Review

Infection by High-Risk Human Papillomaviruses, Epithelial-to-Mesenchymal Transition and Squamous Pre-Malignant or Malignant Lesions of the Uterine Cervix: A Series of Chained Events?

Giovanni Barillari *, Roberto Bei [ID], **Vittorio Manzari and Andrea Modesti**

Department of Clinical Sciences and Translational Medicine, University of Rome Tor Vergata, 1 via Montellier, 00133 Rome, Italy; bei@med.uniroma2.it (R.B.); manzari@med.uniroma2.it (V.M.); modesti@med.uniroma2.it (A.M.)

* Correspondence: barillar@uniroma2.it; Tel.: +39-06-7259-6510

Abstract: Wound healing requires static epithelial cells to gradually assume a mobile phenotype through a multi-step process termed epithelial-to-mesenchymal transition (EMT). Although it is inherently transient and reversible, EMT perdures and is abnormally activated when the epithelium is chronically exposed to pathogens: this event deeply alters the tissue and eventually contributes to the development of diseases. Among the many of them is uterine cervical squamous cell carcinoma (SCC), the most frequent malignancy of the female genital system. SCC, whose onset is associated with the persistent infection of the uterine cervix by high-risk human papillomaviruses (HR-HPVs), often relapses and/or metastasizes, being resistant to conventional chemo- or radiotherapy. Given that these fearsome clinical features may stem, at least in part, from the exacerbated and long-lasting EMT occurring in the HPV-infected cervix; here we have reviewed published studies concerning the impact that HPV oncoproteins, cellular tumor suppressors, regulators of gene expression, inflammatory cytokines or growth factors, and the interactions among these effectors have on EMT induction and cervical carcinogenesis. It is predictable and desirable that a broader comprehension of the role that EMT inducers play in SCC pathogenesis will provide indications to flourish new strategies directed against this aggressive tumor.

Keywords: HPV; inflammation; p53; hypoxia; EMT; uterine SIL; cancer stem cells; uterine cervical carcinoma

1. Introduction

Epithelial cells lining human organs are tightly joined together by means of adherens junctions, are connected to the extracellular matrix via membrane receptors, are oriented according to an apical–basal polarity, and have a limited life span [1].

In multilayered epithelia, dead cells are replaced by young ones arising from the differentiation of stem cells located in the basal layers [1]. This turnover is altered during the repair of a damaged epithelium when epithelial cells died due to the action of harmful agents are replaced in part by the differentiation of stem cells, and in part by the proliferation and migration of epithelial cells that are close to the site of damage [1,2]. Specifically, cells that have survived the harm proliferate due to the ending of contact inhibition and, at the same time, migrate to the site of damage [1,2]. For this to happen, epithelial cells change their phenotype from static to mobile through the EMT process [1,3]. The latter entails sequential events leading epithelial cells to gradually assume a mesenchymal phenotype [1,3]. This being so, in tissues undergoing development, remodeling, or repair, cells that are in diverse states of differentiation, intermediate between the fully epithelial and the fully mesenchymal phenotype, can be simultaneously present [4,5].

The repair process of an epithelium results from an initial inflammatory phase, a midst proliferative phase, and a final, tissue remodeling phase [2,6]. Ultimately, EMT is triggered by inflammatory mediators and sustained by growth, chemotactic, or differentiation factors [1,3]. In epithelial cells, most of these molecules spark signaling pathways which, in turn, activate transcription factors including zinc finger E-box-binding homeobox (Zeb) 1 or 2, basic helix-loop-helix twist homolog (Twist) 1 or 2, and zinc finger SNAI 1 (Snail) or 2 (Slug) proteins [7–11].

The above-mentioned transcriptional regulators act together with noncoding RNAs and chromatin or histone modifiers at promoting the expression of mesenchymal markers while repressing that of the epithelial ones [12–16]. Consequently, epithelial cells which have undergone EMT display a reduced expression of epithelial adherens junction components, such as the epithelial (E)-cadherin, that are replaced with mesenchymal adhesion molecules, like neuronal (N)-cadherin [3]. Other changes in intercellular adhesiveness involve the upregulation of claudin-1 [17], a tight junction molecule that mediates epithelial cell invasion and migration [18]. Moreover, molecules of the epithelial cytoskeleton, such as the cytokeratins, are replaced by components of the mesenchymal cytoskeleton (e.g., vimentin): accordingly, the shape of epithelial cells is converted from cobblestone-like (typical of static epithelial cells) to spindle-like (characteristic of the highly mobile mesenchymal cells) [3,19]. In the meantime, trans-differentiated epithelial cells synthesize enzymes actively digesting the interstitial or pericellular matrices [20].

Variations in the expression of intercellular adhesion or cytoskeletal molecules, as well as the proteolytic degradation of the matrix, cause epithelial cells to separate from each other, lose their apical–basal polarity, and acquire the migratory capabilities that render possible the repair of the damaged epithelium [3].

When the tissue is repaired, cells stop proliferating and moving, and their phenotype is reconverted from mesenchymal to epithelial, through a process termed mesenchymal-to-epithelial transition (MET): the latter involves molecular changes such as N-cadherin or vimentin replacement with E-cadherin and the keratins, respectively [21]. MET is induced by transcription factors (e.g., ELF3/5, GRHL2, and OVOL1/2) or noncoding regulatory RNAs which counteract the activity of the EMT-promoting transcriptional regulators [22–32].

Thus, the EMT that accompanies tissue repair is a transient process, which is very similar to the EMT that occurs during embryogenesis or body growth [3,21]. Precisely because they are transitory and reversible, these types of EMT are physiological [3,21].

However, when the epithelium is subjected to the prolonged action of detrimental agents, EMT persists, leading to severe tissue alterations which, in turn, may form the basis for the development of various pathologies [3,5,6,21].

In particular, EMT participates in the onset, progression, and metastatic spread of carcinomas. This is because EMT: (i) renders epithelial cells susceptible to malignant transformation [33,34]; (ii) facilitates the detachment of transformed epithelial cells from the primary tumor [5,35,36]; (iii) promotes epithelial cell invasion of the peri-tumor matrix and the basement membrane [36–45]; (iv) favors the locomotion of transformed epithelial cells and their spreading throughout the body [21,46–49]; (v) increases the survival of carcinoma cells that have detached from the primary tumor and have reached the circulatory bed or the new site of metastases [50–52]; (vi) reprograms the metabolism of carcinoma cells, adapting it to the changed characteristics of the new microenvironment [53–56].

Among EMT-linked epithelial malignancies is SCC of the uterine cervix, which is the most frequent cancer of the female genital system [57]. Although preventative screenings have significantly decreased cervical SCC-related deaths [58], this malignancy is still a major cause of mortality throughout the world because of its high rate of recurrence and/or metastasization [57]. It is now widely accepted that the aggressive clinical behavior of SCC is triggered by the abnormal and prolonged EMT occurring in its lesions [57].

