CD166 as a Stem Cell Marker? A Potential Target for Therapy Colorectal Cancer?

Abstract

CD166 (Activated leukocyte cell adhesion molecule (ALCAM)) is a member of the immunoglobulin superfamily, which is expressed by various cells in several tissues including colorectal cancer (CRC). Many studies have reported the prognostic predictive value of CD166 as a cancer stem cell marker in CRC. CD166 gained increasing attention regarding tumor progression and metastatic spread in CRC. CD166 potentially represents either diagnostic or therapeutic capacities for CRC. This Mini review aimed to clarify the role and significance of CD166 expression in CRC.

Keywords: CD166; ALCAM; Stem cell; CRC; Immunoglobulin; Cancer Stem Cell

Abbreviations: CSC: Cancer Stem Cell; ALCAM: Activated Leukocyte Cell Adhesion Molecule; CRC: Colorectal Cancer

Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second in women worldwide, accounting for almost 10% of all cases [1,2]. The USA and Europe have high rates compared to Africa and Asia [3,4]. Only in the United States, nearly 135,000 new cases are diagnosed annually that about 50,000 people will die of the disease [5]. In Iran CRC is the third most common cancer in women and the Fifth in men [6]. Two big problems are the high ability of CRC to form secondary tumors, particularly in the lung and liver and the high heterogeneity of the genetic and epigenetic changes among the individual tumors. Continual development of CRC is described on the Figure 1 [7].

Activated leukocyte cell adhesion molecule (ALCAM) also known as CD166, which functions as a cell–cell adhesion molecule in homophilic (ALCAM-ALCAM) and heterophilic (ALCAM-CD6) interactions between adjacent cells in different tissues [8-13]. It is detectable in a wide variety of cell types, including lymphoid bone marrow, cells, hepatocytes, fibroblasts, neuronal cells, myeloid cells, and epithelial cells [14]. CD166, which was first described as a CD6 ligand on leukocytes, is a highly conserved 110-kDa multi domain transmembrane type-I glycoprotein of the immunoglobulin super family [15,16]. It has a variety of functions in normal tissues, such as migration of monocytes across endothelia, intravasation of leukocytes into the central nervous system and T-cell activation [17].

CD166 has been cloned in multiple species and has different names depending on the species and laboratory that cloned it: human melanoma metastasis clone D (MEMD), chicken neural adhesion molecule BEN/SC-1/DM GRASP, mouse/human ALCAM (CD166), rat KG-CAM, HB2 and fish neurolin [18,19].

CD166 is composed of 16 exons and has a size of over 200 kb, with an extracellular domain of 500 amino acids, a transmembrane domain of 22 amino acids and a short cytoplasmic domain of 34 amino acids. It’s consists of five extracellular Ig domains (2 NH2-terminal, membrane-distal variable-(V)-type and 3 membrane-proximal constant-(C2)-type Ig folds) and the human gene for it is located on chromosome 3 (3q13.1q13.2) [20] (Figure 2).

Adhesion molecules are divided into main categories, which include cadherins, integrins, mucins, selectins and immunoglobulins. Adhesion molecules can be involved in tumor cell-endothelial cell adhesion, tumor cell-matrix adhesion or tumor cell-tumor cell adhesion; all of these adhesions are necessary at different times during metastasis or primary tumor formation [19].

The distribution of CD166 in specific cell and tissue offer their involvement in the maintenance and development of tissue architecture, in hematopoiesis, in neurogenesis, immune responses and in tumor progression [21].

CD166 expression is pathologically correlated with aggressive disease in a variety of cancers including breast [23], esophageal [24], prostate [25], melanoma [26], ovarian, bladder and colorectal [27].
Figure 1: Cells of the colon crypt accumulate mutations and start to proliferate. In the green arrows you can see inactivation of antioncogenes, in the red arrows are mentioned most important changes in oncogenes [7].

Figure 2: Topology of ALCAM. The two Ig-like V-type domains and the three Ig-like C2-type domains are shown in red and green; glycosylation sites and the cytoplasmic domain are indicated [20].

