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Review: An Overview on the Pathogenesis of Cervical Cancer

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Abstract

Cervical cancer (CC) is one of the most common and severe malignant gynaecological tumours affecting women worldwide. It remains a global health burden especially in low- and middle-income countries. In Malaysia, CC is classified as the second most common cancer affecting women following breast cancer. The survival rate of CC in Malaysia is the lowest in Malays, followed by Indians and Chinese. This indicates several factors including age and ethnicity may significantly affect the survival rate among CC patients. Persisting infection with high-risk subtypes of the human papilloma virus (HPV) is the main aetiologic factor for the development of CC in addition to other factors that are involved in the pathogenesis of the disease. Genetic modifications such as loss of heterozygosity, mutation and amplification as well as epigenetic mechanisms such as DNA methylation and histone acetylation have been reported to contribute to CC. Besides, local microbiota and environmental factors including smoking, diet and oxidative stress have been associated with the development and progression of CC. Hormonal dysregulation in CC patients and animal models suggest the role of hormones in cervical carcinogenesis. Increased understanding of CC offers the hope to limit the burden of disease and effective prevention programmes is particularly important as the disease is highly preventable. This article aims to discuss and provide a comprehensive overview on the pathogenesis of CC.

Keywords: Cervical cancer, pathogenesis, aetiology, carcinogenesis, HPV

Introduction

Cervical cancer (CC) is the fourth female reproductive tract-associated cancer affecting women worldwide despite its highly preventable nature due to the insufficient screening protocols particularly in low- and middle-income countries (1,2). Around 991 women died of CC in year 2020 in Malaysia, accounting for 3.4% of all cancer deaths (3).

Endocervix and exocervix are the two parts of the cervix lined with glandular cells and squamous cells respectively. The region where the two cell types are located is known as transformation zone, where most CC originate from this zone. CC describes tumours that grow at the lower end of the uterus. It can be divided into two histological types, adenocarcinoma which originates from glandular cells secreting mucus, accounting for 25% of all CC and the more common type, squamous cell carcinoma (SCC) which originates from squamous cells, accounting for approximately 70% of all cases (2,4).

During the early stages of cancer, rarely patients exhibit symptoms however as the cancer progresses, patients manifest symptoms such as post-coital or abnormal vaginal bleeding, profuse malodorous vaginal discharge and pelvic pain.

Human papilloma virus (HPV), particularly the HPV-16/18 strains are the most common cause for CC. Risk factors associated with acquisition of HPV infection such as multiple sexual partners and/or severely impaired immune responses to HPV infection such as individuals with immunodeficiency disorders increases the risk of developing CC (4). This review aimed to discuss updated knowledge on the pathogenesis of CC with insights into the aetiology and progression of the disease.

Pathogenesis of cervical cancer

Genetics

The accumulation of genetic and epigenetic alterations contributes to carcinogenesis. Mutations, deletions, copy-number aberrations, and chromosomal rearrangements are genetic alterations which may result in loss or gain of function in the development of CC.

Loss of heterozygosity (LOH)

LOH is important in tumorigenesis and present as a prognostic factor in numerous malignant neoplasms (5). Several chromosomal regions have been identified to be associated with LOH (5–11). LOH at the tumour suppressor genes contributes to carcinogenesis due to the loss of gene function (5–9). For instance, LOH of the tumour suppressor retinoblastoma gene (Rb) at intron 1 and/or 17 reported in 63% CC patients (7). 3p21 has been identified as a target for LOH in CC with high allelic deletions, suggesting that tumour suppressor genes may be present in this region. The Ras effector gene RASSF1which is located at 3p21.3 may also act as a tumour suppressor gene. Concomitant RASSF1A hypermethylation and LOH at 3p21 in about 67% of CC samples suggests both hypermethylation and LOH are involved in the tumour suppressor gene inactivation (6).

