Review

The expression of CD markers in solid tumors: Significance in metastasis and prognostic value

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Summary. Objective. The clusters of differentiations (CDs) are among the surface markers expressed on different cells in the body, which are involved in the communication of cells with each other and the induction of signaling. Moreover, the evaluation of the ectopic expression of these markers in solid tumors has led to the detection of disease in early stages. In this paper, we have examined the effect of CD markers expression on the function of cancer cells, as well as their importance as the diagnostic and prognostic factors for monitoring the progression of solid tumors. Materials and methods Relevant literature was identified by a PubMed search (1988-2017) of English the language papers using the terms "CD markers", "diagnostic", "prognostic", "predictive marker" and "solid tumors." Discussion. Finally, it can be stated that the evaluation of CDs is not only of diagnostic value at disease onset, but these markers can be used as prognostic and predictive markers to contribute to the treatment of disease and predict its relapse. Conclusion. Monitoring of tumors progression through CDs expressed on circulating tumor cells could be a new diagnostic and prognostic factor in the future.

Key words: CD Marker, Solid Tumors, Diagnosis, Prognosis, Predictive

Introduction

The most important factor increasing the risk of death in cancer patients is the lack of early diagnosis of initial stages of metastasis or relapse. Furthermore, the failure to identify a specific tumor marker for the detection and monitoring of solid tumors could lead to the invisibility of the tumor in the early stages (Qin and Tang, 2004). Tumor markers are factors in plasma or even in tissues that indicate the presence of tumor cells. These markers should be capable of detecting tumor cells much earlier than common diagnostic methods, and on the other hand, the response of cancer cells to treatments can be evaluated by measuring tumor marker levels in the body (Virji et al., 1988). Therefore, to diagnose tumors in the early stages, it is essential to identify a suitable marker for the evaluation and treatment of patients.

CD markers seem to be better diagnosis and prognosis markers in compare to other markers in cancer. CDs comparsion a series of surface antigens (Ags) of different types (Woolfson et al., 2006), which are predominantly expressed on leukocytes and other cells and contribute to various processes, including cell-cell communication and the elicitation of immune responses against foreign agents. In addition, it has recently been noted that these markers are also expressed on tumors and are involved in molecular processes (e.g. self-renewal) in these cells (Chakraborty et al., 2013; Ma, 2013). Moreover, since the expression of CD markers is associated with physiologic changes, their expression on tumor cells is different from normal cells. Hence, the evaluation of these markers as the factors

indicative of physiological and pathological changes occurring in the body can be effective in tracing and detecting the tumor cells in the body (Virji et al., 1988). Several studies have been conducted on the expression of different CD markers on tumor cells and their involvement in molecular mechanisms. However, there have been few studies to date on the assessment of these CD markers as prognostic and predictive markers. Through the identification of biological functions of these markers on cancer cells, they are likely to be used as prognostic factors, as well as for the development of appropriate treatment protocols according to their molecular mechanisms. In this paper, we assessed the expression importance of a number of CD markers as effective factors for disease diagnosis and prognosisof solid tumor cells [e.g. colorectal cancer (CRC) and hepatocellular carcinoma (HCC), as well as their role in response to treatment.

Epigenetic changes regulateCD markers expression

The expression of some CD markers on tumor cells due to epigenetic changes results in the aggressiveness and resistance of these cells to therapeutic agents (He et al., 2011). Epigenetic processes involve a series of changes without substitution in the DNA sequence, which lead to the expression activation or silencing of genes. DNA methylation and histone modification are major epigenetic changes that lead to the formation of a tumor phenotype and the proliferation of tumor (Baba et al., 2009; Kagara et al., 2012). The hyper- and hypo-methylation of CpG islands in the promoters of genes triggers the silencing and activation of gene expression, respectively. Hypomethylation of these regions in the promoter of many CD marker genes (including CD133) results in the increased expression of these markers on tumors, which eventually increases tumor survival. In addition, hypomethylation in the CpG islands has been shown to increase the transcription factor binding to these regions, which enhances the expression of CD markers (Gopisetty et al., 2013). Reduced activity of DNMT1 and DNMT3B enzymes, which methylate CpG islands in gene promoters, is another mechanism that leads to the expression of CD markers on tumor cells. The expression of CD133 has been shown to increase as a result of DNMT1 and DNMT3B inhibition by transformation growth factor-β (TGF-β) (You et al., 2010).

