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Immuno-Histological Role Of CD133 In Pathogenesis Of Gastric Cancer

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Abstract: *The spread of cancer is one of the biggest obstacles at the present time, which has caused panic to people on the health and psychological level, adding to the economic burdens and human losses at the level of most countries of the world. For this reason, most medical institutions and researchers have shown great interest in this field to find the appropriate way out by finding sincere treatments for this problem.The current study includes a review of the immuno-histological role of the CD133 indicator in the development and severity of stomach cancer in order to be a key for applied studies to employ this indicator in the diagnosis or treatment of gastric cancer.*

Keywords: Gastric cancer, CD133, Pathogenesis, immunohistological markers

1.Introduction

The second most common cause of cancer-related death worldwide is gastric cancer (GC).Geographical variation in the prevalence of GC, which may be influenced by genetic and environmental factors [1]. The primary risk factors for distal gastric cancer are an infection with Helicobacter pylori (H. pylori) and dietary factors;whereas proximal stomach cancer is also significantly influenced by obesity and gastroesophageal reflux disease [2].Additional risk factors for gastric cancer include gastric surgery, gastric ulcers and adenomatous polyposis, blood type A, a positive family history, and hereditary factors.despite the fact that histopathology remains the most reliable and cost-effective method, patients are enrolled in the appropriate screening, surveillance, or treatment programs [3, 4]. In recent times, a number of molecules have been found and examined to see if they can be used in the treatment of GC in a clinical setting. Antibodies, immune cells, and chemokines make up the immune response, and their monitoring value for cancer prognosis is extremely high [5]. Recently, CD molecules as CD133 appeared as important factors in function and development many of cells in immuno-histological aspects in additional to immunological reactions [6].

Although the precise physiological function of CD133 is unknown, its widespread presence demonstrates its significance [7]. Although no mechanism has been proposed to link CD133 expression with the phenotype of cancer stem cells (CSCs), the human prominin-1 (CD133) antigen's cell surface expression, particularly that of the AC133 epitope, is one of the ones that has been studied the most frequently in

solid tumors [8]. The present review highlights methodological limitations and pitfalls as well as a variety of analytical tools for the inconsistencies between published data. By facilitating the recruitment of eosinophils, monocytes, T cells, and basophils, immunological markers like CD133 are known to promote tumor cell proliferation, invasion, and angiogenesis [9,10].There are very few studies on the immuno-histological role of CD133 markers as a prognostic or therapeutic factor in GC. To ascertain their significance in the development of GC, it is interesting to address these issues.

1- Immunological Response to Gastric Cancer

The treatment landscape for GC has been altered by remarkable advancements in immuno-oncology. It is essential to acquire a deeper comprehension of tumor immunity because immunotherapy intervenes with the immune response of the tumor rather than directly targeting the cells of the tumor [11,12].

GC cells are found and eliminated by the immune system. Through a process known as immune surveillance, this typically prevents the development of cancer [13]. Tumor-associated antigens (TAA), on the other hand, are antigens that can be found on both normal and tumor cells. Tumour-specific antigens (TSA) are those that are only found on tumor cells. GC-associated genetic mutations usually cause the expression of TSA and TAA [14]. Through endocytosis, tumor-resident dentritic cells (DCs) continuously sample the microenvironment. They process the TSA or TAA into peptides and assemble them on MHC, either in the endosomes for MHC class II or the endoplasmic reticulum for MHC class I [15]. In order for the DC to mature and, consequently, increase the levels of peptide MHC expression, it requires an activation signal, such as a DAMP or PAMP [16,17]. DCs that are activated alter the expression of adhesion molecules and chemokine receptors, making them more responsive to chemokines from the GC draining lymph node (TDLN).The mature DC presents TSA/TAA to CD8+ T cells on MHC class I or CD4+ T cells on MHC class II, initiating an antigen-specific T cell response [18,19]. Cytotoxic T cells (CTLs) require two signals from antigen processing cells (APCs) for successful activation:1) the presentation of the antigen and the binding of the T-cell receptor (TCR) to the peptide-MHC class I molecules; and (2) co-stimulation, T cells' CD28 molecule binding to APCs' CD80 (B7-1) or CD86 (B7-2) co-stimulatory molecules. In the absence of signal 2, immune tolerance to TAA/TSA is induced by signal 1.Since mature DCs express CD80/CD86 at higher levels, they are the only ones that can provide Signal 2 [20,21]. As described for the pathogen response, activated tumor-specific naive T cells proliferate and form effector and memory T cells at this point. With the assistance of CD4+ helper T cells (Th cells), primarily Th1 cells, tumor-specific CD8+ effector T cells, also known as CTLs, travel from the TDLN to the GC and attack tumor cells that present cognate antigen [22]. TILs, or tumor infiltrating T lymphocytes, infiltrate the GC during the effector phase in response to chemokines like CX3CL1, CXCL9, CXCL10, and CCL5[15].Through both direct and indirect means, these TILs eliminate tumor cells .Perforin and granzymes are utilized in the direct mechanism. Several aspects of antigen recognition, presentation, and the killing of tumor cells by effector immune cells (T cells and NK cells) are depicted in Figure 5A (106).An immune synapse (IS, a specialized molecular structure formed between a cytotoxic lymphocyte and a target cell) at the site of antigen recognition is induced by tumor-specific CTL recognition of cognate antigen [19-22]. At the same time, the CTL moves cytotoxic granules to the IS that contain perforin and granzymes. These granules fuse with the CTL cell membrane and release their contents [23]. Perforin polymerizes and inserts into the tumor cell membrane, creating a pore that allows granzyme B to enter the cytoplasm and cause apoptosis in the tumor cells.

