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Advances in Etiology and Treatment of Cutaneous Squamous Cell Carcinoma

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Abstract

Cutaneous Squamous Cell Carcinoma (CSCC) is a common skin malignancy with increasing incidence year by year and is the leading cause of death in patients with skin tumors other than melanoma. The pathogenesis of Cutaneous Squamous Cell Carcinoma has not yet been clarified, limiting the development of related molecular targeted therapies. Surgical resection, radiotherapy, photodynamic therapy and gene therapy can be selected according to the site of disease and histological differentiation. This article reviews the research on the etiology, pathogenesis and treatment of squamous cell carcinoma in recent years.

Keywords

Squamous Cell Carcinoma of Skin, Pathogenesis, Diagnosis, Treatment

1. Introduction

Cutaneous Squamous Cell Carcinoma (CSCC) is a malignant tumor arising from epidermal or adnexal stroma forming cells and is the leading cause of death from non-melanoma skin tumors [1]. A retrospective study of 1905 cases of CSCC in China found that among non-melanotic skin tumors, the incidence of CSCC ranked first (29.4%), slightly higher than that of basal cell carcinoma (28%), and increased by 2.6% per year [2]. As a sub-high incidence of skin cancer, the age of onset of skin cancer in China has also shown a certain tendency of younger age, which seriously affects the quality of life and brings a heavy psychological burden to people [3]. Skin cancer lesions are superficial and easy to contact, and there are many treatments, such as surgical resection, radiotherapy, photodynamic therapy, local drug physical corrosion therapy and gene therapy. It is emphasized in clinical

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practice that the treatment of CSCC should be thorough to avoid metastasis. How to select a comprehensive treatment plan to maximize the preservation or recovery of the appearance and function of the lesion and how to reduce the possibility of recurrence and metastasis of CSCC has always been a matter worthy of in-depth discussion in labor. The pathogenesis of CSCC remains unknown, and advances in molecular targeted therapies have therefore been limited. This article briefly reviews the research progress in etiology, pathogenesis, diagnosis and treatment of this disease.

2. Etiology and Pathogenesis

The pathogenesis of Cutaneous Squamous Cell Carcinoma is very complex, and its pathogenesis is the result of a combination of individual factors and external environmental adverse factors, which are closely related to exogenous injury [4]. A large body of evidence suggests that CSCC is associated with factors such as human age, immune function, certain genetic abnormalities, excessive sun exposure, viral infections, and chemical carcinogens [5] [6]. These factors cooperate with each other, damage the skin, cause skin inflammation, hyperkeratosis and pigmentation, accelerate skin aging, and even cause skin cancer.

2.1. Own Factors

Age: With the increase of age, the probability of skin squamous cell carcinoma also increased gradually [7], Shen Chunming and others [8], through the study of elderly head and face skin tumors, found that with the increase of age, the incidence rate also gradually increased. Foreign studies have shown that more than 80% of skin tumors occur in the elderly over 60 years old [9], older than 75 years old, the incidence of skin cancer in elderly patients. It gradually rises, and this phenomenon may be related to aging of the body and reduced ability of the cells to repair themselves.

Autoimmunity: The development of skin tumors may be associated with decreased autoimmune function [9]. Studies have shown that The incidence of skin cancer is significantly higher in patients with autoimmune disease treatment and organ transplantation after routine use of immunosuppressants such as azathioprine and cyclophosphamide than in normal people, and SCC is more common than basal cell carcinoma [10]. Histological changes of solar keratosis are often found around the diseased skin in such patients, suggesting that the application of immunosuppressive agents can accelerate the development of solar keratosis into SCC.

Some genetic abnormalities: normal people contain proto-oncogenes, and their expression products can promote cell proliferation. However, it can be activated to become an oncogene under specific conditions, resulting in abnormal proliferation and differentiation of cells, which induces carcinogenesis. Abnormal expression of various proto-oncogenes was found in the skin squamous cell carcinoma patients, and the most significant of them were ras and myc gene family [11]. The

tumor cells with high expression of ErbB2 have strong proliferation ability. The expression of ERBB2 gene inhibits the differentiation, maturation and apoptosis of cells, and makes the tumor cells more malignant [12]. When the tumor suppressor gene that inhibits the proliferation of normal cells in the human body is mutated, deleted or inactivated, it will make the cells proliferate inexorably and induce carcinogenesis when they develop into malignant growth. At present, there are many studies on p53, p16, Rb, p21, etc., of which the most closely related to Cutaneous Squamous Cell Carcinoma is p53 gene [13].

2.2. Extrinsic Environmental Factors

Excessive sun exposure: Ultraviolet radiation is clearly defined as a class I carcinogen by the International Cancer Institute (IARC) and is the most important risk factor for CSCC. The most common form of mutation in CSCC is p53 mutation caused by UVR — characteristic C-T and CC-TT pyrimidine dimer conversion [14]. Epidemiological studies have confirmed that UVR is an important cause of CSCC development. In 2017, a study of 14,901 cases of CSCC in the National Cancer Institute SEER database confirmed a significant increase in the incidence and mortality of CSCC in regions with a high UVR index [15]. In the same year, another retrospective study of UVR exposure history in 99 patients with nonmelanoma skin tumors found that CSCC patients had higher SED values for UVR exposure compared to patients with basal cell carcinoma [16].