Enhancer of zester homolog 2 (EZH2) is a component of polycom repressive catalytic complex (PRC2). It has methyltransferase activity, and through the methylation of histone H3, suppresses the expression of tumor suppressor genes and CD markers, which results in solid tumors (such as in glioblastoma) (Abdouh et al., 2009). In tumor cells, EZH2 suppresses and increases the expression of miR-218 and CD133 on tumor cells, respectively. Besides miR-218, there are other miRs suppressing the expression of CD markers on tumor cells, which in fact play the role of tumor suppressors by binding the 3'-untranslated region (3'-UTR) of CD marker mRNAs and prevent their expression (Wang et al., 2016). However, in methylated tumor cells, binding of inhibitory factors to the promoter regions of these miRs reduces their expression and in turn increases the expression of their target genes (CD markers) (Table 1). Therefore, the CD markers expressed on tumor cells could be used as diagnostic and prognostic factors and might also detect the signaling pathways inactivating the tumor suppressors.

CD markers in solid tumors

Liver cancer

Liver cancer is one of the most lethal and invasive malignancies that causes a large number of deaths every year worldwide (Li and Wang, 2016). Liver cancer is

Table 1. Effect of epigenetic changes on the expression of CD markers.

MiRNA	Expression	Disease	CD marker	Mechanisms	Prognosis	Reference
miR-199-5b	Down	Medulloblastoma	CD15	Methylation in the CpGislands at the upstream promoter Binding Hes1 factor to promoter miR-199-5b binding site in the 3'-UTR of CD15	Poor	Andolfo et al., 2012
miR-199a	Down	Ovarian cancer	CD44	Binding site in the 3'-UTR	Poor	Cheng et al., 2012
miR-193a	Down	Ovarian cancer	CD117	Binding of E2F6 to polycomb complex of miR-193a Binding site in the 3'-UTR of CD117	Poor	Cheng et al., 2014
miR-370	Down	Lung cancer	CD105	Binding TRAF4 in the 3'-UTR of miR-370 Binding site in the 3'-UTR of CD105	Poor	Chen et al., 2014; Chen et al., 2015a,b
miR-142-3p	Down	Hepatic and colon cancer	CD133	Binding OCT4 to promoter of miR-142-3p Binding site in the 3'-UTR of CD133	Poor	Shen et al., 2013; Chai et al., 2014
miR-34a	Down	Prostate cancer	CD44	Expression of miR-34a is repressed by p53 Binding site in the 3'-UTR of CD44	Poor	Liu et al., 2011
miR-224 miR-486	Down	Pancreatic ductal adenocarcinomas	CD40	Binding site in the 3'-UTR of CD40	Poor	Mees et al., 2009
miR-200	Down	Lung cancer	CD274	Binding site in the 3'-UTR of CD274	Poor	Chen et al., 2015a

3'-untranslated region; TRAF4: TNF receptor-associated factor 4.

divided into different types based on the affected liver cells, and HCC is the most common form of this cancer (Wallace et al., 2015). Due to the lack of a specific factor, as well as delayed diagnosis of liver cancer, the metastasis and relapse rates of HCC cells are increased in patients, which lead to a reduction in the survival of patients (Han et al., 2014; Azizidoost et al., 2016). Today, it is known that cancer stem cells (CSCs) are sparsely distributed among HCC tumor cells, leading to disease relapse and lack of response to treatment. Several CD markers are expressed on CSCs, including CD13 and CD24 (Ji and Wang, 2012). However, CD133, CD44, and CD90 have been indicated as the most common markers differentiating CSCs from other HCCs. CD133 is a transmembrane glycoprotein that plays an important role in the self-renewal of HCCS, and the tumorigenic potential of CD133$^+$ CSCs is higher than CD133$^-$ ones (Feng et al., 2014). CD44 is another surface marker of CSCs, which causes HCC metastasis through the induction of Epithelial-Mesenchymal Transition (EMT), so that the knockdown of CD44 prevents the metastasis of HCCs (Gao et al., 2015). Moreover, considering the involvement of Wnt/β-catenin pathway in the induction of EMT process and self-renewal of tumor cells, this pathway probably leads to the proliferation of tumor cells via induction of CD44 expression (Shrivastava et al., 2017). CD34 and CD105 (endoglin) are other markers used to evaluate the cellular metastasis of HCC cells, and the angiogenesis rate in cancers such as HCCs can be evaluated as microvascular density (MVD) by these markers. However, recent studies have shown that CD105 is a specific factor to assess angiogenesis and disease progression in HCC due to its expression in new vessels and its distinction between immature and mature vessels (Segatelli et al., 2014; Shahrabi et al., 2016). CD151 is another marker used to evaluate MVD. Considering that the increased CD151 expression is associated with increased release of matrix metalloproteinase 9 (MMP9), the expression of this marker in HCC patients is associated with an unfavorable prognosis (Table 2) (Shi et al., 2010).