Table 1: Loss of heterozygosity associated with cervical cancer

Role	Gene	Chromosomal region	Reference
Tumour suppressor gene	RASSF1A	3p21.3	(6)
	FHIT	3p14.2	
	Rb	13q	(7)
	-	3p12-14.2, 3p21.3-pter, 6q22-25.2	(8)
	-	1p31, 1p36, 1q25	(9)
	-	3p, 18q21.3, 11p15.5	(5)
Immune response gene	HLA	6p21.3	(10)
	HLA II	6p21.21, 6p21.31-21.33	(11)

Mutation

Mutations of tumour suppressor genes such as p53, Rb, PTEN and LKB1, and oncogenes such as PIK3CA, KRAS, EGRF and ERBB2 have been reported in CC. Both tumour suppressor p53 and Rb mutations occur very rarely in initial stages of CC, despite in other cancers (12). Mutation or deletion of p53 gene was found in more than 50% of human tumours. Mutations that result in p53 deactivation usually take place in the central DNA-binding domain, affecting the protein-DNA binding resulting in gene repression (13). Single base-pair substitutions are the most frequently observed p53 gene mutations, mainly between codons 130 and 290 (14). Loss of PTEN function may contribute to cervical carcinogenesis, but to a lesser extent as rare PTEN mutations have been reported (15). However, PTEN may have a role in CC progression and prognosis as suggested by the increased gene mutation rate with tumour progression (16). LKB1 also plays a role in CC progression from HPV-induced dysplasia to invasive cancer in which single nucleotide substitutions or microdeletions were reported in at least 20% of CC (17).

The common mutation rates found in CC can be ranked in the order of PIK3CA, KRAS and EGFR (18,19). As one of the frequently implicated genes in human cancer including CC, PIK3CA encodes p110α protein, the catalytic subunit of phosphoinositide 3-kinase (PI3K) enzyme which plays a pivotal role in P13K pathway for numerous cellular activities.

Mutation of PIK3CA is the most frequently found genetic alteration associated with CC, accounting for 13-36% of CC (20). KRAS protein acts as a GTPase and it regulates cell differentiation, proliferation and survival in CC. ERBB2 mutations have been reported in CC and are associated with poorer prognosis compared to those with wild-type or PIK3CA-mutated invasive CC (21).

Table 2: Mutations associated with cervical cancer

Role	Gene	Type of Mutation	Reference
Tumour suppressor gene	p53	Deletion, substitution	(12,13)
	Rb	Deletion, substitution	(15,22)
	PTEN	Deletion, substitution	(23)
	LKB1	Deletion, substitution	(17)
Oncogene	PIK3CA	Substitution	(19,24,25)
	KRAS	Substitution	(19)
	EGRF	Substitution	(19)
	ERBB2	Substitution	(24)

Amplification

Several genes have been identified to be amplified in CC. Amplification of PIK3CA occurs at a higher rate of 20.3% in adeno/adenosquamous carcinomas compared with SCC (1.4%) (25). EGFR is another gene found to be amplified in which its amplification in 10.2% of SCC was associated with shorter overall survival (19). The amplification rate of ERBB2 amplification reported as 3.8% (21). Vascular endothelial growth factor (VEGF) is a chief mediator of angiogenesis which stimulates the formation of new blood vessels, contributing to tumorigenesis and cancer progression. It has been reported to be overexpressed in 63.07% of patients with cervical carcinoma compared with controls and is associated with poor prognosis (26).

Epigenetics

Epigenetics plays a crucial role in the carcinogenesis and metastasis of CC. DNA methylation and histone acetylation are the two most well-studied epigenetic mechanisms involved in carcinogenesis due to the close interplay between the both processes (27,28). Non-coding RNAs, in particular microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) have also been identified as epigenetic mechanism contributing to tumorigenesis.

DNA methylation

DNA methylation of CpG around the promoters is associated with decreased gene expression while low levels of DNA methylation around the promoters and high levels of gene body methylation have positive correlation with gene expression (29). Compared with HPV-negative squamous carcinoma cell lines, the HPV-positive cell lines show a higher DNA methylation in genic and LINE-1 regions (30). E6 and E7 are the most important HPV oncogenes encoding the oncoproteins E6 and E7 that contribute to host cell transformation in CC. The oncoproteins modulates epigenetic mechanisms including aberrant DNA methylations in host cells (31).

