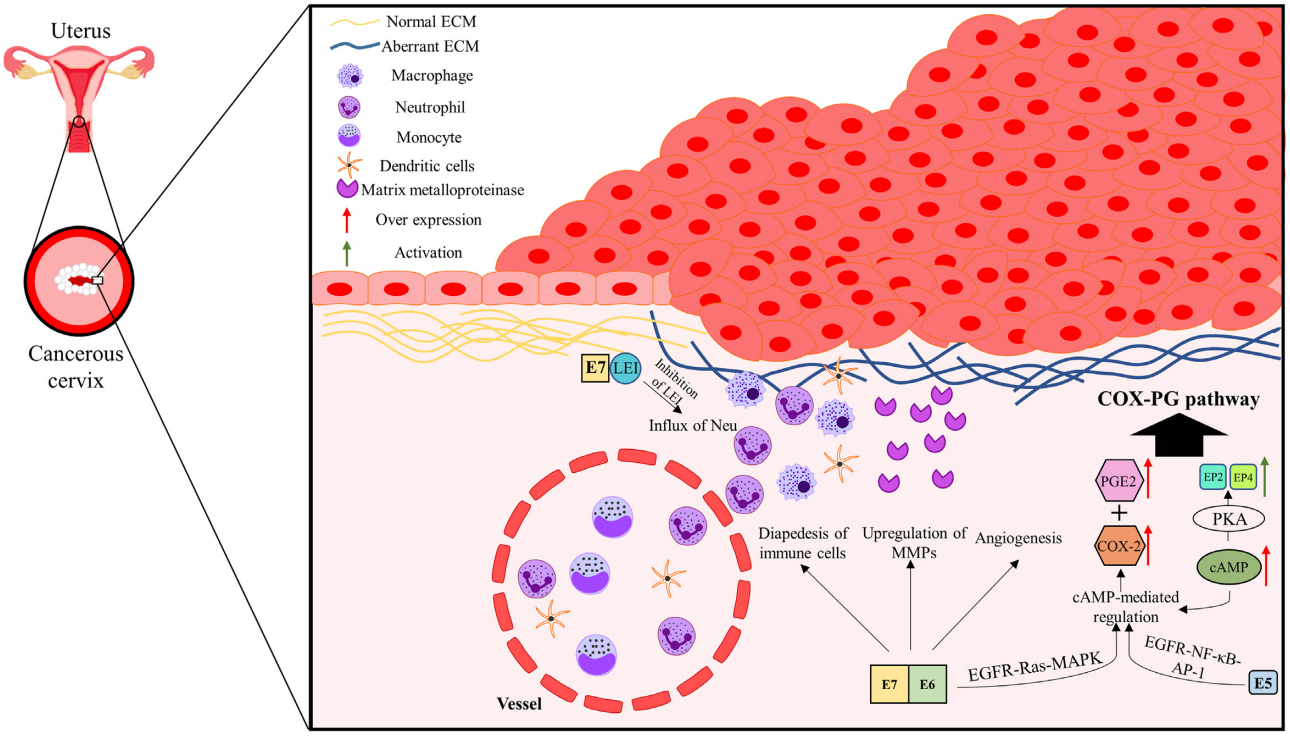

Figure 2. COX-PG pathway in HPV-induced inflammation. HPV E6 and E7 proteins could stimulate the angiogenesis process, diapedesis of innate immune cells such as monocytes, dendritic cells and neutrophils, and upregulation of MMPs. Matrix metalloproteinases alter the normal extracellular matrix to aberrant extracellular matrix. Moreover, E7 increases the influx of neutrophils into the cervical tissue by inhibition of the leukocyte elastase inhibitor (LEI). E6 and E7 are also able to upregulate the expression of cyclooxygenase 2 (COX-2) and prostaglandin E2 (PGE2) by EGFR-Ras-MAPK signaling pathway depending on a cyclic adenosine monophosphate (cAMP)-mediated manner. Another HPV oncogene, E5, could demonstrate this effect by the EGFR-NF-κB-AP-1 signaling pathway instead. Overexpression of cAMP gives rise to the protein kinase A (PKA) mediated-activation of prostaglandin E receptor 2 and 4 (EP2 and EP4). As a result of these phenomena, COX-PG pathway gets induced followed by the induction of chronic inflammation and consequent cervical cancer.

