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Review

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Crosstalk between cell fate and survival pathways during uterine cervical carcinoma progression: a molecular and clinical perspective

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Abstract

The development of uterine cervical cancer is primarily attributed to infection by high-risk human papillomaviruses (HR-HPVs). E5, E6 and E7, the three early oncoproteins of HR-HPVs, have been implicated in initiation and progression of cervical cancer. The intricate molecular mechanisms that orchestrate aberrant cellular transformations to establish carcinoma of the cervical epithelium following viral infections are poorly understood. Here, we discuss how deregulation of three major cell fate regulatory pathways, Hedgehog, Wnt and Notch, and cell survival strategies involving EGFR signaling and G1/S checkpoint contribute towards cervical cancer development and progression. Further exploration of protein interaction database has revealed several genes that are involved in cervical cancer initiation and progression, and the two crucial "driver" genes, MYC and CTNNB1 (β-catenin), have been identified as major players in protein-protein interaction network. GSK3β emerged as the key mediator of crosstalk between Hedgehog, Wnt and Notch signaling pathways. GSK3β regulates cytoplasmic stabilization and nuclear translocation of β-catenin, which further impacts the expression of MYC, critical for cell cycle progression. Collectively, our analyses suggest that combinatorial therapeutic targeting of these proteins may be more effective in blocking cervical cancer initiation and progression.

Keywords: Uterine cervical cancer, hedgehog, Notch, Wnt, G1/S checkpoint, GSK3β, β-catenin, MYC

INTRODUCTION

Uterine cervical cancer is a type of gynecological cancer that is virtually preventable by implementing highly effective primary (HPV vaccine) and secondary (Papanicolaou screening test) preventive measures. Despite significant improvements, these measures have not been appropriately implemented across all countries. As a result, cervical cancer is still the fourth most frequently diagnosed cancer amongst women worldwide, ranking only after breast, lung, and colorectal cancer[1]. In 2020, an estimated 604,127 new cases of cervical cancer (3.1% of all cancers) were reported globally, while approximately 341,831 deaths (3.3% of all cancers) ranked it as the fourth leading cause of cancer-associated death in women[1] [IARC Cervix uteri, source: Globocan 2020, Available from: https://gco.iarc.fr/]. Age-related cervical cancer incidence varied widely between countries and was estimated at 13.1 per 100,000 women worldwide. Globally, the average age at diagnosis of cervical cancer and death was 53 and 59 years, respectively[2]. In thirty-six countries, it is the top-ranked leading cause of cancer-related death, and the most commonly diagnosed female cancer in twenty-three underdeveloped or developing countries in sub-Saharan Africa, Melanesia, South America, and South-Eastern Asia including India[1].

Twelve oncogenic human papillomaviruses (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59), designated as high-risk human papillomavirus (HR-HPV), are classified as group 1 carcinogens by the International Agency for Research on Cancer Monographs and are essential but not enough cause for cervical cancer development[3]. Other significant associated factors include sexually transmittable infections (Human immunodeficiency virus type 1 and *Chlamydia trachomatis*), exposure to diethylstilbestrol (*in utero*), tobacco smoking, a high parity, and long-term use of estrogen–progestogen (combined) oral contraceptives[1]. Some recent studies evaluated the possible connections between the vaginal microbiome (VMB) and cervical cancer. The presence of a large number of anaerobic bacterial species such as *Gardnerella vaginalis*, *Sneathia, Megasphaera*, and *Prevotella* in vaginal microbiota is also associated with cervical cancer development[4].

Apart from all the above etiological and epidemiological factors, different molecular, cellular and signaling pathways and their deregulations are directly associated with the development of cervical cancer. In 2013, Vogelstein *et al.* developed a generalized theory of tumorigenesis by categorizing all the driver genes into twelve cellular pathways that regulate three core cellular processes: cell fate, cell survival, and genome maintenance[5]. Various genetic and epigenetic alterations of these drivers in relation to the development of cervical cancer have also been extensively studied. In this review, we have attempted to understand the association of cell fate and cell survival regulatory pathways and their crosstalk in the initiation and progression of cervical cancer.

CELL FATE REGULATORY PATHWAYS AND THEIR ASSOCIATION WITH CERVICAL CANCER DEVELOPMENT

Several genetic alterations during cancer development perturb the balance between differentiation and proliferation, favoring the latter. This causes a selective growth advantage as differentiating cells eventually die or become quiescent and alters the cell fate program during tumor progression[5]. Pathways that function through this mechanism include Hedgehog, Wnt/APC/β-catenin and Notch signaling cascades. All these pathways are well-studied self-renewal pathways that, through asymmetric cell division, maintain proper stemness and differentiation status of the cell and control mammalian cellular fate[6,7].

Persistent infection by HR-HPVs in the cervical epithelial basal layer disrupts the otherwise normal homeostasis of cervix[8]. Diverse molecular and dynamic communications among the various cells and their microenvironment are essential for maintaining this normal homeostasis[9,10]. The homeostasis is disrupted by carcinogenesis that involves aberrant cellular transformations through sustained perturbations of genomic and epigenomic landscapes, generating tumors comprising heterogeneous cell populations. Such tumors negatively impact the local homeostasis to fulfil their metabolic demands for growth and uncontrolled proliferation, eventually escaping the immune surveillance to invade or metastasize, initiating secondary tumors in distal tissues and organs, thus affecting systemic homeostasis and overall normal physiology[11,12]. Tumor malignancy induces homeostatic distress primarily through the release of a wide array of cytokines, neurohormonal and immune mediators, affecting body and brain functions[12]. Normal cervical epithelial homeostasis is maintained through the precise balance between basal cell proliferation, which increases cell density, and basal layer delamination and epithelial differentiation, which reduces basal cell density. After HR-HPV infection, enhanced basal cell proliferation followed by increased cell density disrupts the normal regulation of epithelial delamination and differentiation, establishing early stages of cervical cancer[8]. During this development, HR-HPVs first establish their infection through the cervical transformation zone (TZ), which comprises ectocervix, squamocolumnar junction, reserve cells and endocervical crypts. Then, damage to the ectocervix, a multilayered stratified squamous epithelium, enables HR-HPVs to reach the basal stem cells[8]. This passage leads to the expression of diverse genes to avoid immune surveillance and favors the permanent establishment of viruses in the basal layer. E6, an HR-HPV oncoprotein, is associated with the deregulation of normal cervical epithelial homeostasis and initial perturbation of the differentiation program, which is otherwise tightly regulated by different stem cell regulatory pathways involving Wnt and Notch signaling systems[8,13]. Deregulation of these pathways by genetic and epigenetic instabilities also disrupts normal cellular differentiation, leading to the erosion of barriers against dedifferentiation[7]. This phenomenon eventually generates cancer stem cells (CSCs) and tumor cell heterogeneity that contribute to the development and progression of cervical cancer[14].

