Chemotherapy for Oral Cancer

Subjects: Oncology

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The increasing incidence of resistance to chemotherapeutic agents has become a major issue in the treatment of oral cancer (OC). Epithelial-mesenchymal transition (EMT) has attracted a great deal of attention in recent years with regard to its relation to the mechanism of chemotherapy drug resistance. EMT-activating transcription factors (EMT-ATFs), such as Snail, TWIST, and ZEB, can activate several different molecular pathways, e.g., PI3K/AKT, NF-κB, and TGF-β.

Keywords: EMT ; chemotherapy ; chemoresistance ; oral squamous cell carcinoma

1. Introduction

As the second leading cause of death globally, cancer still represents a major public health challenge. The latest epidemiological analysis of the incidence of cancer in the USA indicated that 4950 people are diagnosed with cancer every day, with an annual incidence of 1,806,590 [1]. Although not common in developed countries, oral cancer (OC), a type of head and neck cancer (HNC), is still the sixth leading type of cancer in the world, with an estimated incidence of 275,000 cases per year [2]. Two-thirds of OC patients reside in developing countries. There is huge geographic variation in the incidence of OC, with an approximately 20-fold difference between the countries with the lowest and highest rates [3]. In high-risk countries, such as India and Sri Lanka, OC is the main cancer in men and accounts for up to 25% of all new cases of cancer in these countries. However, OC accounts for only 1–3% of all malignancies in countries with low incidence rates, such as the UK [4].

A report by the US Centers for Disease Control and Prevention (CDC) indicated that 36% of patients with OSCC have localized disease, while 43% have locoregional spread and 9% present with distant metastasis at the initial diagnosis [5]. Overall, locoregional recurrence is very common and leads to death in 40–60% of these patients, whereas less than 20% of patients die because of distant metastasis [6]. Frustratingly, the overall five-year survival rates for OC are around 50–60% even after decades of development of cancer treatments [7].

Regardless of diagnostic methods, numerous therapeutic strategies can be applied for OSCC treatment. Chemotherapy is the first-line treatment for various types of cancer, including OSCC [8]. However, the development of chemoresistance represents a challenge in chemotherapy [9]. Previous studies have shown that frequent application of high-dose chemotherapeutic agents has led to the emergence of chemoresistance, where overcoming this issue has become a major goal for researchers around the world.

Cancer cells have been shown to switch between molecular pathways and mechanisms to ensure their proliferation, invasiveness, and resistance to chemotherapeutic agents [10]. During this process, invading cancer cells acquire mesenchymal features, while losing cell polarity and intercellular tight junctions. This transition from epithelial to mesenchymal cells is designated as the epithelial-mesenchymal transition (EMT) [11]. The EMT was first identified in the 1970s as a feature of embryogenesis and wound healing, but its underlying mechanisms have since been studied extensively and used to explain carcinogenesis and tumor invasiveness [12]. The main characteristic of EMT during tumor metastasis is the loss of the adherent junction protein E-cadherin. A number of transcription factors participate in the regulation of E-cadherin, but only a few directly mediate its expression [13]. These EMT-activating transcription factors (EMT-ATFs), which include the Snail, TWIST, and ZEB families, bind specifically to the promoter of E-cadherin through E-boxes and inhibit its transcription [14], and thus play pivotal roles in the dynamic regulation of EMT, tumor metastasis, and resistance to chemotherapy agents [15].

2. Plant Alkaloids

Multivariate analysis showed that interstitial IL-6 expression was a critical and independent factor associated with paclitaxel resistance [16]. A retrospective study with a large sample size also revealed a similar outcome, in that patients with lower IL-6 expression showed a higher rate of sensitivity to chemotherapy than those with a higher level of IL-6

expression (69.3% and 48.1%, respectively) [17]. Although the reason is still unclear, Osuala et al. [18] confirmed that CAFs are the major source of IL-6 secretion. Based on this finding, suppression of interstitial IL-6 expression may reverse paclitaxel resistance.

The evidence outlined above suggests that inhibiting NF-κB and TGF-β signaling, especially the activity of Snail, is vital for resensitization of cancer cells to paclitaxel therapy.

Docetaxel is another representative taxane drug similar to paclitaxel. Their structures and mechanisms of action are largely the same, but they differ in several other aspects, such as tubulin polymer generation. In an ex vivo study, docetaxel also tended to be more potent in different cell lines; docetaxel is considered to be a schedule-independent drug, while paclitaxel is not [19][20]. Riou et al. [21] reported that docetaxel was 1.3–12-fold more effective than paclitaxel after 90 h of exposure, which may have been due to the higher affinity of docetaxel for microtubules.

Several factors have been shown to be associated with docetaxel resistance, including the expression of isoforms of β-tubulin, drug efflux pumps, and activation of survival factors (i.e., PI3K/AKT, mTORC) [22][23][24][25].

3. Future Perspectives

Extensive studies have provided a comprehensive understanding of the molecular pathways and ATFs involved in the EMT of OSCC/HNSCC. These insights have suggested the potential benefits of anti-EMT therapies.

Metformin, vanadium, etc., were shown to suppress markers of mesenchymal differentiation, such as vimentin and N-cadherin, while inducing the expression of E-cadherin. Previous in vivo studies showed that combining chemotherapy agents improved drug sensitivity and reduced the expression of E-cadherin, thus suppressing the EMT [26][27][28].

High-throughput screening systems have also been developed for identifying anti-EMT drugs. In a pilot screen using a novel three-dimensional high-throughput screening system for a test of 1330 compounds, Arai et al. [29] identified nine compounds that were above the thresholds and two of those compounds, the TGF-β-R1 inhibitor SB-525334 and CDK2 inhibitor SU9516, acted as inhibitors of EMT in lung cancer cell lines. Similarly, Germain et al. [30] identified a chemical probe, ML245, through high-throughput screening that restrained CSCs progression by regulating the expression of proapoptotic/mitochondrial maintenance factors and DNA-modifying enzymes.

A great deal of progress has been made in understanding the EMT over the last several decades. It is anticipated that combined administration of antitumor drugs with chemotherapeutic agents, together with the development of innovative high-throughput screening and miRNA technology to acquire specific inhibitors targeting multiple pathways and ATFs, will translate into new clinical treatments for cancer, including OSCC/HNSCC, in the near future.

4. Conclusions

The EMT can promote resistance of cancer cells to a range of chemotherapeutic agents. Several signaling pathways and EMT-AFTs have been shown to play vital roles in this process. Further extensive studies of the complex pathways involved in the EMT and drug resistance, combined with innovative techniques such as high-throughput screening and miRNA-based technologies, will facilitate the development of precise strategies for the treatment of OSCC/HNSCC and other types of cancer.

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