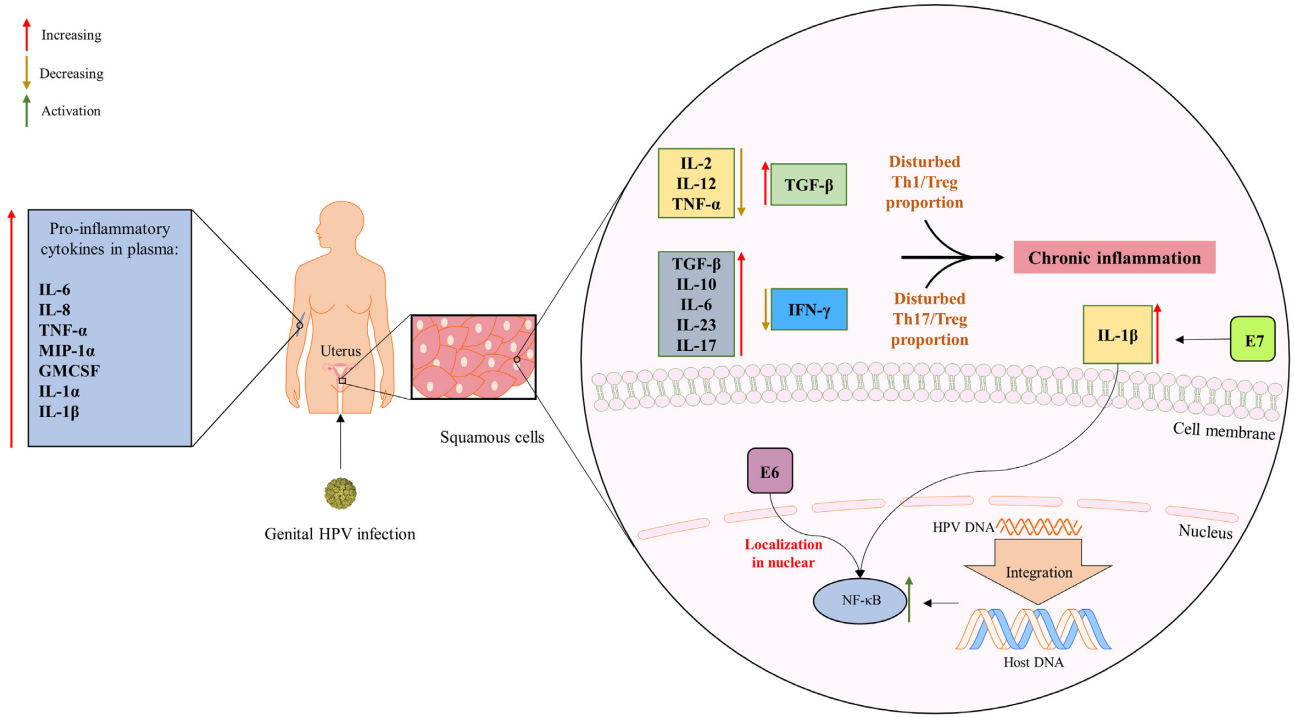

Figure 3. Pro-inflammatory cytokines in HPV-induced inflammation. Several pro-inflammatory cytokines are increased in the plasma of patients with genital HPV infection, including IL-6, IL-8, TNF-α, MIP-1α, GMCSF, IL-1α and IL-1β. By decreasing of IL-2, IL-12 and TNF-α, and increasing of TGF-β in cervical tissue, the ratio of Th1/Treg is disturbed. Moreover, upregulation of TGF-β, IL-10, IL-6, IL-23, IL-17 and downregulation of IFN-γ give rise to the disturbance of Th17/Treg ratio. Eventually, these events lead to the induction of chronic inflammation. HPV E7 could elevate the expression level of IL-1β, which ends in activation of NF-κB molecules. Additionally, HPV E6 localizes these molecules within the nucleus of HPV-infected cells. Overall, the elevated level of NF-κB and its localization into HPV-infected cells could give rise to the induction of chronic inflammation followed by a cervical cancer incidence.

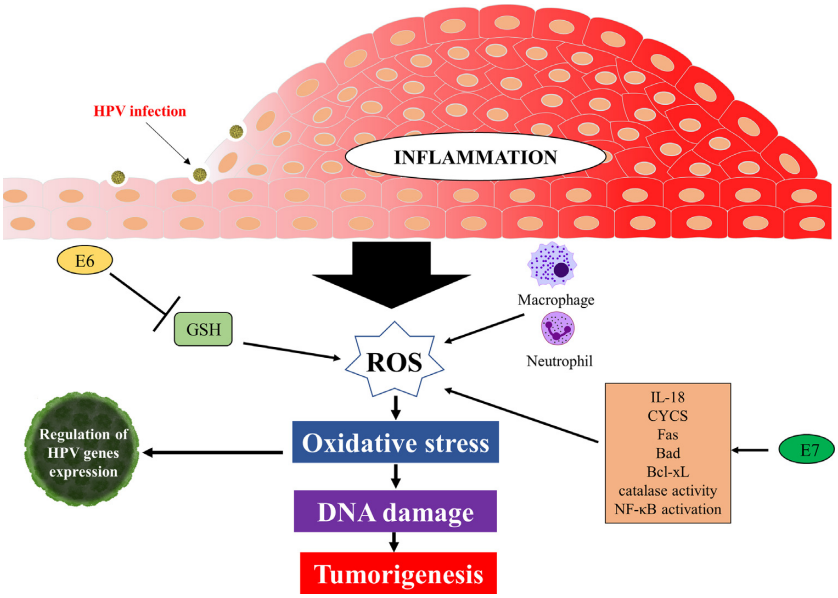

Figure 4. The role of ROS in HPV-induced inflammation and tumorigenesis. Following the HPV-induced inflammation, the neutrophil and macrophage-based production of ROS is increased. Furthermore, HPV E6 protein could elevate the level of ROS by inhibition of GSH. HPV E7 also augments ROS by coordinated modulation of cellular factors such as IL-18, cytochrome-C, Fas, Bad, Bcl-xL, increasing level of catalase activity and NF-κB activation. The production of ROS finally leads to the induction of OS, by which the expression of HPV genes get regulated and repetitive DNA damage occurs. All these events can eventually end in the induction of HPV-associated tumor.

Infection-induced chronic inflammation, one of the main actors in cancer

The normal confrontation against infections is initiated by the production of reactive oxygen and nitrogen species by leukocytes, which lead to the induction of DNA damage in proliferation cells (Maeda and Akaike 1998). While the acute and chronic inflammations have the same mediators, pathways and processes, acute inflammation is resolved after the stimuli (for example infectious agent) are dispelled and the injured tissue ameliorates get stabilized (Munn 2017). Accordingly, the presence of persistent infection and chronic inflammation, as well as repeated tissue damage and tissue restoration could give rise to destructive DNA damage, such as mutations in vital genes. The most remarkable of such mutations can be observed in p53 genes, which are frequently seen in chronic inflammatory disease-associated tumors (Yamanishi *et al.* 2002). Viral infections could contribute to several chronic inflammatory conditions such as atherosclerosis (Hemmat *et al.* 2018). Viruses, in particular, oncogenic viruses, exert their effects directly on cell transformation by incorporating viral oncogenes within the host genome. Furthermore, it is doubtful whether the viral infection-induced inflammation is another mechanism, by which viral infection ends in malignancy (Coussens and Werb 2002). Several viruses are supposed to utilize the second mechanism, including hepatitis B virus (HBV), hepatitis C virus (HCV), human T lymphotropic virus 1 (HTLV-1), Epstein-Barr virus (EBV), Kaposi's sarcoma herpesvirus (KSHV), Merkel cell polyomavirus (MCV) and HPV (Read and Douglas 2014).

HPV-INDUCED INFLAMMATION IN CERVICAL CANCER INDUCTION

For several years the interrelationship between chronic inflammation, the incidence of high-grade squamous intraepithelial neoplasia (HSIL), and invasive cervical cancer (ICC) have been considered (Schwebke and Zajackowski 1997; Castle *et al.* 2001; Hawes and Kiviat 2002). Through the cellular assessment of cervical cancerous tissue compared to a healthy one, it has been demonstrated that the increased count of macrophages in cervical epithelium could aggravate the severity of HPV infection-induced wounds, which leads to an inflammatory condition (Hammes *et al.* 2007). The ambiguous point concerning the relation of HPV infection, chronic inflammation and induction of cancer is the exact cellular mechanisms mediating this relationship. After early HPV infection, this oncogenic virus integrates some parts of its genome to the genome of the host cell, which contains two major HPV oncogenes, E6 and E7 (Doorbar *et al.* 2012). This event gives rise to the excessive production of HPV oncogenes in the HPV-infected cells and repeated release of pro-inflammatory cytokines and subsequent induction of chronic inflammation (Liu *et al.* 2015). As mentioned before, chronic inflammation is associated with repeated tissue injury and amelioration that could lead to the creation and development of mutations in the vital genes such as p53. Thus, it could be understood that the persistent HPV infection and its associated chronic inflammation is responsible for the progression of HPV-induced cancers. As the signaling pathways are accountable for the induction of inflammation (Yeung *et al.* 2018), these cellular pathways could also be the culprit of HPV-induced inflammation as well as cytokines and chemokines.

