Research article

Cell surface markers for mesenchymal stem cells related to the skeletal system: A scoping review

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ARTICLE INFO

ABSTRACT

Multipotent mesenchymal stromal cells (MSCs) have been described as bone marrow stromal cells, which can form cartilage, bone or hematopoietic supportive stroma. In 2006, the International Society for Cell Therapy (ISCT) established a set of minimal characteristics to define MSCs. According to their criteria, these cells must express CD73, CD90 and CD105 surface markers; however, it is now known they do not represent true stemness epitopes. The objective of the present work was to determine the surface markers for human MSCs associated with skeletal tissue reported in the literature (1994–2021). To this end, we performed a scoping review for hMSCs in axial and appendicular skeleton. Our findings determined the most widely used markers were CD105 (82.9%), CD90 (75.0%) and CD73 (52.0%) for studies performed *in vitro* as proposed by the ISCT, followed by CD44 (42.1%), CD166 (30.9%), CD29 (27.6%), STRO-1 (17.7%), CD146 (15.1%) and CD271 (7.9%) in bone marrow and cartilage. On the other hand, only 4% of the articles evaluated *in* situ cell surface markers. Even though most studies use the ISCT criteria, most publications in adult tissues don't evaluate the characteristics that establish a stem cell (self-renewal and differentiation), which will be necessary to distinguish between a stem cell and progenitor populations. Collectively, MSCs require further understanding of their characteristics if they are intended for clinical use.

1. Introduction

The bone marrow (BM) contains cells with self-renewal and differentiation capacity, known as multipotent mesenchymal stromal cells (MSCs) related to the skeletal system, which can differentiate into skeletal lineages (cartilage, bone, hematopoietic support stroma, adipocytes and fibroblasts). These cells represent a population destined to sustain skeletal tissue throughout the life of an individual [1]. Worldwide there has been an increasing need for skeletal tissue regeneration (bone or cartilage), due to an augmentation in trauma, cancer, bone and joint disorders, as well as ageing, associated with a decline in the quality of life. Hence, therapies have been proposed using stem cells, where MSCs would be an ideal source; however, their true nature and location for isolation has not been yet determined, because MSCs reside in different skeletal anatomical sites. Therefore, the aim of this work was to perform a scoping review regarding MSCs' cell surface markers to establish the status reported in the literature.

The concept of post-natal mesenchymal stem cells originated with Friedenstein in 1966 from studies isolating BM stroma [2]. In 1988 Owen and Friedenstein described these BM stromal cells were made up of a heterogeneous population possibly containing stem and progenitor cells with the capacity to differentiate into diverse tissues including bone [3]. Following, Arnold Caplan in 1991 coined the term mesenchymal stem cells (MSCs) to describe a limited population of cells responsible for bone and cartilage formation in the embryo and its repair and turnover in adult tissues [4]. However, the term "mesenchymal" is not appropriate since it refers to a histological description of a cell with migratory capacity in the embryo, which can derive from mesoderm, neural crest or ectoderm [5]. Skeletal tissue has different embryological origins, such as somites, which give rise to the axial skeleton (vertebrae), lateral plate mesoderm forming appendicular bones and neural crest cells developing into the visceral cranium. Therefore, there is not a unique origin to form the skeleton and the term MSCs would be incorrect [5].

Since the year 2000 until now, publications associated with the term "MSCs" have starkly increased. Additionally, the term MSCs has extended into non-skeletal tissues, such as umbilical cord [6], adipose tissue [7] and placenta [8]. Moreover, lack of scientific rigor in defining postnatal skeletal stem cells has been identified [5]. In 2006 the International Society for Cell Therapy (ISCT) in an effort to establish a general consensus regarding multipotent mesenchymal stromal cells proposed a series of characteristics to define MSCs. These criteria included: adherence to plastic under standard culture conditions, expression of cell surface markers CD105, CD90 and CD73; absence of hematopoietic cell surface markers CD45, CD34, CD14, CD11b, CD79a or CD19 and HLA-DR, and last the capacity to differentiate *in vitro* into osteoblasts, adipocytes and chondrocytes, as determined by staining techniques [9]. Despite the fact that over 15 years have passed the same criteria are still used, even though they don't validate a true skeletal stem cell [10]. In 2018 Chan et al. reported "true skeletal stem cells" from fetal and adult tissues with the following cell surface markers: $PDPN^+$, $CD146^-$, $CD73^+$, $CD164^+$ with the capacity of self-renewal and multipotency generating bone, cartilage and stroma progenitors [11]. However, the scientific community has not echoed Chan's work.

