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Is CD34 Truly a Negative Marker for Mesenchymal Stem Cells?

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Abstract

The prevailing school of thought contents that mesenchymal stem cells (MSCs) do not express CD34, and this sets MSCs apart from hematopoietic stem cells (HSCs), which express CD34. However, the evidence for MSCs being CD34- is largely based on cultured MSCs, not tissue-resident MSCs, and the existence of CD34- HSCs is in fact well documented. Furthermore, the Stro-1 antibody, which has been extensively used for the identification/isolation of MSCs, was generated by using CD34+ bone marrow cells as immunogen. Thus, neither MSCs being CD34- nor HSCs being CD34+ is entirely correct. In particular, two studies that analyzed CD34 expression in uncultured human bone marrow nucleated cells both found that MSCs (BMSCs) existed in the CD34+ fraction. Several studies also found that freshly isolated adipose-derived MSCs (ADSCs) expressed CD34. In addition, all of these ADSC studies and several other MSC studies observed disappearance of CD34 expression when the cells were propagated in culture. Thus, available evidence points to CD34 being expressed in tissue-resident MSCs, and its negative finding being a consequence of cell culturing.

Keywords

CD34; Stro-1; Bone marrow; Adipose; Mesenchymal stem cell; MSC marker

Introduction

First identified in bone marrow, mesenchymal stem cells (MSCs) have been reported to reside in most adult tissues (1). In particular, the adipose tissue-derived MSC (ADSC) is a highly promising cell type for clinical applications due to its ease of isolation from an abundant source (2,3). Based on a prevailing view about ADSC's surface marker expression (4), we and others have attempted to localize ADSC in adipose tissue by using CD34 as a defining marker, and the resulting immunohistochemical data indicated the existence of such cells in the capillaries and in the adventitia of larger blood vessels (5-9). However, reviewers of our manuscripts, which are now published (5,9,10), have questioned the use of CD34 as a positive marker because "the consensus" was that CD34 is a negative marker for MSCs. This "consensus" apparently refers to the minimal criteria for MSCs as proposed by The Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy (11). However, in this publication no explanation or reference was provided for why CD34 should be a negative MSC marker. So we searched the literature and found that indeed many studies have described MSCs as lacking CD34 expression. But more importantly we also found that lacking CD34 expression is not necessarily the true nature of

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Declaration of Interest
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MSCs; rather, it is likely a consequence of cell culturing. While this possibility has been briefly mentioned in two review articles (12,13), it apparently has yet to be fully appreciated. Thus, we thought that a dedicated review article on whether CD34 is truly a negative MSC marker should clarify confusions among MSC researchers.

Discovery of MSCs is based on their ability to adhere to plastic surface

The discovery of MSCs has generally been credited to Friedenstein and colleagues, who used a "colony-forming unit-fibroblasts (CFU-F)" approach to isolate fibroblast-like cells from murine bone marrow, spleen, and thymus that adhere to and form colonies on plastic surface (14). These cells are now called MSCs or BMSCs, the latter indicating their bone marrow origin. Thus, it is obvious that one of the most distinctive features of MSCs is their ability to adhere to plastic surface, as opposed to other bone marrow cells, such as hematopoietic stem cells (HSCs), which cannot. Thus, in early MSC studies a link between adherence to plastic surface and lack of CD34 expression already existed.

How did MSCs become CD34-

In the paper by Dominici et al (11), which proposes minimal criteria for human MSC, there was no explanation or citation for why CD34 is a negative MSC marker. An exhaustive search of the literature found that the first paper that described human MSC as lacking CD34 expression was published in 1999 by Pittenger et al (15). In this study human BMSCs were cultured as monolayers on plastic surface for undisclosed numbers of passages and then determined to be CD34- by flow cytometry. The finding of lacking CD34 expression was thus based on MSCs that grew on plastic surface, not MSCs that reside in the bone marrow. Most if not all subsequent studies that identified MSCs as lacking CD34 expression were also based on plastic-adherent MSCs. Importantly, these plastic-adherent MSCs were often compared to HSCs that were grown in suspension, leading to the conclusion that MSCs were CD34- while HSCs CD34+. In at least one occasion bone marrow cells from mice were even intentionally "immunodepleted" with anti-CD34 antibody for the purpose of "enriching" the MSC population (16). This procedure of course would have "depleted" not only CD34+ HSCs but also CD34+ MSCs.

