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Review

# CD26 a cancer stem cell marker and therapeutic target

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ABSTRACT

Cancer stem cells (CSCs) comprise a tumor subpopulation responsible for tumor maintenance, resistance to chemotherapy, recurrence and metastasis. The identification of this cell group is very important, but there is still no consensus on its characterization. Several CSC markers have been described, like CD133, CD24, CD44 and ALDH1, but more research to identify new markers to facilitate the identification of CSC in a heterogeneous tumoral mass is required. Thus, this article describes the CD26 expression as a CSC marker and the role that it plays in different types of cancer. CD26 expression correlates with some characteristics of CSCs, like the formation of spheres in vitro, formation of new tumors, and resistance to chemotherapy. CD26 is therefore suggested as an auxiliary marker for CSC in different types of cancer, and as a potential therapeutic target.



## 1. Introduction

Cancer cells were initially considered as a fairly homogeneous set inside a tumor. Nowadays, it is known that a single tumor includes regions with varied degrees of cellular differentiation. In recent years, an increasing body of evidence points to the existence of a cell subpopulation with low differentiation, called cancer stem cells (CSCs) [1]. These cells differ from other populations of the tumor in the presence of stem cell markers [2], and have specific characteristics, such as resistance to traditional chemotherapy and radiotherapy [3], apart from the capacity for self-renewal, being able to initiate the development of a new tumor [4].

CSCs were initially identified in acute myeloid leukemia (AML), where the presence of a cellular hierarchy was characterized. These CSCs presented a cell surface phenotype $CD34^+/CD38^-$, and were capable of reproducing an AML when injected in diabetic mice [5,6]. After isolation of CSCs in AML, they were identified in solid tumors. In 2003, Al-Haaj et al. [2] isolated $CD44^+/CD24^-$ cells from breast cancer tumors, which had greater ability to produce new tumors in immunodeficient mice, when compared with other cell subpopulations. Currently CSCs have been characterized in different types of tumors, such as prostate [7], colorectal [4], melanoma [8], pancreatic [9] and cervical cancers [10].

The identification of the CSCs is usually performed by using cell surface markers, which require previous knowledge of the markers used in the CSCs of the tissue of interest. The most commonly used include CD133, CD44, CD24 and CD90 [11]. Furthermore, in solid tumors, it is possible to identify the side population (SP), characterized by the expulsion of Hoestch33342® dye within CSCs due to the presence of efflux pumps in these cells [12]. Aldehyde dehydrogenase 1 (ALDH1) activity has also been used as a functional stem cell marker to isolate CSCs [13].

In recent years, the role of CD26 in CSCs has been widely studied in several types of cancer. This enzyme is expressed on a variety of cell types, and has peptidase activity, being able to cleave and degrade many biologically active peptides [14]. It also has other non-enzymatic functions, acting as the major binding protein for adenosine deaminase (ADA) [15], interacting with extracellular matrix proteins [16], and participating in different signalling pathways [17]. Recently, the CD26 glycoprotein was correlated with CSCs in colorectal cancer cells $CD133^+$ [18]. In addition, CD26 was highly expressed in CSCs of patients with malignant mesothelioma (MM) [19]. Thus, CD26 is suggested as an auxiliary marker for the isolation of this cell subpopulation.

The aim of this study is to provide an overview, in a systematic review format, of the expression profile of CD26 in CSCs, focusing

*Abbreviations:* CSC, Cancer stem cells; AML, Acute myeloid leukemia; SP, Side population; ALDH1, Aldehyde dehydrogenase 1; ADA, Adenosine deaminase; MM, Malignant mesothelioma; GBM, Glioblastoma multiforme; LSC, Leukemia stem cells; CML, Chronic myeloid leukemia; ER, Estrogen receptors.

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on the role of the expression of this enzyme in different types of tumors.

## 2. Method

An electronic search was conducted in December 2014, for papers indexed in PubMed database. The search strategy included the combination of the terms "Cancer Stem Cell, CSC, Cancer-initiating cell or CIC" and "CD26 or DPPIV". Eligible articles for inclusion in this review should describe any possible relationship between CSCs and CD26 in different cancer types. This research strategy afforded to identify 15 articles and after reviewing their abstracts all papers were chosen. Data for this review were extracted from the original studies on CSCs and CD26 found in the search.

## 3. Results and Discussion

It has been reported that tumors are composed of a hierarchy of cells, and this set is often more complex than some human organs. Considering the different populations of cells that form the tumor, CSCs have been subject of several studies in recent years, which have characterized these cells in different types of cancer. One of the main points concerning CSCs to be investigated and discussed is the identification of this population within the tumor microenvironment. Several markers have been characterized for the identification of CSCs, and it is known that the combination of markers qualifies the isolation of CSCs. Thus, CD26 has emerged in recent years as a potential marker for CSCs in different types of cancer. In the Table 1 of this review, we present a summary of articles that demonstrate the expression of CD26 in CSCs.