Henceforth, after decades the biological definition of true MSCs remains a topic of discussion. Despite the lack of knowledge, an interest still prevails regarding this cell population for therapeutic purposes. Moreover, *in vitro* cell culture can modify protein expression properties [1]. To date it is not clear whether cell epitopes can ascertain MSCs; hence, the objective of this work was to identify from the literature which cell surface markers have been used to characterize hMSCs related to the skeletal system, since tissue of origin has been used indiscriminately. Additionally, this review assessed if markers were determined from *in vitro* studies or established by immunohistochemistry (IHC) from tissues *in situ*.

Table 1

Terms and keywords selected for each evaluated variable. A search in Medline (PubMed), Scopus and Web of Science was performed using equations for all three variables.

Variable	Keywords	Equation
Skeletal stem cells	"Skeletal stem cells" "Mesenchymal stem cells" " Stromal stem cells" "Mesenchymal Stromal stem cells"	"Skeletal stem cells" OR "Mesenchymal stem cells" OR "stromal stem cells" OR "Mesenchymal Stromal stem cells"
AND		
Cell Surface marker	"Surface markers" Biomarkers "clusters of differentiation" Identification	"Surface markers" OR Biomarkers OR "clusters of differentiation" OR Identification
AND		
in situ and *in vitro*	"*in vivo*" "*in vitro*" "Cell culture" "*in situ*"	"*in vivo*" OR "*in vitro*" OR "Cell culture" OR culture OR "*in situ*"
NOT		
		Equine OR Bovine OR Rhesus OR Rat OR Mice OR Rodent OR Rabbit OR Porcine OR Canine OR Ovine OR Cryconservation OR Adipose OR "Umbilical Cord" OR Placenta OR "Dental pulp" OR Neuron OR Hepatitis OR Arterio* OR Skin OR Murine OR Mucosa OR Pancreatic* OR animal.

2. Materials and methods

PRISMA guidelines were used to perform a scoping review to identify in the literature cell surface markers that have been utilized to identify possible MSCs *in vitro* and *in situ* based on indexed publications in Medline (PubMed), Scopus and Web of Science databases. The following search equation was used "skeletal stem cells, mesenchymal stem cells, cell surface markers, *in vitro, in vivo* and *in situ*", which should be included in the title, abstract or keywords (Table 1). Year of publication was not restricted, where the last date of search was July 26, 2022.

For this study, no review protocol was required since this work was not associated with a clinical trial.

A total of 462 articles was obtained in PubMed (the search was refined by including only humans and NOT taking into account the following: Hematopoietic* OR peripheral blood OR menstrual blood OR cardio* OR "salivary glands" OR synovial OR papilla OR heart* OR denta* OR muscle OR Cornea* OR synovi* OR "Schwann cell" OR vascular OR brain OR odont* OR neural OR liver OR hepatic OR aorta OR amniotic OR muscle OR adipo* OR uro* OR Menstrual OR Ovari* OR cord OR endometr* OR periodontal* OR ligament OR tendon OR synovi* OR cardio* OR diabetes OR jelly OR lung OR colo* OR spleen or kidney). In contrast, initially 2716 articles were found in Scopus; however, after applying the filter "human" and "humans" from the listing "Refine results" a total of 1749 articles were attained. Last, in Web of Science 660 publications were identified for a total of 2871 articles. With this total an excel table was created with information containing author, year of publication and journal assigning a number to each retrieved article. Eighteen observers revised the 2871 articles. After this first selection a total of 172 articles were selected based on inclusion and exclusion criteria. Exclusion criteria included: animals (2.4%), visceral skeleton (0.7%), synovial tissue (0.5%), commercial stem cells also considering TERT MSCs (3.7%), other tissues other than bone and cartilage (25.2%), articles not in English (0.2%), non-research articles (25.8%) and non-related (35.6%). Following, only three observers performed a second round of revision where duplicated articles were excluded, for a final total of 152 articles where 94.8% of the initial 2871 articles were omitted (Fig. 1).

3. Results

The objective of the present work was to determine MSCs *in vitro* or *in situ* cell surface markers associated with skeletal tissue according to what has been reported in the literature for Medline (PubMed), Scopus and Web of Science. Based on what has been published MSCs were classified according to their anatomical location: bone marrow (82.0%) and cartilage (11.3%). Furthermore, for 6.7% of the publications out of the 152 articles did not describe site of isolation. Moreover, for some publications more than one anatomical site was characterized, for example bone marrow and cartilage. Additionally, for the 152 articles evaluated the most frequent cell surface markers were $CD105^+$, $CD90^+$ and $CD73^+$, followed by $CD44^+$, $CD166^+$, $CD29^+$, STRO-1$^+$, $CD146^+$ and $CD271^+$ (Fig. 2).

