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Review

Recent advances in head and neck squamous cell carcinoma — A review

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ABSTRACT

The current review presents the results of the most recent studies performed on different aspects of human head and neck squamous cell carcinoma, including radiosensitivity induction, efficiency improvement of monoclonal antibodies using low-intensity ultrasound, chemical compounds such as toll-like receptor (TLC) agonists, dasatinib, resveratrol and niclosamide, nuclear inhibition of cancer using STAT3 decoy oligonucleotide, efficiency of anti-EGFR monoclonal antibodies in detection of head and neck cancers and other related issues.

Contents

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Introduction

Head and neck cancer refers to a group of biologically similar cancers affecting the lip, oral cavity (mouth), nasal cavity, pharynx, larynx and paranasal sinuses [7,43]. The most common type of head and neck cancer (90%) is squamous cell carcinoma (SCC). Head and neck squamous cell carcinoma (HNSCC) exhibits highly malignant phenotypes characterized by the extensive invasion into surrounding tissues and metastasis to distant organs, even at an early stage [20,35]. Approximately, 560,000 new cases of HNSCC and 300,000 deaths are reported annually throughout the world [32], being regarded a main cause of mortality in humans. During the recent years several efforts have been made on various aspects of human head and neck cancers, including detection techniques, treatment strategies, and mechanisms involved in cancer initiation and progression. In addition, several strategies have been proposed and evaluated to induce tumor sensitivity to radiation or anticancer drug. The current review comprises a number of the most important and updated studies on human head and neck cancers and provides a scientific basis for understanding new advancements using previous relevant studies.

Head and neck cancers and EGFR

Head and neck cancers (HNC) are associated with enhanced expression and activity of EGFR. The main EGFR downstream signaling pathways involved in HNSCC are RAS/RAF/MEK/ERK, PI3-K/AKT, STAT (Fig. 1), PLC/PKC, EGFR nuclear signaling (Fig. 2) and the Src pathways. So far, several anti-cancer drugs have been developed to suppress these pathways, among which are monoclonal antibodies cetuximab and panitumumab (which target the extracellular domain of EGFR) as well as erlotinib (which targets intracellular tyrosine kinase domain). A major drawback correlated with such EGFR inhibitors is the development of resistance mechanisms in cancers cells, consequently resulting in poor prognosis. Therefore, identification of mechanisms responsible for resistance and overcoming them will be helpful in improving the efficiency of treatment strategies.

In vitro studies on HNSCC

Radiosensitivity induction in HNSCC cancer

Dasatinib enhances radiosensitivity in HNSCC cancer. Among SFK (Src family kinases) members, Yes (v-Yes-1 yamaguchi sarcoma viral oncogene) and Lyn (v-yes-1 Yamaguchi sarcoma viral-related oncogene homolog) are responsible for nuclear translocation of EGFR via phosphorylation at Y1101 [13]. Nuclear EGFR increases DNA repair through interaction with DNA-dependent protein kinase (DNA-PK), resulting in decreased radiosensitivity [48]. A recent study carried out in vivo model indicates that inhibition of nuclear EGFR via SFK inhibitor dasatinib (DSB) can enhance radiosensitivity via decreasing the repair of radiation-induced DNA damage [48]. When it is used as a single agent, DSB is an inefficient agent in HNSCC inhibition [4], while it offers significant cancer inhibition potency when combined with radiation.