Hedgehog signaling

Hedgehog (HH) signaling is one of the major self-renewal pathways during early embryogenesis. Canonical HH signaling pathway consists of three ligands, Indian hedgehog (IHH), Desert hedgehog (DHH) and Sonic hedgehog (SHH), a 12 transmembrane receptor called Patched 1 (PTCH1), a class F G protein-coupled receptor (GPCR) as well as signal transducer called Smoothened (SMO), a cytoplasmic protein named SUFU and three transcription factors (GLI1, GLI2 and GLI3)[15]. In the absence of ligands, GLI2/3 are attached to the SUFU by KIF7. Glycogen synthase kinase (GSK-3β), protein kinase A (PKA) and CK1α then phosphorylate GLI2/3, a phenomenon triggered by cyclic AMP but initiated by G protein-coupled receptor 161 (Gpr161). As a result, Cullin 1 (CUL1) and β transducin repeat-containing protein (β-TrCP) remove the C-terminal transcriptional activation domain of GLI2/3, converting them into repressors (GLI2R and GLI3R) [Figure 1A][16]. However, binding of ligands to the receptors and coreceptors initiates HH signaling cascade that promotes degradation of SUFU and translocation of activated GLI (GLI^A), either full-length GLI1 or truncated GLI2/3 into the nucleus [Figure 1B][17,18]. GLI2 acts as the major activator to trigger the expression of GLI1, the principal effector molecule and a transcription factor, which leads to the hyper-activation of several target genes associated with cell differentiation, proliferation, cell cycle progression, apoptosis, tissue patterning, DNA damage, angiogenesis, vascularization and cell-cell adhesion[17,19]. All these signaling components and cellular processes are manipulated by tumor cells during carcinogenesis as well as metastasis[20].

Both upregulation and downregulation of HH pathway components are frequently associated with various types of cancer, including cervical cancer. Chaudary *et al.* observed elevated expression of SHH (89%), IHH (85%), GLI1 (79%) and SMO (33%) in 85 human cervical carcinoma samples[21]. Addition of SHH ligand is

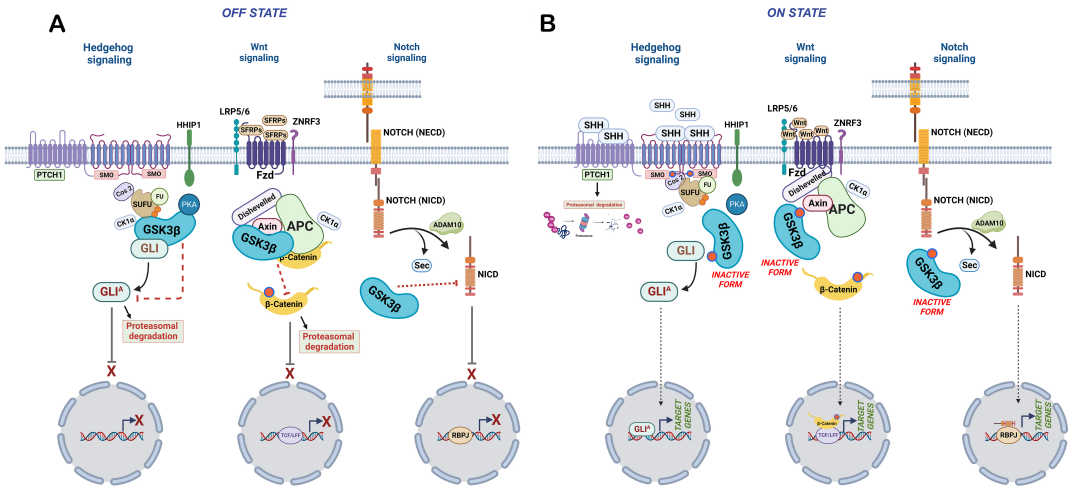

Figure 1. Cell fate regulatory canonical Hedgehog, Wnt and Notch signaling pathways in cervical cancer. (A) "*OFF STATE*" describes the cytoplasmic stabilization of GSK3β followed by proteasomal degradation or cytoplasmic restriction of the effector molecules; GLI^A, β-catenin and NICD for the three pathways, respectively, in the absence of ligands or in the presence of antagonists. As a result, no target genes are expressed. (B) "*ON STATE*" describes the inactivation of cytoplasmic GSK3β by the influence of suitable ligands. This helps in the nuclear translocation of effector molecules and the expression of their target genes. Created with BioRender.com.

associated with cell proliferation and migration of cervical cancer cells, while inhibition of SMO and GLI reduced cell numbers significantly and induced apoptosis by upregulating pro-apoptotic protein cleaved caspase 3[22]. Immunohistochemical analysis of 102 human uterine cervical cancer samples showed that reduced expression of PTCH1 was concordant with its genetic and epigenetic alterations due to deletion/promoter methylation during cervical cancer development[23]. The same study also correlated the high nuclear expression of GLI1 with reduced PTCH1 expression[23]. The landscape of genomic alterations in cervical carcinomas revealed an association of high expression of GLI2 with its copy-number gain[24]. In the presence of HPVE6, an elevated expression of SMO/GLI and loss of negative regulator SUFU further suggested a possible crosstalk between this etiological factor and signaling pathway, which facilitates cancer progression[25]. A recent study reported that SUFU is also involved in the suppression of tumor cell migration and DNA damage repair by inhibiting the activity of a transcriptional factor, ZNF281[26].

Notch signaling

Notch signaling is another pathway associated with cell division, differentiation, and survival[27]. Deregulation of both canonical and non-canonical Notch signaling plays diverse essential roles during cervical cancer progression. In canonical Notch pathway, transmembrane Notch receptors NOTCH1, NOTCH2, NOTCH3, and NOTCH4 of one cell interact with DSL (Delta, Serrate, and Lag2) ligands (Jagged 1, 2 and Delta-like 1, 3 and 4) present in the adjacent cells [Figure 1A][28]. This interaction triggers two sequential proteolytic cleavages in the NOTCH receptor. The first cleavage is a type of S2 cleavage, which is catalyzed by ADAM10 or TACE (TNF-α-converting enzyme; also known as ADAM17) metalloproteases to produce a substrate for S3 cleavage. This second cleavage is mediated by γ-secretase, an enzyme complex that contains presenilin, nicastrin, PEN2 and APH1, and releases active Notch intracellular domain (NICD)[28,29]. Subsequently, NICD is transported to the nucleus and heterodimerizes with DNA binding protein RBP-J (recombination signal sequence-binding protein Jκ), also known as CSL (*C*BF1, *S*u(H) and *L*AG-1) protein [Figure 1B]. The co-activator Mastermind (Mam) and other transcription factors replace co-repressors (Co-R), and are recruited to the CSL complex, helping NICD to act as a transcriptional activator of genes containing RBP-J binding sites[28,29]. In non-canonical, otherwise known as RBP-J or CSL-independent NOTCH signaling pathway, cell adhesion is promoted through R-Ras activation by NICD. It

may also interact with IKKα and LEF1 to regulate the NF-κB pathway or the Wnt pathway[30]. In the presence of HPV, non-canonical Notch signaling pathway can initiate human cervical carcinogenesis via PI3K pathway, by avoiding interaction with CSL[31].

