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Leading article/Artykuł redakcyjny
Review/Praca poglądowa

Cancer stem cells in head and neck squamous cell carcinoma

Nowotworowe komórki macierzyste w rakach głowy i szyi

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ARTICLE INFO

Article history:
Received: 27.10.2013
Accepted: 31.10.2013
Available online: 05.11.2013

Keywords:
- Head and neck squamous cell carcinoma
- HNSCC
- Cancer stem cells
- Tumor markers
- Tumorigenesis

Słowa kluczowe:
- raki głowy i szyi
- nowotworowe komórki macierzyste
- markery nowotworowe
- nowotworzenie

ABSTRACT

Recent studies have demonstrated that cancer stem cells (CSC) play an important role in the pathobiology of head and neck squamous cell carcinomas (HNSCC). This subpopulation of undifferentiated, self-renewing cells is responsible for resistance to conventional anti-cancer therapy, cancer recurrence, metastasis and ability to form a heterogeneous tumor. CSC are identified on the basis of specific markers, including membrane proteins or cell enzymes, or by using their self-renewal properties. As their resistance to standard HNSCC treatment may eventually lead to the lack of treatment success, there is an urgent need to better understanding CSC biology and identify them as potential target new treatment modality.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy in humans and constitutes 6–10% of all malignant tumors [1]. Every year, there are six thousand new cases noted in Poland and over 500 000 in the world, mainly among people in the 6–7th decade of life [2, 3]. High morbidity and mortality, lack of expected

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0030-6657/$ – see front matter © 2013 Polish Otorhinolaryngology - Head and Neck Surgery Society. Published by Elsevier Urban & Partner Sp. z o.o. All rights reserved.
http://dx.doi.org/10.1016/j.otpol.2013.10.010

response to radio- and chemotherapy and significant reduction in the quality of life among patients after surgical procedures in the head and neck region are related to the need for seeking more effective methods of treatment and prevention of disease recurrence [4]. Despite advancements in the field of oncology and great methods of detecting the disease at earlier stages in the last 30 years, we still observe high morbidity and resistance to conventional therapy. Surgical treatment and frequent local recurrences significantly reduce patients' quality of life [5, 6]. Research studies from recent years are dominated by the hypothesis that there is a small population of cells within the main tumor mass containing stem cell features [7, 8]. Recent studies indicate that a small population of cancer cells is highly tumorigenic, undergoes self-renewal and has an ability to differentiate into cells that normally constitute the bulk of the tumors. It is believed that existence of cancer stem cells (CSC) may be the reason for the lack of effectiveness of previous treatment methods [9, 10]. Targeted elimination of these cells is considered to provide a new framework for head and neck cancer treatment. It is also suggested that learning about previously unknown molecular mechanisms determining the occurrence and development of head and neck tumors will allow for acquiring considerably better therapeutic results. This review discusses the proposed role of cancer steam cells in tumorigenesis and a potential influence of cancer steam cell hypothesis on clinical management of head and neck cancers.

Cancer stem cell theory

Previously accepted stochastic model of oncogenesis presented in 1976 by Nowel was based on an assumption that neoplasm develops from a single mutated cell that, due to the influence of mutagens, underwent various genetic and epigenetic changes, transforming into a neoplastic cell [11]. This model also explained the pathophysiologic bases for development of preneoplastic lesions (dysplasia) and subsequent, gradual progression to neoplasm, as in *e.g.* colon cancer. In this model, neoplastic disease is considered a proliferative disease (Fig. 1). It is thought that all neoplastic cells are identical and possess the same capacity to proliferate and carcinogenesis. This model exerted great influence on development of current anti-cancer therapies. However, stochastic model of oncogenesis did not explain fundamental facts regarding *e.g.* phenotypic heterogenicity of neoplastic cells as well as tumorigenesis potential and ability to metastasize characterizing only a small proportion of tumor cells (<10%) [12, 13]. Based on the above mentioned observations, a new theory of oncogenesis, relating to a cancer stem cell (CSC) model, was put forward [8]. According to the American Association for Cancer Research (AACR) Workshop on CSC, neoplastic stem cells are defined as cells within the tumor that are capable of self-renewal as well as of differentiation into various types of cells of the same line, ensuring phenotypic heterogenicity of the tumor [7]. According to "cancer stem cell hypothesis" malignant stem cells are located at the top of the hierarchy among tumor cells, as they are the only ones that exhibit proliferative properties. Existence of CSCs was implied as long as 40 years ago. The most data on this topic come from research on hematological malignancies. Presence of those cells *in vivo* was first confirmed in acute myeloid leukemia (AML) in 1997 [14]. In 2003, Al-Hajj et al. proved the presence of CSC in solid tumors. They experimentally confirmed the ability of transplanted stem cells to restore a phenotypically heterogeneous structure of a tumor [15]. Existence of CSCs in HNSCC was first described in 2007 by Prince, who isolated them due to the presence of CD44+ surface marker [7]. Neoplastic stem cells most likely derive either from normal stem cells, in which mutations accumulated resulting in genetic instability, or from mutated progenitor stem cells. CSC have a lot in common with normal stem cells. Among other things, they possess the ability to proliferate indefinitely and to self-renew [16, 17]. CSCs exhibit greater expression of signaling pathways responsible for tumor growth and inhibition of apoptosis, ensuring immortality of neoplastic cells. Because of their longevity, tissue stem cells undergo various genetic and epigenetic changes that, acquired in time, lead to transformation into CSCs. Under normal circumstances, as a result of asymmetrical stem cell division, two groups of cells may coexist within the same niche: one being dedicated to restoring a stem cell reserve and the second beginning the process of differentiation (Fig. 2a) [18]. Thus, the stem cell pool does not become depleted. In carcinogenesis, this process is entirely different. Two identical stem cells are formed in the course of symmetrical

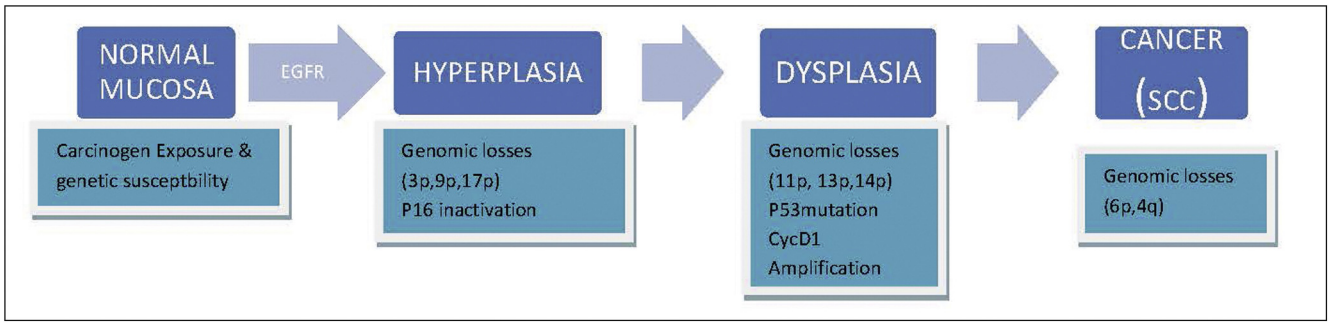

Fig. 1 – Clonal genetic model of molecular progression of head and neck cancer (acc. [37] with modif.)
Abbreviations: CycD1=cyclin D1 gene; p16 = p16INK4A cyclin-dependent kinase inhibitor gene; p53 = p53 tumor suppressor gene
Ryc. 1 – Genetyczny model klonalnej progresji nowotworów głowy i szyi