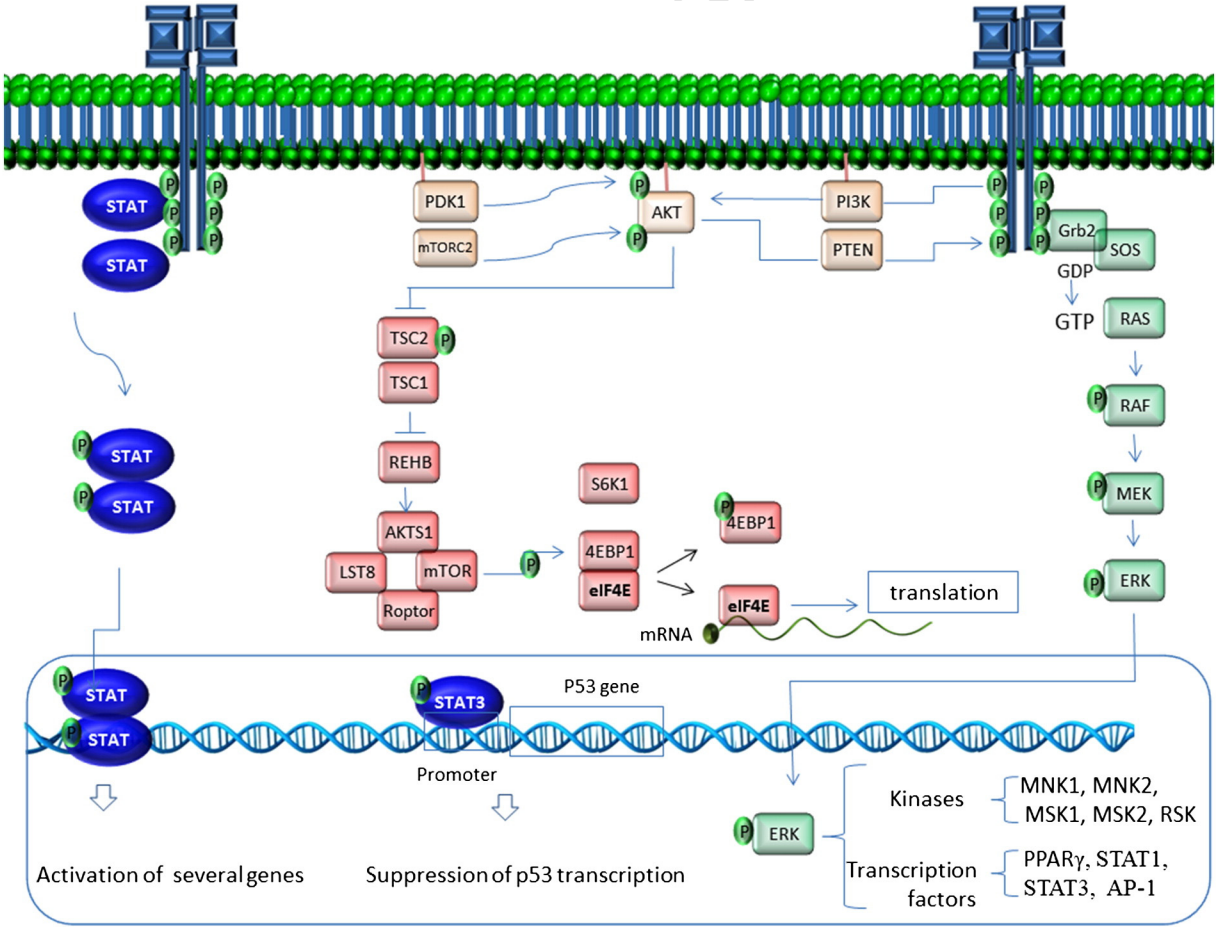

Fig. 1. RAF/RAS/MEK/ERK, PI3K/AKT and STAT pathways. Activation of RAF/RAS/MEK/ERK, PI3K/AKT finally leads to phosphorylation of several kinases and activation of a number of transcription factors. Upon activation of PI3K/AKT pathway, eIF4E is released and initiates the translation of some genes. This pathway is attenuated naturally by tumor suppressor PTEN, which dephosphorylates the AKT. After phosphorylation, STATs are dimerized and translocate into the nucleus, where they activate expression of several genes mostly involved in cell proliferation. STAT3 inhibits the transcription of p53 gene by occupying its promoter, indirectly resulting in enhanced cell proliferation.

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