The first article that reported the CD26 expression in CSC used samples of colorectal tumors. CSC labeled with CD133 was isolated and the expression of CD26 accompanied the increased expression of CD133, being suggested as an auxiliary marker of indifferentiation and metastasis [18]. A similar result was also found in samples of patients with colorectal cancer. In this study, CD26 showed a similar expression pattern found in other indifferentiation markers (CD44 and ALDH), featuring CD26 as a CSC marker [26]. A similar profile was also observed when CSCs were induced in vitro, in colorectal cancer cell lines of epithelial origin (HCT116) and in two adenocarcinoma cell lines (HT29 and Caco-2) [24].

A study with human MM showed that when sphere formation was induced, there was an increase in CD26 expression in CSC of cell lines of epithelial (H226, Meso-1, Meso-4 and H2052) and sarcomatoid origin (JMN, H2452 and H-28), as well as in patient samples. The results show an increase in CD26 expression and also in CD24 and CD9 in these cells, suggesting that these proteins may be potential CSC markers in MM [19]. Moreover, after the growth of immortalized cells of glioblastoma multiforme (GBM) in spheroids, the expression of indifferentiation markers, such as Nanog, Oct-4 and CD133 was observed, as well as increased expression of CD26 [22]. These results demonstrate the ability of these cells to grow in spheroids and show that CD26 may be used as a CSC marker in MM and GBM.

The patterns of gene expression in leukemia stem cells (LSC) from patients with chronic myeloid leukemia (CML), analyzed by microarray, showed a phenotypic pattern $CD34^{+}/CD38^{-}/ALDH^{High}$. Besides, an increase in CD26 expression was also observed, which was confirmed by the qPCR technique [25]. This result was also confirmed in another study with LSC, where CD26 showed high expression together with BCR/ABL1, an oncoprotein considered essential for CML manifestation [20,33].

In some cancers, CD26 shows a heterogeneous expression pattern, depending on the cell line and individual characteristics of each tumor. CD26 expression in CSC of four cell lines was evaluated in breast cancer (MCF-7, MDA-MB231, H5578T and MCF10) and seven samples of patients with high-grade lesion. Only the cancer cell line of glandular origin (H5578T) showed high expression of CD26. However, a high CD26 expression was observed in five patient samples, independently of estrogen receptors (ER), since CD26 is expressed both in $ER\alpha^{+}$ and $ER\alpha^{-}$ patients [30]. A similar result was observed in gastric cancer, with heterogeneous pattern, where the four cell lines studied showed CD26 expression (GSU, MKN1, MKN7 and MKN45), while other two were negative (AGS and NUGC3) [31]. Thus, CD26 is presented as a CSC marker in gastric and breast cancer, depending on the individual characteristics of the cell subpopulation under study, and requires the association of other indifferentiation markers. In gastric cancer, Lgr5 has been described as CSC marker in adenocarcinoma samples. Its expression followed the increase of markers like CD44, ALDH1 and CD26 in CSC [28].

Considering that the expression of CD26 correlates with the expression of indifferentiation markers, it is necessary to know the roles that this enzyme plays in CSC. In human colorectal cancer, CSC $CD133^{+}$ with high CD26 expression showed an increased ability to form new tumors when injected in mice, compared to CSC $CD133^{+}$ with low expression of CD26. The tumors formed were

**Table 1**
CD26 profile expression in CSC of clinical samples/tumor cell line.

| Author, year | Tissue study or tumor cell line | Methods |
|---|---|---|
| Herrmann et al., 2014 [20] | Peripheral blood of patients with chronic myeloid leukemia (CML) | Flow cytometry, immunohistochemistry |
| Okamoto et al., 2014 [21] | Mesotelioma cell lines: Meso-1, MSTO, NCI-H2452, and NCI-H226 | Flow cytometry, microarray, knockdown |
| Qu et al., 2014 [22] | Sample of glioblastoma multiforme tumor | RT-PCR |
| Apostolou et al., 2013 [23] | Colon cancer stem cells | Real-time PCR |
| Gemei et al., 2013 [24] | Colorectal cancer cell lines: HT29, HCT116, Caco-2, GEO, LS174T | Immunophenotyping, flow cytometry |
| Gerber et al., 2013 [25] | Peripheral blood of patients with CML | Real-time PCR, RT-PCR |
| Suzuki et al., 2013 [26] | Sample of colorectal cancer tumors and cell lines Caco-2, DLD-1, HCT116, HT29 and SW480 | Flow cytometry |
| Tilan et al., 2013 [27] | Sample of Ewing sarcoma tumors | Western blot, immunohistochemistry, flow cytometry |
| Wu et al., 2013 [28] | Sample of gastric cancer tumors | Immunohistochemistry |
| Zhou et al., 2013 [29] | Colorectal cancer cell line SW620 | Real-time PCR |
| Leccia et al., 2012 [30] | Sample of breast cancer tumors and cell lines MCF-7, MDA-MB231 (MDA), Hs578T, and MCF10 | Flow cytometry |
| Nishikawa et al., 2012 [31] | Gastric cancer cell lines: AGS, NUGC3, GSU, MKN1, MKN7, MKN28, MKN45 and MKN74 | Flow cytometry |
| Yamazaki et al., 2012 [32] | Sample of malignant mesothelioma tumors | Flow cytometry, microarray |
| Ghani et al., 2011 [19] | Sample of malignant mesothelioma tumors | Flow cytometry |
| Pang et al., 2010 [18] | Sample of colorectal cancer tumors, sample metastasis and xenografts | Flow cytometry, knockdown |