Cyclooxygenase-prostaglandin (COX-PG) pathway

The COX-PG pathway plays an important role as the central regulator of inflammation and cancer. Several motives have been introduced to induce COX-2 production, such as growth factors (i.e. epidermal growth factor), lipopolysaccharides (LPSs) and pro-inflammatory cytokines (IL-2 and TNF-α) (Hinz, Cheremina and Brune 2008). Overall, the overexpression of COX-2 is indicated in diverse kinds of cancer; by its functions, enhanced metastasis, suppressed cellular apoptosis, angiogenesis and cellular proliferation occur (Sales *et al.* 2001; Cao and Prescott 2002; Sobolewski *et al.* 2010). It has been shown that HPV oncoproteins (E5, E6 and E7) might stimulate COX-PG pathway as the result of upregulation of COX-2 expression and E type of PGs (PGE) (Fig. 2) (Sales *et al.* 2002; Libra *et al.* 2009; Adefuye and Sales 2012). COX-2 expression and also PGE2 production is illustrated to be concentrated in several sites of cervical epithelium, cervical vessels and inflammatory cells (Kulkarni *et al.* 2001; Sales *et al.* 2001; Ferrandina *et al.* 2002; Sales *et al.* 2002; Kim *et al.* 2004), and also the overexpression of COX-2 also has been found in cervix cancerous cells, when compared to normal cells (Kulkarni *et al.* 2001). Moreover, a significant link has been reported between the expression of COX-2 and matrix metalloproteinases (MMPs) in some kinds of cancers which show that the decreased expression of COX-2 results in the reduced level of MMPs (Sivula *et al.* 2005; Liu *et al.* 2015). Tremendous remodeling of the extracellular matrix (ECM), which is caused by MMPs, leads to a conversion in the vasculature, which follows by extravasation of immune cells and angiogenesis (Aggarwal *et al.* 2006; Libra *et al.* 2009; Adefuye and Sales 2012). Some studies report an association between such MMPs transcription and HPV E6 and E7 transcription in remodeling and differentiation of tissue (Nuovo *et al.* 1995; Libra *et al.* 2009). Furthermore, comforted activation and the elevated influx of neutrophils within the tissue owing to the formation of E7-leukocyte elastase inhibitor complex and downregulation of those inhibitors as well as the overexpression and activation of MMPs, which facilitate the diapedesis process of neutrophils into the inflammation sites (da Silva Cardeal *et al.* 2006; Kolaczkowska *et al.* 2009).

Activation of EGFR signaling pathways shows that the overexpression of EGFR leads to the increased production of COX-2 (Kim *et al.* 2004). The production of amphiregulin (a member of the EGF family) and subsequent activation of EGFR-Ras-mitogen-activated protein kinase (MAPK) signaling, which gets triggered by HPV E6 and E7, gives rise to the activation of COX-2 promoter and increased expression level of COX-2 during a complicated signaling cascade (corepressor/coactivator exchange) (Subbaramaiah and Dannenberg 2007). HPV E5 has been shown to be associated with the upregulation of COX-2 expression as well. However, its function is exerted through nuclear factor kappa light chain enhancer of activated B-cells (NF-κB)-activated proteins 1(AP-1)-involved the EGFR signaling pathway (Kim *et al.* 2010).

As mentioned before, PGEs play an essential part in the COX-PG pathway. PGE2 could join with PGEs receptors (EP1, EP2, EP3, EP4) and exert its effects through this connection (Narumiya and FitzGerald 2001). However, only 2 types (EP2 and EP4) of these receptors are shown to be involved in cervical cancer and are upregulated during this cancer remarkably (Sales *et al.* 2001). In comparison with normal cervical cells, cAMP are also upregulated in cervical cancerous cells (Sales *et al.* 2001). The activation of EP2 and EP4 are mediated by the protein kinase A (PKA) pathway, following stimulation of adenylate cyclase and elevated level of cAMP (Coleman, Smith and Narumiya 1994). It is

identified that there is an association between COX and cAMP activation, by which COX activity is considered to be regulated by cAMP as a primary second messenger (Narumiya and FitzGerald 2001; Sales *et al.* 2001). Nevertheless, other EPs need to be investigated, to see whether they play any role in cervical cancer progression.

Pro-inflammatory cytokines and immune cells

Pro-inflammatory cytokines, including IL-6, IL-8, TNF-α, macrophage inflammatory protein 1 alpha (MIP-1α), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-1α and IL-1β are remarkably increased in plasma of patients with HPV infections (Fig. 3), followed by a decreased lymphoproliferative response (Kemp *et al.* 2010). High-risk HPV E6 and E7 could barricade IL-1β function to lessen the innate immune response against HPV-infected cells, and simplify the life cycle and persistence of HPV, by which cell transformation and subsequent carcinogenesis could take place (Niebler *et al.* 2013). There is some evidence that proves regulatory T cell (Treg) involvement through the ICC incidence. Accordingly, changes in the cytokine pattern of patients with HPV-associated cervical lesions recommend that the chronic inflammation, accompanied by inconsonance of T helper 1 (Th1)/Treg proportion, give rise to facilitated tumor progression and immune evasion (Fig. 3). Such changes are manifested as a diminution of IL-2, IL-12 and TNF-α and vice versa, the increment of transforming growth factor-beta (TGF-β) (Peghini *et al.* 2012). It has been illustrated that Th1 cells infiltrated in cervical tumor site could change M2-macrophages to activated M1-macrophages in order to create a tumor-rejecting microenvironment (Heusinkveld *et al.* 2011).

NF-κB activation following the integration of HPV DNA, within the host genome, might play a considerable role in cervical cancer induction. Besides the common targets of HPV oncoproteins (E6 and E7) and subsequent inhibition of p53 and pRB cellular tumor suppressors, these viral proteins correlate with the activation of NF-κB, which leads to irrepressible cell cycle and cellular transformation (Senba and Mori 2012). HPV E6 localizes this transcription factor in the nucleus of the HPV-infected cell (Fig. 3). E6 and E7 are demonstrated to have an association with elevated levels of NF-κB activation, which means that this factor plays a crucial role in the transmission of chronic inflammation to malignancy and cancer (James, Lee and Klingelhutz 2006; Senba *et al.* 2011). As well as HPV E6 and E7, IL-17 manifests an ability to stimulate the NF-κB pathway, which subsequently leads to the cellular proliferation and invasion of cervical cells. It has been reported that IL-17 could be elevated by the activity and overexpression of the HPV E6 protein (Chang *et al.* 2010; Lv *et al.* 2018). Consequently, it has been indicated that the expression of IL-1β could be upregulated by E7, which results in the expression of NF-κB. On the other hand, it is shown that HPV E6 hampers the transcription of IL-1β. The exact mechanisms involved in the IL-1β-mediated inflammation upon the HPV infection still remains uncovered (Ainouze *et al.* 2018). In terms of TNF-α protective effects against HPV infection, it has been shown that the inhibition of this cytokine, to suppress TNF-α-mediated apoptosis and its antiproliferative efficacy, could be an essential phenomenon in HPV oncogenicity (James, Lee and Klingelhutz 2006; Scott *et al.* 2013). A recent study has illustrated a striking upregulation in TGF-β, IL-10, IL-6, IL-23 and IL-17 expression, and downregulation of interferon γ (IFN-γ) expression in ICC patients (Fig. 3). The expression of CCR6 and chemokine receptor CCL20 is shown to be elevated in the cervical tumor. Actually, the presence of CCL20 had a direct correlation with the number of Th17 in ICC (Yu, Lou and He 2015). Hence, immune responses should be repressed during cervical cancer progression. Furthermore, a significant fluctuation in T helper 17 (Th17)/Treg ratio in patients with ICC was indicated, which suggests an important role for the disturbance of Th17/Treg ratio in ICC occurrence (Zhang *et al.* 2011; Chen *et al.* 2013).