Notch pathway was previously reported for its differentiation-promoting role during cervical cancer development from normal cervical epithelium[32]. This pathway plays both oncogenic and tumor suppressor functions in cervical cancers. In HPV16-induced primary human keratinocytes, activated Notch1 cooperates with HPV16 oncogenes E6 and E7, and promotes cellular transformation[33]. The RT-PCR analysis of over-expressed Notch1/JAGD1 revealed its association with tumor progression in human cervical cancer and poor patient survival[34]. A recent study further supported this proliferation of cervical cancer cells through DARS-AS1/miR-628-5p/JAG1 axis that activates Notch signaling pathway[35]. Both NOTCH1 mRNA and protein overexpression in cervical cancer cells were involved in tumorigenesis and suppression of apoptosis[36]. This pathway also facilitates anoikis resistance followed by cell migration and epithelial-to-mesenchymal transition when transfected with E6/E7 in an Akt-dependent manner[37,38]. The Cancer Genome Atlas (TCGA) project found that 15% of cases of primary squamous cell cervical carcinoma were associated with the loss of function alteration (deep deletion, truncating mutation, missense mutation) of FBXW7, a negative regulator of Notch pathway[24]. TCGA data also revealed copy number variations (CNVs) of NOTCH target genes, including HES1, CCND1, and Myc[24,27]. Overexpression of both HES1 and HES5 was associated with late-stage cervical cancer cases, but the poor prognosis was also observed in patients with early-stage cervical cancer[39]. NOTCH1 signaling modulates tumorigenic properties in cervical cancer cells through RhoC[40]. During its tumor suppressor functions, decreased NOTCH1 expression was found to be correlated with an increase in NUMB expression in cervical cancer compared to cervical intraepithelial neoplasia[41]. In vitro transient overexpression of Intracellular Notch (ICN1, 2, 3, 4) was associated with decreased cell proliferation[42]. A recent study revealed that low mRNA expressions of NOTCH1 and NOTCH3 were concordant with their high promoter methylation (92% and 61%, respectively)[43]. Further, Rodrigues *et al.* showed that meta-analysis of TCGA data was consistent with altered expression of Notch pathway components in > 80% of primary cervical cancer samples[27].

Wnt signaling

During embryonic development, critical regulation of cellular physiology involving proliferation, differentiation, adhesion, and polarity is associated with Wnt signaling pathway[44]. Depending on the particular combination of receptor and ligand, Wnt pathways are of three types: canonical, non-canonical planar cell polarity (PCP) pathway and non-canonical Wnt/calcium pathway. In canonical pathway, canonical Wnt ligands (Wnt1, Wnt2, Wnt3, Wnt3A, Wnt7 and Wnt8) bind to canonical Frizzled receptors (FZD1-5, FZD7-8 and FZD10) as well as LRP5/6 coreceptors (low-density lipoprotein receptor-related protein 5/6). These initiate intracellular signaling by sequestering the β-catenin degradation complex composed of the tumor suppressor adenomatous polyposis coli (APC), the scaffolding protein Axin, two kinases: CK1α (casein kinase 1α), GSK3β (glycogen synthase kinase 3β), and a phosphatase Protein phosphatase 2A (PP2A)[40]. This event helps in the stabilization of β-catenin in the cytoplasm by sequential phosphorylation at the C-terminal of β-catenin via Src (Y333) and Akt (S552). Finally, EGFR-mediated phosphorylation at Y654 further facilitates the PKA-mediated phosphorylation at S675 and nuclear translocation of β-catenin [Figure 1B]. In the nucleus, β-catenin can bind with members of the TCF/LEF (T-cell factor/lymphoid enhancer factor) family of transcription factors and recruit the transcriptional Kat3 co-activators p300 and/or CBP (CREB-binding protein) to transcribe Wnt target genes (c-MYC, Cyclin D1, EGFR, and CD44 *etc.*) and stimulate chromatin modifications[40]. In various cancers, epithelial-to-mesenchymal transition (EMT) is promoted by the down-regulation of E-cadherin (usually tightly associated with β-catenin in normal epithelium), which triggers the nuclear translocation of β-catenin, and activation of canonical Wnt signaling[45]. The absence of Wnt ligand-receptor interaction stimulates the

degradation complex, which then sequesters β-catenin through Axin and APC. CK1α then phosphorylates near the N-terminus of β-catenin at Ser45, while GSK3β phosphorylates at Thr41, Ser37 and Ser33. This phosphorylation recruits β-transducin-repeat containing protein 1 (β-TRCP1) at the phosphorylated N-terminus of β-catenin, causing ubiquitination of β-catenin by an E3 ligase [Figure 1A][40]. The term non-canonical pathway refers to a group of Wnt-dependent planar cell polarity (PCP) and Wnt/calcium signaling pathways that do not lead to the cytoplasmic stabilization of soluble β-catenin. In the planar cell polarity pathway, frizzled receptor (FZD6) mediates cellular signals through activation of c-Jun N-terminal Kinase (JNK), which further helps in nuclear translocation of transcription factor c-Jun[45]. Another non-canonical pathway, the Wnt/Ca^{2+} pathway, triggers the release of endoplasmic Ca^{2+} to the cytoplasm, possibly via G-proteins, and is involved in the activation of Phospholipase C (PLC) and Protein kinase C (PKC). Elevated Ca^{2+} can activate the phosphatase calcineurin, which dephosphorylates transcription factor NF-AT, inhibiting its nuclear accumulation. Higher levels of cytoplasmic calcium activates CamKII (calcium-calmodulin-dependent kinase II), PKC (protein kinase C), and calcineurin, which triggers activation and nuclear translocation of NFATs (nuclear factors of activated T cells) to initiate transcription of various genes[46].

Aberrant canonical Wnt signaling pathway contributes as a key player in stimulating the clonal selection of cancer stem cells (CSCs), and initiation, maintenance and development of various cancers, including cervical cancer[44,47]. Aberrant activation of Wnt pathway has been suggested as the *second hit* in HPV-immortalized human keratinocyte transformation during cervical cancer development[48]. Increased nuclear β-catenin expression is frequent in cervical cancer patients, whereas β-catenin mutation was a rare event here[48,49]. Frequent promoter hypermethylation of SFRP1, SFRP2, SFRP4, and SFRP5 during cervical cancer development were reported by different studies[50,51]. Ectopic expression of SFRP5 was involved in low expression of Wnt/beta-catenin downstream genes that suppressed colony formation and invasion of cervical cancer cells *in vitro*[51]. Rescued expression of SFRP1 and SFRP2 in CaSki cells suppressed nuclear accumulation of beta-catenin and reduced cancer cell growth. The same study also revealed that ectopic expressions of both proteins were associated with epithelial marker E-cadherin overexpression, and lower expression of SLUG, TWIST and SNAIL, the *three musketeers* of EMT[52]. Promoter of another negative regulator DKK1 was also hypermethylated, and its low expression during cervical cancer development is inversely correlated to the high TWIST expression[53,54]. AXIN and APC, two other critical components of β-catenin destruction complex, were rich in CpG islands in their promoters and were found to be methylated in cervical cancer[53]. Upstream activation of the Wnt/β-catenin pathway also resulted from overexpression of pathway activators such as Wnt ligands (WNT6, WNT10B and WNT14), frizzled receptors (FZD7. FZD10), and dishevelled (DVL1) in cervical cell lines[55-59]. A study also revealed that low expression of APC is associated with its deletion or promoter hypermethylation during the development of uterine cervical cancer. This study also revealed that overexpression of WNT3 and medium to high (74%-95%) expression of β-catenin/p-β-catenin (Y654) were related to the poor overall survival of patients[60]. Recently, it was reported that GSK3β was transcriptionally repressed by DAX1[61]. As a result, reduced proteasomal degradation, as well as increased nuclear accumulation of β-catenin, was observed. This phenomenon additionally promoted cell growth, tumorigenicity, and tumorsphere formation through activation of the Wnt/β-catenin pathway[61]. Further, TCGA data showed that 83% of all cervical cancer samples showed at least one mutation within the Wnt pathway components[62]. Feng *et al.* reported LGR6-mediated activation of Wnt/β-catenin pathway through the overexpression of TCF7L2 leading to β-catenin/TCF7L2/LGR6 feedback loop in $LGR6^{high}$ cervical cancer stem cells[63]. A recent Gene set enrichment analysis (GSEA) confirmed the interaction between OTX1 and Wnt9b[64]. This study showed that OTX1 silencing inhibited the overexpression of the Wnt antagonists such as APC, GSK3β and AXIN2 and increased levels of Wnt9b and β-catenin during cervical cancer progression[64].