The expression of maintenance methyltransferase DNMT1 is regulated by the complex conformed by the tumour suppressor p53, transcription factor Specificity Protein 1 (SP1), and the Histone Deacetylases (HDAC) 1 and 6 (32). Inactivation of tumour suppressor p53 gene by E6 protein contributes to upregulation of DNMT1, leading to DNA hypermethylation which is associated with cervical carcinogenesis. Repression of p53 by E6 protein occurs through the ubiquitin pathway with the involvement of the cellular protein E6-associated protein (E6AP) (33). Direct binding of E7 oncoprotein to DNMT1 results in upregulation of methyltransferase enzyme activity and enzyme stabilization. Hypermethylation of tumour suppressor cyclin A1 (CCNA1) promoter by E7-DNMT1 complex is strongly correlated with HPV-associated CC (34). Interaction of E7 with transcription factors may also direct DNMT1 to result in gene silencing (32,34). Hypermethylation in a distant regulatory CpG island by E7 oncoprotein results in a significant downregulation of the major histocompatibility complex (MHC-I) α-subunit HLA-E (34). Hypermethylation of promoter directed by E7 results in a downregulation of

chemokine CXCL14, an important immune evasion mechanism that enables persistent HPV infection (34). The cell adhesion molecule E-cadherin was found to be downregulated in CC (35). Augmentation of DNMT amount and activity by E7 protein results in decreased gene expression of cellular E-cadherin (36). Hypermethylation of CpG islands in promoter regions of CDH1 encoding E-cadherin is commonly reported in invasive CC (37).

Hypomethylation in promoter genes have also been reported. Hypomethylation in the gene promoter/exon 1 of STK31 in the HPV16/18-positive cell lines HeLa, SiHa and CaSki CC cell lines was reported by Yin et al (38). Overexpression of collagen XVII encoded by COL17A1 in CC is associated with increased local dissemination. Hypomethylation of COL17A1 promoter is correlated with elevated gene expression in CC and other epithelial cancers (39).

Histones modifications

The increased expression of HDACs1 and HDACs2 identified in cervical dysplasia and invasive carcinoma by gene silencing mechanism through removal of acetyl group were reported (40). E6 and E7 HPV oncoproteins can target cellular proteins including HDACs and HATs and affect cell growth and proliferation through the alteration of the chromatin structure (27). Binding of HPV-E7 protein from HPV high-risk types to HDACs occurs through the intermediary protein Mi2β that can modify the structure of chromatin via histone deacetylation and ATP-dependent nucleosome repositioning (41). Interaction between HPV-16 E6 protein with p300/CBP co-activator protein results in a significant decrease in the transcriptional activity of p300 and may contribute to cellular transformation (42).

Studies on changes in histones at a global level have reported that there is a loss of monoacetylated and trimethylated forms of histone H4 associated with hypomethylation of DNA repetitive sequences in cancer cells. A significant association between modifications of histone H3 (phosphorylation and acetylation) with progression of CC from cervical intraepithelial neoplasia I (CIN I) to CIN II and CIN III has been reported (27).

Transformation of the cervical cells infected by HPV may also involve in the activation of canonical Wnt signalling pathways. Epigenetic silencing of secreted Wnt antagonists has been observed in various cancers. Another study have demonstrated histone deacetylation in cervical carcinoma HeLa cell line has resulted in transcriptional repression of DICKKOPF-1 (DKK-1) encoding a secreted Wnt antagonist (43).

Non-coding RNAs

Based on a study reported, 29 miRNAs were differentially expressed in cervical tumour tissues, among which upregulation involved 13 miRNAs while 16 miRNAs were downregulated (44). The possible epigenetic mechanisms associated with abnormal miRNA expression related to the pathogenesis of CC include DNA methylation and histone deacetylation. Evidence has been found for methylation-mediated transcriptional repression of miR-149, miR-20 3, miR-375, miR-432, miR-1286, miR-641, miR-1290, miR-1287, and miR-95 in cervical carcinogenesis (45–47). Interaction between the viral oncoproteins, HPV-16 E2 and E6 with RNA results in pre-RNA splicing suppression and affects the gene expression (48). Presence of HPV-16 E6 protein suppresses the expression of tumour suppressive miR-23b through DNA methylation of the host gene C9orf3. c-MET gene which is implicated in several cancers is one of the target genes of miR-23. c-MET gene overexpression was observed in solid tumours including uterine cervix carcinomas (49). B Muralidhar et al reported that more than 50% of advanced cervical SCC demonstrated a chromosome 5p gain with miRNA processor Drosha as the most significantly upregulated transcript following the gain. Drosha affects the expression of cancer-associated miRNAs that may be involved in the regulation of protein-coding genes and serves as an oncogene in cervical SCC (50,51).

