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Progress in the Study of Significant Mutated Genes and Molecular Biological Factors in Cervical Tumors

Jiajing Liang[1,2#], Xiuling Wei[1,2#] & Shibo Zhao[3]

[1] Department of Obstetrics and Gynecology, Southwest Hospital and Baise People's Hospital, Affiliated to the Right River College of Ethnic Medicine, Guangxi 533000, China
[2] Collage of Graduate, Youjiang Medical University for Nationalities, Guangxi 533000, China
[3] Collage of Clinical Medicine, Youjiang Medical University for Nationalities, Guangxi 533000, China
Correspondence: Shibo Zhao, Collage of Clinical Medicine, Youjiang Medical University for Nationalities, Guangxi 533000, China.
[#] These authors shared first authorships.

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Abstract

Cervical cancer is the most prevalent gynecologic malignancy in developing countries, with incidence and mortality rates continuing to rise. Despite widespread research on cervical cancer, the specific mechanisms and synergistic factors underlying its occurrence remain unclear. In recent years, there has been a growing interest in the relationship between gene mutations and cervical cancer. Numerous studies have demonstrated that alterations in oncogenes, tumor suppressor genes, and related regulatory genes are closely associated with the development and progression of cervical cancer. The application of genome sequencing technology in malignant tumors has allowed for the identification of additional gene mutations in cervical cancer. By identifying significantly mutated genes, we can further target malignancy driver genes, which may be the key to uncovering the intrinsic mechanisms of sexual tumors. Therefore, a review of the current status of research on mutated genes in cervical cancer and factors associated with recurrence after treatment of early-stage cervical cancer can provide new insights for mechanistic studies, diagnosis, and targeted therapy of cervical cancer.

Keywords: cervical tumor, genetic study, early-stage cervical cancer, recurrence factors, prognosis, research progress

1. Introduction

Cervical cancer is the most common malignancy in women and its incidence has been increasing year by year, especially among younger women. Its incidence is second only to breast cancer. Although the use of the human papillomavirus (HPV) vaccine and cervical cancer screening have significantly reduced the incidence of cervical cancer, it remains high in developing countries. In China, the incidence and mortality rates of cervical cancer have risen to the top of the list of malignant tumors affecting the female

reproductive tract. The clinical application of cervical cancer screening and triple-step screening technology has led to the early detection and timely treatment of more and more cervical cancer patients, improving their tumor-free survival. However, the recurrence of early-stage cervical cancer patients after treatment is becoming a growing concern.

In recent years, both domestic and foreign scholars have conducted research and analysis on factors related to possible recurrence in patients with early-stage cervical cancer, with significantly mutated genes and molecular biological factors being popular areas of investigation. This paper aims to review the relevant literature published in this field at home and abroad. While it is well known that HPV infection is the primary cause of cervical carcinogenesis, most women experience only transient infections. Only about 1% of women with persistent high-risk HPV infection will develop cervical cancer.

The pathogenesis and associated risk factors for the development of cervical cancer are not yet fully understood. Significantly mutated genes are genes that may have biological significance at the genetic level, and their identification can help to target disease driver genes by considering mutation hotspots, function, and evolutionary conservatism screening. For example, human leukocyte antigen A (HLA-A), cysteine aspartate-specific protease 8 (CASP8), ErbB-2 receptor tyrosine kinase 3 (ErbB-3) and transforming growth factor β type II receptor (TGFBR2) are significantly mutated genes in cervical cancer. Although the mechanisms of other genes have been more thoroughly explored in cervical cancer and related fields, the study of HLA-A, CASP8, ErbB-3, and TGFBR2 is still in its infancy. As the first significant mutated genes detected in cervical cancer, there are still few reports on the exploration of their related mechanisms in this field. In this paper, we review the newly identified significant mutated genes HLA-A, CASP8, ErbB-3, and TGFBR2, as well as other biological factors associated with cervical cancer.

2. Associated Significant Genes

2.1 HLA-A

The human major histocompatibility complex, HLA, is located at 6p21.31 and is an important component of the host cell-mediated immune response to viral infection. It is closely related to human immune system function and tumor development. HLA is mainly divided into class I and class II genes. The classical HLA class I genes, HLA-A, HLA-B, and HLA-C, are expressed on most nucleated cells and encode classical HLA class I molecules (endogenous antigen-presenting molecules) that present peptide antigens to CD8+ cytotoxic T cells. CD4+ T lymphocytes mediate immunity. Studies have shown that immunosuppressed individuals are more likely to develop persistent HPV infection, cervical intraepithelial neoplasia (CIN), and carcinoma, suggesting that the evasion of immune surveillance may be associated with the transformative potential of HPV and the rapid progression of cervical cancer. Altered HLA expression is a common mechanism by which tumors evade host immune surveillance. Complete loss of human HLA-Ⅰ molecules leads to resistance to cytotoxic T lymphocyte-mediated lysis.