CELL SURVIVAL REGULATORY PATHWAYS AND THEIR ASSOCIATION WITH CERVICAL CANCER DEVELOPMENT

Cell cycle checkpoints, especially G1/S checkpoint, and EGFR signaling pathway are the two interesting aspects of cell survival regulation. Both were reported to be involved in the development of diverse human cancers, including cervical cancer. Two important tumor suppressor genes (TSGs) RB1 and p53, also the guardians of cell cycle, control the G1/S checkpoint in normal cells [Figure 2][65]. HR-HPV infection is the most important etiological factor in cervical cancer development. The two main oncoproteins of HR-HPV, E6 and E7, play a crucial role in the progression of this disease[66]. E6 and E7 can deregulate all the major hallmarks of cancer and can achieve uncontrolled cell growth and proliferation by deactivating growth suppressors[67]. In HR-HPV-infected cells, E6 and E7 interact with p53 and RB1, respectively, and inhibit their normal tumor-suppressing activities [Figure 2][66]. HR-HPV E6 first interacts with host E6-associated protein (E6-AP), an E3 ubiquitin ligase, through their conserved LXXLL motif. This pair again forms a heterotrimeric complex with p53 (E6/E6-AP/p53 complex) that ultimately leads to the proteasomal degradation of p53, thereby preventing p53-mediated apoptosis[66,67]. E6 also inhibits apoptosis and increases chromosomal instability through the degradation of pro-apoptotic proteins, BAX and BAK[66]. This oncoprotein is further associated with the activation of reverse transcriptase telomerase (hTERT) that prevents telomere shortening, contributes to persistent proliferation and promotes immortalization[66,67]. E6 oncoprotein also inhibits the degradation of SRC-family kinases that are involved in the growth stimulation of HR-HPV-infected cells[66].

In HR-HPV-infected cells, another oncoprotein, E7, is involved in the inactivation of RB1 that controls G1/S phase transition in otherwise normal cells[66]. Under normal conditions, RB1 remains bound to the E2F family of transcription factors until the cells are fully equipped to enter the S phase, thereby preventing the expression of S phase genes[64]. E7 oncoprotein disrupts the association of RB1-E2F complex by targeting RB1 for proteasomal degradation, releases E2F transcription factors that constitutively activate E2F-responsive genes and induce hyperproliferation by forcing abnormal cell-cycle progression through premature S-phase entry[66,67]. The released E2F then transcribes cyclins E (CCNE1), cyclin A (CCNA1) and $p16^{INK4A}$ (CDKN2A). $p16^{INK4A}$ along with other INK4 family members ($p15^{INK4B}$, $p18^{INK4C}$, and $p19^{INK4D}$) inhibits cell cycle progression by blocking CDK4/6, thus acting as a tumor suppressor[67]. Surprisingly, the expression of $p16^{INK4A}$ in HR-HPV infected cells is upregulated by E7 oncoprotein[66]. For the survival of the RB1-depleted cervical cancer cells, $p16^{INK4A}$ is overexpressed to inhibit CDK4/6 function. This phenomenon is supported by cellular senescence and epigenetic de-repression through the H3K27-specific demethylase KDM6B, rather than inactivation of RB1[67]. Simultaneously, E7 is also involved in the inactivation of cyclin-dependent kinase inhibitors CIP1/WAF1 (p21) and KIP1 (p27) [Figure 2]. Thus, it is evident that apoptosis must be primarily prevented by E6 and further E7-mediated cell cycle deregulation synergizes cell immortalization and malignant transformation in normal cervical epithelium[66,67].

Apart from this mechanism, RB1 was downregulated through its deletion and/or promoter methylation during cervical cancer progression[68]. The same study also showed that alterations (deletion/promoter methylation) of RBSP3 were associated with overexpression of phosphorylated-RB1 (p-RB1) in cervical cancer tumor samples and poor prognosis of patients[68]. A tumor suppressor candidate, LIMD1, was associated with RB1 and inhibited the growth and metastases of cancer cells[69]. Both RBSP3 and LIMD1 are associated with the unphosphorylated state of RB1 and the negative regulator of cell cycle progression [Figure 2]. Chakraborty *et al.* showed that reduced protein expression of LIMD1 was associated with progression of cervical cancer development and correlated to its deletion/promoter methylation status[70].

EGFR is frequently overexpressed in cervical dysplasia and cancers[71]. Immunohistochemical analyses in 53 primary cervical cancers showed overexpression (64%) of EGFR protein that corresponded with lymph

