Functions of CD34

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CD34 is primarily known as a biomarker for hematopoietic stem cells (HSCs) and hematopoietic stem precursor cells, but it has also been identified as a marker for several non-hematopoietic cells. All three proteins in the CD34 family share similar structural characteristics, including the presence of serine, threonine, and proline residues in their extracellular domains. These domains are heavily glycosylated and sialylated, which gives the proteins an effective size range of 90–170 kDa and defines the CD34 family as a subfamily of sialomucins.

CD34 regenerative stem cell cancer stem cells

1. CD 34 and Hematopoietic Cells

When used for medical purposes, CD34 levels are monitored in order to ensure quick bone marrow transplantation and may further be applied as a specific label in selective cell sorting in order to enhance an embryonic hematopoietic cell population [1]. Despite the fact that sometimes it is believed that CD34 is only a stem cell indicator, its presence in bone marrow or blood specimens indicates a mixture of both hematopoietic stem and precursor cells [2]. The human hematopoietic cells are subsequently differentiated from CD34+ precursor cells through a decreased level of CD90 and the absence of CD38, human leukocyte antigen, and a range of markers of the adult hematopoietic cells [3].

Human CD34+ hematopoietic cells (HSCs) are also characterized by the ability to differentiate into all hematopoietic lineage cells and possess a high proliferative capacity [3]. Information provided by the literature indicates that CD34+ HSCs and their precursors are able to proliferate into new cell lines, such as cardiomyocytes, respiratory epithelial cells, and hepatocytes [4][5].

2. CD 34 Multipotent Mesenchymal Stromal Cells (MSC)

Multipotent stromal cells (MSCs) are located in almost all adult tissues and are a predominant and versatile cell type that is widely researched for therapeutic applications in regenerative medicine [6]. In addition to their well-documented in vitro capacity for mesenchymal differentiation, MSCs have also been shown to possess various other properties. These include their ability to release paracrine factors that promote wound healing, their capacity to create specialized niches within tissues, their ability to modulate immune responses, and their immune privileged status. These properties have made MSCs an attractive therapeutic tool for a wide range of medical applications, including tissue repair, autoimmune disorders, and transplantation [7].

Two past studies have reported CD34 expression in MSCs, both of which focused on fat-derived MSCs [8][9]. While one study focused on the structural characteristics and roles of CD34 protein in association with MSC [9], the other study questioned the hypothesis about CD34 being a specific negative biomarker of multipotent stromal cells [8]. Therefore, Lin et al. reviewed the evidence according to which, CD34 appeared to be an essential marker in the initial MSC investigation, thus pointing to Simmons' investigation, which shows that newly isolated CD34+ bone marrow stem cells build a consistently higher percentage of fibroblastic population comparable to CD34-cells [10].

Additionally, some researchers have proposed that CD34 could potentially serve as a positive biomarker for MSCs with a specific association with vascularization. These cells may be referred to as vascular progenitor cells, suggesting that they have the ability to differentiate into endothelial cells and contribute to blood vessel formation. The potential of CD34+ MSCs as a source for vascular progenitor cells has been explored in various studies, highlighting their potential therapeutic applications for cardiovascular diseases and tissue engineering. However, further research is needed to fully understand the role of CD34 in MSCs and its potential for vascularization [8].

Cells that exhibit CD34 expression constitute at least a fraction of the entire MSC network, while this particular subgroup exhibits particular features. CD34 appears to be linked to a greater efficiency of new cell colony formation and possesses a lasting proliferation capacity [11]. CD34+ MSCs are known to express a range of common stromal cell markers, such as CD90, CD105, and CD73, as well as other markers such as CD271 and Stro-1 that have been identified as MSC-specific markers. Additionally, CD34+ MSCs may also express markers that are associated with other cell types, such as CD45, which is commonly found on hematopoietic cells, and CD133, which is expressed on a variety of progenitor and stem cells. The co-expression of these markers suggests that CD34+ MSCs may represent a heterogeneous population of cells with diverse functional properties [11][12].

CD34+ MSCs have been shown to have a greater pattern of endothelial transdifferentiation [13], which is also observed in embryonic stem cell-derived MSCs, thereby strongly implying that CD34 is a marker of early human MSCs [14].

3. CD 34 and Muscle Stem Cells

Muscle satellite cells, also known as muscle stem cells, are small precursor stromal cells that reside in skeletal muscle tissue and have the ability to differentiate into mature muscle cells. CD34 protein is widely used as an indicator for identifying these cells, as it is expressed on the surface of satellite cells, making it a useful marker for identifying and isolating them for further study. The differentiation and proliferation of satellite cells are crucial for muscle growth and regeneration, making them an important focus of research in the field of muscle biology [15].

In vivo, these muscle cells are quiescent until they are stimulated in order to supply myonuclei for muscle fibers during high-intensity physical activity or during muscle injury. The activation of these types of cells, which is believed to be for differentiation, corresponds to a significant upregulation of CD34. Moreover, it is speculated that CD34 may play a fundamental role in regulating muscle progenitor cell differentiation by establishing and sustaining a population of satellite cells [16].