Studies have demonstrated that the expression of HLA molecules is a crucial prognostic factor in patients with various types of tumors, including rectal, endometrial, ovarian epithelial, and prostate cancers (Mehta AM, Jordanova ES, Kenter GG, et al., 2008). A small study evaluating cervical cancer cell suspensions found that 90% of tumors exhibited alterations in the HLA gene, including mutations, loss of heterozygosity, and other genetic alterations (Litwin TR, Clarke MA, Dean M, et al., 2017). Among these, partial deletion of HLA-class I molecule expression in cervical cancer can result in the loss of tumor antigen expression and immune cell recognition, which may be associated with poorer overall and disease-free patient survival.

In a study published in Nature, whole-genome sequencing of cervical squamous carcinoma tissues revealed that mutations in HLA-A and HLA-B accounted for 8% and 6%-9% of cases, respectively. HLA-A was defined as a significant mutated gene in cervical carcinoma for the first time. Ferns et al. (Ferns DM, Heeren AM, Samuels S, et al., 2016) also observed a trend of complete loss of HLA-A in primary cervical squamous cell carcinoma by examining different cervical cancer tissues. Significant loss of HLA-A was evident in cervical squamous cell carcinoma metastases, and only significant loss of HLA-B/-C was detected in cervical adenocarcinoma. Furthermore, this study found that abnormal expression of HLA class I genes

was also associated with tumor size and involvement parameters.

2.2 CASP8

Caspases are a family of aspartic acid-based cysteine proteases whose members are abnormally expressed or active in a variety of pathological states, including malignancy. Caspase-8, encoded by CASP8 on chromosome 2q33, is an apical Caspase that acts on death receptor-ligand interactions to induce apoptotic processes, and its activation leads to downstream Caspase activation, which can alter cell behavior in various ways from apoptosis, necrosis, cell adhesion and migration (Keller N, Ozmadenci D, Ichim G, et al., 2018). Under normal conditions, Caspase-8 exists as a monomeric zymogen, and membrane-associated death receptor signaling complexes such as the death-inducing signaling complex (DISC) bind to Caspase-8 to promote zymogen maturation and thus apoptosis. In recent years, it has also been found that Caspase-8 can also act through signaling pathways such as Toll-like receptors, antigen receptors, microtubule scaffolds of the death domain, and unlinked integrins (Graf RP, Keller N, Barbero S, et al., 2014).

Caspase-8 inactivation is essential for tumor evasion of the apoptotic process; therefore, reduced Caspase-8 expression or dysfunction promotes the development, progression, and treatment resistance of various malignancies, such as head and neck cancer, colorectal cancer, gastric cancer, and neuroblastoma (Mandruzzato S, Brasseur F, Andry G, et al., 1997; Gao W, Weng J, Gao Y, et al., 2013; Lu H, Jiang PC, Zhang XD, et al., 2015). In cervical cancer, Caspase-8 has been identified as a significantly mutated gene. Aréchaga-Ocampo et al. (Laniewski P, Barnes D, Goulder A, et al., 2018) showed differential expression of Caspase-8 and Caspase-9 in cervical cancer samples and cell lines, suggesting multiple alterations of the Caspase pathway in cervical cancer. Ekonomopoulou et al (Clarke MA, Rodriguez AC, Gage JC, et al., 2012) showed that Caspase 8 and Caspase-9 were differentially expressed in cervical cancer by Wu et al (Reis Machado J, da Silva MV, Cavellani CL, et al., 2014) found that Tumor necrosis factor α-induced protein8 (TNFAIP8) was found in HeLa cells of cervical cancer. Wang et al. (Richards KH, Wasson CW, Watherston O, et al., 2015) found that inhibition of Caspase-8/-3/-9 activity significantly reduced the activity of B-cellassociated protein 31 (B-CAP 31) in cervical cancer HeLa cells, and that silencing of TNFAIP8 increased the sensitivity to cisplatin treatment and promoted the role of Caspase-3/-8 in apoptosis. Kong et al (Zheng JJ, Song JH, Yu CX, et al., 2019) found that ubiquitin ligase Cullin7 (CUL7), an important member of the Cullin family, promoted ubiquitination of Caspase-8 by promoting the development of cervical cancer. CUL7, an important member of the Cullin family, was found to prevent Caspase-8 activation by promoting Caspase-8 ubiquitination modification, thereby limiting exogenous apoptotic signaling. The search for molecular regulators of tumor cell growth has been an important goal of malignancy research, and the in-depth study of Caspase-8 and apoptosis mechanism may be important for the prevention and treatment of cervical cancer and the development of Caspase-8 as a predictor of malignancy.