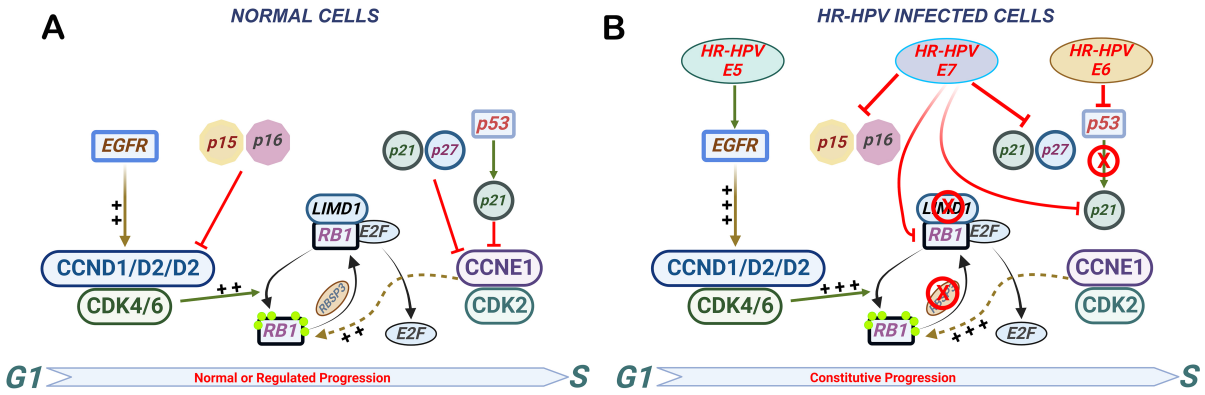

Figure 2. Cell survival regulatory pathways in cervical cancer. (A) In healthy cervical epithelial cells, RB1 normally associates with LIMD1 to sequester E2F during early G1 phase. Initially, CCND1/D2/D3-CDK4/6 complex phosphorylates RB1, which is further phosphorylated by CCNE1-CDK2 complex in late G1. Free E2F then only impacts the expression of cell cycle regulatory genes. Cyclin-CDK complexes are also negatively controlled by p15, p16, p21 (positively regulated by p53) and p27. EGFR positively regulates the CCND's expression but in a controlled manner. Phosphorylated RB1, also dephosphorylated by RBSP3, further complexes with E2F, resulting in normal control of cell cycle progression. (B) In the presence of HR-HPV oncoproteins, E5, E6 and E7, normally functioning cellular systems are completely jeopardized. E5 gets involved in constitutive activation of EGFR that helps in overexpression of CCNDs. On the other hand, E6 and E7 are associated with the degradation of p53 and RB1, respectively. E7 also deregulates p15, p16, p21 and p27. LIMD1 and RBSP3 are inactivated by genetic and/or epigenetic alterations. CCND1/D2/D3-CDK4/6 and CCNE1-CDK2 complexes constitutively phosphorylate RB1. Thus, E2F is free to transcribe cell cycle regulators abnormally, and the cell cycle loses its brake. Created with BioRender.com.

node metastasis[72]. EGFR amplification might be critical for cervical squamous cell carcinoma progression and strongly correlated with clinical parameters in addition to protein expression[73]. However, in cervical cancer, EGFR activating mutations were uncommon[73,74]. TCGA data analysis identified novel recurrent focal amplification (17%) at EGFR locus (7p11.2)[62]. High HPV16 E6 mRNA expression was associated with elevated membrane expression of EGFR[75]. It was also suggested that another less explored HPV oncoprotein, E5, immediately interacted with EGFR post-infection, and activated the downstream Ras-Raf-MAP kinase pathway or PI3K-Akt pathway that led to altered cell proliferation, angiogenesis, and apoptotic signaling in cervical cancer cells[76,77]. A recent study established a feedback loop between the JNK-dependent activation of EGFR signaling pathway and HPV E6/E7 expression that promotes cell proliferation, survival and EMT[78].

In Figure 3, we have summarized the cellular and molecular mechanisms that aberrantly transform the normal cervical epithelium to initiate cervical cancer. Stabilization of membrane EGFR by E5 oncoprotein of HR-HPVs along with degradation of p53 and RB1 by E6 and E7 oncoproteins of HR-HPVs, respectively, are involved in cell cycle deregulation. On the other hand, genetic and epigenetic alterations of different cell fate regulatory genes and/or proteins stabilize their effector molecules in the cell nuclei. These transcription factors then drive the expression of different genes, which further control cell survival strategies and deregulate cell cycle progression [Figure 3]. Together, these major events are critically linked to uterine cervical cancer initiation and progression.

HOW DO THESE PATHWAYS CROSSTALK?

The information we have gathered until now tells us about cell cycle progression through deregulation of cell fate and cell survival strategies adopted by tumor cells. However, how easily can they maintain this relationship amidst the complex milieu of diverse cellular functions? Ongoing research is behind this *Holy Grail*.

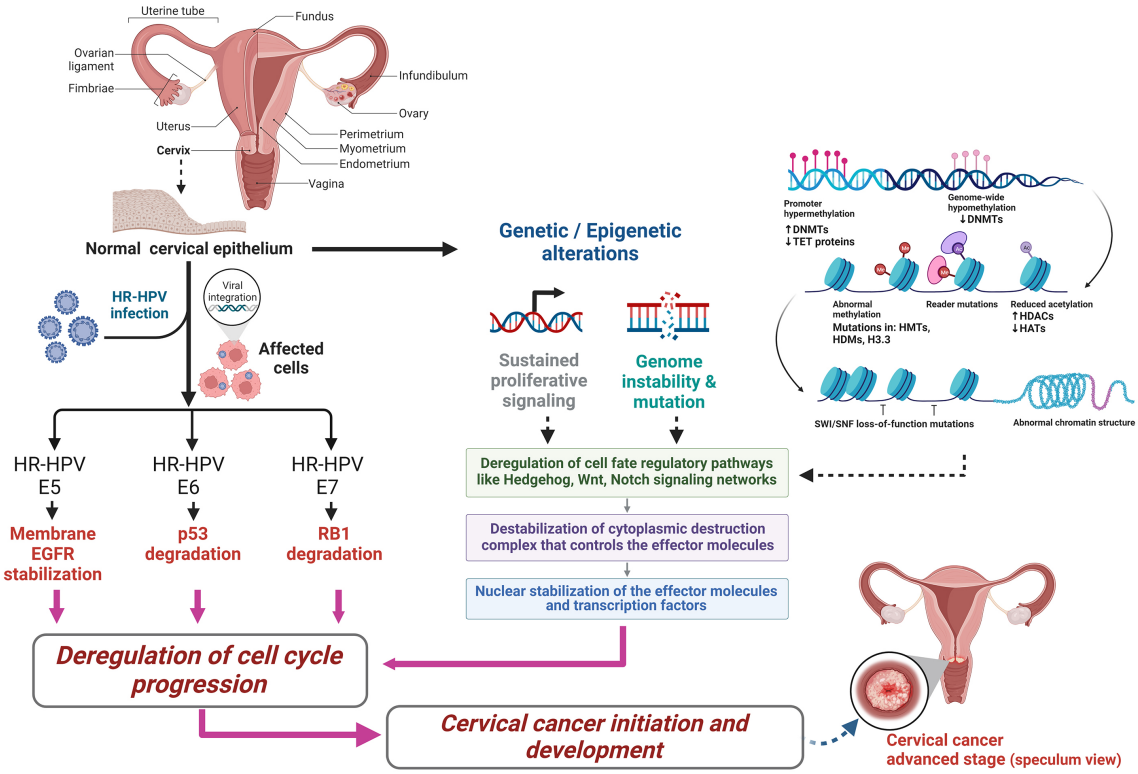

Figure 3. Summary of deregulation of cell fate and cell survival regulatory pathways under the influence of HR-HPVs during cervical cancer initiation and development. The cell regulatory systems are generally destabilized by HR-HPV oncoproteins, while the cell fate regulators are disrupted primarily by genetic and/or epigenetic alterations. Both systems cooperate to aberrantly transform healthy cervical cells and deregulate cell cycle progression. Created with BioRender.com.