Citation: Dana H, Marmari V, Mahmoodi G, Mahmoodzadeh H, Ebrahimi M, et al. (2016) CD166 as a Stem Cell Marker? A Potential Target for Therapy Colorectal Cancer?. J Stem Cell Res Ther 1(6): 00041. DOI: 10.15406/jscrt.2016.01.00041
Discussion

CD 166 is a marker of CRC stem cells that it has potential as a therapeutic target for CRC [27,28]. CD166 is important for cell survival and motility, cell growth, and also for invasion during metastases and tumor progression. Overexpression, loss, or malfunction of CD166 may contribute to the detachment of tumor cells and therefore to local invasion and tumor progression [22].

Tachezy et al. [12] evaluated the expression of CD166 in CRC. This study was performed to retrospectively evaluate the expression of CD166 in CRC. The expression of CD166 in CRC tissues of primary and metastatic sites and to determine whether ALCAM could serve as a diagnostic and prognostic marker [12]. Expression of CD166 in CRC has been analyzed by several groups with conflicting results [29]. In CRC a pathologically altered CD166 expression has been observed and could be associated with tumorigenesis and tumor progression [22]. In human CRC, aberrant cell surface CD166 expression is strongly correlated with a 15-month shortened survival [27].

In a research the expression of CD166 in CRC with using immunohistochemical staining with a semiquantitative scoring system, cytoplasmic and membranous immunoreactivity were analyzed. In research the expression of CD166 in CRC with using immunohistochemical staining with a semiquantitative scoring system, cytoplasmic and membranous immunoreactivity were analyzed. 58.6% had strong cytoplasmic staining and 30.6% had strong membranous staining (compared with normal epithelium) of the 111 CRC studied. Membranous CD166 expression correlated significantly with shortened patient survival. The authors proposed that upregulation of CD166 is an early event in the malignant transformation in CRC because it was identified in cancers, which are considered to be precursor lesions [19].

CD166 shedding in CRC, defined as detection of the intracellular domain in the absence of the corresponding extracellular domain, was significantly elevated in patients with CRC and correlated with reduced survival. Conversely, retention of intact CD166 was associated with improved survival, thereby confirming that CD166 shedding is associated with poor patient outcome [30].

Conclusion

CD166 is considered as a stem cell marker in colorectal cancer. Stem cells are determined as cells with the capability to perpetuate themselves through self-renewal and to produce mature cells of a special tissue through differentiation. As with other membrane proteins, CD166 represents a potential target for therapy, and its utility as a drug target may be further enhanced by ligand-induced endocytosis.

Concentrate on cancer initiation and progression has dominated the endeavor to better guide therapeutic approaches and understand disease pathology. As such, Cancer stem cell (CSC) hypothesis, which suggests that cancer is driven by cells harboring stem cell-like qualities, offers one explanation for why many current therapeutic approaches ultimately result in relapse of disease. Today the techniques that are commonly used in chemical therapy for the treatment of cancer, only target the differentiated or differentiating cells which form a major part of the tumor mass. The fact, that these cells only form the tumor volume but they cannot generate new cell and do not play a role in the disease progression and the development of tumor, is not noticed. In this hypothesis, some CSCs or cancer-initiating cells may be quiescent and, thus, evade eradication by standard cytotoxic therapies designed to target proliferating cells. These surviving cells can then proceed to support tumor growth and have the potential to initiate recurrent or metastatic disease [27]. The focus on these facts, and as CD166 is assumed as stem cells marker and is expressed highly in colorectal cancer, it can be an appropriate remedial potential to treat them.

CD166 is a cell-surface antigen that is proposed as the antigen of cancer stem cell in CRC. Active immunotherapy encompasses a diverse range of strategies, some of which target multiple, undefined antigens whereas others specifically target a particular antigen or a group of antigens. Recently, the recognition of the tumor related antigen has introduced a new foundation in the immunotherapy of special antigens. The major aim of the vaccine experiments initiated from the last decade was to induct the specific immune response against the cancer antigens [31,32].