HPV viral proteins may modulate multiple lncRNAs in host cells. The lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) acts as a tumour oncogene in CC. MALAT1 is overexpressed in solid tumour and is associated with proliferation, apoptosis, migration and invasion of tumour cells (52). In earlier stages of CC, there is a downregulation of lncRNA HOX transcript antisense RNA (HOTAIR) expression but upregulation of HOTAIR was observed in HPV-16 positive cervical carcinomas and HPV-positive cell lines with higher HPV-16 E7 protein expression (32). Increased HOTAIR levels in patients with CC is associated with poor prognosis (53). Thymopoietin pseudogene 2 (TMPOP2) or lncRNA-EBIC which was reported to be upregulated in human CC tissues and cell lines interacts with the transcription repressor EZH2 to repress E-cadherin expression in cancer cells (54). Several lncRNAs act as tumour suppressors in CC. For instance, downregulation of lncRNAs growth arrest-specific transcript 5 (GAS5), IDH1-AS1, lnc-CCDST, Maternally Expressed Gene 3 (MEG3), STXBP5-AS1, tumour suppressor candidate 8 (TUSC8) and XLOC_010588 is associated with cervical carcinogenesis (55).

Microbiota

Local microbiota plays an important role in persistent HPV infection and cancer progression (56). The microbiome of a healthy female genital tract consists mainly of *Lactobacillus* species, providing protection against exogenous bacteria and virus by creating a low pH environment (57). Dysbiosis of the microbiome attributed to factors such as hormonal levels, hygiene habits, and sexually transmitted diseases (STD) may favour the outgrowth of certain groups of bacteria, affect the overall health of an individual and has been associated with oncogenesis (58,59). Changes in the composition of vaginal microbiome characterized by *Lactobacillus* depletion and overgrowth of non-*Lactobacilli* species, typically anaerobic bacteria and *Lactobacillus iners* dominance has been associated with preinvasive disease, increased disease severity, and disease invasiveness in patients with CIN (56). *L. crispatus* which produces lactic acid and secretes protective proteins is significantly associated with a healthy vaginal microbiome whereas *L. iners* dominance reported in CIN patients produces low amounts of lactic acid and is not involved in the production of the protective peptide (57).

Bacterial vaginosis (BV), characterized by similar vaginal microbiomes as CIN such as reduced *Lactobacilli* abundance, increased anaerobes predominance, and increased diversity may be involved in the development of CC, as suggested by the findings of cervical cytological abnormalities which are more often in those with disturbance of vaginal microbiomes (60). Production of lactic acid by *Lactobacilli* to maintain local pH lower than 4.5 in addition to bacteriocin production which inhibits pathogens are the major protective mechanisms associated with *Lactobacilli*. Formation of microcolonies by the *Lactobacilli* prevents the pathogen adhesion to the epithelial cells and triggering of host defenses by the pathogens (58). BV-related bacterial, mucosal, and immune complications may contribute to increased susceptibility to HPV infection, HPV persistence and CIN. Dysbiosis of vaginal microbiome results in weakened defense mechanisms and increases the susceptibility to viral infections. Elevated production of epithelial-lining-degrading enzymes associated with BV also contributes to the initiation of infection by HPV (56). Measurement of cervicovaginal cytokine levels in women with BV has reported an elevated cytokine interleukin (IL)-1β and lowered levels of anti-inflammatory molecule secretory leukocyte protease inhibitor (SLPI). Anti-inflammatory state induced by lactic acid and inhibition of toll-like receptor (TLR) agonists-elicited inflammation by lactic acid contribute to the anti-inflammatory effects of lactic acid. Depletion of lactic acid and thus decreased anti-inflammatory effects may increase the risk of HIV infection related to the cervicovaginal inflammation (61). As vaginal dysbiosis, gut dysbiosis is associated with the development of cancer through the alteration of normal host responses but the establishment of its role in cervical carcinogenesis require further studies (59).