In view of these findings, the present review deals with the mechanisms by which EMT is induced in uterine cervical SCC, favoring the clinical progression and metastasization of this tumor.

2. The E5, E6, and E7 Proteins of HR-HPVs Trigger EMT in Cervical Epithelial Cells

The cervix is the lower end of the uterus and consists of two different areas: the endocervix, which continues with the body of the uterus, and the ectocervix which projects into the vaginal cavity [59]. While the endocervix is lined with a monostratified cylindrical epithelium, the ectocervix is covered by a multilayered non-keratinized squamous epithelium that is continuously renewed via the migration of immature cells of the basal layers towards the superficial layers, where cells differentiate until they undergo desquamation [60–62].

During puberty, the cylindrical epithelium that covers the area of the endocervix next to the ectocervix is replaced by a multilayered squamous epithelium: this area, which is termed the "transformation zone", is the one in which SCC develops most frequently [58,60–62].

The onset of SCC is for almost all cases associated with infection with DNA viruses belonging to the HPV family, with HPV16 being the most prevalent HR-HPV type [62–64].

Once sexually transmitted, HR-HPVs reach the cells of the basal layer of the ectocervical epithelium: there the viruses actively replicate, this implying the expression of the viral genome and the synthesis of its products, the E5, E6, and E7 transforming proteins included [62–69].

In the epithelial cells of the uterine cervix basal layer, E5 increases the protein levels of the receptor for the highly mitogenic epidermal growth factor (EGF) via a block of its degradation that normally follows its stimulation by EGF [68,69]. In addition, E5 enhances the mitogenic activity of endothelin-1 and downregulates the expression of the cyclin-dependent protein kinase inhibitors $p21^{WAF/CIP1}$ and $p27^{KIP1}$, thus promoting cell cycle progression [69]. Furthermore, E5 hampers the adhesive interactions among epithelial cells mediated by connexin 43: this reduces the contact inhibition, further contributing to the proliferation of epithelial cells [68]. At the same time, E5 inhibits epithelial cell differentiation by downregulating the expression of the fibroblast growth factor receptor (FGFR)2b [68–70]. Because of all these activities, E5 favors the proliferation of immature basal cells and, at the same time, hampers their differentiation (Table 1) [68–70].

Table 1. The HR-HPV-E5 protein: activities and biological effects with a role in cervical carcinogenesis.

E5 Activity	Effect on HPV-Infected EC
Inhibition of EGFR degradation, enhancement of ET-1 growth effect, p21 and p27 downregulation, cx43 counteraction	Proliferation
Downregulation of the expression of epithelial FGFR2b	Lack of differentiation
Reduction in CD1d and MHC levels on the plasma membrane	Impaired clearance by immune cells
Fas downregulation and Bax degradation	Survival
Induction of the expression of mesenchymal FGFR2c, activation of AKT and MAPK	EMT and tumorigenic behavior

The findings summarized herein are from references [68–70]. Abbreviations: AKT: protein kinase B; Bax: B-cell lymphoma 2-associated X protein; CD: cluster of differentiation; cx: connexin; EC: epithelial cells; EGFR: epidermal growth factor receptor; EMT: epithelial-to-mesenchymal transition; ET: endothelin; Fas: tumor necrosis factor receptor superfamily member 6; FGFR: fibroblast growth factor receptor; HPV: human papillomavirus; MAPK: mitogen-activated protein kinase; MHC: major histocompatibility complex.

For its part, the HPV-E6 protein drives the degradation of the p53 oncosuppressor cellular protein via the ubiquitin ligase-cellular proteasome system (Figure 1) [51,65]. This event is followed by the upregulation of p53-repressed factors, such as the Bcl-2 protein and the telomerase enzyme (Figure 1), leading to an alteration in the kinetic of cervical epithelial cell renewal [50,51,66].
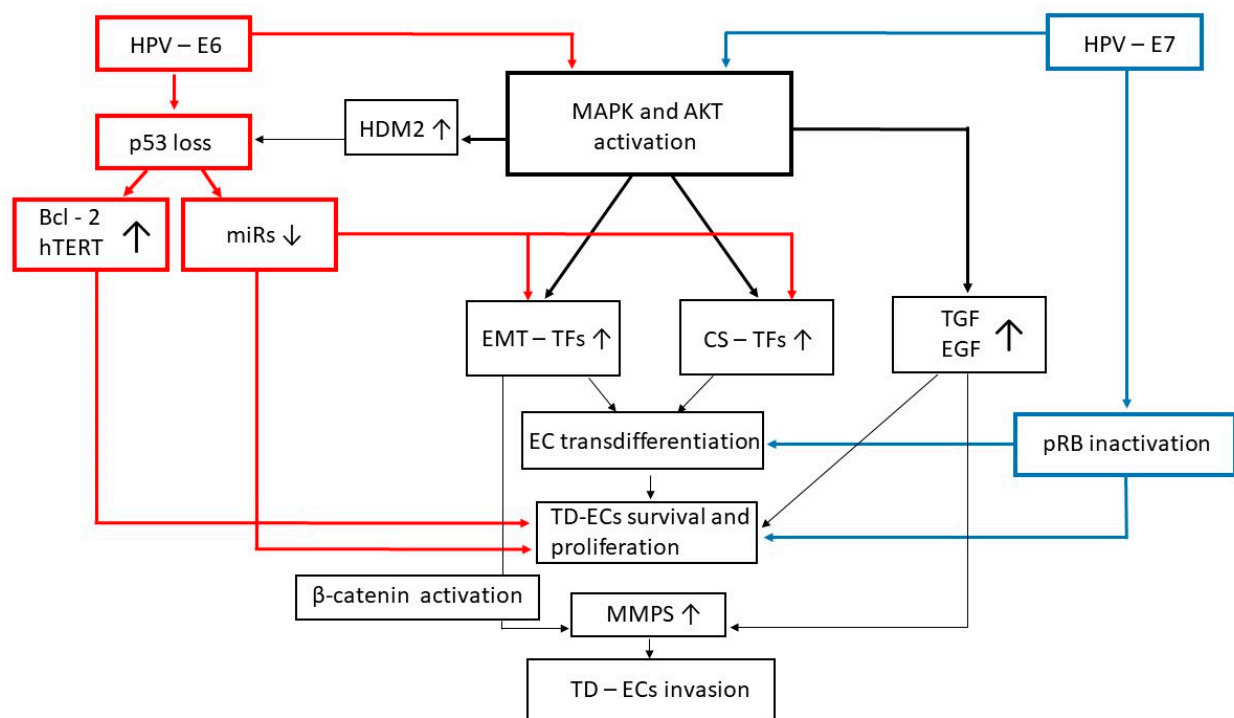
Figure 1. The E6 and E7 proteins of high-risk HPVs exert activities that make them capable of directly converting epithelial cells into mesenchymal, stem-like cells. Arrows symbolize directions of connections. Abbreviations: AKT: protein kinase B; CS: cellular stemness; EC: epithelial cells; EGF: epidermal growth factor; EMT: epithelial-to-mesenchymal transition; HPV: human papillomavirus; HDM2: human double minute 2; hTERT: human telomerase reverse transcriptase; MAPK: mitogen-activated protein kinase; miR: microRNA; MMP: matrix metalloproteinase; pRb: retinoblastoma protein; TD: trans-differentiated; TF: transcription factor; TGF: transforming growth factor.