HPV-INDUCED OXIDATIVE STRESS

The wide-scale production of ROS could be harmful to the cellular genome, which is responsible for elevating oxidative DNA damages and consequently promoting related cancers (Wiseman and Halliwell 1996). According to the high metabolic activity of cancerous cells, oxidative stress (OS) is significantly more obvious in these cells, by which cellular proliferation gets enhanced (Szatrowski and Nathan 1991; Sosa *et al.* 2013). Similar to chronic inflammation, HPV oncogenesis could be accelerated by OS (De Marco 2013). HPV-motivated inflammation could also increase the neutrophil and macrophage-based production of ROS (Bartsch and Nair 2006; Ponath and Kaina 2017). HPV oncogenes, E6 and E7, play a pivotal role in this phenomenon. E6 decreases the amount of glutathione (GSH) and catalase activity, which boosts the production of ROS followed by extensive DNA damage (Fig. 4). However, E7 acts in the opposite way and decreases ROS production (Cruz-Gregorio *et al.* 2018). HPV E6 is not able to suppress p53 function by itself and this protein is not fully sufficient for the p53 inhibition process. Many factors are involved in E6-mediated suppression of p53 (De and Marcante 1993; Abdulkarim *et al.* 2002; Divya and Pillai 2006; Munagala *et al.* 2011) including OS. Oxidative stress activation is associated with the regulation of HPV RNAs expression and their splicing template (Mouret *et al.* 2005; De Marco *et al.* 2007). Additionally, HPV E7 is demonstrated to be correlated with the elevated persistence to the H_2O_2-mediated cell death, by coordinated modulation of cellular factors such as IL-18, cytochrome-C, Fas, Bad, Bcl-xL, increasing level of catalase activity, and NF-κB activation (Fig. 4) (Shim *et al.* 2008). Eventually, besides the well-known oncogenic roles of HPV E6 and E7, these oncoproteins seem to execute their cellular transformation activity by inducing OS in the HPV-infected cells.

RELATION Of microRNAs and HPV-Induced Inflammation

MicroRNAs (miRNAs), a member of small non-coding RNAs, could alter the translation patterns of messenger RNAs (mRNAs) (Ambros and Chen 2007). HPV oncoproteins (E6 and E7) can dysregulate the expression of miRNAs to expedite the oncogenic process of HPV-induced cancers. These miRNAs are reported to be involved in several signaling pathways, particularly the ones which result in the induction of chronic inflammation (Chiantore *et al.* 2016; Gao *et al.* 2016; Satapathy *et al.* 2017). It is believed miRNAs, which are involved in such pathways (including JAK/STAT3, MAPK, Wnt/β-catenin, NF-κB, TGF-β/Smad and PI3K/Akt/mTOR (Hou *et al.* 2015), might participate in the occurrence of chronic inflammation and subsequently the incidence of cancer. Several miRNAs are demonstrated to have a lot of roles in some inflammatory signaling pathways during cervical cancer (Table 1). However, the association of these miRNAs and the induction of chronic inflammation need to be investigated further.

Table 1. List of miRNA involved in the inflammatory signaling pathways through cervical cancer.

Signaling pathways	miRNA	Effect	Target	Cell line	Reference
β-catenin	miR-135a	upregulation	SIAH1	HeLa, CaSki, SiHa	(Leung *et al.* 2014)
NF-κB	miR-429	downregulation	IKK BETA	C33A, HeLa	(Fan *et al.* 2017)
	miR-130a	undetermined	PTEN	HeLa, CaSki	(Feng *et al.* 2016)
PI3K/Akt	miR-21	upregulation	undetermined	HeLa, SiHa	(Song *et al.* 2016)
	miR-181a	upregulation	undetermined	End1/E6E7	(Xu *et al.* 2016)
	miR-221	upregulation	PTEN	HeLa, SiHa	(Du *et al.* 2016)
	miR-491	downregulation	HTERT	HeLa, SiHa, MS751	(Zhao *et al.* 2015)
	miR-494	upregulation	PTEN	HeLa, CaSki, SiHa	(Yang *et al.* 2015)
	miR-196a	upregulation	FOXO1, P27KIP1	HeLa, CaSki, SiHa	(Hou *et al.* 2014)
MTOR	miR-634	downregulation	MTOR	undetermined	(Cong *et al.* 2016)
	miR-99amiR-99b	downregulation	MTOR	HeLa	(Wang *et al.* 2014)

AGING AND THE PROGRESSION OF HPV-INDUCED INFLAMMATION TO CANCER

The alteration of immune responses in old people is associated with their susceptibility to several diseases, and especially viral infections (Weiskopf, Weinberger and Grubeck-Loebenstein 2009). It has been shown that aging could have negative effects on the production of IL-2 and IFN-γ, and also the function of T cells and Th1 effectiveness (Thoman and Weigle 1982; Haynes *et al.* 1999; Tesar *et al.* 2006). Furthermore, aging could deteriorate innate immune responses, particularly the regulation of inflammatory cytokine production (Renshaw *et al.* 2002; Panda *et al.* 2010). The upregulation of well-known inflammatory cytokines, IL-1, IL-6 and TNF-α, is demonstrated to have a correlation with aging (Ershler 2003). In particular, the elevated level of IL-6 could give rise to the altered differentiation of Th17 (Bettelli *et al.* 2006). The prevalence of HPV infection among older women is shown to be approximately 1 in 16 in women aged between 57 and 85 years old (Lindau *et al.* 2008). Overall, it could be concluded that there is a probable association between HPV infection in old age and the occurrence of inflammation followed by an incidence of cervical cancer.