Environmental

Smoking

Smoking is a major behavioural risk factor for persistent infection by high-risk HPV (hrHPV) and development of CIN and eventual CC in addition to other risk factors. Two most common histological types of CC, SCC and adenocarcinoma share numerous risk factors including increased sexual partners, younger age at first sexual encounter and full-term pregnancy and prolonged use of oral contraceptive, with the exception of smoking (62,63). Current tobacco smoking is associated with increased risk for SCC but not adenocarcinoma of the cervix in a meta-analysis of six case-control studies enrolling 5,649 SCC cases and 910 adenocarcinoma cases (62), supported by another meta-analysis of 12 epidemiological studies enrolling 8,097 invasive SCC cases, 1,374 invasive adenocarcinoma cases and 26,445 women without carcinoma of the cervix (63). Numerous studies have reported the positive associations between smoking, both active and passive, with the risk of cervical precancer and cancer (64–67). Inconsistent results were found for the relation of passive smoking with CC. A recent systematic review and meta-analysis in 2018 concluded that passive smoking may increase the risk of CC but the levels of cigarette exposure were not investigated (68).

There are several mechanisms proposed on the cervical carcinogenesis caused by cigarette smoking. Exposure of DNA of the epithelial cells in the cervix to the carcinogenic nicotine and cotinine and other metabolic products such as polycyclic hydrocarbons and aromatic amines may contribute to cervical carcinogenesis (69). Interaction between the carcinogen benzo[a]pyrene (BaP) in cigarette smoke with the HPV may enhance HPV persistence and promote carcinogenesis and cancer progression (70). Carcinogens in the cigarette smoke may induce changes in the immune systems such as elevated T lymphocytes, suppressed activity of T lymphocytes, low levels of circulating immunoglobulins except IgE and increases the risk of acquisition or persistent HPV infection (71). Besides, tobacco smoking was also strongly associated with aberrant methylation of p16 promoter in squamous cell CC and high-grade dysplasia (72).

Diet

The association of food intake/diet with the occurrence of different cancers including CC have been studied however limited to significant validation. This is mainly due to the factor of hormonal dysregulation which is the main cause for most of the diseases/ disparities in women. Overall, there are seven important hormones regulating the entire homeostasis of women health (73). These hormones are significantly associated with certain category/group of food which is presented in Figure 1.

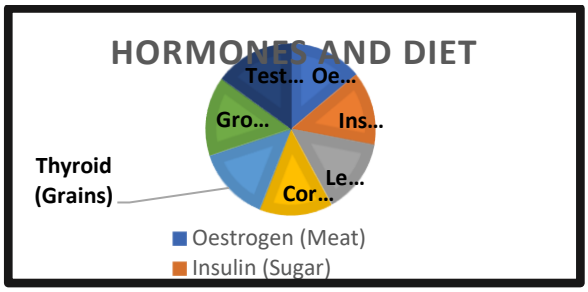

Figure 1: Association between hormones and diet

In line to this, studies have reported on the relationship of dietary pattern and CC from different perspectives. There is a higher risk of CIN for those with high scores for semi-western diet with the characteristics of a higher intake of bread, dairy products, eggs, and soft drinks as well as a higher fat intake ratio (74). Evaluation of dietary data in a recent case-control study shows the significant association of unhealthy dietary pattern characterized by higher intake of snack, fat dairies, French fries, mayonnaise, soft drinks, sugars, refined grains, solid oil, nuts and boiled potato with HPV infection and CC (75), consistent with the findings of other studies (74,76). Higher levels of saturated fatty acids, n-6 polyunsaturated fatty acids and simple carbohydrate contained in these diets are associated with inflammation which plays a role

in cervical carcinogenesis. Patients with CC have reported a markedly elevated levels of inflammatory markers such as sTREM-1, TNFα, IFNβ, IL-1β, and IL-6 compared to the healthy controls (77). On the contrary, dietary consumption of fruits, vegetables and green tea are found to provide protective effects against cervical carcinogenesis. Antioxidants, vitamins and carotenoids act as the preventive and reductive factors of CC (76).

