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Review Article

Cancer Stem Cells and Sonic Hedgehog Signaling in Head and Neck Cancer: Potential Targets for Overcoming Chemoradiation Resistance

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Abstract.

Cancer stem cells (CSC) are a small and distinct population of cancer cells that possess self-renewal and differentiation ability and are relatively resistant to treatment including chemotherapy and radiotherapy. Sonic hedgehog (SHH) and related signaling molecules are critical to embryonic development and regulate both proliferation and differentiation of various types of stem cells, including CSC. This article provides a brief overview of the SHH signaling pathway, summarizes the correlation between SHH signaling and treatment resistance of cancer cells and discusses the recent advances in targeting this signaling cascade to overcome treatment resistance. We proposed that CSC and their related the SHH signaling pathway might be potential targets for overcoming chemoradiation resistance of head and neck cancer cells. This has been under investigation by our comprehensive team treating head and neck cancers.

Keywords **:** Cancer stem cell, Sonic hedgehog, Chemoradiation, Resistance

綜合評論

頭頸癌之癌症幹細胞與 Sonic Hedgehog 訊息傳導：具克服放射化學治療抵抗性潛力之標靶

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中文摘要

癌症幹細胞是具備自我更新及分化能力且對放射及化學治療較不敏感之一小群特殊癌細胞。Sonic Hedgehog (SHH)及其相關訊息傳導分子對胚胎發育非常重要，並且能調節包括癌症幹細胞等多種幹細胞之增生及分化。本文將簡介 SHH 訊息傳導路徑，扼要說明其與癌症治療抵抗性之關連，並討論如何利用標靶於 SHH 路徑以克服治療抵抗性之近期研究發展。

我們藉此提出利用標靶於 SHH 訊息傳導路徑以克服頭頸癌放射及化學治療抵抗

性之假說。此假說經本院頭頸癌聯合治療小組研究中。

關鍵字: 癌症幹細胞、Sonic Hedgehog、放射化學治療、抵抗性

CANCER STEM CELLS

Solid tumors are usually histologically heterogeneous and contain various types of cells including tumor, stromal, and infiltrating immune cells. Inside various kinds of solid tumors, a subpopulation of cancer cells possessing characteristics resembling normal stem cells has been identified, namely, cancer stem cells (CSC). It has been widely accepted that CSC are a small minority of cancer cells that possess the ability to extensively proliferate and form new tumors even starting at a small amount [1-5]. CSC share with normal stem cells the capacity to replicate without losing the ability to proliferate. They can self-renew, giving rise to another malignant stem cell and undergo differentiation toward phenotypically diverse nontumorigenic cancer cells [2]. Similar to normal stem cells, CSC are thought to be relatively quiescent, to be resistant to drugs and toxins, and to possess active DNA repair capacity [6]. To define CSC, several key characteristics have been described as follows: (1) the CSC subpopulation can be separated from the other cancer cells by distinctive cell surface markers or by strong drug transporter activity pumping out the substrate dye Hoechst 33342 to be detected as "side population" in flow cytometric analysis; (2) the CSC can be serially transplanted through multiple generations, indicating a self-renewal property; (3) tumors originating from the CSC contain mixed populations of tumorigenic and nontumorigenic cells, suggesting a differentiation activity.

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CANCER STEM CELLS IN HEAD AND NECK CANCER

Using methods similar to those used to identify the tumorigenic subpopulation of cells from breast cancer, Mark et al. reported the isolation of a highly tumorigenic subpopulation of cancer cells from squamous cell carcinoma of head and neck (HNSCC). They generated single-cell suspensions from HNSCC specimens and identified that $CD44^+$ HNSCC cells possessed tumorigenic potential in immunocompromised mice by serial dilution experiments [7]. The differentiation ability of $CD44^+$ cells was demonstrated by content of a mixture of $CD44^+$ and $CD44^-$ tumor cells in tumors arising from purified $CD44^+$ cells. Serial re-transplantation of both $CD44^+$ and $CD44^-$ populations indicated that only the $CD44^+$ population could initiate new tumors in vivo. They also found that the $CD44^+$ cells expressed CK5/14, a marker for the basal region in normal squamous epithelium where the normal tissue stem cells are known to reside. Moreover, the differentiation marker involucrin stained areas of the tumors that were $CD44^-$. These findings provide a clue that the carcinogenesis of HNSCC may be organized into a developmental hierarchy, during which CSC may play a role.

CHEMORADIATION RESISTANCE AND CSC

Concurrent chemoradiation (CCRT) has been widely accepted as a standard treatment for locally advanced head and neck cancers [8,9] or for organ preservation to provide a better quality of life [10]. Radiation therapy (RT) and chemotherapy (CT) are often given over multiple sessions to allow for the recovery of normal tissue between administration of treatment fractions. However, surviving cancer cells can also proliferate during the interval between sessions. "Ac-