Cytokines like type I IFN, IFN-, and TNF are secreted as indirect mechanisms [24]. After clearance, the remaining CD8+ T cells differentiate into T memory cells, which can maintain their anti-cancer properties and elicit a more rapid and potent immune response to tumor cells upon their next encounter [25].

The NK cell is yet another important type of cell in the early response to GC.As a part of the innate immune system, NK cells can directly kill tumor cells and act in a non-specific manner against them. Hematopoietic and solid tumors have been linked to this kind of immune response against cancer [12,25].

2.Cluster of Differentiation and gastric cancer

Cluster of Differentiation (CD) molecules are thought to be ideal targets for cancer immunotherapy because they play a crucial role in immunity. The anti-tumor immune response is inhibited by CD73, according to numerous studies. T-cell infiltration into the tumor site, for instance, increased when CD73 was silenced [26,27]. Jin and co.discovered that CD73 was linked to T-cell suppression and tumor cell expansion. In addition, in vivo studies have demonstrated that the anti-tumor immune response is suppressed by tumor cells' CD200 signal [27]. There is mounting evidence to suggest that CD molecules and cancer patients' prognoses are linked. In some malignant tumors, for instance, overexpression of CD274 is linked to a poor prognosis and resistance to antitumor therapy. Additionally, a poor prognosis was linked to the presence of CD9 expression and CD133 (+) cells in gastric cancer [28]. Additionally, CD molecules serve as a biological cancer marker. Expression of CD274 in tumor cells has been shown to be a useful biomarker for predicting the prognosis of cancer. In patients with esophageal and gastric cancer, expression of CD166 (ALCAM) is a sign of a poorer chance of survival [23,29]. Increased infiltration of CD56 (+) NK cells in tumor tissues and CD86 expression in lymphoma cells are potential indicators of a helicobacter pylori-dependent tumor. Gastric carcinoma cells were helped to grow, invade, and migrate by CD97, which also helped exosomes form a premetastatic niche. As a result, it is critical to investigate novel strategies for targeting CD molecules in GC cancer. These strategies have the potential to improve clinical outcomes for cancer immunotherapy [29,30].

2- Structure and Function of CD133 Biomarker

CD133 also called AC133, prominin-1, is a transmembrane glycoprotein of 865 amino acids with a complete sub-atomic load of 120 kDa. This protein comprises of a N-terminal extracellular space, five transmembrane areas with two huge extracellular circles, and a 59 amino acids cytoplasmic tail [26,31]. Five transmembrane fragments what separate two little intracellular circles (IC1 and IC2), two huge extracellular circles (EC2 and EC3), and an intracellular C-terminal area (IC3) (Figure 1). The two extracellular circles contain nine putative N-glycosylation destinations; five on EC2 area and four on EC3 space [32]. Glycosylation of CD133 yields a 120 kDa protein and changes the general tertiary construction and solidness of CD133. The CD133 quality, prominin 1 (PROM1), is situated on chromosome 4 in people and chromosome 5 in mice and is just roughly 60% homologous from primates to rodents [32]. Record of human CD133 is driven by five elective advertisers, three of which are situated on CpG islands and are somewhat managed by methylation. These advertiser districts frequently bring about elective joining of CD133 mRNA, bringing about CD133 underlying variations with possibly one of a kind jobs [33,34].

