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Review Article

Molecularly-targeted therapy for the oral cancer stem cells

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Summary Human cancer tissues are heterogeneous in nature and become differentiated during expansion of cancer stem cells (CSCs). CSCs initiate tumorigenesis, and are involved in tumor recurrence and metastasis. Furthermore, data show that CSCs are highly resistant to anticancer drugs. Cetuximab, a specific anti-epidermal growth factor receptor (EGFR) monoclonal antibody, is used in cancer treatment. Although development of resistance to cetuximab is well recognized, the underlying mechanisms remain unclear. Lapatinib, a dual inhibitor of epidermal growth factor receptor (EGFR)/ErbB2, has antiproliferative effects and is used to treat patients with ErbB2-positive metastatic breast cancer. In this review, cetuximab and lapatinib-resistant oral squamous cell carcinoma (OSCC) cells proliferation and migration signal transduction passway is discussed by introducing our research.

Contents

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1. Introduction

Cancer tissue is a complex ''organ''. The tumor tissue microenvironment is composed of a variety of cells, including tumor cells, cancer stem cells, inflammatory cells, and cancerassociated fibroblasts, along with blood vessels (Fig. 1). It is possible that cancer stem cells participate in the processes that lead to resistance to therapy and the establishment of distant metastases.

The epidermal growth factor receptor [(EGFR)/ErbB1/HER1] is a member of the ErbB tyrosine kinase family. All receptors of the ErbB family activate and regulate diverse cellular processes, including proliferation, survival, adhesion, migration and differentiation [1]. Ligand binding potentiates receptor interaction with either a homologous molecule (homodimerization), a different ErbB-family receptor [2—5]. Upregulation of EGFR expression in many human epithelial cancers is associated with advanced tumor stage and an unfavorable prognosis [6,7]. Thus, EGFR is considered to be not only a useful prognostic biomarker but also a promising therapeutic target, have been developed and used in cancer treatment.

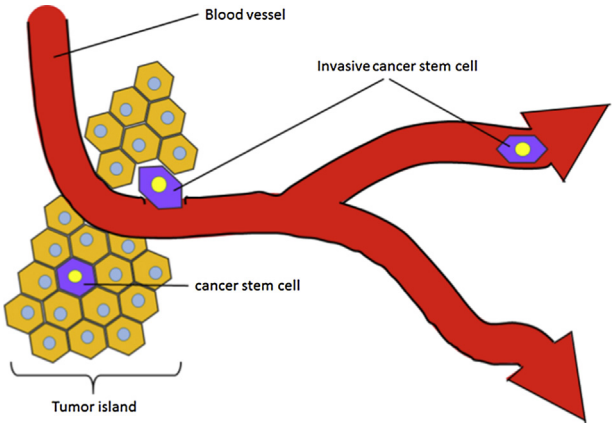

Figure 1 Cancer tissue is a complex ''organ''. The tumor tissue microenvironment is composed of a variety of cells, including tumor cells, cancer stem cells along with blood vessels. The cancer stem cells are rare cells found primarily in the invasive edge of tumors close to blood vessels.

Molecularly-targeted therapies, which include monoclonal antibodies and small molecule inhibitors, such as EGFR, have significantly changed the treatment of cancer over the past 10 years. These drugs are now a component of therapy for many common malignancies, including breast, colorectal, lung, and pancreatic cancers, as well as oral cancer. The mechanisms of action and toxicities of targeted therapies differ from those of traditional cytotoxic chemotherapy. Targeted therapies are generally better tolerated than traditional chemotherapy. Targeted therapy has raised new questions about the tailoring of cancer treatment to an individual patient's tumor, the assessment of drug effectiveness and toxicity, the economics of cancer care, and resistance following treatments.

Cetuximab is a chimeric IgG1 monoclonal antibody that binds with high affinity to the extracellular domain of EGFR [8]. The antibody blocks EGFR activation by preventing tyrosine kinase-mediated phosphorylation of the protein [9]. Cetuximab has been prescribed for patients with metastatic colorectal cancer (mCRC) [10—14] and head and neck squamous cell carcinoma (HNSCC) [15—19]. For clinical setting of metastatic or recurrent oral cavity cancers, cetuximab 400 mg/m^2 IV loading dose on day 1, followed 250 mg/m^2 IV weekly until disease progression.

The EGFR/ErbB2 dual inhibitor lapatinib is used to treat ErbB2-positive breast cancer. Despite intensive efforts investigating a large number of ligands identified for EGFR, ErbB3 and ErbB4, no direct ligand for ErbB2 binding has been identified. However, ErbB2 dimerizes with other ErbB receptors and acts as a co-receptor [20], and overexpression of ErbB2 can induce transformation of cells without the ligand [21]. In addition, since heterodimeric formation of ErbB2 with other ErbBs can enhance ligand binding, receptor tyrosine phosphorylation, and cell proliferation compared with EGFR homodimers, lapatinib has better efficacy than those of single inhibitors of EGFR signal transduction for preventing tumor growth and survival [22]. For clinical use, oral lapatinib 1500 mg daily or oral lapatinib 1000 mg daily in combination with intravenous trastuzumab 2 mg/kg weekly (after the initial 4 mg/kg loading dose).

However, use of EGFR inhibitors containing cetuximab or lapatinib is resistance following treatments. Thus, it is important to understand not only how cetuximab or lapatinib acts but also the mechanisms of resistance. In this

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