Simultaneously with the effects promoted by E5 and E6, the HPV-E7 protein binds and inactivates the retinoblastoma tumor suppressor cellular protein (pRb) (Figure 1), thus synergizing with E5 and E6 in impeding infected cells to exit the cell cycle and differentiate [66].

It is noteworthy that, while proliferating, HPV-infected basal epithelial cells migrate towards the superficial layers of the cervical epithelium [62]. In the majority of cases, these HPV-promoted phenomena are limited to causing a thickening of uterine ectocervical epithelium or, at most, benign flat warts [62]. In a small percentage of cases, however, the abnormal growth of immature basal cells and their migration towards the superficial layers of the cervical epithelium lead to the development of hyperplastic and/or dysplastic lesions termed squamous intraepithelial lesions (SILs) [62,71,72].

Two types of SILs are known: low-grade SIL (L-SIL) and high-grade SIL (H-SIL) reference [61,71,72].

L-SIL, also defined as grade 1 cervical intraepithelial neoplasia, consists of proliferating and keratinized immature basal cells whose nuclei are surrounded by vacuoles: these cells represent the manifestation of a productive HPV infection and can constitute up to 1/3 of the cervical epithelium [71,72]. L-SIL generally undergoes spontaneous involution until it disappears, progressing into H-SIL only in 20–30% of cases [71–73].

H-SIL encompasses grade 2 and 3 cervical intraepithelial neoplasia. The former is characterized by hyper-keratinized epithelial cells that colonize 2/3 of cervical basal layers [71,72]; whereas grade 3 cervical intraepithelial neoplasia represents the early stages of HPV-induced carcinogenesis, and it is made up of highly dysplastic cells that undergo atypical mitosis and occupy the 2/3 of the entire epithelium, including the superficial layers [71,72].

When its DNA does not integrate into the genome of the host cell, HPV is generally neutralized by the immune system: under this circumstance, the abnormal proliferation of basal cells ceases, the warts and SILs regress and the cervical epithelium returns to normal [62].

However, the E5, E6, and E7 oncoproteins actively counter host immune response directed against the HR-HPVs. Specifically, E5 reduces the levels of the CD1d receptor on the plasma membrane of HPV-infected epithelial cells, thereby impairing their recognition by natural killer cells (Table 1) [69]. In addition, E5 can retain the major histocompatibility complex/human leukocyte (MHC/HLA) class I antigens in the endoplasmic reticulum: as a consequence, E5-expressing epithelial cells display low MHC/HLA-I antigen levels on their surface (Table 1), and this jeopardizes their disruption by cytotoxic T cells [68,69]. In addition, E5 further hinders the clearance of HR-HPV-infected cervical epithelial cells by downregulating the expression of MHC class II antigens induced by the inflammatory mediator interferon (IFN)γ on the surface of these cells [68,69]. For their part, the E6 and E7 proteins of the HR-HPVs halt IFN capability of reverting the inhibitory effect that E5 has on MHC/HLA-I [68,69]. Moreover, E5 prolongs the survival of HR-HPV-infected epithelial cells by downregulating the expression of the cell death Fas receptors and by promoting the degradation of the proapoptotic Bax protein (Table 1) [68,69]. The inhibition of the anti-HPV immune response and, in general, the reduction in the apoptosis of cervical cells infected with these viruses, extends the duration and the intensity of HR-HPV infection, thus increasing the likelihood of cellular transformation. In fact, when E5, E6, and E7 succeed at hindering the immune response and HR-HPV load is high, the viral DNA integrates into the genome of host cells [74–77]: in such an eventuality the HPV-E5 gene is lost, while the HPV-E6 and E7 proteins are overexpressed and their carcinogenic effects are intensified [66–69,77]. As a consequence, the entire cervical epithelium is replaced by poorly differentiated cells displaying abnormal nuclei and atypical mitoses [71,72]. In 20–50% of H-SIL cases, these cells may degrade the epithelial basement membrane via the synthesis of proteolytic enzymes, thus initiating the development of an invasive SCC [73,78].

Of importance, results from clinical studies indicate that, as compared to normal cervical epithelium, the expression of the EMT-promoting Zeb 1, Twist 1 or 2, and Snail transcription factors is progressively increased during the onset of uterine cervical SIL and its progression to SCC [79–86]. Consequently, the level of both claudin-1 and vimentin increases, while that of E-cadherin is reduced [17,87]. These phenomena parallel L-SIL progression to H-SIL and finally to SCC, and are predictive of SCC metastasis to lymph nodes [17,87].

As for physiological EMT, that also accompanies SCC onset or progression occurs gradually, explaining why cells with intermediate phenotypes between the fully epithelial and the decidedly mesenchymal ones can be found in the squamous lesions of the uterine cervix [88–97]. Such a variety of phenotypes could depend on the multitude of EMT promoters that may be present in the cervix of HPV-infected women, and on the temporal sequence according to which cervical epithelial cells are exposed to these factors.

In this context, it has to be highlighted that, while downregulating the epithelial FGFR2b, HPV-E5 drives the expression of the mesenchymal FGFR2c variant, whose signaling leads to EMT, cellular invasiveness, and tumorigenic behavior (Table 1) [70].

Still in this regard, in vitro studies performed with SCC cell lines have shown that the E6 and E7 proteins of HR-HPVs can directly trigger EMT via the induction of Twist2, Zeb, Slug, or Snail expression and nuclear translocation [83,98–100]. This is because both the E6 and E7 proteins of HR-HPVs can turn on the mitogen-activated protein kinases (MAPK)/extracellular-regulated kinases (ERK) and/or the phosphoinositide 3 kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathways (Figure 1) [101–104]. Triggering of these signaling pathways actuate the expression of Snail, Slug, Twist, and Zeb, as well as other EMT-promoting transcription factors (Figure 1), including STAT3 and nuclear factor-κB (NF-κB) [7–11].

On its part, also E5 can turn on both PI3K/AKT and MAPK/ERK (Table 1), either directly or via EGFR activation [68,69]: this explains why in cervical L-SILs the expression of HPV-E5 parallels that of the Snail, Slug or Zeb transcription factors [70].

Moreover, E5, E6, and E7 enhance the activity, and/or upregulate the expression, of EMT promoters such as EGF and transforming growth factor (TGF)-β1 (Table 1 and Figure 1) [68,69,100,105].