CD166 expression is a positive prognostic marker for overall survival of CRC patients, and its detection might help to optimize the existing prognostic staging system. Elevated expression in higher differentiated tumors might indicate a potential role in the early steps of tumorigenesis, and its loss might be associated with reduced cellular adhesion, resulting in a higher metastatic potential of the tumor [12].

References
1. Forghanifard MM, Moghbeli M, Raeossadati R, Tavassoli AL, Javadani Mallak A, et al. (2013) Role of SALLA4 in the progression and metastasis of colorectal cancer. J Biomed Sci 20:6.
2. Sørensen CG, Karlson WK, Pommergaard HK, Burchardt J, Rosenberg J (2016) The diagnostic accuracy of carcinoembryonic antigen to detect colorectal cancer recurrence - A systematic review. Int J Surg 25: 134-144.
3. Peravali R, Hall N (2015) Colorectal cancer: features and investigation. Medicine 43(6): 299-302.
4. Haggar FA, Boushey RP (2009) Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clin Colon Rectal Surg 22(4): 191-197.
5. American Cancer Society (2015) Cancer facts & figures.
6. Ramezani Darya Sar R, Nad Ali F, Modirian M, Arjinmpdpr M, Salvati F, et al. (2011) Program national comprehensive of cancer control. Ministry of Health and Medical Education. Islamic Republic of Iran.
7. Pitule P, Čedliková M, Treška V, Králiková M, Liška V (2013) Assessing colorectal cancer heterogeneity: one step closer to tailored medicine. Journal of Applied Biomedicine 11(3):115-129.
8. Fernández MM, Ferrugat F, Cárdenas Delgado VM, Bracallente C, Bravo AI, et al. (2016) Glycosylation-dependent binding of galectin-8 to activated leukocyte cell adhesion molecule (ALCAM/CD166) promotes its surface segregation on breast cancer cells. Biochimica et Biophysica Acta 1860(10): 2255-2268.
9. Chappell PE, Garner LI, Yan J, Metcalfe C, Hatherley D, et al. (2015) Structures of CD6 and Its Ligand CD166 Give Insight into Their Interaction. Structure 23(8): 1426-1436.
10. Wagner M, Bilinska M, Pokrzywlo Dragan A, Sobczyński M, Cyrl M, et al. (2014) ALCAM and CD6 - multiple sclerosis risk factors. J Neuroimmunol 276(1-2): 98-103.
11. Anderson ER, Hessman CR, Levin TG, Monne M, Wong M (2010) The Role of colorectal cancer stem cells in metastatic disease and therapeutic response. Cancers 3(1): 319-339.

12. Tachezy M, Effenberger k, Zander H, Minner S, Gebauer F, et al. (2012) ALCAM (CD166) expression and serum levels are markers for poor survival of esophageal cancer patients. Int J Cancer 131(2): 396-405.

13. Al Shehri FS, Azeem EM (2015) Activated leukocyte cell adhesion molecule (ALCAM) in saudi breast cancer patients as prognostic and predictive indicator. Breast Cancer (Auckd) 9: 81-86.

14. Fujiwara K, Ohuchida K, Sada M, Horioka K, Urich CD, et al. (2014) CD166/ALCAM expression is characteristic of tumorigenicity and invasive and migratory activities of pancreatic cancer cells. PLoS One 9(9): e107247.

15. Ni C, Zhang Z, Zhu X, Liu Y, Qu D, et al. (2013) Prognostic value of CD166 expression in cancers of the digestive system: A systematic review and metaanalysis. PLoS One 8(8): e70958.

16. Sun Y, Wang Y, Cao Q, Yu H, Zheng D, et al. (2015) Expression and Role of CD166 in the chronic kidney disease. Iran J Pediatr 25(5): e543.