Oxidative stress

Oxidative stress has reported to be involved in the pathogenesis of CC. Oxidative stress results from the dysregulation of the oxidant-antioxidant balance. As a result, free radicals, specifically the reactive oxygen species (ROS) are generated in excessive amount, causing lipid peroxidation and damage of DNA, RNA and protein, leading to mutations that can accumulate and contribute to the malignant cell transformation (78). Increased ROS production is commonly reported in cancer cells. ROS also possesses pro-apoptotic, pro-survival and mitogenic effects in addition to its mutagenic effects which may lead to carcinogenesis. Oxidative modification of transcription factors and genes involved in proliferation and apoptosis by ROS enhances cell division. ROS has reported to activate the P13K and hypoxia-inducible factor (HIF) pathways as well as metabolic adaptations which play a role in cellular proliferation and survival, contributing to tumorigenesis (79).

Oxidative stress, hrHPV and chronic inflammation may act synergistically in cervical carcinogenesis. Oxidative stress and inflammation enhance the integration of hrHPV viral genome into host genome, resulting in upregulation of HPV oncoproteins E6 and E7 which can interact with the tumour suppressors such as p53 and pRb, eventually leading to the development of CC (80,81). HPV infection triggers the activation of inflammatory responses, altering the balance of generation and removal of ROS and overproduction of ROS can then lead to cell damage. Besides, E6*, a shorter isoform of oncoprotein E6 results in reduced expression of superoxide dismutase isoform 2 and glutathione peroxidase, leading to elevated ROS levels that enhance the oxidative DNA damage (82). The reduced expression of tumour suppressor miR-34a caused by E6 decreases the expression of TrxR2 which possesses antioxidant potential, results in the promotion of cancer (83).

Nuclear factor erythroid 2-related factor 2 (NRF2) is part of the antioxidant system of the cervical epithelial tissue. It is bound to the Kelch-like ECH-associated protein 1 (Keap1) which mediates the degradation of factors involved in cell survival and apoptosis by ubiquitin-proteasome pathway and NRF2 is normally expressed at low levels due to the activity of Keap1. Modification of cysteine residues on Keap1 upon exposure to stress causes the nuclear translocation of NRF2 to bind to the antioxidant-responsive elements (AREs), inducing the transcription of antioxidant enzymes which reduces the oxidative stress. However, overexpression of NRF2 due to the loss of function of the tumour suppressor Keap1 is associated with the development and progression of cancer as NRF2 promotes proliferation and inhibits programmed cell death (84). Elevated level of NRF2 has been reported in SiHa and C33A cervical cell lines (85).

Hormonal dysregulation

Oestrogen

The steroid hormone oestrogen plays a pivotal role in the reproductive, musculoskeletal, cardiovascular and central nervous systems of both males and females. Implicated in several cancers such as breast cancer, endometrium cancer and colon cancer, oestrogen and its receptor ERα may contribute to cervical carcinogenesis, persistence and progression, as suggested by the HPV transgenic mouse models (86). In human models, the role of oestrogen was hypothesized based on the increased risk of CC with prolonged use of oral contraceptives containing oestrogen with or without progesterone as well as the higher CC risk with increased number of pregnancies (87,88). As

opposite to that observed for oestrogen, progesterone was suggested to inhibit cervical carcinogenesis as supported by the decreased risk of CC in women infected by HPV who used the synthetic progesterone, medroxyprogesterone acetate (MPA) (89). In normal physiological process of the menstrual cycle, the epithelial cells in the uterine cervix proliferate and differentiate in response to the oestrogen levels and this leads to epithelial hyperplasia. ERα is vital in mediating the carcinogenic activities of oestrogen, as demonstrated by the failure of HPV transgenic mice which were deficient of ERα to develop cervical hyperplasia when they were administered with oestrogen. Binding of oestrogen to its cytosolic receptors induces homo- or hetero-dimerization of ERs, translocation of the oestrogen-bound ERs to the nucleus then results in activation or repression of the genes of interest by classical and non-classical pathways (90). Cervical dysplasia may lead to CC if left untreated (91). Infection by the high-risk subtypes of HPV promotes the aberrant squamous differentiation of cells in the cervical transformation zone, contributes to atypical squamous metaplasia which then progresses to CIN and ultimately CC. Alterations of the CC microenvironment by high-risk HPV oncogenes with or without oestrogen can also contribute to the cervical carcinogenesis (90).