Undoubtedly, however, the induction of EMT in HPV-infected cervical epithelial cells strongly depends on E6's capability of driving p53 degradation [51]. In fact, this event causes p53 to no longer activate the transcription of microRNAs (miRs) that otherwise would have blocked Zeb, Slug, or Twist expression (Figure 1), thereby hindering EMT [34,106–109].

miR-34 and miR-203, together with the miR-200 family members, are among the p53-transcribed miRs which are reduced in HPV-infected epithelial cells: downregulation of these miRs follows E6-promoted p53 degradation, and it is paralleled by an increase in Snail or Zeb levels, EMT and cell invasion (Figure 1) [34,51,107]. Since the p53-transcribed miRs repress not only the phenotypic plasticity, but also the survival, growth, invasion, and migration of SCC cells, a reduction in their expression influences not only the phenotype of SCC cells but also the clinical course of SCC [106,110–113]. For instance, miR-34 levels are significantly lower in L-SIL than in normal cervical epithelium, even lower in H-SIL, and extremely low in invasive SCC [51]. Worthy of interest is the fact that given the pro-apoptosis effect and growth suppressive activities of miR-34, its downregulation in cervical SIL or SCC correlates with the increased survival and replicative capacity of HPV-infected cervical epithelial cells (Figure 1) [51].

These phenomena are amplified in cells where E6-induced p53 loss is accompanied by the functional impairment of pRB caused by the HPV-E7 oncoprotein. In fact, the simultaneous inactivation of p53 and pRB strongly upregulates Snail, Slug, and Zeb1 expression, and readily converts epithelial cells from static to motile and invasive (Figure 1) [114,115].

On the other hand, when overexpressed and/or hyperactivated, Snail, Slug, and Zeb1 can directly counteract p53 and pRb activity, further downregulating tumor suppressive miRs, and rendering epithelial cells susceptible to malignant transformation [33,34]. In agreement with these findings, the concurrent inactivation of p53 and pRB has been shown to give rise to mesenchymal-like tumors in animal models [116].

Taken together, all these findings indicate that the E5, E6, and E7 oncoproteins of the HR-HPVs cooperate in inducing the proliferation and trans-differentiation of cervical epithelial cells. However, it has to be highlighted that while in L-SIL lesions the DNA of HR-HPVs is found in the epithelial cytosol, most of HSILs and the very vast majority of SCCs are associated with viral DNA integration into the host cell genome [68–70]. In agreement with the fact that this event causes the loss of the E5 gene [68,69,77], the latter is expressed in cervical L-SILs [70] but not in cervical carcinomas [68]: this underlies the established belief that E5 plays a role mostly in the early stages of cervical carcinogenesis [63,66–69,77].

3. Inflammation Cooperates with the E6 and E7 Proteins of HR-HPVs at Promoting EMT in Normal or Neoplastic Uterine Cervical Epithelial Cells

As with many other types of dysplastic or neoplastic lesions [117], the development of uterine cervical SILs and their progression to SCC are respectively preceded and accompanied by an inflammatory reaction [118–121]. The latter often follows the infection of the uterine cervix with HPV (Figure 2) as well as other microbial agents, and it accompanies the immune response directed against these pathogens and/or the reparation of the tissue damage caused by them [122,123].
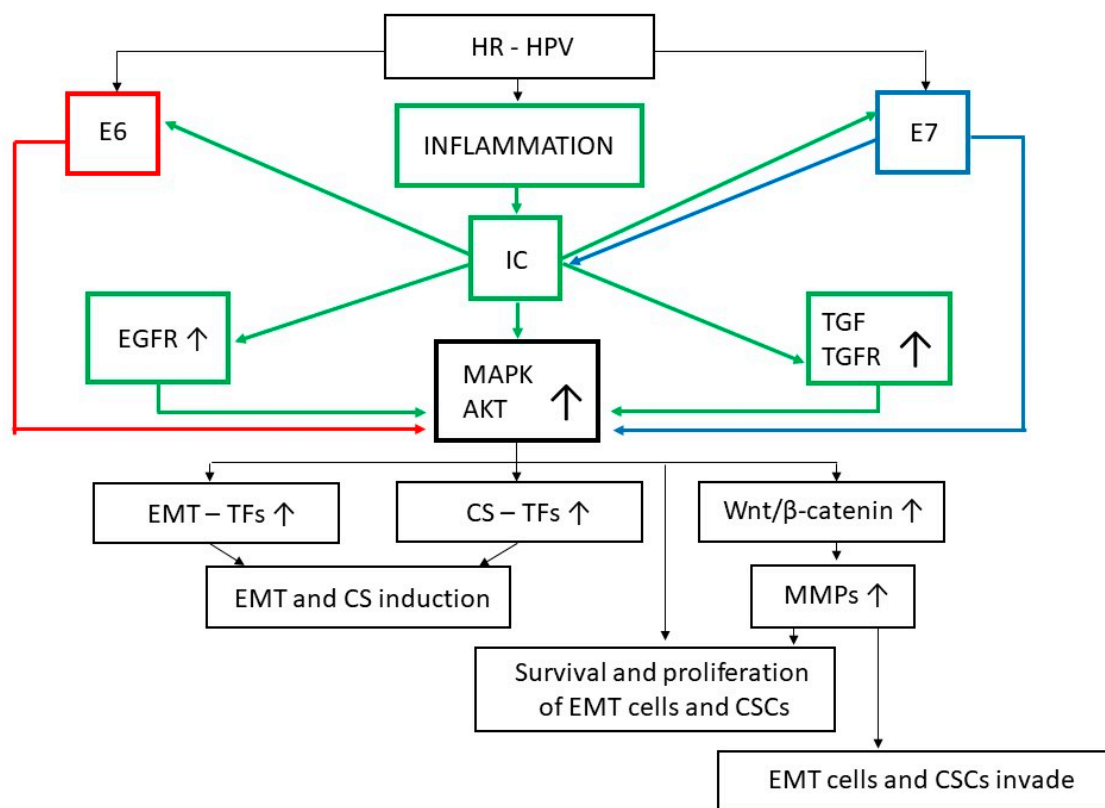
Figure 2. Inflammatory cytokines cooperate with the HPV-E6 and HPV-E7 proteins at inducing the appearance of epithelial/mesenchymal hybrids or stem-like cells, and at favoring their survival, growth, and invasiveness. Arrows symbolize directions of connections. Abbreviations: AKT: protein kinase B; CS: cellular stemness; CSC: cancer stem cell; EGFR: epidermal growth factor receptor; EMT: epithelial-to-mesenchymal transition; HR-HPV: high-risk human papillomavirus; IC: inflammatory cytokines; MAPK: mitogen-activated protein kinase; MMP: matrix metalloproteinase; TF: transcription factor; TGF: transforming growth factor; TGFR: transforming growth factor receptors; Wnt: wingless-type mouse mammary tumor virus integration site.