Hedgehog, Notch and Wnt pathways act through their effector molecule(s), GLI1/2/3, RBPJ, also known as CSL (*C*BF1, *S*u(H) and *L*AG-1) and β-catenin (CTNNB1), respectively. Functionally, all these effectors are transcription factor(s) and they work with other transcriptional co-factors to transcribe their downstream genes. These sets of genes drive cell proliferation and growth progression. The Hedgehog pathway effector(s), GLI proteins, can directly bind to the promoter of its target genes, regulating their expression[79]. GLI1 and GLI3 proteins recognize the 5'-GACCACCCA-3' sequence, while GLI2 binds at the 5'-GAACCACCCA-3' sequence[79]. The major target genes of Hh signaling pathway include PTCH1, PTCH2, and GLI1 itself; while others are HHIP, proliferation-promoting genes (CCND1 and MYC), cell cycle regulators (CCND2, CCNE1), apoptosis regulator (BCL2), epithelial-to-mesenchymal transition genes (SNAIL), stem cell self-renewal (NANOG and SOX2), Notch pathway ligand (JAG1), and different members of Wnt signaling pathway[79,80]. The target genes for canonical Notch signaling are largely governed by the DNA binding Su (H) motif of CSL (RBPJ), and recognize the consensus 5'-CGTGGGAA-3'[81,82]. A nuclear complex consisting of CSL, NICD, Mastermind, p300 and HAT induces the transcriptional activation of downstream targets of Notch pathway that include HES1, HES5, HES7, HEY1, HEY2 and HEYL[83]. Additionally, MYC, CCND1 and p21/Waf1 are also targets of Notch signaling pathway[29]. Activation of the canonical Wnt pathway during the development of cancer leads to nuclear translocation of Y654-p β-catenin. There it interacts with TCF/LEF, its co-transcriptional activator, that binds to 5'-CCTTTGATC-3' sequence and transcribes target genes (PDK1, MTC1, MYC, CCND1, COX2, AXIN2, EGFR and CD44)[84]. Nuclear β-catenin further interacts with NICD and controls the expression of Notch ligand genes, including DLL1, DLL3, DLL4, JAG1 and JAG2, due to the presence of TCF/LEF-binding site within the promoter region of these genes[83].

Activation of Hedgehog and Wnt signaling pathways accelerates nuclear accumulation of GLIs and β-catenin, respectively, while both pathways are connected by molecules such as GSK3β, CK1α, SUFU, p53, PTEN, SMO and KRAS[85]. Effector molecules GLIs and β-catenin are involved in the activation of Notch pathway ligands, cell cycle regulators and EGFR. GLI1 is involved in the transcription of G1/S cyclins (CCND1 and CCNE1)[80]. CCND1 is also a target gene of β-catenin[84]. Deregulated expression of these cyclins with their respective CDKs can influence aberrant cell cycle progression during tumorigenic development. RB1, along with LIMD1 and E2F, controls cell cycle progression through G1/S phase [Figure 2][69]. Sequential phosphorylation or degradation of RB1 allows the progression of cell cycle through this phase. CCND1-CDK4/6 complex is involved in phosphorylating RB1 during the early G1 phase, whereas degradation of RB1 is facilitated by HPVE7 oncoprotein during the early infection stage by HR-HPV [Figure 2][66,86]. During late G1 phase, CCNE1-CDK2 further hyper-phosphorylates RB1[87]. In the S-phase, RB1 is fully phosphorylated by CCNA1-CDK2 complex and this state is maintained until mitosis is initiated[87]. Abnormal progression of cell cycle can be controlled by dephosphorylation of RB1, which is mediated by RBSP3 [Figure 2]. However, as mentioned earlier, downregulation of this gene/protein cannot rescue RB1 and the cell from deregulation of crucial signaling pathways.

The network

Using the STRING database, we predicted functional interactions among the cell fate and cell survival regulatory pathway proteins and constructed a protein-protein interaction (PPI) network based on both known and predicted PPIs [Figure 4][88]. Further, hub genes of the PPI network were identified using Cytoscape (version 3.9.1) with additional CytoHubba plug-in[89]. Nested network style and yFiles radial layout algorithm (yFiles Organic Layout and yFiles Remove Overlaps) were used to redraw the network [Figure 4]. We then calculated node degrees for each protein to determine the most influential proteins in the network. MYC, CTNNB1, GSK3B, SHH, GLI2, AXIN1, EGFR, GLI3, NOTCH1 and RBPJ were sequentially identified as the top 10 hub proteins using the Bottleneck method in this network [Figure 4][90]. Among these proteins, the genes encoding MYC, CTNNB1, AXIN1, EGFR and NOTCH1 proteins are classified as the potent "driver" genes, while the rest are "passengers"[5]. This observation suggests that hub proteins might play precise but critical roles in cervical cancer progression. Furthermore, these proteins might also be potential therapeutic targets in the future, being extracted by Bottleneck method[91]. Here, our discussion primarily focuses on the top three proteins in the analyzed network according to their connectivity levels.

DISCUSSION

From our analyses, MYC, CTNNB1 and GSK3β appeared as the most crucial and connected proteins in the network [Figure 4]. GSK3β is established as the first level of crosstalk molecule because of its involvement in regulating all three cell fate pathways. It is an unconventional serine/threonine protein kinase (STK) that generally requires pre-phosphorylated substrates for phosphorylation. Cytoplasmic stabilization of GSK3β is associated with the "*OFF STATE*" of Hedgehog, Notch and Wnt signaling systems [Figure 1A]. In this state, all the effector molecules of these pathways, GLI, NICD and CTNNB1, are trapped in the cytoplasm by their respective destruction complex and are unavailable for nuclear translocation. As a result, no downstream target genes of these pathways are expressed to regulate cellular fate. In the "*ON STATE*", the signaling dynamics of the three pathways change completely [Figure 1B]. HR-HPVE5 induced EGFR/MAPK pathway phosphorylates GSK3β at its Serine9 position[92]. This phosphorylated GSK3β cannot hold back GLI, NICD and CTNNB1 in the cytoplasm further. As a result, nuclear translocation of these transcription factors induce the expression of their respective target genes, which initiate the next level of deregulation in cells. Thus, GSK3β appears as the "non-hub–bottleneck node" protein in this network as it is involved in connecting all the three major cell fate regulatory pathways [Figure 5].

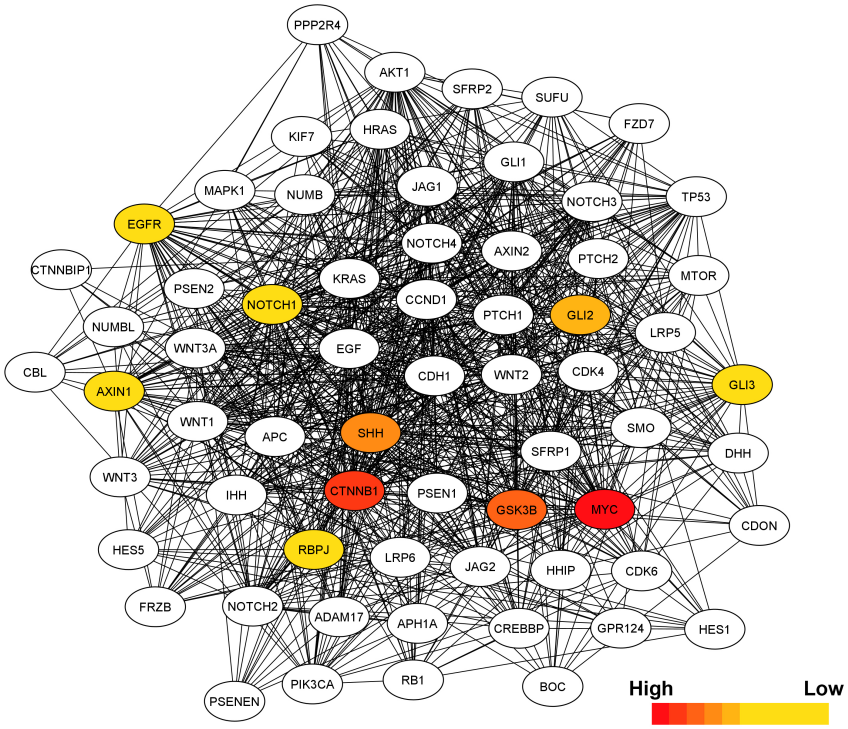

Figure 4. Protein-protein interaction (PPI) network with known genes of cell fate and cell survival regulatory pathways. MYC, CTNNB1, GSK3B, SHH, GLI2, AXIN1, EGFR, GLI3, NOTCH1 and RBPJ are identified as the top 10 hub proteins using the Bottleneck method. Among these proteins, MYC, CTNNB1 and GSK3B appeared as the most connected hub proteins in the network. Color bar indicates high (red) to low (yellow) connectivity of the protein hubs.