CONCLUSION

The association of inflammation and incidence of different types of cancers has been considered for several years. Cervical cancer, one of the most important cancers in females, is believed to be accelerated by inflammation. Regarding HPV as the main cause of this cancer, this virus might prepare an inflammatory circumstance, by which the process of cervical cancer get expedited (Subbaramaiah and Dannenberg 2007). HPV oncogenes (E5, E6 and E7) are demonstrated to be the principal suspects of the incidence of inflammation. The COX-PG pathway has been shown to play a critical role in the inflammation induced in HPV-infected cervical cells. Besides their common oncogenicity functions, HPV oncogenes agitate the expression of COX-2 and PGE2. These proteins are the central members of COX-PG pathway, by which the HPV-induced inflammation develops within the cervical cells. Furthermore, several pro-inflammatory cytokines, measured in the plasma of HPV-positive patients, are demonstrated to be increased and include IL-1 (α and β), IL-6 and TNF-α (Kemp *et al.* 2010).

Next to the preparation of the inflammatory condition, HPV oncogenes are correlated with the induction of OS and consequent DNA damage. OS activation could support the transformation activity of HPV E6 and E7 and also could precipitate the carcinogenesis of HPV (De Marco 2013).

The role of miRNAs in the induction of HPV-induced inflammation needs to be investigated in further studies. However, it is predicted that miRNAs, which are reported to be involved in the inflammation pathways (at least in the in-vitro situation), could also be suspected of being involved in the progression of cervical cancer. Aging, according to its effects on the elevation of pro-inflammatory cytokines, might have an association with the high chance of activation of inflammation followed by cervical cancer. However, the exact roles of aging and induction of HPV-induced inflammation need to be considered. Recently, it has been shown that HPV infection could effect the occurrence of autoimmunity with low ability (Donmez *et al.* 2019). This function might be associated with the inflammation induced by this virus.

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REFERENCES

Abdulkarim B, Sabri S, Deutsch E *et al.* Antiviral agent Cidofovir restores p53 function and enhances the radiosensitivity in HPV-associated cancers. *Oncogene* 2002;**21**:2334–46.

Adefuye A, Sales K. Regulation of inflammatory pathways in cancer and infectious disease of the cervix. *Scientifica (Cairo)* 2012;**2012**:548150.

Aggarwal BB, Shishodia S, Sandur SK *et al.* Inflammation and cancer: how hot is the link? *Biochem Pharmacol* 2006;**72**:1605–21.

Ainouze M, Rochefort P, Parroche P *et al.* Human papillomavirus type 16 antagonizes IRF6 regulation of IL-1β. *PLoS Pathog* 2018;**14**:e1007158.

Ambros V, Chen X. *The Regulation of Genes and Genomes by Small RNAs*. The Company of Biologists Ltd, 2007.

Arbyn M, Castellsagué X, de Sanjosé S *et al.* Worldwide burden of cervical cancer in 2008. *Ann Oncol* 2011;**22**:2675–86.

Balkwill F, Coussens LM. Cancer: an inflammatory link. *Nature* 2004;**431**:405–6.

Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 2001;**357**:539–45.

Bartsch H, Nair J. Chronic inflammation and oxidative stress in the genesis and perpetuation of cancer: role of lipid peroxidation, DNA damage, and repair. *Langenbecks Arch Surg* 2006;**391**:499–510.

Bettelli E, Carrier Y, Gao W *et al*. Reciprocal developmental pathways for the generation of pathogenic effector T(H)17 and regulatory T cells. *Nature* 2006;**441**:235–8.

Bouvard V, Baan R, Straif K *et al*. A review of human carcinogens—Part B: biological agents. *Lancet Oncol* 2009;**10**:321–2.

Brigati C, Noonan DM, Albini A *et al*. Tumors and inflammatory infiltrates: friends or foes? *Clin Exp Metastasis* 2002;**19**: 247–58.

Cao Y, Prescott SM. Many actions of cyclooxygenase-2 in cellular dynamics and in cancer. *J Cell Physiol* 2002;**190**:279–86.

Castle PE, Hillier SL, Rabe LK *et al*. An association of cervical inflammation with high-grade cervical neoplasia in women infected with oncogenic human papillomavirus (HPV). *Cancer Epidemiol Biomarkers Prev* 2001;**10**:1021–7.

Catarino R, Petignat P, Dongui G *et al*. Cervical cancer screening in developing countries at a crossroad: Emerging technologies and policy choices. *World J Clin Oncol* 2015;**6**:281.

Chang YH, Yu CW, Lai LC *et al*. Up-regulation of interleukin-17 expression by human papillomavirus type 16 E6 in nonsmall cell lung cancer. *Cancer* 2010;**116**:4800–9.

Chen Z, Ding J, Pang N *et al*. The Th17/Treg balance and the expression of related cytokines in Uygur cervical cancer patients. *Diagn Pathol* 2013;**8**:61.

Chiantore MV, Mangino G, Iuliano M *et al*. Human papillomavirus E6 and E7 oncoproteins affect the expression of cancer-related microRNAs: additional evidence in HPV-induced tumorigenesis. *J Cancer Res Clin Oncol* 2016;**142**:1751–63.

Coleman RA, Smith WL, Narumiya S. International Union of Pharmacology classification of prostanoid receptors: properties, distribution, and structure of the receptors and their subtypes. *Pharmacol Rev* 1994;**46**:205–29.

Cong J, Liu R, Wang X *et al*. MiR-634 decreases cell proliferation and induces apoptosis by targeting mTOR signaling pathway in cervical cancer cells. *Artif Cells Nanomed Biotechnol* 2016;**44**:1694–701.

Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002;**420**:860–7.

Cruz-Gregorio A, Manzo-Merino J, Gonzaléz-García MC *et al*. Human papillomavirus types 16 and 18 early-expressed proteins differentially modulate the cellular redox state and DNA damage. *Int J Biol Sci* 2018;**14**:21–35.

da Silva Cardeal LB, Brohem CA, Corrêa TC *et al*. Higher expression and activity of metalloproteinases in human cervical carcinoma cell lines is associated with HPV presence. *Biochem Cell Biol* 2006;**84**:713–9.

De Marco F. Oxidative stress and HPV carcinogenesis. *Viruses* 2013;**5**:708–31.

De Marco F, Perluigi M, Foppoli C *et al*. UVB irradiation down-regulates HPV-16 RNA expression: implications for malignant progression of transformed cells. *Virus Res* 2007;**130**:249–59.

De FM, Marcante M. HPV-16 E6-E7 differential transcription induced in Siha cervical cancer cell line by interferons. *J Biol Regul Homeost Agents* 1993;**7**:15–21.

Divya CS, Pillai MR. Antitumor action of curcumin in human papillomavirus associated cells involves downregulation of viral oncogenes, prevention of NFkB and AP-1 translocation, and modulation of apoptosis. *Mol Carcinog* 2006;**45**:320–32.

Donmez HG, Tanacan A, Unal C *et al*. Human papillomavirus infection and autoimmune disorders: a tertiary center experience. *Pathog Dis* 2019;**77**:ftz028.

Doorbar J, Quint W, Banks L *et al*. The biology and life-cycle of human papillomaviruses. *Vaccine* 2012;**30**:F55–70.