17. Miyata T, Yoshimatsu T, So T, Oyama T, Uramoto H, et al. (2010) Cancer stem cell markers in lung cancer. Personalized Medicine Universe 4: 40-45.

18. King JA, Ofori Acquah SF, Stevens T, Al Mehdi AB, Fodstad O, et al. (2004) Activated leukocyte cell adhesion molecule in breast cancer: prognostic indicator. Breast Cancer Res 6(5): 478-487.

19. Ofori Acquah SF, King JA (2008) Activated leukocyte cell adhesion molecule: a new paradox in cancer. Transl Res 151(3): 122-128.

20. Weidle UH, Eggle D, Klostermann S, Swart GW (2010) ALCAM/CD166: cancer-related issues. Cancer Genomics Proteomics 7(5): 231-244.

21. Swart GW (2002) Activated leukocyte cell adhesion molecule (CD166/ALCAM): Developmental and mechanistic aspects of cell clustering and cell migration. Eur J Cell Biol 81(6): 313-321.

22. Ihnena M, Kohler N, Kerstenc JF, Mide Langoscha K, Becka K, et al. (2010) Expression levels of activated leukocyte cell adhesion molecule (ALCAM/CD166) in primary breast carcinoma and distant breast cancer metastases. Disease Markers 28: 71-78.

23. Kulasingam V, Zheng Y, Soosaipillai A, Leon A, Gion M, et al. (2009) Activated leukocyte cell adhesion molecule: A novel biomarker for breast cancer. Int J Cancer 125(1): 9-14.

24. Clauditz TS, Rheinbaben KV, Lebek P, Minner S, Tachezy M, et al. (2014) Activated leukocyte cell adhesion molecule (ALCAM/CD166) expression in head and neck squamous cell carcinoma (HNSCC). Pathol Res Pract 210(10): 649-655.

25. Erturk K, Tastekin D, Bilgin E, Serilmaz M, Bozboy HU, et al. (2016) Serum activated leukocyte cell adhesion molecule and intercellular adhesion molecule-1 in patients with gastric cancer: Can they be used as biomarkers? Biomed Pharmacother 77: 86-91.

26. Tomita K, Bokhoven AV, Jansen CFJ, Bussemakers MIG, Schalken JS (2000) Coordinate recruitment of E-cadherin and ALCAM to cell–cell contacts by a-catenin. Biochem Biophys Res Commun 267(3): 870-874.

27. Levin TG, Powell AE, Davies PS, Silk AD, Dismuke AD, et al. (2010) Characterization of the intestinal cancer stem cell marker CD166 in the human and mouse gastrointestinal tract. Gastroenterology 139(6): 2072-2082.

28. Dana H, Mahmoodi G, Marmari V, Mazraeh A, Ebrahimi M (2016) An overview of cancer stem cell. J Stem Cell Res Ther 1(4): 00029.

29. Fanali C, Lucchetti D, Farina M, Corbi M, Cufino V, et al. (2014) Cancer stem cells in colorectal cancer from pathogenesis to therapy: controversies and perspectives. World J Gastroenterol 20(4): 923-942.

30. King JA, Ofori Acquah SF, Stevens T, Al Mehdi AB, Fodstad O, et al. (2004) Activated leukocyte cell adhesion molecule in breast cancer: prognostic indicator. Breast Cancer Res 6(5): R478-R487.

31. Hansen AG, Freeman TJ, Arnold SA, Starchenko A, Jones Paris CR, et al. (2013) Elevated ALCAM shedding in colorectal cancer correlates with poor patient outcome. Cancer Res 73(10): 1-10.

32. Melero I, Gaudernack G, Gerritsen W, Huber C, Parmiani G, et al. (2014) Therapeutic vaccines for cancer: an overview of clinical trials. Nat Rev Clin Oncol 11(9): 509-524.

33. Guo C, Manjili MH, Subjeck JR, Sarkar D, Fisher PB, et al. (2013) Therapeutic cancer vaccines: past, present and future. Adv Cancer Res 119: 421-475.