Among the three effector molecules, CTNNB1 or β-catenin established itself as the second-level hub protein in this network [Figure 4]. Even though GLI and NICD function as transcription factors of several target genes that are associated with deregulation of cell growth and survival, CTNNB1 is the key player. After phosphorylation of GSK3β at Serine9, dissociation from the E-cadherin (CDH1) pool and cytoplasmic stability of CTNNB1 increase due to Akt-mediated phosphorylation of β-catenin at S552[93]. Next, EGFR/Src mediated S333 and Y654 phosphorylation facilitates nuclear translocation of this protein. Finally, Protein kinase A (PKA) phosphorylates the C-terminal Serine675 that promotes transcriptional activity of β-catenin[93]. In the nucleus, phosphorylated (C-terminal) and hyperactivated CTNNB1 drives aberrant upregulation of CCND1, MYC, EGFR, MMP7, COX-2, CD44 and many epithelial-to-mesenchymal transition (EMT) related proteins[84,94]. Expression of these diverse proteins then sets a cascade of deregulation in cells. CCND1 and MYC give cells growth advantages positively supported by EGFR signaling cascade[95]. EFGR also provides a positive feedback loop to CTNNB1 for its nuclear translocation[93]. β-catenin is involved in the expression of SNAIL1, an essential EMT marker, overexpression of which is directly associated with loss of cell-cell junction as well as cell invasion and metastasis in cancer[96]. CTNNB1 can be projected as the junctional hub or the first "hub-bottleneck node" protein as it is controlled under the cell fate pathways and, on the other hand, has the ability to control different regulatory proteins associated with diverse cellular processes, including cell growth and differentiation during cancer development [Figure 5].

The highest level of connectivity was observed through MYC protein in this network [Figure 4]. MYC has been identified as the target protein of effector molecules of all three cell fate regulatory pathways[79,80,84,97]. MYC, acting as a transcription factor, regulates ~15% of all genes involved in diverse cellular mechanisms,

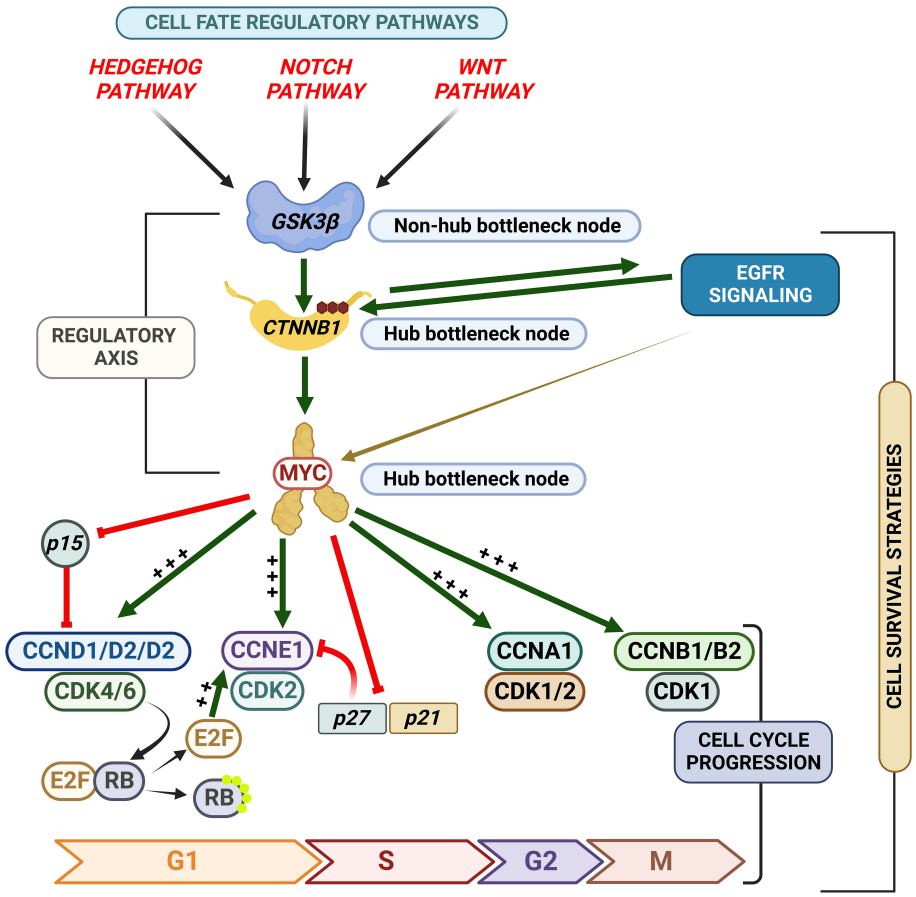

Figure 5. Crosstalk between cell fate and cell survival pathways during cervical cancer development. GSK3β, CTNNB1 and MYC co-operatively mediate crosstalk between cell fate and cell survival regulatory mechanisms. GSK3β, a "non-hub-bottleneck node" protein in this network, acts as the crosstalk molecule between all three major cell fate regulatory pathways. MYC is the most connected protein and the "hub-bottleneck node" in this network, as it controls cell survival strategies along with cell cycle progression. CTNNB1, another "hub-bottleneck node" of this network, is the connector between GSK3β and MYC. Thus, GSK3β/CTNNB1/MYC regulatory axis concurrently controls cell fate and cell survival strategies during cervical cancer initiation, development and progression. Created with BioRender.com.

including cellular proliferation and differentiation, and cell cycle progression[98,99]. Deregulation of MYC is reported in ~70% of all human cancers and its aberrant expression is directly correlated with tumor initiation and maintenance[99]. Further, this protein has the ability to regulate all the hallmarks of cancer[99]. MYC tethers with MYC-associated factor X (Max) and binds to E-boxes with the consensus (sometimes non-consensus) core sequence 5'-CACA/GTG-3' and impacts transcriptional activation of several target genes involved in cell cycle regulation[100]. The major target proteins in this category are CCND1, CCND2, CCND3, CCNE1, CCNE2, CCNA2, CCNB1, CDK1, CDK2, CDK4, CDK6, CDK7 (a subunit of cyclin-dependent kinase (CDK) activating kinase (CAK)), CDC25A and E2F1[101].