Du J, Wang L, Li C *et al*. MicroRNA-221 targets PTEN to reduce the sensitivity of cervical cancer cells to gefitinib through the PI3K/Akt signaling pathway. *Tumor Biol* 2016;**37**:3939–47.

Dueñas-González A, Lizano M, Candelaria M *et al*. Epigenetics of cervical cancer. An overview and therapeutic perspectives. *Mol Cancer* 2005;**4**:38.

Dyson N, Howley PM, Münger K *et al*. The human papilloma virus-16 E7 oncoprotein is able to bind to the retinoblastoma gene product. *Science* 1989;**243**:934–7.

Ershler WB. Biological interactions of aging and anemia: a focus on cytokines. *J Am Geriatr Soc* 2003;**51**:S18–21.

Fan JY, Fan YJ, Wang XL *et al*. miR-429 is involved in regulation of NF-κBactivity by targeting IKKβ and suppresses oncogenic activity in cervical cancer cells. *FEBS Lett* 2017;**591**:118–28.

Feng Y, Zhou S, Li G *et al*. Nuclear factor-κB–dependent microRNA-130a upregulation promotes cervical cancer cell growth by targeting phosphatase and tensin homolog. *Arch Biochem Biophys* 2016;**598**:57–65.

Ferrandina G, Lauriola L, Zannoni GF *et al*. Expression of cyclooxygenase-2 (COX-2) in tumour and stroma compartments in cervical cancer: clinical implications. *Br J Cancer* 2002;**87**:1145–52.

Gao D, Zhang Y, Zhu M *et al*. miRNA expression profiles of HPV-infected patients with cervical cancer in the Uyghur population in China. *PLoS One* 2016;**11**:e0164701.

Genther Williams SM, Disbrow GL, Schlegel R *et al*. Requirement of epidermal growth factor receptor for hyperplasia induced by E5, a high-risk human papillomavirus oncogene. *Cancer Res* 2005;**65**:6534–42.

Georgescu SR, Mitran CI, Mitran MI *et al*. New insights in the pathogenesis of HPV infection and the associated carcinogenic processes: the role of chronic inflammation and oxidative stress. *J Immunol Res* 2018;**2018**:5315816.

Getahun F, Mazengia F, Abuhay M *et al*. Comprehensive knowledge about cervical cancer is low among women in Northwest Ethiopia. *BMC cancer* 2013;**13**:2.

Gross G, Pfister H. Role of human papillomavirus in penile cancer, penile intraepithelial squamous cell neoplasias and in genital warts. *Med Microbiol Immunol* 2004;**193**:35–44.

Hammes LS, Tekmal RR, Naud P *et al*. Macrophages, inflammation and risk of cervical intraepithelial neoplasia (CIN) progression—clinicopathological correlation. *Gynecol Oncol* 2007;**105**:157–65.

Hatterschide J, Bohidar AE, Grace M *et al*. PTPN14 degradation by high-risk human papillomavirus E7 limits keratinocyte differentiation and contributes to HPV-mediated oncogenesis. *Proc Natl Acad Sci USA* 2019;**116**:7033–42.

Hawes SE, Kiviat NB. *Are Genital Infections and Inflammation Cofactors in the Pathogenesis of Invasive Cervical Cancer?* Oxford University Press, 2002.

Haynes L, Linton PJ, Eaton SM *et al*. Interleukin 2, but not other common γ chain–binding cytokines, can reverse the defect in generation of CD4 effector T cells from naive T cells of aged mice. *J Exp Med* 1999;**190**:1013–24.

Hemmat N, Baghi HB. Human papillomavirus E5 protein, the undercover culprit of tumorigenesis. *Infect Agent Cancer* 2018;**13**:31.