Inflammation of the uterine cervix involves its infiltration by activated leukocytes releasing a variety of cytokines among which tumor necrosis factor (TNF)α, interleukin (IL)-1, or IL-6 are detected in most uterine SILs or SCCs [120,124–127]. Of interest, as with activated leukocytes, SCC cells also constitutively produce IL-1, IL-6, and TNFα [128–130], thereby contributing to an increase in the intratumoral concentration of these cytokines. In this context, it is significant that TNFα promotes the gene expression of HPV-E6 and HPV-E7, and that the latter protein upregulates TNFα expression in a reciprocal fashion (Figure 2) [131,132].

Noteworthy, IL-1, IL-6, or TNF tissue levels correlate positively with the stage of progression of cervical disease, from healthy epithelium to L-SIL, and from this to H-SIL and SCC [118–122,124,126,127,133].

At variance with IL-1, IL-6, or TNF, the concentrations of inflammatory IFNγ decrease in uterine cervical SILs or SCC, as compared to normal cervical epithelium [134–136]. It is worthy of note that SCC regresses in patients treated with IFNγ [137]. Despite this clinical evidence, however, IFNγ is known to synergize with IL-1 and TNF at promoting EMT and cellular invasion [138,139]. In fact, exposure of either normal or tumor epithelial cells to IL-1, TNFα, or IFNγ upregulates the expression of the EGF receptor (EGFR) (Figure 2) [140–146]. Specifically concerning cervical epithelial cells, when EGF is released by tissue-infiltrating inflammatory cells [147], it binds to EGFR driving glycogen synthase kinase 3β inactivation, and the consequent upregulation and nuclear accumulation of EMT-promoting transcription factors (Figure 2) [148,149].

As for inflammatory cytokines, the expression of EGFR increases from L-SIL to H-SIL and from the latter to SCC, as compared with the healthy cervical epithelium [148,150,151]. This phenomenon coincides with the fact that, while in healthy cervical epithelium EGFR is expressed almost exclusively in the basal layer, in SIL and especially in SCC the EGFR is present in all layers, these being infiltrated with migrating and proliferating basal cells [62,71,72]. In this regard, it has to be highlighted that, besides directly upregulating EGFR, the inflammatory IL-1, IL-6, TNFα, or IFNγ promotes epithelial cell migration [152–155]. Taken together, these results describe one of the many cases in which inflammation favors cancer onset or progression, rather than counteracting them [117].

Still about this, it is noteworthy that in addition to EGFR, the TNFα, IL-1, and/or IFNγ upregulate also the expression of TGF-β1 and its type I and II receptors (Figure 2) reference [139,156–159]. In this regard, one should consider that TGF-β1 is arguably the most powerful inducer of EMT in both normal and transformed epithelial cells [3,13,148,160–166]. In particular, following its release by inflammatory leukocytes, TGF-β1 binds to, and phosphorylates, the TGF-β receptor II expressed on the surface of either normal or tumor epithelial cells [166,167]. Upon its activation, the TGF-β receptor II phosphorylates the TGF-β receptor I, this leading to the aggregation of the Smad 2, 3, and 4 cytoplasmic proteins into a trimeric complex which enters the nucleus, thereby promoting Snail, Zeb1, Zeb2, or Twist gene expression (Figure 2) [166,167].

Similar to what happens for inflammatory cytokines and EGFR, an increase in TGF-β1 expression in the uterine cervix has been shown to accompany L-SIL progression to H-SIL [168,169]. Some authors have reported that the upregulation of TGF-β1 is transient since its levels in the lesions are reduced when H-SIL evolves into SCC [168,169]. In contrast, other studies have found that TGF-β1 protein levels also augment during SIL progression to SCC and that this parallels the upregulation of HPV-E7 [170] which, as specified already, can promote TGF-β1 expression [105].

It is worthy of the greatest interest that, HPV-E5, E6, and E7, as well as IL-1, IL-6, TNFα, IFNγ, EGF, and TGF-β1, are capable of triggering the MAPK/ERK and/or the PI3K/AKT/mTOR pathways, leading to the activation of EMT-promoting transcription factors (Figure 2) [7,9,11,14,68,69,123,146,161,171–184].

Therefore, the aberrant activation of the PI3K/AKT/mTOR and/or MAPK/ERK pathways observed in uterine SIL or SCC [185,186] is most likely due to the concurrent activities of inflammatory mediators, growth factors, and HR-HPV oncoproteins.

The strong activation of AKT and MAPK, and the cross-talks between these signaling pathways, rapidly induce the EMT pro-invasive phenotype in cervical epithelial cells, thereby promoting SIL and its progression to invasive SCC [9,17,79–85,87,185–187]. In addition, activated AKT and MAPK effectively sustain the survival and proliferation of the epithelial–mesenchymal hybrids (Figure 2) [188,189]. These phenomena are magnified when HPV-E6 nullifies p53 ability to arrest the growth or promote the death of cells whose genomic integrity has been compromised by carcinogens, HR-HPVs included: in such an eventuality, epithelial–mesenchymal hybrids with damaged DNA survive and proliferate uncontrollably [107,109,190,191].