2.3 ErbB-3

The human epidermal growth factor receptor (HER) family of tyrosine kinase transmembrane protein receptors, including ErbB-1 [epidermal growth factor receptor (EGFR) or HER-1], ErbB-2 (HER-2), ErbB-3 (HER-3), and ErbB-4 (HER-4), are involved in a variety of complex and tightly controlled signaling pathways that regulate cell proliferation, migration, invasion, and survival (Paolini F, Curzio G, Melucci E, et al., 2016). -EGFR and HER-2 are established proto-oncogenes and their overexpression leads to the development of malignant tumors. itself has minimal kinase activity and needs to be regulated by its ligand to form a heterodimer with another member of the family, which in turn triggers multiple signaling cascades leading to downstream effects (Collier TS, Diraviyam K, Monsey J, et al., 2013). Activation of the PI3K/protein kinase B (AKT) pathway is essential for cancer cells to evade cell death upon exposure to toxic stimuli (Gupta SM & Mania-Pramanik J, 2019), while the HER-3 intracellular structural domain has six potential sites of heterodimerization. The intracellular structural domain of HER-3 has six potential PI3K binding sites that strongly activate the PI3K pathway when these sites interact with subunits in PI3K (Verlingue L, Hollebecque A, Lacroix L, et al., 2018), thus suggesting that activation of this pathway can increase the development of metastasis in malignant tumors. Overexpression or aberrant activation of the

receptor tyrosine kinase family or its direct downstream targets leads to activation of MAPK/ERK, which in turn leads to activation of multiple substrates and cell proliferation; this pathway is more active in cell proliferation and invasion than the PI3K/AKT pathway (Burotto M, Chiou VL, Lee JM, et al., 2014). It has been demonstrated that ErbB-3 is overexpressed in a variety of malignancies such as melanoma, breast cancer, and pancreatic cancer, and its activation is closely related to the development of malignancies, poor prognosis, and drug resistance (Capparelli C, Purwin TJ, Heilman SA, et al., 2018; Morrison MM, Williams MM, Vaught DB, et al., 2016; Liles JS, Arnoletti JP, Tzeng CW, et al., 2010; Du J, Zhou S, Wang L, et al., 2018). The genome sequencing of cervical cancer tissues revealed ErbB-3 as a new significant mutated gene in cervical cancer, which provides new clues for the study of cervical cancer pathogenesis. The expression levels of ErbB-3 mRNA and its protein were higher in both squamous and adenocarcinoma than in normal tissues. After silencing ErbB-3 expression in small interfering RNA (siRNA) transfected cervical squamous carcinoma cells, the proliferation, migration, invasion ability and mitogen activated protein three kinase (MTK-1) protein expression of cancer cells were also significantly decreased. Sollome et al (Winkle SM, Throop AL & Herbst-Kralovetz MM, 2016) found that ErbB-3 could regulate cell migration and extracellular acidification by interacting with MTK-1, and it was hypothesized that ErbB-3 might act synergistically with MTK-1 to promote cervical carcinogenesis and metastasis. WNT1 (Wnt FamilyMember 1, WNT1) and ErbB-3 expression inhibited the proliferation of cervical cancer cells.

In recent years, there has been growing interest in ErbB-3 as a potential therapeutic target for malignant tumors. Targeting antibodies against ErbB-3 have shown promising results in interfering with tumor cell growth through a variety of mechanisms. These drugs are currently in the preclinical and clinical stages of development, and their findings could provide new directions for the treatment of cervical cancer in the future.

2.4 TGFBR2

TGF-β plays an important role in normal cell development and homeostasis in vivo, and dysregulation of its response and downstream signaling pathways can lead to a variety of diseases, including the initiation, progression, and metastasis of malignancies. TGFBR2 is the receptor to which TGF-β directly binds and functions, and its encoding gene is located at 3p22 with serine/threonine kinase activity (Shannon B, Yi TJ, Perusini S, et al, 2017). TGFBR2, as a key molecule functioning in the TGF-β TGF-β type I interacts with the intracellular structural domain of the complex formed by type II receptors to phosphorylate specific serine and threonine by type II kinase, which in turn activates type I receptor kinase through transphosphorylation, which in turn phosphorylates downstream cellular effectors and other substances to initiate intracellular downstream cascade reactions, such as the most common SMAD signaling pathway. In tumor cells, amino (N)-terminal glycosylated TGFBR2 prevents TGF-β from binding to it, making the cells resistant to TGF-β signaling, thereby reducing the sensitivity of cancer cells to TGF-β signaling and promoting tumorigenesis (Winkle SM, Throop AL & Herbst-Kralovetz MM, 2016).