CD133 is found in numerous cell lines and most grown-up tissues except for mature peripheral blood leukocytes, despite the fact that it is commonly known that the declaration of this biomarker is more limited to undifferentiated cells that incorporate endothelial progenitor cells, hematopoietic stem cells, fetal brain stem cells, kidney stem

cells, prostatic epithelial stem cells and liver stem cells [11,33].

Regardless of different speculations, the natural capability of CD133 is as yet not surely knew. Initially, CD133 was known as a surface marker of hematopoietic undifferentiated organisms and forebear cells, yet CD133 has likewise as of late been accounted for as a marker of CSCs in strong diseases like cerebrum growths, cellular breakdown in the lungs, liver disease, colon disease, pancreatic malignant growth, and prostate malignant growth [2,16]. What's more, in cellular breakdown in the lungs, bosom disease, hepatocellular carcinoma, gastric malignant growth, and pancreatic malignant growth, CD133 articulation has been accounted for to be unequivocally related not exclusively to cancer movement, yet additionally to therapy opposition [35].

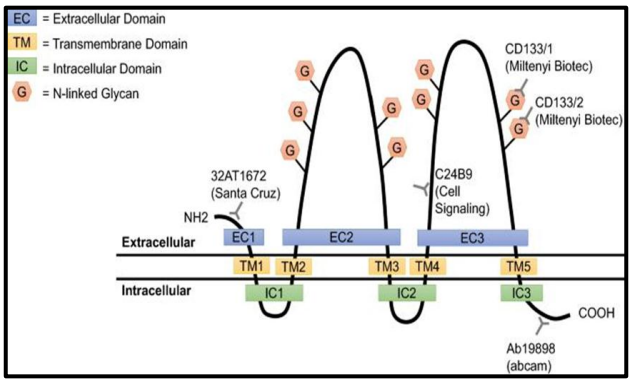

Figure (1): Show structure of CD133

3- Role of CD133 in Gastric Cancer

Prominin-1, also known as CD133 or AC133, is a transmembrane glycoprotein with a total molecular weight of 120 kDa and 865 amino acids. This protein has a 59-amino acid cytoplasmic tail, five transmembrane domains with two large extracellular loops at its N-terminus, and an extracellular domain at its N-terminus [22,31]. Figure 2 depicts five transmembrane segments that divide an intracellular C-terminal domain (IC3), two large extracellular loops (EC2 and EC3), and two small intracellular loops (IC1 and IC2).There are nine potential N-glycosylation sites in the two extracellular loops;four on the EC3 domain and five on the EC2 domainThe tertiary structure of CD133 is altered, as is its stability, and glycosylation results in the production of a 120 kDa protein. Prominin 1 (PROM1), a CD133 gene, is only approximately 60% homologous between primates and rodents [22]. It is on chromosome 4 in humans and chromosome 5 in mice. Five alternative promoters drive human CD133 transcription, three of which are located on CpG islands and partially methylated. Alternative splicing of CD133 mRNA is frequently the result of these promoter regions, resulting in CD133 structural variants with potential distinct functions [36,37]. Although it is common knowledge that the expression of this biomarker is more restricted to undifferentiated cells, such as endothelial progenitor cells, hematopoietic stem cells, fetal brain stem cells, kidney stem cells, prostatic epithelial stem cells, and liver stem cells, CD133 is found in many cell lines and the majority of adult tissues, with the exception of mature peripheral blood leukocytes [28,38].

The biological function of CD133 is still poorly understood, despite various theories. In the past, CD133 was known as a surface marker for hematopoietic stem cells and progenitor cells. However, more recently, it has been found to be a marker for CSCs in solid cancers like prostate cancer, lung cancer, colon cancer, pancreatic cancer, and brain tumors [39]. CD133 expression has also been found to be strongly linked to treatment resistance and tumor progression in pancreatic, lung, breast, hepatocellular carcinoma, gastric, and breast cancers [40].

Stomach cancer remains one of the diseases that need broader studies to reveal the mechanism of its impact on the body. Our attempts to reveal the mechanism of development of this disease by examining the role of CD133 at the histological and immunological level, as in the following paragraphs.