Many studies relied on CD34 being a positive MSC marker

In 1991 Simmons and Torok-Storb (17) published a paper titled "CD34 expression by stromal precursors in normal human adult bone marrow", and it provided a detailed analysis of uncultured BMSCs with convincing evidence that BMSCs are CD34+. Specifically, these investigators sorted human bone marrow nucleated cells on the basis of CD34 expression and found that greater than 95% of detectable CFU-F were recovered in the CD34+ fraction. While the "detectable CFU-F" was based on cytometric (light scatter) characteristics of CFU-F, a more recent study by Kaiser et al (18) assayed CFU-F based on their ability to grow on plastic surface. Specifically, the authors also sorted human bone marrow nucleated cells on the basis of CD34 expression. The sorted cells were then seeded in 24-well plates and observed for formation of fibroblast-like colonies. The results showed that fibroblast-like cells grew in 19 out of 87 wells from the CD34+ fraction while no growth was observed from the CD34- fraction. Furthermore, for confirmation of MSC phenotypes, the fibroblast-like cells from the CD34+ fraction were verified by their ability to differentiate into chondrocytes, osteoblasts and adipocytes. Importantly, after in vitro expansion, all of the cells that originated from the CD34+ fraction became CD34-. Thus, while CFU-F (BMSCs) were mostly derived from CD34+ bone marrow cells, they became CD34- in cell cultures.

In another 1991 paper published by Simmons and Torok-Storb (19) CD34+ human bone marrow cells were used as immunogen to generate a panel of hybridomas. These

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hybridomas were then screened by several criteria, including selection against a panel of T- and B-cell lines to eliminate hybridomas that produced antibodies against any T- and B-cell-lineage markers. An antibody produced by one of the hybridomas that fulfilled these criteria was named Stro-1, apparently for its presumed specificity against bone marrow stromal cells. In any case, the Stro-1 antibody has since been utilized in hundreds of studies for the isolation and/or identification of MSCs from various tissues (20,21), and, apparently due to the recognition of Stro-1 antibody's widespread usage, Kolf et al (22) stated in a MSC review article that "Stro-1 is by far the best-known MSC marker". So, it seems ironic that while Stro-1 is presumably the best-known MSC marker, CD34, which critically contributed to the generation of the Stro-1 antibody, has become one of the best-known negative MSC markers.

The disappearing CD34

In their CD34 paper Simmons and Torok-Storb (17) discussed that definitive proof of CD34 expression in BMSCs requires biochemical analysis of the cell surface molecules identified by CD34 antibodies and for evidence of CD34 expression in these cells. However, the authors also pointed out the technical difficulties in carrying out these analyses because BMSCs exist at an extremely low frequency within the bone marrow and they tend to lose CD34 expression during cell culture. They further cited two studies that also observed cell culture-associated loss of CD34 expression. First, Watt et al (23) found that primary cultures of umbilical cord vein endothelial cells were nonreactive with CD34 antibody despite their reactivity in tissue sections. Second, Fina et al (24) detected CD34 messenger RNA in cultured endothelial cells despite their lack of binding to CD34 antibodies, suggesting that in cell culture the CD34 protein is either downregulated or modified to a form that is nonreactive with CD34 antibodies. In more recent years this cell culture-associated loss of CD34 expression has continued to be observed in endothelial cells (25-27) and in MSCs of various tissue origin (1,7,18,28-30). In support of this notion, a recently accepted manuscript specifically mentions loss of CD34 expression in MSCs upon in vitro cultivation (31). However, it should be pointed out that, despite the prevailing evidence that cultured MSCs are CD34-, a few studies have reported persistent CD34 expression in cultured murine BMSCs (32,33). Of particular interest is the finding that BMSCs from different mouse strains expressed different levels of CD34, with those from B1/6 and BALB/c strains expressing at high and low levels, respectively (33).

HSCs can also become CD34-

CD34 is a universally accepted HSC marker. However, in 1996 Osawa et al (34) reported the identification of CD34- HSCs and that, despite being CD34-, these cells remained capable of reconstituting the lymphohematopoietic system. These findings were soon confirmed in several subsequent studies (35-40). In addition, CD34- HSCs were found able to reverse to CD34+, and vice versa (38,40,41). Together, these findings led to the proposal of the "stem cell cycle" theory, which contends that HSCs circulate in the peripheral blood as CD34+ cells and can return to the bone marrow to become quiescent CD34- stromal fibroblast-like cells (i.e., MSCs) (42). However, the idea of a common hematopoietic-mesenchymal stem cell remains controversial (43), and the suggestion of MSCs being CD34- was still based on cultured, not tissue-resident MSCs.