Testosterone

Testosterone is an androgen produced in the ovaries with physiological activities in the female reproductive, cardiovascular and musculoskeletal systems. There is a positive association between the testosterone concentration and female sexual function and testosterone may be used to treat sexual dysfunction in women (92). A prospective study reported the association between invasive cervical carcinoma and free testosterone in premenopausal women and total testosterone in postmenopausal women, suggesting the involvement of testosterone in the development of CC (93). The role of testosterone in the pathogenesis of CC may also be related to oestrogen as both testosterone and oestrogen are biochemically closely related in which the testosterone is the biosynthetic precursor of oestradiol (92,93).

Insulin

Insulin-like growth factor 1 (IGF-1) has been associated with the development and progression of CC by stimulating cellular proliferation. IGF-1 receptors were found to be highly expressed in CC cells compared with normal epithelial cells. Secreted by the β cells of the pancreatic islets of Langerhans, insulin is involved in the regulation of the blood glucose levels by promoting glucose uptake into cells from the circulation and regulating the metabolism of carbohydrate, lipid and protein (94). Type 2 diabetes characterised by insulin resistance, and relative insulin deficiency is a well-known risk factor of cancer which plays a role in tumorigenesis and progression of tumour. Hyperglycaemia and hyperinsulinemia promote cellular proliferation and reduce programmed cell death without altering the cell cycle. Binding of endo- or exogeneous insulin to both insulin and IGF-1 receptors results in glucose uptake into the cancer cells and proliferation, metastasis and invasion of the cancer cells (95). A recent systematic review and meta-analysis by Chen et al also reported that diabetes is associated with poorer CC prognosis (96).

Leptin

Leptin is a metabolic hormone mainly secreted by the adipose tissue and it is involved in the regulation of energy homeostasis, appetite, body weight, reproductive function and angiogenesis. Elevated levels of leptin in obese subjects reflects the state of leptin resistance in these patients as leptin reduces food intake and body weight (97). A meta-analysis reported the association between obesity and higher risk of CC (98). Activation of multiple signalling pathways by leptin suggests its role in the pathogenesis and progression of neoplasms. Leptin was reported to cause in a marked increased growth of the HeLa cells, with significant upregulation of oncogenic c-myc and the downstream anti-apoptotic bcl-2 in the cells.

There was also a remarkable correlation between the leptin levels and grades of cervical carcinoma, suggesting the role of leptin in the progression of CC (97).

Cortisol

The steroid hormone cortisol synthesized in the zona fasciculata layer of the adrenal cortex is also known as the stress hormone. Its functions include the mediation of stress response and regulation of metabolism, inflammation and immune response. Activation of the hypothalamus-pituitary-adrenal (HPA) axis in response to stress causes the release of cortisol from the adrenal cortex, allowing the body to remain in the alert state (99). Elevated secretion of glucocorticoid during chronic stress compromises the cell-mediated immunity by disrupting the equilibrium between the activity of type 1 T-helper (Th1) cell and Th2 cell, favouring the humoral immune response mediated by Th2 cells but suppresses the cell-mediated immunity mediated by Th1 cells which plays a role in the clearance of hrHPV, thus promoting the persistent infection by hrHPV and contributes to the development of CC. A recent study reported that both chronic stress and diurnal cortisol are associated with baseline hrHPV positivity and HPV-mediated cervical carcinogenesis (100).

Conclusion

Cervical cancer remains a serious health issue in developing countries with wide variation in incidence and mortality in various regions of the world. Persisting infection with the sexually transmitted HPV infection is the main cause of cervical carcinogenesis, and therefore factors that are associated with the acquisition of HPV infection or impaired immune response to HPV infection increase the risk of CC. Genetics, epigenetics, microbiota, environmental as well as hormonal factors are involved in the development and progression of CC, and with the enhanced knowledge on the pathogenesis of the disease, effective prevention programmes and treatment modalities can be established to limit the disease burden of CC.

Conflict of Interest

There was no potential conflict of interest relevant to this article.

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