Macrophages are divided into two types of M1

(CD68$^+$) and M2 (CD206) based on function and expression of a series of markers on their surface. The M1 type plays an important role in suppressing the growth of cancers by stimulating immune responses, while the M2 type increases tumor cell proliferation by suppressing immune responses (Dong et al., 2016). Accordingly, it has been shown that the increased expression of CD68 and CD206 markers could be used to evaluate prognosis in patients, so that the overexpression of CD68 and CD206 has been associated with favorable and poor prognosis, respectively (Table 2). In addition to prognostic value, the CDs expressed on HCC cells can be used to analyze the response rate of patients to treatments. It is essential to target immune system inhibitor markers such as CD152 on cancer cells in order to revive inflammatory responses of immune system against cancer cells (Table 3).

Colorectal cancer

This malignancy is ranked third and second in terms of prevalence in males and females, respectively. CRC cells are metastable to liver in 70-80% of cases (Jemal et al., 2011). Liver is the organ producing thrombopoietin (TPO) and CD110 as the TPO receptor is expressed by CRC cells. Hence, the chemotactic property between TPO and its receptor probably leads to the metastasis of CRC cells to the liver (Gao et al., 2013). On the other hand, CRC cells can metastasize to lymph nodes if CD133 and CXCR4 are expressed on their surface (Silinsky et al., 2013). However, if this is the case, the Wnt/β-catenin signaling pathway will be disrupted and CRC metastasize to the liver (Michl et al., 2015; Ahmadzadeh et al., 2016). Besides, the expression of CD200 (which leads to the suppression of immune responses) is increased on CD133$^+$ CD44$^+$ cells relative to CRC CD133$^-$ CD44$^-$ cells, which is associated with the activation of Wnt/β-catenin pathway that ultimately results in the suppression of the immune system (Zhang et al., 2016). Conversely, the 90K glycoprotein (a type of tumor suppressor) has a number of domains to which CD9 and CD82 are bound to inactivate the Wnt/β-

Table 2. The expression of CD makers in cancers and their diagnostic and prognostic value.

Type of cancer	Commonly identified CD markers	Prognostic CD markers	Diagnostic CD markes	Type of sample	Type of diagnostic technique	Reference
liver	CD133, CD44, CD90, CD105, CD34, CD151, CD206, CD68	CD151, CD68, CD206	----------	Tissue, Cell line	IHC, Flow cytometery, RT-PCR	Ho et al., 2005; Zhu et al., 2015; Zhao et al., 2016; Ren et al., 2017
colorectal	CD66, CD110, CD133, CD44, CD2, CD89, CD200	CD110, CD133, CD44, CD200	CD66	Tissue, Cell line, peripheral blood	IHC, Flow cytometery, RT-PCR	Lee et al., 2010; Gao et al., 2013; Kim et al., 2013; Michl et al., 2015
lung	CD117, CD176, CD166, CD88, CD103CD66	CD88, CD103	CD66	Tissue, Cell line, peripheral blood	IHC, Flow cytometery, RT-PCR	Guo and Ward, 2005; Herpel et al., 2011; Lin et al., 2011; Zhou et al., 2013; Tachezy et al., 2014; Djenidi et al., 2015
Breast	CD44, CD24, CD133, CD14, CD200, CD4 CD8, CD4 CD25	CD44, CD133, CD14	----------	Tissue, Cell line, peripheral blood	IHC, Flow cytometry, ELISA	Wang et al., 2012; Celik et al., 2016; Jang et al., 2016; Lv et al., 2016; Tampaki et al., 2017

IHC:Immunohistochemistry;RT-PCR:Reversetranscription polymerase chain reaction; ELISA: enzyme-linked immunosorbent assay.

catenin signaling pathway (Lee et al., 2010). Thus, the CDs expressed on CRCs can activate or suppress the Wntβ-catenin pathway according to their physiological functions and the activation of this pathway is associated with a poor prognosis.