CD34 does not present expression for every satellite muscle cell; however, it is used to identify them along with several other markers, such as CD56 [15]. The first myogenic progenitors studied do not possess the ability to manifest CD34; CD34 expression is first identified as satellite muscle cells develop [17].

Complementary tests further speculate that CD34+ cells may possess the capacity to be more than just muscle progenitors. Separate MSC-like cells that display mesenchymal differentiation were also detected in muscle satellite cells by identifying expression patterns of CD34 [18].

Past studies have also proposed that CD34+ cells found inside the interstitial spaces of muscles may be similar to those from the endothelium based on their expression pattern. Such myoendothelial cells exhibit augmented muscle regeneration capacity when compared to cells that express either muscle stem cells or endothelial patterns [19].

The differences found in the characteristics of satellite muscle cells can be explained by the existence of different subgroups of CD34+ cells with unique differentiation potentials. Markers expressed together with CD34 also affect the differentiation process. As an example, CD34+ cells co-expressing the endothelial marker CD31 exhibit angiogenic differentiation. Nevertheless, CD34+ CD31 cell populations show higher potential for differentiation of adipose and muscle tissue [20].

4. CD34 and Endothelial Cells

CD34 is generally considered to be a biomarker for vascular endothelial precursor cells [21]. These bone marrow tissue-derived cells are circulating in the peripheral blood, and their value in proangiogenic therapies has been amply documented [22]. The characteristics of CD34+ endothelial cells are frequently related to those of hematopoietic cells, as these two cell types can be identified and isolated within blood samples by using CD34 as an antigen; therefore, these cells are used in various vascular pathologies [23]. In addition, these cells possess the ability to form new types of cells, such as osteoblasts and cardiomyocytes [24].

Matsumoto suggests from his research the hypothetical presence of an overlap between osteoblasts and endothelial progenitor cells [25]. It is hypothesized that in the bone marrow there are a number of CD34+ precursor cells, which possess the ability to differentiate into endothelial cells as well as osteoblasts. A number of studies have highlighted the use of circulating CD34+ cells for healing broken bones, which frequently have a poor recovery because of insufficient circulation in the area of the fracture [25].

It is believed that there may be a subgroup of mature non-circulating endothelial cells that exhibit CD34 expression and are predominantly situated in the smaller blood vessels, whereas the vast proportion of endothelial cells from larger blood vessels does not exhibit CD34 expression [21]. Unlike the usual biology of endothelial cells, all cells that exhibit CD34 expression have an elongated cell shape without narrow junctions [26].

In the past, research on in vivo cultures has revealed the presence of CD34 protein expression within endothelial cells originating in the umbilical vein; although when grown in vitro, expression is essentially absent and only a small population of cells preserve CD34 expression [21]. These particular cells mentioned previously display unique morphological features as well as numerous filopodia; in addition, CD34 is very well expressed within these filopodia, where angiogenesis is most active, thus highlighting the important functional role of CD34 in progenitor cell activity [26].

5. CD 34 and Cancer Stem Cells (CSCs)

Based on information available in the literature, CD34 has been identified in various cancers, such as gastric, breast, thyroid, colorectal, and skin cancer [27]. CD34 has also been utilized as a biomarker to assess angiogenesis in multiple malignancies, such as cervical cancer, gastric cancer, lung cancer, and oral squamous cell carcinoma [27].

In recent years, an increase in CD34 expression, Ang II, and vascular endothelial growth factor has been documented in patients with severe hepatocellular carcinoma [28]. Therefore, as well as for regenerative stem cells, in the case of CD34 expression on cancer cells and CSCs, CD34 was linked with endothelial progenitors and adult cells and angiogenesis. In addition, it is very likely that CD34+ cells found in different mature tissues are endothelial precursor cells, which need future studies to be fully confirmed [27].

In 2006, a group of researchers led by Clarke published a study on the potential involvement of CD34 in tumor development. The study was conducted on mice and involved injecting them with a tumor-promoting substance to induce tumorigenesis. The researchers found that mice lacking the CD34 protein failed to activate angiogenesis, a process that involves the growth of new blood vessels, and therefore developed fewer tumors compared to wild-type mice. CD34 is a protein that is primarily found on the surface of hematopoietic stem cells, which give rise to different types of blood cells. Angiogenesis is a critical process in tumor development, as it provides the growing tumor with a blood supply and nutrients necessary for its survival and growth. Clarke et al.'s findings suggest that CD34 may play a crucial role in angiogenesis and, consequently, tumor development. By comparing CD34 knockout mice with wild-type mice, they were able to demonstrate the importance of CD34 in angiogenesis and tumor growth. Their study provides valuable insights into the molecular mechanisms underlying tumorigenesis and may have implications for the development of new cancer therapies targeting CD34 or related pathways [29].

CSCs are a small subpopulation of cells within a tumor that are believed to be responsible for driving tumor growth and metastasis. These cells possess the ability to regenerate and produce different types of malignant cells that make up the tumor. One of the defining characteristics of CSCs is their expression of certain cell surface biomarkers. These biomarkers are also found in human embryonic cells, adult stem cells, and normal cells. Understanding the biology of CSCs is critical for the development of new cancer treatments that target these cells. By targeting CSCs, it may be possible to eradicate the tumor and prevent its recurrence. However, more research is needed to fully understand the mechanisms underlying CSCs and develop effective therapies that can selectively target them [27][29].