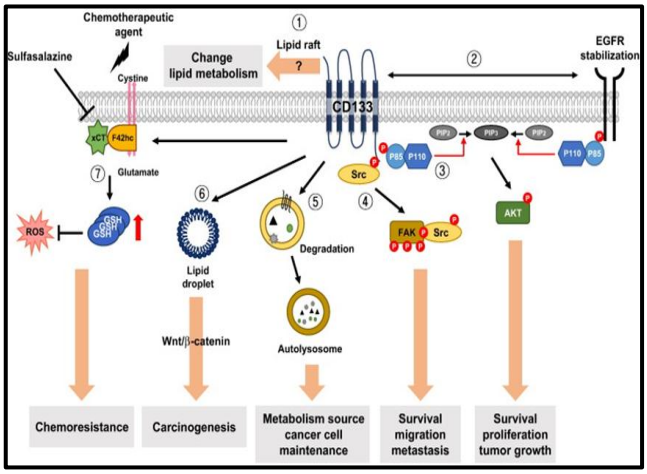

Figure (2): show role of CD133 in cancer development [19]

-Immunological role of CD133 in Gastric cancer

In our current study, we did not find the specific role that CD133 plays in stomach cancer [7]. We also found a difference in the opinions of studies about this, but some immunological studies indicated its role in inhibiting or stimulating some immune cells that have an active role in the malignant response, such as DC and CD8, where we noticed that CD133 has an inhibitory effect on the effectiveness of these cells in eliminating cancerous cells [22,36]. However, Tumor immune cells can have both pro- and anti-tumorogenic effects, exhibit functional and phenotypic plasticity, and are diverse. It is interesting to note that the precise location of various subsets of immune cells in relation to CD133 and their distribution have been proposed as useful indicators for predicting the behavior of tumors.In fact, T cells, B cells, neutrophils, and macrophages—parts of the tumor microenvironment that may influence the therapeutic response—are increasingly being considered in the field.For instance, previous research has shown that knocking down cyclic GMP-AMP synthase-stimulator of interferon genes (STING) promotes the GC of tumor-associated macrophages (TAM) into the pro-inflammatory subtype and induces the apoptosis of GC cells, highlighting the negative function of STING in TAMs17 [38,48]. As a result, analyzing the spatial relationships between individual cellular and acellular components may helpMultiple markers need to be used together in order to accurately identify particular subsets of immune cells that are part of a tumor.Importantly, advances in multiplex immunohistochemistry (m-IHC) have made it possible to simultaneously detect multiple antigens in situ at the resolution of a single cell [9,27]. The immune response to tumor cells is primarily triggered by CD8-positive cytotoxic T cells. However, the so-called cancer-immunity cycle (CD133) can correct a number of steps in the process [2,12]. These steps include: (1) the production of tumor antigens by tumor cells and the processing of released tumor antigens by antigen presenting cells (APCs) like dendritic cells (DCs); (2) the presentation of tumor antigens on the surface of APCsThe immune response is boosted when additional tumor antigens are released by the tumor cells that are destroyed or inhibited by CD133 or T cells.It has been reported that some receptors and their ligands either promote or inhibit each step[40-48].

Finally, it is important to say that the immunological evaluation of CD133 played a major role in determining its role, but there are still many questions that can be accurately resolved when evaluating this indicator at the histological level or gene expression.

-Immunohistology of CD133 in gastric cancer

Immunohistochemistry (IHC) is a powerful method that uses the specific binding of an antibody to an antigen to locate specific antigens in cells and tissues [41]. The light microscope is typically used to detect and examine these antigens.Cancers;In some cancers, specific tumor antigens are up- or de novo expressed.Sample, enzyme or dye activation, and microscope inspection of the antigenDiseases like cancer can be better diagnosed with the aid of immunohistochemistry.It can also be used to

distinguish between various types of cancer [42].

We found many studies that depended on the immuno-histological method for the detection of CD133. However, those studies differed in determining the histological role of CD-133 in gastric adenocarcinoma in the different stages of gastric cancer, as CD-133 was identified in the cytoplasm and cell membrane of the poorly well differential gastric adenocarcinoma stage, while it was found more clearly located in the cell membrane and cytoplasm of cancer cells in the stage of depth invasive adenocarcinomas [43]. By activating the Wnt signaling pathway and increasing the expression of vascular endothelial growth factor-A (VEGF-A) and interleukin-8, CD133 can also promote angiogenesis.As a result, CSCs may view CD133 as their "Achilles' heel," as blocking this protein will also block the signaling pathways that are involved in cell proliferation. [44].