Viral Infections: Human papillomavirus (HPV) is highly epitheliotropic and causes infected cells to proliferate excessively until malignant transformation. The study of Leigh *et al.* showed 84.1% positivity for human papillomavirus in SCC in the immunosuppression group [17]. Among more than 100 subtypes of human papillomavirus discovered so far, 5/16/18 human papillomavirus DNA has a high detection rate in skin cancer tissues, HPV-16 gene products E6 and E7 proteins can bind to tumor suppressor proteins p53 and PRb, so that p53 cannot repair damaged DNA, and human papillomavirus infection can aggravate the malignancy of skin cancer. Through investigation, it was found that OKF26 gene subtype of HHV-8 could be detected in virus detection of some SCC patients, with a positive rate of 21.95%, and it was speculated that HHV-8 had a certain adjuvant carcinogenic effect in the occurrence and development of SCC [18].

Certain Chemical Carcinogens: Many common chemical carcinogens, such as arsenic and polycyclic aromatic hydrocarbons, have been demonstrated to be associated with CSCC. A systematic review by Yen *et al.* found that ethanol intake was also significantly associated with an increased risk of CSCC, and their meta-analysis results confirmed that this association was dose-dependent [19].

3. Pathogenesis

Skin carcinogenesis involves abnormalities in key genes and pathways involved in regulating cell survival, cell cycle, and genomic stability and is a multi-step process in the stepwise accumulation of genetic and epigenetic alterations [20]. The

pathogenesis of CSCC involves multiple gene and pathway driver gene mutations [21]. TP53 mutation is an early event in skin carcinogenesis, which can occur in up to 90% of CSCC and is often thought to be caused by ultraviolet radiation [22]. Mutations in TP53 (79%), NOTCH-1/2/4 (69%), and CDKN2A (48%) gene were observed in metastatic CSCC [23]. Epidermal growth factor receptor genes are often mutated and overexpressed in CSCC [24]. MicroRNAs involved in the regulation of gene post-transcriptional expression have been a hot topic in the field of basic research in recent years, and Bai *et al.* found that high expression of MiR-217 can promote the development of CSCC by directly acting on PTRF (Polymerase I and Transcript Release Factor), and MiR-217 was significantly negatively correlated with PTRF expression in CSCC, while overexpression of PTRF in CSCC significantly alleviated the promoting effect of MiR-217 on cancer [25].

4. Diagnosis

Because of the heterogeneity of CSCC histiocytes, the histological grade should be comprehensively determined according to the area with the lowest degree of tumor differentiation and the proportion. Less than 25% of undifferentiated cells were grade I, 25% to 50% of undifferentiated cells were grade II, 50% to 70% of undifferentiated cells were grade III, and almost all undifferentiated cells were grade IV. Among them, grade III and IV are poorly differentiated squamous cell carcinoma, with severe invasion and possible high metastasis, and the prognosis is poor if timely and reasonable treatment is not performed. Well-differentiated tumor cells had intercellular bridges with large cell bodies, and keratinized beads, dyskeratotic cells, and squamous vortex were observed. Poorly differentiated tumor cells have small cell bodies, scant cytoplasm, hyperchromatic nuclei, often many atypical nuclear clefts, and no keratinizing beads or dyskeratotic [26]. Undifferentiated or poorly differentiated CSCC is similar to a variety of spindle cell tumors in pathological findings and requires immunohistochemical staining for differentiation.

5. Treatment

5.1. Surgical Treatment

Surgical treatment is currently the main treatment for CSCC. However, traditional surgical treatment can completely remove the tumor, but

At the same time of tumor resection, a large number of normal tissue defects and severe changes in skin appearance increase the negative impact on patients. Therefore, while completely removing the lesion, it is necessary to take into account the repair of the wound after resection, so as to retain or restore the appearance and function of the local area to the greatest extent.

1) Standard resection plus postoperative margin evaluation is the conventional treatment for CSCC [27]. It is recommended to perform extended 4-mm resection for primary low-risk CSCC ≤ 2 cm in diameter and 6-mm resection for those > 2 cm in diameter, and histological tumor clearance can be achieved in 95% of cases.

For primary high-risk CSCC, with the increase of risk factors and the diameter of the lesion, the safe resection margin should be gradually enlarged, and the lesion < 1 cm in diameter should be enlarged by at least 4 mm for resection, at least 6 mm for those 1 to 1.9 cm, and at least 9 mm for those ≥ 2 cm. Histopathological examination of the resection margin is required after resection to determine the histological clearance of the tumor. 14% to 15% of primary and 23% to 50% of recurrent CSCC have subclinical invasion (clinically invisible, histopathologically confirmed only), and the extent of subclinical invasion of recurrent CSCC is greater than that of primary [28], so attention should be paid to the margin examination of recurrent CSCC. If the postoperative margin is positive, standard resection with postoperative margin evaluation should be performed again if tolerated by the patient.