Hemmat N, Ebadi A, Badalzadeh R *et al*. Viral infection and atherosclerosis. *Eur J Clin Microbiol Infect Dis* 2018;**37**:2225–33.
Herberhold S, Hellmich M, Panning M *et al*. Human polyomavirus and human papillomavirus prevalence and viral load in non-malignant tonsillar tissue and tonsillar carcinoma. *Med Microbiol Immunol* 2017;**206**:93–103.
Heusinkveld M, de Vos van Steenwijk PJ, Goedemans R *et al*. M2 macrophages induced by prostaglandin E2 and IL-6 from cervical carcinoma are switched to activated M1 macrophages by CD4+ Th1 cells. *J Immunol* 2011;**187**:1157–65.
Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *FASEB J* 2008;**22**:383–90.
Hou T, Ou J, Zhao X *et al*. MicroRNA-196a promotes cervical cancer proliferation through the regulation of FOXO1 and p27(Kip1). *Br J Cancer* 2014;**110**:1260–8.
Hou X, Yang F, Liu W *et al*. Signaling pathways that facili-tate chronic inflammation-induced carcinogenesis. *J Cell Signal* 2015;**1**:9.
Hwang SG, Lee D, Kim J *et al*. Human papillomavirus type 16 E7 binds to E2F1 and activates E2F1-driven transcription in a retinoblastoma protein-independent manner. *J Biol Chem* 2002;**277**:2923–30.
Iuliano M, Mangino G, Chiantore MV *et al*. Human papillomavirus E6 and E7 oncoproteins affect the cell microenvironment by classical secretion and extracellular vesicles delivery of inflammatory mediators. *Cytokine* 2018;**106**:182–9.
James MA, Lee JH, Klingelhutz AJ. Human papillomavirus type 16 E6 activates NF-κB, induces cIAP-2 expression, and protects against apoptosis in a PDZ binding motif-dependent manner. *J Virol* 2006;**80**:5301–7.
Kemp TJ, Hildesheim A, García-Piñeres A *et al*. Elevated systemic levels of inflammatory cytokines in older women with persistent cervical human papillomavirus infection. *Cancer Epidemiol Biomarkers Prev* 2010;**19**:1954–9.
Kim GE, Kim YB, Cho NH *et al*. Synchronous coexpression of epidermal growth factor receptor and cyclooxygenase-2 in carcinomas of the uterine cervix: a potential predictor of poor survival. *Clin Cancer Res* 2004;**10**:1366–74.
Kim MK, Kim HS, Kim SH *et al*. Human papillomavirus type 16 E5 oncoprotein as a new target for cervical cancer treatment. *Biochem Pharmacol* 2010;**80**:1930–5.
Kim SH, Oh JM, No JH *et al*. Involvement of NF-κB and AP-1 in COX-2 upregulation by human papillomavirus 16 E5 oncoprotein. *Carcinogenesis* 2009;**30**:753–7.
Kiyono T, Hiraiwa A, Fujita M *et al*. Binding of high-risk human papillomavirus E6 oncoproteins to the human homologue of the Drosophila discs large tumor suppressor protein. *Proc Natl Acad Sci USA* 1997;**94**:11612–6.
Kolaczkowska E, Grzybek W, van Rooijen N *et al*. Neutrophil elastase activity compensates for a genetic lack of matrix metalloproteinase-9 (MMP-9) in leukocyte infiltration in a model of experimental peritonitis. *J Leukoc Biol* 2009;**85**:374–81.
Kulkarni S, Rader JS, Zhang F *et al*. Cyclooxygenase-2 is overexpressed in human cervical cancer. *Clin Cancer Res* 2001;**7**:429–34.
Kuper H, Adami HO, Trichopoulos D. Infections as a major preventable cause of human cancer. *J Intern Med* 2000;**248**:171–83.
Lee SS, Weiss RS, Javier RT. Binding of human virus oncoproteins to hDlg/SAP97, a mammalian homolog of the Drosophila discs large tumor suppressor protein. *Proc Natl Acad Sci USA* 1997;**94**:6670–5.
Leung CO, Deng W, Ye TM *et al*. miR-135a leads to cervical cancer cell transformation through regulation of β-catenin via a SIAH1-dependent ubiquitin proteosomal pathway. *Carcinogenesis* 2014;**35**:1931–40.
Libra M, Scalisi A, Vella N *et al*. Uterine cervical carcinoma: role of matrix metalloproteinases (review). *Int J Oncol* 2009;**34**:897–903.
Lindau ST, Drum ML, Gaumer E *et al*. Prevalence of high-risk human papillomavirus among older women. *Obstet Gynecol* 2008;**112**:979.
Liu N, Huang J, Sun S *et al*. Expression of matrix metalloproteinase-9, cyclooxygenase-2 and vascular endothelial growth factor are increased in gastrointestinal stromal tumors. *Int J Clin Exp Med* 2015;**8**:6495–501.
Liu X, Ma X, Lei Z *et al*. Chronic inflammation-related HPV: a driving force speeds oropharyngeal carcinogenesis. *PLoS One* 2015;**10**:e0133681.
Lv Q, Wu K, Liu F *et al*. Interleukin-17A and heparanase promote angiogenesis and cell proliferation and invasion in cervical cancer. *Int J Oncol*. 2018;**53**:1809–17.
Maeda H, Akaike T. Nitric oxide and oxygen radicals in infection, inflammation, and cancer. *Biochemistry (Mosc)* 1998;**63**:854–65.
Mantovani A, Allavena P, Sica A *et al*. Cancer-related inflammation. *Nature* 2008;**454**:436–44.
Mathur SP, Mathur RS, Rust PF *et al*. Human papilloma virus (HPV)-E6/E7 and epidermal growth factor receptor (EGF-R) protein levels in cervical cancer and cervical intraepithelial neoplasia (CIN). *Am J Reprod Immunol* 2001;**46**:280–7.
McLaughlin-Drubin ME, Huh KW, Munger K. Human papillomavirus type 16 E7 oncoprotein associates with E2F6. *J Virol* 2008;**82**:8695–705.
Mittal S, Banks L. Molecular mechanisms underlying human papillomavirus E6 and E7 oncoprotein-induced cell transformation. *Mutat Res Rev Mutat Res* 2017;**772**:23–35.
Mouret S, Sauvaigo S, Peinnequin A *et al*. E6$*$ oncoprotein expression of human papillomavirus type-16 determines different ultraviolet sensitivity related to glutathione and glutathione peroxidase antioxidant defence. *Exp Dermatol* 2005;**14**:401–10.
Munagala R, Kausar H, Munjal C *et al*. Withaferin A induces p53-dependent apoptosis by repression of HPV oncogenes and upregulation of tumor suppressor proteins in human cervical cancer cells. *Carcinogenesis* 2011;**32**:1697–705.
Munn LL. Cancer and inflammation. *Wiley Interdiscip Rev Syst Biol Med* 2017;**9**:e1370.
Narumiya S, FitzGerald GA. Genetic and pharmacological analysis of prostanoid receptor function. *J Clin Invest* 2001;**108**:25–30.
Ni J, Wang M, Wang M *et al*. CCND1 G870A polymorphism and cervical cancer risk: a case–control study and meta-analysis. *J Cancer Res Clin Oncol* 2011;**137**:489–94.
Niebler M, Qian X, Höfler D *et al*. Post-translational control of IL-1β via the human papillomavirus type 16 E6 oncoprotein: a novel mechanism of innate immune escape mediated by the E3-ubiquitin ligase E6-AP and p53. *PLoS Pathog* 2013;**9**:e1003536.
Nuovo GJ, MacConnell PB, Simsir A *et al*. Correlation of the in situ detection of polymerase chian reaction-amplified metalloproteinase complementary DNAs and their inhibitors with prognosis in cervical carcinoma. *Cancer Res* 1995;**55**:267–75.
Panda A, Qian F, Mohanty S *et al*. Age-associated decrease in TLR function in primary human dendritic cells predicts influenza vaccine response. *J Immunol* 2010;**184**:2518–27.

Peghini BC, Abdalla DR, Barcelos AC *et al.* Local cytokine profiles of patients with cervical intraepithelial and invasive neoplasia. *Hum Immunol* 2012;**73**:920–6.

Pillai MR, Sreevidya S, Pollock BH *et al.* Polymorphism at codon 72 of p53, human papillomavirus, and cervical cancer in South India. *J Cancer Res Clin Oncol* 2002;**128**:627–31.

Ponath V, Kaina B. Death of monocytes through oxidative burst of macrophages and neutrophils: killing in trans. *PLoS One* 2017;**12**:e0170347.

Proctor MJ, Talwar D, Balmar SM *et al.* The relationship between the presence and site of cancer, an inflammation-based prognostic score and biochemical parameters. Initial results of the Glasgow Inflammation Outcome study. *Br J Cancer* 2010;**103**:870.

Read SA, Douglas MW. Virus induced inflammation and cancer development. *Cancer Lett* 2014;**345**:174–81.

Renshaw M, Rockwell J, Engleman C *et al.* Cutting edge: impaired Toll-like receptor expression and function in aging. *J Immunol* 2002;**169**:4697–701.

Sales KJ, Katz AA, Davis M *et al.* Cyclooxygenase-2 expression and prostaglandin E2 synthesis are up-regulated in carcinomas of the cervix: a possible autocrine/paracrine regulation of neoplastic cell function via EP2/EP4 receptors. *J Clin Endocrinol Metab* 2001;**86**:2243–9.

Sales KJ, Katz AA, Howard B *et al.* Cyclooxygenase-1 is up-regulated in cervical carcinomas: autocrine/paracrine regulation of cyclooxygenase-2, prostaglandin e receptors, and angiogenic factors by cyclooxygenase-1. *Cancer Res* 2002;**62**:424–32.

Sarkar S, Alam N, Chakraborty J *et al.* Human papilloma virus (HPV) infection leads to the development of head and neck lesions but offers better prognosis in malignant Indian patients. *Med Microbiol Immunol* 2017;**206**:267–76.