4. Cyclic Hypoxia Exacerbates EMT and Favors the Appearance of Stem-Like Cells in Cervical Squamous Lesions

During tumor progression, the proliferating cancer cells at the beginning infiltrate the tissue area where they developed, and then move towards its periphery, hence increasing the size of the neoplastic mass: at this point, local vessels cannot satisfy the strong demand that the growing tumor has for oxygen and nutrients [192,193]. As a consequence, an acidified and hypoxic microenvironment is produced leading to the activation of the hypoxia-inducible factor (HIF)-1 (Figure 3) [192,193].
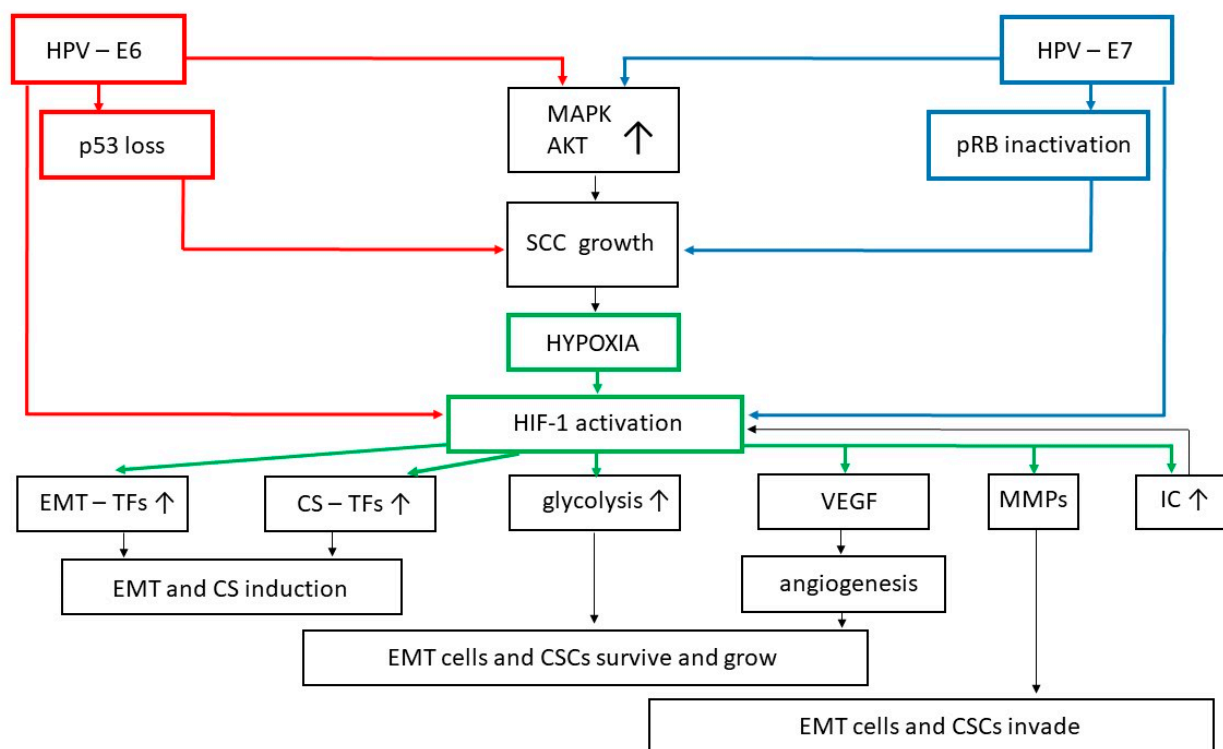
Figure 3. The HPV-E6 and E7 proteins strengthen HIF-1 capability of promoting EMT and cellular stemness. Arrows symbolize directions of connections. Abbreviations: AKT: protein kinase B; CS: cellular stemness; CSC: cancer stem cell; EMT: epithelial-to-mesenchymal transition; HPV: human papillomavirus; IC: inflammatory cytokines; MAPK: mitogen-activated protein kinase; MMP: matrix metalloproteinase; pRb: retinoblastoma protein; SCC: squamous cell carcinoma; TF: transcription factor; VEGF: vascular endothelial growth factor.

HIF-1 is a transcription factor consisting of a constitutively expressed subunit HIF-1β and an oxygen-regulated subunit HIF-1α [193]. Under normal oxygen tension (normoxia), post-translational modifications of the HIF-1α subunit trigger its degradation via the ubiquitin–proteasome pathway [193]. In hypoxia, HIF-1α is stabilized and interacts with transcriptional coactivators to promote the expression of target genes such as that coding for vascular endothelial growth factor (VEGF)-A: the latter, in turn, stimulates angiogenesis, that is the formation of new blood vessels directed at nourishing the growing tumor (Figure 3) [182,190,192,193].

In the proliferating lesions of the uterine cervix, the expression of HIF is highest in areas that are distant from the pre-existing vessels and close to necrotic zones [194]. Of interest, hypoxic tumor areas are often infiltrated by inflammatory macrophages secreting TNFα, IL-1, and IL-6 which, as cited earlier, are effective inducers of EMT [182].

Between HIF-1 and inflammatory mediators, reciprocal interactions occur, some of which are started or mediated by AKT signaling [195,196]. In particular, HIF-1 directly activates the expression of IL-1, IL-6, or TNF (Figure 3) [196–198], as well as that of chemotactic factors recruiting inflammatory cytokine-releasing macrophages [199]. On the other hand, TNFα or IL-6 upregulates HIF-1α gene expression [200,201], while IL-1β increases HIF-1α protein levels by acting post-transcriptionally (Figure 3) [195]. In the HPV-infected cervix, HIF-1α is also stabilized by the E6 and E7 proteins, which block the degradation of HIF-1α protein by the cellular proteasome (Figure 3) [101–104,202–204]. This effect, which again is mediated by E6 or E7 capability of activating the ERK1/2 and PI3K/AKT signaling pathways, leads to an increase in VEGF-mediated tumor angiogenesis (Figure 3), this being particularly evident during H-SIL evolution into invasive SCC [205–207]. Lately, the newly formed vessels will provide the tumor with additional metastatic routes [190,192,193].

However, tumor-associated new vessels are highly dysfunctional and, as such, they are not capable of satisfying in full or constantly the great oxygen request by the growing neoplasm [190,192]. As a consequence, phases of hypoxia and normoxia are interspersed in the tumor tissues [190]. During the hypoxic phase, HIF-1 drives EMT in carcinoma cells by activating Snail, Twist, or Zeb expression (Figure 3), either directly or by recruiting the NF-kB transcription factor and/or the TGFβ/Smad signaling pathways [182,190]. When the oxygen level in the tumor tissue returns to normal, HIF is inactivated, and EMT gradually and/or partially converts into MET via ELF3/5, GRHL2, and OVOL1/2 transcriptional activity [190]. This condition, which is termed "cyclic hypoxia", frequently occurs in SCC tissues [208]: there, the continuous interchange of the epithelial and mesenchymal phenotypes favors the appearance in the lesions, and the persistence therein, of poorly differentiated cells, which resemble stem cells [209,210].

Here it has to be highlighted that in post-natal life stem cells normally reside in specifically dedicated body areas, the basal layer of the multilayered epithelia included: there, stem cells continuously differentiate into mature cells, and self-renew in order to keep their number constant [107,191]. In particular, during physiologic tissue growth or renewal, stem cells replicate each giving rise to two cells of which one remains stem and one differentiates: such a peculiar replication is defined as "asymmetric division", and it also occurs in the repair of lesions of limited extension [107,191]. In contrast, when the tissue injury is extensive, resident stem cells initially proliferate, each of them eventually giving rise to two stem cells (symmetric division), and so on until some of the numerous stem cells that have been produced differentiate into two mature cells [191].

The balance between pro-differentiation and antidifferentiation stimuli that a stem cell receives from the microenvironment is modulated by a variety of transcription factors. Among them, HIF-1 is very effective as it promptly stimulates the Oct4 and Sox2 transcription factors at inducing the stem cell phenotype (Figure 3) [107]; at the same time, HIF-1 favors stem cell survival by promoting lactate production via glycolysis (Figure 3), a metabolic program which is exacerbated in both stem and cancer cells, rendering them less dependent on oxygen supply than non-transformed, well-differentiated cells [54,211].

In addition to HIF-1 activation promoted by local hypoxia, the expression of stemness markers in cervical squamous lesions could result from the degradation of p53 driven by the E6 protein of HR-HPVs [51]. This is because functional p53 represses the expression of stem cell factors including Oct4, KLF4, LIN28A, Sox2, and c-myc by acting on them directly or through the activity of miRs, such as miR-34a and miR-145 (Figure 1) [34,191,212,213]. Furthermore, inhibitory interactions exist between p53 and other stemness-related genes such as STAT3 and Piwi-l [214,215].