2) Microcontrolled-surgery MCS is a surgical technique for the removal of skin tumors by processing skin tissues in horizontal sections and examining them under a microscope until all boundaries are tumor-free. There are two techniques for microcontrolled surgery: mohs microsurgery (MMS) and 3D histology, which differ because the former uses frozen sections while the second uses paraffin sections [29]. Intraoperative examination of tumor resection boundaries by means of frozen sections by MCS is done to confirm that the tumor is completely removed before incision closure, and MCS also avoids unnecessary removal of uninvolved tissue, which is important for tumors located at critical anatomical sites [30]. MMS was the first technical designed to ensure complete tumor removal and avoid unnecessary removal of healthy tissues [31]. Since its introduction, MMS has been considered the first-line surgical procedure for locally invasive, high-risk skin cancer resection. MMS is particularly useful when unaffected tissues must be maximally preserved. MCS provided the highest R0 (*i.e.*, microscopic absence of cancer cells at the primary tumor site) resection rate (>90%) and a lower recurrence rate (0% - 4%) compared with conventional surgery (3.1% - 8.0%).

5.2. Radiation Therapy

It is usually used for patients who cannot be treated surgically, or combined with surgery and other adjuvant regimens for comprehensive treatment. However, its use in postoperative radiotherapy (PORT) for Cutaneous Squamous Cell Carcinoma (CSCC) with perineural invasion is controversial [32]. The National Comprehensive Cancer Network recommends: for CSCC < 2 cm in diameter, the total radiation dose is 45 - 50 Gy, 2.5 - 3 Gy per fraction; for CSCC > 2 cm in straight diameter, the total radiation dose is 50 - 60 Gy, 2.5 Gy per fraction, or the total radiation dose is 60 - 66 Gy, 2 Gy per fraction. Radiation therapy has a high risk of secondary tumors and should be used with caution in younger patients, usually in patients over 60 years of age. Contraindications are genetic diseases that predispose to skin cancer, such as nevoid basal cell carcinoma syndrome, Li Fraumeni syndrome (hereditary tumor syndrome caused by pathogenic mutation of TP53 gene), and relative contraindications are connective tissue related diseases, such

as lupus erythematosus and scleroderma. Radiation therapy can lead to adverse events such as pigmentation/hypopigmentation, chronic ulceration, and increased incidence of NMSC.

5.3. Photodynamic Therapy (PDT)

It can be used for local treatment of CSCC in situ and should be used with caution for invasive CSCC. It is a novel anti-tumor model that has been applied in recent years. However, its mechanism of action is not fully clarified, and data show that photodynamic therapy is to use the characteristics of high-uptake photosensitizers of tumor cells, use a laser corresponding to wavelength 122 to irradiate tumor cells, use singlet oxygen or other reactive oxygen species produced by photosensitizers, directly and efficiently induce apoptosis or lead to tumor tissue necrosis through non-apoptosis pathways to kill cancer cells. PDT treatment produces much less toxic side effects than chemoradiotherapy damage to the patient's body, which is easy to operate and has a significant effect, and has gradually become recognized as an effective means of cancer prevention and treatment [33].

5.4. Targeted Therapy

It is mainly epidermal growth factor receptor (EGFR) inhibitors. EGFR is a transmembrane glycoprotein with extracellular binding-domain, as well as an intracellular tyrosine-kinase domain-domain that regulates cell proliferation through pathways such as MAPK and PI3K [34]. Including cetuximab and panitumumab. Cetuximab alone or in combination with radiation therapy or platinum-based chemotherapeutic agents has some effects on advanced CSCC and can be used as a second-line agent for systemic therapy [35]. panitumumab monotherapy is safe and effective in the treatment of CSCC, but its indication for CSCC has not been approved [36].

5.5. Other Treatments

Cryotherapy, laser therapy, photodynamic therapy, electrochemical therapy, sonodynamic therapy, and local drug therapy (e.g., imiquimod cream, interferon, 5-FU, etc.) can be performed clinically for well-differentiated and small CSCC.

6. Summary

Squamous cell carcinoma of the skin is a common skin cancer. Its occurrence is the result of multiple factors and multiple links, and its exact etiology and pathogenesis are still the current research hotspots. At present, there is no simple and efficient treatment for this disease, and surgical resection is the main treatment, but there are some defects in simple surgical treatment. During the treatment process, the treatment plan can be adjusted according to the dynamic changes of the patient's condition, and the multidisciplinary cooperation of plastic surgery, oncology, dermatology and other disciplines can be used. After treatment, patients should be informed to avoid the risk factors of CSCC as much as possible, the

importance of sun protection should be emphasized, and education should be given to patients to enable them to have the ability to initially assess their own skin condition, which is conducive to timely treatment and reduce the possibility of recurrence, in order to achieve better clinical efficacy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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