This clearly indicates that MYC controls the expression of all the major cell cycle regulators. Sequential phosphorylation of RB1 by various cyclin-CDK complexes throughout different phases of cell cycle allows the activation and accumulation of E2F transcription factors[87,101,102]. This phenomenon induces the expression of S phase-related proteins that are involved in DNA replication[101]. Finally, MYC-regulated CCNB1/B2-CDK1 complex helps the cells during the M-phase transition [Figure 5][102-104]. MYC also functions as a transcriptional repressor while binding with MYC-interacting zinc finger protein-1

(Miz-1)[100]. Surprisingly, the most important proteins in this group, CDKN2B ($p15^{INK4B}$), CDKN1A ($p21^{CIP1/WAF1}$) and CDKN1B ($p27^{KIP1}$), are cyclin-dependent kinase inhibitors that interfere with cell cycle progression [Figure 2][102]. These proteins either inhibit the interaction between cyclin and CDK, or block the cyclin-CDK complex to impose a regulation on growth-promoting activity. In response to continuous growth signaling, cells always adopt this gatekeeping measure to avoid abnormal and uncontrolled proliferation. MYC-mediated repression of CDKN2B, CDKN1A and CDKN1B removes these cell cycle brakes and overcomes the mortality of cell growth. Thus, MYC appeared as the central hub protein and the second "hub-bottleneck node" in this network, connecting the two major core cellular processes, cell fate and cell survival systems [Figure 5].

CONCLUDING REMARKS AND FUTURE DIRECTIONS

From the above discussion, it is clear that cell fate and regulatory pathways work together via the three important crosstalk molecules, GSK3β, CTNNB1 and MYC. These three proteins are involved through a common axis to regulate cells' fate followed by their survival [Figure 5]. GSK3β can directly regulate the nuclear translocation of CTNNB1 as well as CTNNB1-dependent expression of MYC[105]. On the other hand, GSK3β is also involved in the degradation of MYC by phosphorylating it at Threonine58[106,107]. MYC further stimulates cell cycle progression and proliferation through both overexpression and under-expression of positive and negative regulators of cell cycle, respectively [Figure 5]. GSK3β, CTNNB1 and MYC are collectively associated with multiple "driver genes" such as CCND1, CDH1, CDKN2A, CDKN2C and many others, which are critical for the regulation of cell cycle progression, cellular differentiation and survival[5]. CTNNB1 and MYC were identified as functionally altered proteins in the integrated cell circuit, which were genetically reprogrammed to manifest the six hallmarks of cancer and dictate malignant growth[108]. MYC was also identified as one of the four original "Yamanaka factors" (collectively known as OSK*M*)[109]. It can manipulate cell fate to generate induced pluripotent stem cells (iPSCs) from somatic cells. Self-renewal properties and associated signaling pathways, along with reprogramming potency of iPSCs by the influence of Yamanaka factors, are also mimicked by cancer cells to produce stemness among themselves[110]. GSK3β, CTNNB1 and MYC have the ability to influence diverse cellular functions, thus affecting cell physiology to initiate and develop cancer.

GSK3β, CTNNB1 and MYC are directly associated with the progression of cervical cancer. Inactivation of GSK3β enhances cervical cancer progression and invasion, and induces drug resistance[111]. Nath *et al.* also showed that activation of GSK3β with nimbolide and iAkt (Akt inhibitor-VIII) can induce apoptosis, and these two molecules can be further exploited for therapeutic interventions of cervical cancer[111]. The oncogenic character of CTNNB1 in cervical carcinogenesis was deciphered years ago[112,113]. Suppression of β-catenin expression is associated with anti-proliferative activity and tumor inhibition in cervical cancer[114]. CTNNB1-mediated inhibition of cervical cancer cell proliferation was also reported via NHERF1-induced suppression of alpha-actinin-4 expression[115]. On the other hand, LGR5-induced overexpression of β-catenin was associated with cervical cancer growth, further indicating its oncogenic character during cervical cancer development[116]. CTNNB1 is also an EMT marker for cervical cancer[114]. All these oncogenic roles make β-catenin a potent "druggable" target, although this cannot be fully achieved due to adverse side effects. Only a small-molecule MSAB is known to directly target Armadillo repeat region 2 of CTNNB1 and inhibit its oncogenic signal[117]. Different classes of therapeutic agents such as enzyme inhibitors, β-catenin/TCF antagonists, and transcriptional regulators have been developed to target β-catenin indirectly[114,118]. XAV939, K-756, and WXL-8 are the tankyrase inhibitors that stimulate β-catenin degradation by stabilizing Axin[114]. PFK115-584 and CFP049090 inhibit β-catenin/TCF complex in a dose-dependent manner[119]. Aspirin and indomethacin attenuate β-catenin by modulating TCF activity[120]. Some other molecules like CRT3, iCRT5, iCRT14, BC21, BC23, HI-B1 also inhibit β-catenin-TCF4 interaction and suppress tumor

growth[114]. PRI-724 was reported to inhibit the interaction between CTNNB1 and its transcriptional co-activator CBP[121].

MYC gene amplification and protein overexpression in HR-HPV-infected cervical lesions and cervical cancer were reported previously[122,123]. Fluorescence *in situ* hybridization (FISH) experiments revealed altered MYC expression in HR-HPV-infected cervical cancer cells due to HR-HPV genome integration within the MYC locus (chromosome band 8q24)[64]. Additionally, using FISH, amplification of MYC was investigated in cervical epithelial exfoliated cells for screening of precancerous lesions of cervical carcinoma[124]. Frequent inactivation of FBW7 in cervical cancer (13%) promotes overexpression of MYC and cancer progression[125]. MYC has been described as the "undruggable" target for many decades[99]. But recently, both direct and indirect therapeutic targets of MYC are in clinical trials[99,126,127]. Omomyc, one of the most promising therapeutic drugs directly targeting MYC, is currently under pre-clinical trial[126]. Among the different alternative approaches to inhibit MYC, targeting MYC transcription and translation, as well as its stability, are crucial[127]. The main indirect approach to inhibit MYC is to target MYC/MAX heterodimer. Different small molecule inhibitors such as 10058-F4, 10074-G5, Mycro3, MYCMI-6 and KJ-Pyr-9 were reported to interfere with MYC/MAX interaction[126].

Collectively, we have attempted to understand the critical roles of three important cell fate regulatory pathways, Hedgehog, Wnt and Notch, in the initiation and progression of cervical cancer. We further identified crosstalk molecules among these pathways, which are involved in the regulation of cellular growth, proliferation and survival. Finally, we have discussed the available drug regime against the identified valuable crosstalk molecules. We found that all available therapeutic approaches are primarily targeting a single molecule at a time. This might not be effective in treating cervical cancer or other cancers due to the complexities of disease progression and possible deregulation of crucial cellular processes. We predict that applying combinatorial therapies against the crosstalk molecules may achieve better clinical outcomes in the future.

DECLARATIONS

Authors' contributions

Drafted and edited the review, created figures and analyzed data: Samadder S
Data mining, analysis and presentation: Paul P
Edited the review and created figures: De A

Availability of data and materials

All data mined and/or generated for creating PPI network will be made freely available upon request.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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