The expression of CD66 by CRC cells is reduced in the early stages of CRC but is increased with disease progression and expansion, which is associated with resistance against anoikis (a form of programmed cell death) (Kim et al., 2013). There are long (L) and short (S) domains on the cytoplasmic side of CD66 and the L domain shows a good response to treatment. A number of other CDs are expressed on CRC cells, which are known as predictive markers. CD47 is an example of mentioned CD markers which activates the anti-dependent cell mediated cytotoxicity phenomenon (ADCC) (Table 3).

Lung cancer

Lung cancer is a malignancy with a high mortality rate in patients (Normanno et al., 2016). CD133 is not only expressed on CSCs of lung cancer, but it is known as a diagnostic marker for circulatory tumor cells (CTCs) in this type of cancer, so that the detection of CTCs in peripheral blood (PB) can indicate the metastasis of cancer cells. Therefore, CD133 could be used as a diagnostic marker for lung cancer CTCs in the early stages of metastasis (Hou et al., 2013). Therefore, targeting CD133 may be effective in preventing the progression of cancer cells (Table 3). Other markers expressed on CSCs are listed in Table 2, among which the CD66 is expressed to a higher extent in malignant cells than in normal cells. Therefore, monitoring of CD66 in patients can lead to disease diagnosis (Zhou et al., 2013). On the other hand, CD66 targeting is also associated with increased activity of the immune system and improved survival of patients (Table 3).

In normal conditions, C5a interaction with its receptor (CD88) leads to inflammation via activation of immune cells (Guo and Ward, 2005). Recently, however, it has been shown that such an interaction in lung cancer leads to the decreased expression of CD62E (E-selectin) and eventually an increase in EMT and metastasis. Furthermore, the overexpression of CD9 can increase the apoptosis of tumor cells due to calretinin expression that ultimately reduces metastasis (Gu et al., 2013; He et al., 2013). It has been shown that CD317 (H.M1.24) targeting can lead to increased complement-mediated tumor lysis (Table 3). CD103 is another marker expressed on immune cells such as CD8^{+} T-cells and tumor infiltrating lymphocytes (TILs) but CD103 expression is decreased in patients with lung cancer, leading to increased proliferation of cancer cells. Therefore, the reduction in CD103 expression may be associated with an unfavorable prognosis (Djenidi et al., 2015). Finally, we can say that the evaluation of immune markers as prognostic factors may prove helpful in monitoring the progression of tumor cells.

Breast cancer

This is one of the most common cancers among women. Human epidermal growth factor receptor (HER2) is an important marker in breast cancer, which is used as a prognostic and diagnostic factor (Krishnamurti and Silverman, 2014). CD24 and CD44 are two markers expressed on breast CSCs. However, the expression of CD24 and CD44 in HER2 positive CSC cells and CSC HER2 negative cells has been indicated, respectively. Moreover, HER2 positive CSCs are more aggressive than HER2 negative ones probably due to CD24 expression by the former (Jang et al., 2016). Given the expression induction of hypoxia inducible factor (HIF) through the activation of PI3K/AKT pathway, HIF is likely to enhance the aggressivenessof HER2 positive

Table 3. Expression of CD makers and their response to treatment.

Cancer	Predictive CD markers	Function	Type of treatment	Response	Reference
Liver	CD133	Activation of ERK pathway	Sorafenib	Ineffective	Hagiwara et al., 2012; Chen et al., 2016; Duffy et al., 2017
	CD279	Phosphorylation of ERK	Sorafenib+anti-PD-1	Good	
	CD152	Suppression of T-cells	Tremelimumab+ TACE	Good	
Colorectal	CD66	Apoptosis	Chemotherapy-5-FU	Good	Tseng et al., 2013; Gao et al., 2014; Steinert et al., 2014; Yamamoto et al., 2015
	CD47	Mediated phagocytosis by macrophage	mAb	Good	
	CD147	Apoptosis and arrested cell cycle	5-FU	Good	
Lung	CD133	Expression ABCG2 and CXCR4	Cisplatin	Ineffective	Bertolini et al., 2009; Wang et al., 2009; Hong et al., 2015
	CD317	Induced ADCC and CDC	mAb	Good	
	CD66	Sensitive to anoikis	8F5m Ab+Paclitaxel	Good	
Breast	CD166	-----------	Taxane-free adjuvant chemotherapy	Good	Ihnen et al., 2008; Zhou et al., 2015; Onishi et al., 2017
	HER2 with CD3	Stimulate T-cell	Specific Ab	Good	
	CD24	Reduce expression drug resistance factor	Chemotherapy-5-FU	Good	