Satapathy S, Batra J, Jeet V *et al.* MicroRNAs in HPV associated cancers: small players with big consequences. *Expert Rev Mol Diagn* 2017;**17**:711–22.

Schiffman M, Castle PE, Jeronimo J *et al.* Human papillomavirus and cervical cancer. *Lancet* 2007;**370**:890–907.

Schoppmann SF, Birner P, Stöckl J *et al.* Tumor-associated macrophages express lymphatic endothelial growth factors and are related to peritumoral lymphangiogenesis. *Am J Pathol* 2002;**161**:947–56.

Schwebke JR, Zajackowski ME. Effect of concurrent lower genital tract infections on cervical cancer screening. *Genitourin Med* 1997;**73**:383–6.

Scott ME, Shvetsov YB, Thompson PJ *et al.* Cervical cytokines and clearance of incident human papillomavirus infection: Hawaii HPV cohort study. *Int J Cancer* 2013;**133**:1187–96.

Senba M, Buziba N, Mori N *et al.* Human papillomavirus infection induces NF-κB activation in cervical cancer: a comparison with penile cancer. *Oncol lett* 2011;**2**:65–68.

Senba M, Mori N. Mechanisms of virus immune evasion lead to development from chronic inflammation to cancer formation associated with human papillomavirus infection. *Oncol Rev* 2012;**6**:e17.

Shacter E, Weitzman SA. Chronic inflammation and cancer. *Oncology (Williston Park)* 2002;**16**:217–26.

Shim JH, Kim KH, Cho YS *et al.* Protective effect of oxidative stress in HaCaT keratinocytes expressing E7 oncogene. *Amino Acids* 2008;**34**:135–41.

Sivula A, Talvensaari-Mattila A, Lundin J *et al.* Association of cyclooxygenase-2 and matrix metalloproteinase-2 expression in human breast cancer. *Breast Cancer Res Treat* 2005;**89**:215–20.

Sobolewski C, Cerella C, Dicato M *et al.* The role of cyclooxygenase-2 in cell proliferation and cell death in human malignancies. *Int J Cell Biol* 2010;**2010**:215158.

Song L, Liu S, Zhang L *et al.* MiR-21 modulates radiosensitivity of cervical cancer through inhibiting autophagy via the PTEN/Akt/HIF-1α feedback loop and the Akt-mTOR signaling pathway. *Tumor Biol* 2016;**37**:12161–8.

Sosa V, Moliné T, Somoza R *et al.* Oxidative stress and cancer: an overview. *Ageing Res Rev* 2013;**12**:376–90.

Subbaramaiah K, Dannenberg AJ. Cyclooxygenase-2 transcription is regulated by human papillomavirus 16 E6 and E7 oncoproteins: evidence of a corepressor/coactivator exchange. *Cancer Res* 2007;**67**:3976–85.

Szalmás A, Tomaić V, Basukala O *et al.* The PTPN14 tumor suppressor is a degradation target of human papillomavirus E7. *J Virol* 2017;**91**:e00057–17.

Szatrowski TP, Nathan CF. Production of large amounts of hydrogen peroxide by human tumor cells. *Cancer Res* 1991;**51**:794–8.

Tesar BM, Walker WE, Unternaehreret J *et al.* Nurine myeloid dendritic cell-dependent toll-like receptor immunity is preserved with aging. *Aging Cell* 2006;**5**:473–86.

Thoman ML, Weigle WO. Cell-mediated immunity in aged mice: an underlying lesion in IL 2 synthesis. *J Immunol* 1982;**128**:2358–61.

Tommasino M. The human papillomavirus family and its role in carcinogenesis. In: *Seminars in Cancer Biology*. Elsevier, 2014, 13-21.

Tsung K, Dolan JP, Tsung YL *et al.* Macrophages as effector cells in interleukin 12-induced T cell-dependent tumor rejection. *Cancer Res* 2002;**62**:5069–75.

Wahl LM, Kleinman HK. *Tumor-Associated Macrophages as Targets for Cancer Therapy*. Oxford University Press, 1998.

Wallace NA, Galloway DA. Novel Functions of the Human Papillomavirus E6 Oncoproteins. *Annu Rev Virol* 2015;**2**:403–23.

Wang L, Chang L, Li Z *et al.* miR-99a and-99b inhibit cervical cancer cell proliferation and invasion by targeting mTOR signaling pathway. *Med Oncol* 2014;**31**:934.

Weiskopf D, Weinberger B, Grubeck-Loebenstein B. The aging of the immune system. *Transpl Int* 2009;**22**:1041–50.

White EA, Munger K, Howley PM. High-Risk Human Papillomavirus E7 Proteins Target PTPN14 for Degradation. *MBio* 2016;**7**:e01530–16.

Wiseman H, Halliwell B. Damage to DNA by reactive oxygen and nitrogen species: role in inflammatory disease and progression to cancer. *Biochem J* 1996;**313**(Pt 1):17–29.

World Health Organization. *Cervical Cancer*. http://www.who.int/cancer/prevention/diagnosis-screening/cervical-cancer/en/ (12 September 2018, date last accessed).

Xu H, Zhu J, Hu C *et al.* Inhibition of microRNA-181a may suppress proliferation and invasion and promote apoptosis of cervical cancer cells through the PTEN/Akt/FOXO1 pathway. *J Physiol Biochem* 2016;**72**:721–32.

Yamanishi Y, Boyle DL, Rosengren S *et al.* Regional analysis of p53 mutations in rheumatoid arthritis synovium. *Proc Natl Acad Sci USA* 2002;**99**:10025–30.

Yang YK, Xi WY, Xi RX *et al.* MicroRNA-494 promotes cervical cancer proliferation through the regulation of PTEN. *Oncol Rep* 2015;**33**:2393–401.

Yeung YT, Aziz F, Guerrero-Castilla A *et al.* Signaling pathways in inflammation and anti-inflammatory therapies. *Curr Pharm Des* 2018;**24**:1449–84.

Yu Q, Lou XM, He Y. Preferential recruitment of Th17 cells to cervical cancer via CCR6-CCL20 pathway. *PLoS One* 2015;**10**:e0120855.

Yun HY, Kim MW, Lee HS *et al*. Structural basis for recognition of the tumor suppressor protein PTPN14 by the oncoprotein E7 of human papillomavirus. *PLoS Biol* 2019;**17**:e3000367.

Zhang Y, Ma D, Zhang Y *et al*. The imbalance of Th17/Treg in patients with uterine cervical cancer. *Clin Chim Acta* 2011;**412**:894–900.

Zhao Q, Zhai YX, Liu HQ *et al*. MicroRNA-491-5p suppresses cervical cancer cell growth by targeting hTERT. *Oncol Rep* 2015;**34**:979–86.