Additionally, the inflammatory mediators or growth factors with a role in cervical carcinogenesis may contribute to the induction of stemness by activating PI3K/AKT/mTOR or MAPK-ERK and, consequently, Zeb, Snail, and Twist transcriptional activity, which includes the expression of stemness markers (Figures 1–3) [34,107,109,191]. In addition, activated AKT or MAPK upregulates the human/murine double minute (H/MDM) 2 protein (Figure 1) which, by hindering p53 transactivation activity, induces stemness and/or causes stem cells to exit quiescence and progress through the cell cycle, thereby triggering stem cell expansion [107]. However, H/MDM2 is also capable of driving Slug degradation [109]. Therefore, because of this dual effect, H/MDM2 is likely to have an important role in the modulation of epithelial cell plasticity.

In view of the impact that HIF-1, p53, Zeb, Snail, and Twist have on EMT, it is easy to understand why cells displaying EMT features together with stem cell markers including nestin, aldehyde dehydrogenase 1, the cholesterol-binding CD133, and the glycosaminoglycan receptor CD44 are present in uterine cervical SCC lesions [88–90,92,96,97].

When a malignant transformation is achieved, carcinoma cells may lose any index of differentiation and acquire decidedly stem characteristics (Figures 1–3) [216,217]. These cells, termed cancer stem cells (CSCs), are very invasive and vital, being capable of self-renewal like normal stem cells [94,107,191,216,218,219]. Of interest, CSCs are found in

uterine SCC from its early stage of development (i.e., H-SIL or SCC in situ), so much so that they have been proposed as markers for the preventive diagnosis of this tumor [90–92,94,95,220,221].

The CSCs, whose number in the SCC lesions directly parallels the tumor grade reference [91,92,94,95,222] are believed to arise from the dedifferentiation of mutated somatic cells and/or the transformation of stem cells [107]: both of these events are largely attributable to the loss of p53 which is undoubtedly one of the key steps in HR-HPV-promoted cervical carcinogenesis. In fact, given that functional p53 guarantees stem cells differentiation and prevent the reconversion of differentiated cells into stem cells, p53 loss causes terminally differentiated somatic cells to revert to stem-like and proliferate; likewise, the functional impairment of p53 triggers adult stem cells to acquire pluripotency and to undergo symmetric divisions [107,191].

In this context, one should consider that markers of EMT and stemness characterize not only uterine CSCs but also the stem cells residing in the basal layer of the cervical epithelium [91,93–95,218]. This has suggested that uterine SCC could be initiated by the transformation or the abnormal activation of basal stem cells [223,224]. Such a hypothesis is supported by the finding that the "transformation zone", that is the area of the cervix in which SCC develops more frequently is particularly rich in stem cells [58,60–62].

5. EMT and Cellular Stemness Not Only Facilitate SCC Cells Invasion and Spreading, but also Increase SCC Cells Resistance to Anticancer Chemo- or Radiotherapy

Invasive uterine SCC is started when carcinoma cells degrade the basement membrane of the cervical epithelium and penetrate into the underlying stroma [78]. Tissue-infiltrating abilities are especially evident in carcinoma cells that have undergone EMT reference [187,209,210,225]. In this context, one should consider that Twist, Snail, and other EMT-promoting transcription factors activate the expression of basement membrane-degrading proteolytic enzymes [226–229]. Among them, the matrix metalloproteinases (MMPs) are pivotal to SCC cell invasion (Figures 1–3) [230]. It is worth noting that two members of the MMP family, MMP-2 and MMP-9, are considered as SCC prognostic markers since their expression level positively correlates with the progression of L-SIL to H-SIL, pre-invasive SCC, and, finally, invasive SCC [230].

It has to be highlighted that the EMT transcription factors can promote MMP expression also in an indirect fashion, that is by downregulating E-cadherin and thereby disassembling the intercellular junctions constituted by E-cadherin/cytoplasmic β-catenin complexes: this event, in turn, causes the translocation of cytoplasmic β-catenin to the nucleus where it cooperates with NF-kB at activating MMPs expression [20,231].

The β-catenin is the fundamental component of the wingless-type mouse mammary tumor virus integration site (Wnt) pathway, a signaling axis important to tissue homeostasis because of its impact on cell survival, proliferation, differentiation, and locomotion [232]. It is noteworthy that a deregulated activity of Wnt/β-catenin participates in the onset and progression of uterine cervical SCC where it associates with EMT [233,234]. This is easily predictable given that β-catenin transcriptional activity is stimulated by signaling pathways that are strongly activated by EMT-promoting factors with a role in cervical carcinogenesis, including IL-1, IL-6, TNFα, EGF, and TGF-β1 (Figure 2) [235–248]. Specifically regarding TGF-β1, the most powerful promoter of EMT in uterine epithelial cells, an increase in its levels such that occurring in cervical squamous lesions causes in epithelial cells an abnormal activation of the Smad proteins and PI3K/AKT/mTOR or MAPK/ERK signaling, which synergize at promoting β-catenin nuclear translocation, MMP expression and cellular invasion (Figure 2) [13,160–165,171,179,183,249–253]. For its part, EGF cooperates with TGF-β1 at promoting MMP expression and cellular invasiveness (Figure 2) [254]. These molecular events, which confer a pro-oncogenic phenotype to the epithelial–mesenchymal hybrids [171,179,183,251,253], are particularly stressed in HR-HPV-infected cells, where the E6 and E7 proteins downregulate Wnt/β-catenin inhibitors such as the miR-34a and the Na+/H+ exchanger tegulatory factor 1 protein [255,256].

As for the EMT canonical transcription factors and the Wnt/β-catenin axis, HIF is also capable of inducing the expression of MMPs (Figure 3), as well as further extracellular matrix-degrading enzymes [182,257]. Indeed, hypoxia is deeply involved in tumor evolution from the pre-invasive to the invasive phase [258]. In particular, when compared with well-oxygenated SCCs, the SCCs undergoing cyclic hypoxia show a high probability of metastasizing, this being due to their richness in epithelial–mesenchymal hybrids [209,210].

Upon basement membrane degradation, cancer cells reach the stroma driven by growth factors or nutrients [190]. When cells from the primary tumor invade the surrounding stroma, cellular hybrids in which the mesenchymal characters are more expressed than the epithelial ones are present in carcinoma invasive front, where they act as "leader" cells [190]. In contrast, hybrids in which epithelial markers are more abundant than the mesenchymal ones aggregate to each other and follow the leading cells in the invasion path [190]. In accordance with their EMT phenotype, invading leader cells synthesize a new matrix rich in fibronectin and other non-collagenous glycoproteins [259]: such a "soft" matrix does not hinder cellular locomotion but, on the contrary, favors it by providing the cells with mechanical support [21,260].

Cancer cells move through the tissues via the use of long protrusions of the cell membrane and cytosol which result from the polymerization of actin and the maturation of an actin-myosin contractile apparatus [261]. Such phenotypic changes are triggered by Twist 1 or other EMT transcription factors upon their activation by EGF and/or TGF [261]. The rearrangement of the cytoskeleton is followed by the recruitment of MMPs and CD44, both expressed by the uterine cervical SCC cells [88,230], to the forming protrusions: there, CD44 and the MMPs may aggregate, giving rise to macromolecular complexes which on one side mediate cancer cell adhesion to the extracellular matrix, and on the other induce matrix degradation [261].

