Targeting the Tumor Stroma for Oral Cancer Therapy

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Opinion

Histopathological diagnosis is commonly used to identify oral cancer. However, morphological diagnosis alone cannot clarify the biological malignancy and prognosis of this disease. Findings from cancer stem cell research and cancer genetic analysis help guide the design of cancer studies. In addition, the environmental niche, which includes cancer stem cells (CSCs) and/or cancer associated fibroblasts (CAFs), influences the behavior of the cancer cells and therefore the prognosis [1,2]. We utilize oral cancer samples to evaluate specific mesenchymal cell surface markers and to clarify cell properties and functions that may not be predicted by the pathological diagnosis [3]. Most cancers of the oral cavity are squamous cell carcinomas, with various degrees of malignancy. Spindle cell carcinoma (SpCC) is composed of a biphasic mixture of epithelial and mesenchymal cells [4]. SpCC is a subtype of poorly differentiated oral squamous cell carcinoma (OSCC) diagnosed by immunostaining of pathological specimens [5]. This traditional analysis can lead to diagnostic difficulties due to the range of histological patterns seen in SpCC. As it is a rarely diagnosed tumor, the characteristics of SpCC remain unclear [6]. Therefore, it is difficult for basic researchers and clinicians to determine the appropriate diagnosis and treatments. It is critical to understand the pathological and genetic characteristics of SpCC, including the gene expression patterns in the tumor microenvironment, to increase our understanding of this rare cancer.

Current oral cancer treatments are organ specific and mainly use reagents that target squamous cell carcinoma in the head and neck regions. For example, the EGFR-targeting reagent cetuximab is well known for its application in malignant disease of the head and neck. However, prior research demonstrated that cetuximab is not effective in cases of recurrent or advanced SpCC [6]. This underscores the necessity of identifying other cell components that can be targeted. Our group demonstrated that a cetuximab-resistant recurrent SpCC sample expressed the mesenchymal stem cells (MSCs) markers platelet-derived growth factor receptor α (PDGFRα) and Nestin. Prospective cell analysis by using a flow cytometer revealed that recurrent SpCC cells expressed the CSC marker CD44v, which was identified in both EpCAM positive epithelial cells and PDGFRα positive mesenchymal cells. These results indicate that CSCs survived in both parenchymal and mesenchymal tissues. Cultured cells expressed legacy MSC markers such as CD73, CD90, and CD105, and they showed features such as colony forming, migration, and differentiation abilities. Our group demonstrated the utility of imatinib, which is known to inhibit the protein tyrosine kinase activity of Bcr-Abl and PDGFRα, in targeting PDGFRα-expressing stromal cells. Imatinib had a more potent inhibitory effect on the cultured cells and was more effective in inducing cell death relative to the cetuximab-treated group.

Perspectives

In our previous study, we evaluated the characteristics of cancer cells obtained from tissues in addition to conventional pathological diagnosis. By using a flow cytometer, it was possible to analyze the expression of markers several hours later. This strategy enables early prediction of the possible effects of chemotherapy and is expected to identify new markers and help develop drugs aimed at specific molecular targets. Analysis of the proliferation and migration abilities of the cancer cells, as well as drug response tests, can be used to further determine specific patient characteristics. This information, in combination with pathological analysis, helps inform diagnostic and treatment decisions and makes it possible to further...
elucidate the biological malignancy and prognosis of cancers as compared with pathological diagnosis alone. Our approach can contribute to the development of disease-specific individualized treatments that are essential for rare cancers with histologic types.

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