The origin of cancer stem cells is a topic of ongoing debate and speculation in the scientific community. Although the precise source of these cells remains controversial, there are several theories regarding their potential origins, including from precursor cells, stem cells, or even differentiated cells that have undergone reprogramming within the tumor microenvironment. Understanding the origin of CSCs is critical for developing targeted cancer therapies that can effectively eliminate these cells and prevent tumor recurrence [27][30].

Despite significant advances in cancer research, relapse of cancer and/or metastasis remain major challenges in the field. CSCs have been implicated in the development of these phenomena, as they are thought to play a critical role in tumor initiation, growth, and metastasis. Because CSCs are resistant to conventional cancer therapies, they may be responsible for the failure of many treatments to eradicate the disease completely. In recent years, there has been growing interest in the use of CSC-targeted therapies for cancer treatment. By selectively targeting CSCs, it may be possible to eliminate the source of tumor growth and prevent relapse and metastasis. However, there is still much to learn about the biology of CSCs and their role in cancer development, and further research is needed to develop effective treatments that can specifically target these cells while sparing healthy tissue [27].

The expression of various drug resistance receptors in CSC has been linked to chemotherapy resistance. In addition, enhanced DNA repair capabilities in CSC have been linked with the development of radiation resistance in some types of malignancies. Therefore, CSCs were considered promising targets for cancer therapy and medicine discovery. A greater comprehension of cell surface biomarkers expressed on CSCs will allow their isolation and enrichment [27].

The earliest proof of CSCs was demonstrated in acute myeloid leukemia by Lapiod et al. back in 1994 [31]. During the study, Lapiod et al. discovered a specific subpopulation of CSC, characterized by the presence of CD34 and the absence of CD38. To further investigate the role of these cells in the initiation and progression of AML, they were transplanted into mice with severe combined immunodeficiency (SCID). The results of this study confirmed that these CD34+CD38- cells were responsible for initiating leukemia [31].

According to the study conducted by Park et al., hepatic cancer may develop from transformed CD34+ stem cells in the liver, suggesting that stem cells not only play a role in organ and tissue regeneration but may also contribute to the development of cancer. Furthermore, CD34+ cell populations isolated from PLC/PRF/5 liver carcinoma have the ability to generate multiple types of liver cancer in mice. Therefore, this leads to the hypothesis that CD34+ hepatocellular cells may be a subtype of hepatic CSCs [32].

A recent study carried out by Yin P. et al. revealed that a subset of cells found in uterine leiomyoma exhibit characteristics of stem cells. These cells have been classified into three categories based on their expression of CD34: CD34+/CD49b+, CD34+/CD49b-, and CD34-/CD49b-. Among these categories, CD34+/CD49b+ cells were found to be the most prevalent. It is speculated that CD34+ cells, which are known to be endothelial progenitors, may play a role in angiogenesis and contribute to cancer stemness and metastasis in the context of CSCs. The data from the study also suggested that the use of CD34 could be useful in isolating these side population cells for further molecular investigation [33].

The study by Natarajan Aravindan and colleagues aimed to investigate the role of CD34+ cancer stem cells (CSCs) in high-risk neuroblastoma (HR-NB) patients. The researchers found that CD34 expression in NB was associated with MYCN amplification, advanced disease stage, and progressive disease after clinical therapy. CD34+ was also correlated with poor survival in patients with N-MYC-amplified HR-NB. Further analysis of the genetic landscape of CD34+-NB-CSCs identified significant up- and down-modulation of genes compared with NB-CSCs that lack CD34. The study suggests that careful consideration should be exercised for autologous stem-cell rescue with CD34+ selection in NB patients due to the risk of reinfusing NB-CSCs that could lead to post-transplant relapse [34].

6. CD34 in Clinical Applications

Despite the potential of embryonic stem cells to differentiate into various cell types during the blastocyst stage, most adult stem cells have limited potential for tissue regeneration. Hematopoietic stem cells are a well-known source of adult stem/progenitor cells. However, CD34+ cells in adult human circulating/peripheral blood have also been found to contain hematopoietic and endothelial progenitor cells, making them an essential source of stem/progenitor cells. Previous research has focused on identifying ways to guide stem cells towards tissue renewal [35]. Past studies have shown that tissue ischemia triggers the mobilization of endothelial precursor cells from the bone marrow into the bloodstream by upregulating cytokines, leading to their migration and incorporation into regions of neovascularization. Based on this breakthrough, multiple studies have demonstrated the therapeutic value of EPCs in various pathologies [35].

The initial investigations into the therapeutic uses of CD34 centered around the transplantation of purified CD34+ hematopoietic progenitor cells for hematopoietic reconstitution. Studies involving irradiated baboons showed that transplantation of these purified CD34 cells resulted in the eventual restoration of normal blood cell numbers [27][36].

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