PD-1: Programmed cell death protein1; 5-FU: 5- Fluorouracil; mAb: monoclonal antibody; Ab: antibody; CDC; complement-dependent cytotoxicity; ADCC: Antibody-dependent cellular cytotoxicity; CXCR4: C-X-C chemokine receptor type 4.

CSC cells due to increased angiogenesis (Hosonaga et al., 2014; Kim et al., 2014). On the other hand, the expression of CD24 reduces the activity of MAPK signaling pathway, which reduces the proliferation of cancer cells. Moreover, it increases the apoptosis of the cancer cells by suppressing the CD44-induced NF-kB pathway (Ju et al., 2011). On the other hand, CD44$^+$ALDH^{high} breast cells can metastasize toward this organ through the interaction with factors released by lungsuch as osteopontin (Chu et al., 2014; Rahim et al., 2014). CD133 is expressed on CSCs as well as CD44. Recent research has shown that CD133$^+$ ALDH$^+$ cells cause increased angiogenesis (Lv et al., 2016). CD146 is another marker expressed on CSCs, leading to the increased expression of Ki-67 (which increases cell proliferation) as well as enhancing angiogenesis as a co-receptor with VEGFR2. Therefore, the expression of CD146 is associated with metastasis and disease relapse (Tampaki et al., 2017).

T regulatory (Treg) and T helper (Th) cells are characterized by the expression of CD4$^+$/CD25$^+$ and CD4$^+$/CD8$^+$ markers, respectively. Th/Treg ratio plays a crucial role in the control of tumors. Recent research has indicated that the Th/Treg ratio is reduced in breast cancer patients relative to healthy people due to increasing Treg cells in advanced (IV stage) breast cancer (Wang et al., 2012). The expression of CD200 on immune cells and interaction with its receptor (CD200R) results in immune system suppression and increased proliferation of tumor cells (Rezaeeyan et al., 2017). However, recent results have shown that the soluble CD200 leads to the release of inflammatory cytokines (e.g. IL-1β), preventing metastasis and relapse of tumor cells (Celik et al., 2016). It is interesting to note that in other malignancies like chronic lymphocytic leukemia (CLL), the secretion of soluble CD200 leads to the production of a number of CD markers in addition to those mentioned on tumor cells, the targeting of which may affect the course of disease improvement. Finally, targeting CD24 and CD3 additionally to HER2 would prevent the proliferation of cancer cells and stimulate the immune system against cancer cells, respectively (Table 3).

Discussion and future perspective

Cancer is a disease that is difficult and even impossible to control and treat due to the lack of diagnosis at disease onset. The absence of a specific or common marker to detect tumor cells is the main factor for uncontrolled progression of this disease (Huse and Aldape, 2014). Although a variety of markers have been raised to identify and evaluate the progression of cancer cells, it seems that the identification of CD markers expressed on CTCs in PB has a higher clinical prognostic value due to straightforward measurement and cost-effectiveness compared to other markers (Hou et al., 2013; Liu et al., 2013). In addition to prognostic value of CD markers expression, these markers could be used as predictive markers to evaluate patients responses to

chemotherapy and even radiotherapy. For example, CD133 is a marker expressed in CSCs of various cancers, the expression of which is associated with an unfavorable prognosis and shows variable responses to different therapies (Tables 2, 3). Also, given that CSCs from different solid tumors possess a series of common markers like CD133 and CD44, these markers may be not only be used to detect CSCs in different cancers but to design a common integrated therapeutic approach to target these cells (Table 3). In addition, the expression of CD44 and other CSC markers can be due to the activation of Wnt/β-catenin signaling pathway. Finally, tracing the activation of this pathway in solid tumors can be considered as a prognostic factor with respect to the markers expressed via this pathway (Shrivastava et al., 2017).

Finally, it is understood that the evaluation of CD markers in solid tumors might be useful as a diagnostic factor in monitoring the disease development and treatment response.

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