CD34- or CD34+: does it matter?

Despite extensive research the function of CD34 remains uncertain. Because this review is focused on CD34 as a cellular marker rather than its function, interested readers can find excellent discussion on possible CD34 functions in these published articles (12,44,45). In regard to HSCs, for which CD34 is a well-accepted marker, it is interesting to note that two

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independently created CD34-deficient mouse strains exhibited only subtle but different alterations in their hematopoietic system. Specifically, one strain had a decreased number of progenitor cells but a normal number of mature cells (46). The other strain however had normal numbers of both progenitor and mature cells, with the only abnormality being a mild reduction in inflammatory trafficking of eosinophils (47). One possible explanation for these mild alterations could be functional compensation by CD34-related proteins (45). In any event, in bone marrow reconstitution experiments, HSCs isolated from the second CD34 knockout strain nevertheless exhibited impaired ability to cross the vascular endothelium en route to the bone marrow (48). Thus, the function of CD34 appears to relate to HSC trafficking, as it may act as an anti-adhesive molecule, enabling greater cellular mobility and homing efficiency to the bone marrow (45). On the other hand, CD34 can also act as a pro-adhesive molecule for HSC interaction with the stromal environment (44).

Perhaps due to the prevailing notion that MSCs are CD34-, there has been no study that investigates possible alterations in the MSCs of CD34-deficient mice. Attempts however have been made to compare functional differences between CD34+ and CD34- MSCs isolated from the same individuals. In one study microarray analysis revealed higher vascular gene expression in a CD34+ than in a CD34- murine BMSC clones (32). The CD34+ clone also induced a higher level of angiogenic responses when transplanted subcutaneously. The authors thus concluded that CD34 expression correlates with enhanced vasculogenic and angiogenic potential. In another study human ADSCs were sorted into CD34+ and CD34- fractions, and which were then compared for various biological functions (49). The results showed that CD34+ cells were more proliferative and had a greater ability to form colonies. On the other hand, CD34- cells had a greater ability to differentiate into adipogenic and osteogenic lineages. Thus, the authors suggested that CD34 expression correlates with replicative capacity and stemness, and loss of CD34 expression might be related to lineage commitment. However, it should be pointed out that reversibility of CD34 expression in HSCs is well documented (38,40-42), and reversal of CD34 expression from negative to positive has also been demonstrated in BMSCs (50,51) and ADSCs (52) as a consequence of differentiation into hematopoietic or endothelial cells. Thus, the CD34 expression status in HSCs and MSCs appears to depend on their environment, and can change from positive to negative, and vice versa, as they relocate from one tissue compartment to another. More importantly though, for therapeutic application both freshly isolated (CD34+) and cultured (CD34-) ADSCs have been shown to be effective in treating various diseases in animal experimentations (2,3). Thus, similar to the situation with HSCs (53), CD34 expression or not does not seem to affect the therapeutic efficacy of MSCs.

Conclusions

Due to their scarcity BMSCs have been overwhelmingly investigated in cell-culture settings. On the other hand, ADSCs are more abundant and have been frequently studied in their freshly isolated state (10). The latter situation thus permitted the characterization of MSCs without the influence of cell culturing, and their CD34 positivity thus realized. Furthermore, the use of CD34 as a positive MSC marker permitted the identification of MSCs as being intimately associated with the vasculature, and consequently our proposal that MSCs are vascular stem cells (VSCs) (2,3,10). Whether our hypothesis is correct or not, there is little doubt that MSCs are increasingly believed to reside near or within blood vessels, and CD34 is one of the most frequently used markers for this recognition (8,30,54-56). This of course does not exclude the possibilities that certain MSCs are not perivascularly associated and certain subsets of MSCs might indeed be CD34-. Furthermore, it should be re-emphasized that differences in CD34 expression between human and murine BMSCs have been noted (33).

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In the MSC "consensus" paper (11) the authors stated: "these criteria will probably require modification as new knowledge unfolds." Thus, based on evidence presented above we propose to modify the minimal criteria for MSCs as to include a distinction between their tissue-resident and cell-culture states.

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