Depending on the physiological aspect and the chemical nature of the gastric tissue occupied by the cancer, the studies differed in considering CD-133 as a screening factor, and this is related to the ratio of CD-133 in the biological sample, as some studies confirmed that the few communities in the cancer cells containing CD-133. A positive result does not appear at the beginning or before the diagnosis of cancer, so this indicator can be relied on to determine the severity of the cancer, but not its diagnosis [24,42].

5.Effect Helicobacter pylori on CD133 Expression for Gastric Cancer Progression

Although genetic factors, alcohol consumption, and diet all have the potential to influence the etiology of GC, infection with Helicobacter pylori is still the most common cause, accounting for more than 70% of cases [45].Distal/non-cardia gastric cancer, which is histomorphologically categorized as intestinal type and is characterized by a stepwise progression to cancer with low-grade dysplasia, high-grade dysplasia, intramucosal adenocarcinoma, and invasive adenocarcinoma, is typically caused by the bacterial infection [46,47].

While the connection between CD133 articulation in GC and patient results has been moderately broadly examined, a stepwise expansion in CD133 during the prior phases of illness has likewise as of late been proposed [48,49]. Until now, existing examinations have either related this stepwise expansion in CD133 articulation with the H. pylori-driven Correa pathway of carcinogenesis, or have not explored the connection among articulation and disease status [50].

Yiming and coworkers have done a meta-analysis of 8 studies, including 603 cases of gastric cancer, and found that CD133 overexpression was linked to a worse prognosis, a higher TNM stage, lymph node metastasis, and vascular and lymphatic invasion [51].Likewise, Yu *et al*, have looked at 31 cases of gastric cancer and compared the levels of CD133 mRNA in gastric cancer samples to those in non-cancerous gastric mucosa from the same patient. The results showed that the level of CD133 mRNA was linked to the cancer status, size, stage, and presence of metastasis. This result agrees with the observation made by Wen *et al*., that gastric cancer tissues had higher levels of CD133 mRNA than non-neoplastic gastric tissues [52].Intriguingly, gastric cancer has been linked to an increase in the SC population caused by H. pylori. This is thought to be caused by both direct DNA damage and the disruption of SC differentiation, as well as increased local SC proliferation and recruitment from the bone marrow in response to persistent bacteria-induced gastritis and tissue atrophy [53,54].As a result of these observations, it has been hypothesized that an expanding SC population in *H. pylori* (+) patients accounts for the previously observed rise in CD133 levels during *H. pylori*-associated carcinogenesis [55].

6.Role of CD133 in Immunotherapy for GC

Putting CD133 as a potential therapeutic target for antibody-drug conjugates in gastric cancer [56], putting the possibility of molecular targeting therapy in the most aggressive form of the disease into perspective. Utilizing peptide linkers, recent advancements in ADCs demonstrated improved efficacy and cell-specificity for antigen-expressing cells. Specifically, a monoclonal antibody that is anti-human CD133.In addition, in three distinct xenograft models, the combination treatment of cisplatin and anti-CD133 CAR-T reduced the infiltration of CD133-positive stem cell-like cells and slowed tumor progression. Based on these findings, it appears that the combination strategy of cisplatin and anti-CD133 CAR-T can simultaneously target normal and stem cell-like gastric cancer cells to improve treatment outcomes [57-59]. Although expression of CD133 as a prognostic marker has been found in colorectal cancer and brain tumors, it is still unknown whether CD133 can be used as a prognostic marker in non-small cell lung cancer, pancreatic cancer, ovarian cancer, hepatocellular cancer and other types of cancer. Due to the lack of a comprehensive study linking CD133 expression to clinicopathological features and prognosis, it is still unclear whether CD133 is a marker for gastric cancer prognosis [59,60].

7.Conclusion

CD133 is a decent immuno-histological biomarker that can foresee growth repeat and metastasis in gastric carcinoma. In any case, studies with respect to disease undeveloped cells (CSCs) are still in their underlying stages particularly those connected with CD133 in gastric malignant growth. Further examinations are expected to affirm the job of CD133 in growth repeat and metastasis and subsequently advance finding more suitable treatment modalities including designated quality treatment.

Ethical Approval

The specimens of this study took the patient's approval for adult patients, precious and the consent of the irrigation for young people in age as the law and directives of the human rights organizations with adequate information in an ethical manner.

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