TGFBR2 gene is a common target of microsatellite instability mutations and microsatellite stability mutations, and its low expression or mutation is found in CIN, cervical, rectal, ovarian, lung and breast cancers, and its low expression is associated with an increased risk of prostate, nasopharyngeal, breast and colon cancers (Li B, Zhang L, Zhao J, et al, 2019; Shannon B, Yi TJ, Perusini S, et al, 2017; Park JS, Rhyu JW, Kim CJ, et al, 2003; Ding L, Liu C, Zhou Q, et al, 2019). The coexistence of low TGFBR2 expression and high human telomerase reverse transcriptase (hTERT) expression was associated with poor survival, with a higher risk ratio for overall survival than in patients with low TGFBR2 expression alone. Meanwhile, knockdown of TGFBR2 expression in HeLa cells increased cell proliferation, invasion, telomere homeostasis, and reduced apoptosis. Cai et al (Munguía-Moreno JA, Díaz-Chavéz J, García-Villa E, et al, 2018) found that TGFBR2 silencing enhanced cell proliferation and migration by silencing and overexpressing TGFBR2 in SiHa cells, and conversely TGFBR2 expression upregulation inhibited this effect. As a target gene of miR-17-15p, miR-17-15p overexpression inhibits TGFBR2 expression, which in turn promotes tumor development. Therefore, in-depth studies on the regulation of TGFBR2 activity and its mechanism of action in malignant tumors have important applications

in the targeted treatment of cervical cancer.

3. Grouping Biological Factors

Recent medical studies have found that protein and gene expression in cervical tissues are associated with the recurrence of early cervical cancer. Dingjun Zhu et al. have reported that E6-HPV16 or E7-HPV16 promotes MT1-MMP, MMP-2/9 activity and contributes to the metastasis of cervical cancer cells (Park JS, Rhyu JW, Kim CJ, et al, 2003; Ding L, Liu C, Zhou Q, et al, 2019; Munguía-Moreno JA, Díaz-Chavéz J, García-Villa E, et al, 2018). The expression of matrix metalloproteinases (MMPs) and their inhibitors, tissue inhibitors of matrix metalloproteinases (TIMPs), in cervical cancer has been studied in domestic and international literature. MMPs and TIMPs are indicators of recurrence assessment in early-stage cervical cancer, but further research is needed to understand the mechanisms underlying their role in recurrence.

Recent studies have shown the potential value of long non-coding RNA (lncRNA) and microRNA in predicting cervical cancer prognosis, treatment response, recurrence, and drug resistance. One example of a lncRNA is cCHE1, which has been found to be significantly associated with lower overall survival (OS) and recurrence-free survival (RFS) in patients with high CCHE1 expression (Dingjun Zhu, Mei Ye & Wei Zhang, 2015; Chen Y, Wang CX, Sun XX, et al, 2017; Liu M, An J, Huang M, et al, 2018) in cervical cancer tissues. Another study showed that miR-492 is highly expressed in early cervical cancer positive lymph nodes, and tissue inhibitor of metalloproteinases 2 (TIMP2) is its direct and functional target. Liu M et al. (Paolini F, Curzio G, Melucci E, et al, 2016) studied 104 patients with FIGO IIB to IIIB cervical cancer and found that the miR-492/TIMP2/MMP10 axis is a molecular mechanism of abnormal cell migration in cervical cancer and plays an important role in the recurrent metastasis process.

In recent years, domestic and foreign scholars have found in genetic aspects that Twist, Snail, and YB-1 genes are upregulated in the tissue and plasma of early cervical cancer (I-IIa), and the expression level is related to the invasiveness of tumor cells, and high expression is closely related to the recurrence of early cervical cancer after surgery (Xin-Qin Kang & Lin Liu, 2017; Soyi Lim, Chae-Min Lee, Jong-Min Park, et al, 2014). The correlation between the recurrence of early cervical cancer and protein and gene expression in cervical tissues is the current research direction to better improve patient prognosis in the future and improve the theoretical basis for molecular-level prediction, targeted therapy, and gene therapy.

4. Outlook

Gene mutations play an irreplaceable role in the development of cervical cancer. To date, several new significant mutated genes have been identified in cervical cancer by genome sequencing technology, but there are still many genes whose mechanisms of action have been rarely reported in studies. In recent years, there have been more studies on the factors associated with recurrence at home and abroad, which are more in agreement with the results of multiple factors acting together.

The exploration of the detection of significantly mutated genes in cervical cancer tissues and the role they play in the development of cervical cancer and the in-depth mechanism is of profound significance for the future diagnosis, targeted therapy, and prevention of cervical cancer.

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