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Cancer stem cells in oesophageal squamous cell carcinoma: Identification, prognostic and treatment perspectives

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Contents

Abstract

Cancer stem cells (CSCs) are a vital subpopulation of cells to target for the treatment of cancers. In oesophageal squamous cell carcinoma (ESCC), there are several markers such as CD44, ALDH, Pygo2, MAML1, Twist1, Musashi1, Side population (SP), CD271 and CD90 that have been proposed to identify the cancer stem cells in individual cancer masses. It has also been demonstrated that stem cell markers like ALDH1, HIWI, Oct3/4, ABCG2, SOX2, SALL4, BMI-1, NANOG, CD133 and podoplanin are associated with patient's prognosis, pathological stages, cancer recurrence and therapy resistance. Finding new cancer stem cell targets or designing drugs to manipulate the known molecular targets in CSCs could be useful for improvements in clinical outcomes of the disease. To conclude, data suggest that CSCs

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in oesophageal squamous cell carcinoma are related to resistance to therapy and poor prognosis of patients with ESCC. Therefore, innovative insights into CSC biology and CSC-targeted therapies will help to achieve more effective management of patients with oesophageal squamous cell carcinoma.

Keywords: Cancer stem cell; Oesophageal squamous cell carcinoma; CSC markers; CSC biology

1. Introduction

Oesophageal cancers rank as the eighth most common cancer in the world and the fourth highest cause of cancer-related mortality [1]. Oesophageal cancers have diverse histological features with different biological behaviour [2–6]. The most common histological type of oesophageal cancer in high incidence areas in the world is oesophageal squamous cell carcinoma (ESCC) [7]. Improvement in the understanding of the molecular biology of ESCC could help in prediction of prognosis in patients with ESCC through improved ability to detect, classify and treat the disease [8–13]. In the clinical aspect, for example, pre-operative chemo-radiation is adopted as a standard way of treatment for patients with ESCC and in patients with ESCC who undergo this pre-operative chemo-radiation therapy, histological evaluations are important to predict the response to the treatment [14]. Also, histological regression of the primary cancer as indicated by the percentage of residual viable cancer cells is an important prognostic factor [15]. Cancer stem cells (CSCs) may be related to the survival of these residual viable cancer cells and may thus be important factors for prognosis and treatment selection. In this review, markers for CSCs in ESCC, the role of CSCs in therapy resistance as well as the role of CSCs in diagnosis, prognosis and treatment of patients with ESCC will be discussed. This information may help to improve better management of patients with ESCC.

2. Cancer stem cells and therapy resistance of ESCC

Many studies and clinical trials showed that there were no significant improvements in overall survival of patients with ESCC treated with surgery alone or in combination with chemo-radiotherapy [16–24]. Furthermore, some studies reported a higher chemoradiotherapy treatment-related mortality in patients with ESCC [22,25,26]. The current concept to explain this increased mortality and therapy failure is that CSCs are mainly responsible for treatment resistance and are the principal cause of cancer relapses and may be prevalent enough in the disease to make this impact [27–33].

Therapy resistance caused by CSCs has been associated with multiple factors that are unique to CSCs. These include increased expression of drug transporters (such as ATP-binding cassette [ABC] transporter), intracellular detoxification of substances that mediate drug efflux and metabolism, deregulation of anti-apoptotic proteins, increased capacity of DNA damage repair and alterations in cell-cycle kinetics as well as tumour micro-environments [34]. Several signalling pathways such as Notch, Wnt and Hedgehog have also been implicated in the chemo-resistance of CSCs in ESCC [35–38]. Thus, CSCs can contribute to therapy resistance through modulation of intrinsic and/or extrinsic factors. Evidence from preclinical and clinical studies demonstrated that most therapeutic agents effectively destroy the highly proliferating cells that form the bulk of the cancer rather than the relatively quiescent CSCs [27]. Therefore, the elimination of non-CSCs by such treatments allows more space for CSCs to expand and evolve into a more aggressive cancer with higher self-renewal potential [39–44].

3. Functional identification of CSC markers in ESCC

CSCs are cells that have the capacity of self-renewal, meaning they undergo asymmetric divisions to produce more CSCs and a variety of differentiated daughter cells forming the bulk of tumour [45,46]. The translational definition of CSCs and the gold standard for exhibiting ‘stemness’ in CSCs is the ability to regenerate primary tumour in immunocompromised mice. This xenotransplantation demonstrates the capacity of specific cells (CSCs) to reproduce the variety of differentiated cells present in the original primary cancer [45]. Different biomolecules are used as markers to detect and isolate of these self-renewal cells (CSCs) in various cancers. A well-defined panel of markers for CSC in ESCC has not been identified and characterized. Nevertheless, some molecules are being used to functionally identify the CSCs in ESCC. The details of these CSC markers that have been identified in various ESCCs to date are summarized in Table 1.

CD44, a cell-surface antigen, is the major marker used in isolation and detection of oesophageal squamous cell carcinoma. Stem cells in the oesophageal squamous epithelium which express CD44 act as tumour initiating/cancer stem cells as they showed higher tumourigenic potential *in vivo* [47]. CD44 is a receptor for hyaluronic acid which in turn acts as an activator for tyrosine kinase receptor. The action of CD44 stimulates cell proliferation by modulating MAPK (mitogen-activated protein kinase) and PI3K/AKT (phosphatidylinositol-3 kinases/protein kinase B) signalling pathways [48,49]. Also, CD44 has different isoforms (CD44s, CD44v2, CD44v3, CD44v6 etc.) and these variants have significant impact on tumour initiation and