Migrating leader cells need a lot of energy, which they obtain from glycolysis [190]: as discussed before, glycolysis is strongly stimulated in cellular hybrids upon HIF-1 activation (Figure 3) [54,211]. Once more, the phenotypic plasticity of the epithelial–mesenchymal hybrids favors their locomotion. In fact, a leader cell that has consumed all the available energy is replaced by a follower cell, full of energy, which then takes on more decidedly mesenchymal characteristics [190].

When they reach lymphatic or blood vessels, tumor cells adhere to the vascular wall and, again because of the activity of MMPs and other proteolytic enzymes, degrade it and intravasate [258]. Indeed, SCC cells can be isolated from the blood of patients with advanced cervical cancer [262–264]. It is noteworthy that the number of circulating SCC cells is predictive of tumor metastases and/or it inversely correlates with patients' disease-free survival [263,264]. However, only a small percentage of the tumor cells that circulate in the blood or lymph can resist the apoptosis resulting from the lack of the solid support provided by the extracellular matrix, which epithelial cells, including carcinoma cells, need to survive [21,190]. It is relevant that most of the surviving cells are epithelial–mesenchymal hybrids or CSCs: this is because both phenotypes imply the strong activation of pro-survival signaling pathways including PI3K/AKT, NF-kB, and Wnt/β-catenin, and the inactivation of the pro-apoptosis proteins, such as p53 [21,190,258]. In this regard, it is interesting to note that many of the circulating trans-differentiated tumor cells overexpress EGFR, the activation of which is known to strongly support epithelial cell survival [265,266]. Moreover, because of their ability to aggregate with platelets, circulating cellular hybrids and CSCs are protected from either the stress generated by blood flow turbulence or from the attack by immunocompetent cells [190,267].

When circulating tumor cells reach a vessel whose caliber is smaller than the diameter of the metastatic embolus, they stop, adhere to endothelial cells, degrade the vessel wall, and pass into the extravascular territory which may eventually become the site of metastasis [190,268]. The new environment can be hostile to metastasized cells, as it often differs from the one in which the tumor has originated; nonetheless, the phenotypic plasticity of metastasized cells favors their survival [190]. In fact, once the cancerous

epithelial–mesenchymal hybrids have arrived in the secondary site, some of them undergo a MET, returning to assume the original epithelial phenotype [190,258]. While EMT is associated with SCC initiation, invasion, and spreading, MET favors the anchorage-dependent growth of carcinoma cells [269].

However, the EMT to MET switch occurs slowly and often incompletely, causing tumor epithelial–mesenchymal hybrids and CSCs to persist in cervical SCC metastases: this is particularly evident in hypoxic areas where activated HIF-1 stimulates glycolysis at levels that guarantee the tumor cell hybrids and CSCs a certain independence from the vessels of the metastatic site [88,209,210,222,270,271].

From a medical point of view, it is of concern that CSCs are inherently protected from apoptosis triggered by the DNA-damaging chemotherapeutic or radiations [88,222,272]. Once again, this results from the constitutive activation of AKT or Wnt signaling, or from E6-promoted p53 degradation leading to the upregulation of p53-repressed survival factors, such as Bcl-2 [21,51,94,107,190,216,218,219,258].

Indeed, clinical data indicate a poor prognosis for patients affected by uterine cervical SCC rich in epithelial–mesenchymal hybrids and CSCs [92,271–273]. This is particularly evident in scarcely oxygenated uterine SCCs where HIF-1 is activated to promote EMT and stemness [209,210,270]. Most disappointingly, radiotherapy worsens the situation. In fact, the proportion of CSCs over total cancer cell number in cervical SCC tissues increases after radiation therapy [97], likely because of the radiations-induced vessel damage, and the resultant hypoxia [274].

6. Concluding Remarks and Future Directions

SCC of the uterine cervix is a leading cause of death among women worldwide, although its onset can be prevented in the first instance by anti-HPV vaccination [275] and, in the second instance, through screening programs for the detection and surveillance of squamous precancerous lesions [58,276]. If H-SIL is present, its surgical removal will be advisable which, however, does not cancel the possibility of relapse [276].

Concerning the treatment of advanced cervical SCC, the failure of conventional antineoplastic therapy invokes the design and evaluation of novel therapeutic approaches. Given the role that EMT plays in the onset, progression, or metastatization of SCC, and in its resistance to anti-tumor chemotherapy or radiations, particular attention should be paid to drugs countering the EMT process and possibly eradicating CSCs within cervical SCC.

In this regard, it has to be highlighted that switching off the PI3K/AKT/mTOR, MAPK/ERK, or Wnt/β-catenin signaling pathways can revert EMT to MET and halt tumor cell invasion [107,232,234,277–280]. In addition, antagonists of hypoxia-responsive genes have been shown to inhibit SCC cell invasion [281]. Moreover, H/MDM2 inhibitors can promote the differentiation of CSCs and, at the same time, augment their sensitivity to conventional cytotoxic drugs [107]. Similarly, a restored expression of p53-transcribed miRs, such as miR-34a and miR-203, diminishes cancer cell resistance to chemotherapeutic agents [34,51].

Definitely, a deeper understanding of the interplay among the HR-HPV proteins, oncosuppressor genes, cellular regulators of gene expression, inflammatory mediators, and growth factors involved in cervical carcinogenesis could provide clues to developing new strategies hindering the onset, growth, metastatization, or recurrence of uterine SCC.

Abbreviations

AKT	protein kinase B
CSC	cancer stem cell
E-cadherin	epithelial-cadherin
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EMT	epithelial-to-mesenchymal transition
ERK	extracellular-regulated kinase
FGFR	fibroblast growth factor receptor
HIF	hypoxia-inducible factor
HLA	human leukocyte antigen
H/MDM2	human/murine double minute 2
HR-HPV	high-risk human papillomavirus
H-SIL	high-grade squamous intraepithelial lesion
IFN	interferon
IL	interleukin
L-SIL	low-grade squamous intraepithelial lesion
MAPK	mitogen-activated protein kinase
MET	mesenchymal-to-epithelial transition
MHC	major histocompatibility complex
miR	microRNA
MMP	matrix metalloproteinase
mTOR	mammalian target of rapamycin
N-cadherin	neuronal-cadherin
NF-kB	nuclear factor-kappa B
PI3K	phosphoinositide-3-kinase
pRb	retinoblastoma protein
SCC	squamous cell carcinoma
SIL	squamous intraepithelial lesion
TGF	transforming growth factor
TNF	tumor necrosis factor
VEGF	vascular endothelial growth factor
Wnt	wingless-type mouse mammary tumor virus integration site
Zeb	zinc finger E-box-binding homeobox

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