3.1. Bone marrow cell surface markers

Most studies isolated cells from bone marrow (92.1%) from the following anatomical sites: femur, hip, iliac crest, vertebra and knee. The most frequent cell surface markers from cells cultured *in vitro* were those proposed by the ISCT ($CD105^+$, $CD73^+$ and $CD90^+$),
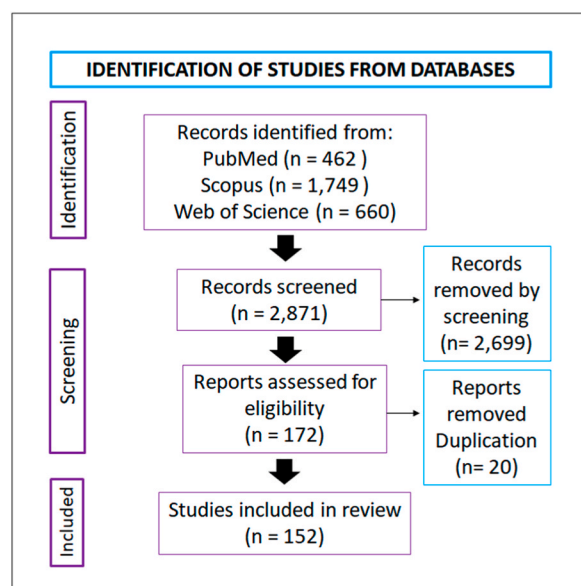

Fig. 1. Article selection. Literature search was performed in three databases Medline (PubMed), Scopus, and Web of Science obtaining a total of 2871 articles. After a revision performed by 18 observers, 152 articles were selected.
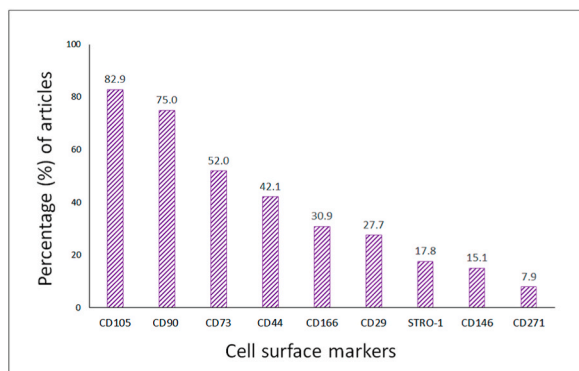
Fig. 2. Percentage of articles evaluating cell surface markers *in vitro*. The most frequently used markers agree with those proposed by ISCT 2006: CD105 (82.9%), CD90 (75.0%), CD73 (52.0%), followed by CD44 (42.1), CD166 (30.9%), CD29 (27.7%), STRO-1 (17.8%), CD146 (15.1%) and CD271 (7.9%).

followed by CD44^{+}, CD166^{+}, CD29^{+}, STRO-1^{+}, CD146^{+} and CD271^{+} (Table 2).

3.2. Cartilage cell surface markers

11.3% of the articles evaluated cell surface markers from cells cultured *in vitro* from cartilage tissue. As previously described for bone marrow the most frequent markers were CD105^{+}, CD90^{+} and CD73^{+}, followed by CD44^{+}, CD166^{+}, CD29^{+}, STRO-1^{+} and CD146^{+} (Table 3).

Fig. 3 summarizes cell surface markers identified in the literature in bone marrow and cartilage.

Table 2
Cell Surface markers assessed from *in vitro* studies in cells isolated from bone marrow in femur, hip, iliac crest, vertebra and knee. Negative cell surface markers were not included, such as CD45, CD34, CD14, CD11b, CD79a, CD19 and HLA-DR.

Cell Surface marker	Anatomical site	Reference
CD105, CD90 and CD73	Femur	[12–28]
	Iliac crest	[29–68]
	Hip	[69–75]
	Vertebra	[17,20,76]
	Knee	[77–81]
	Not described	[82–109]
CD44	Femur	[13,15,17,22,26,110]
	Hip	[75,111]
	Iliac crest	[32,36,37,40,44,47,53,55,59,112]
	Vertebra	[76]
	Knee	[78–81]
	Not described	[83–85,91,95,97,99,107,113]
CD166	Femur	[15,17,22,114,115]
	Hip	[71,111,116]
	Iliac crest	[37,46,47,52,117]
	Vertebra	[17]
	Knee	[79,80]
	Not described	[33,84,85,104,107]
CD29	Femur	[18,22,115]
	Hip	[111]
	Iliac crest	[35,36,39,47,48,57,68,78,80,118]
	Knee	[67,69,70]
	Not described	[83,84,87,100,105,107,113]
STRO-1	Femur	[22,27,119,120]
	Hip	[73,116]
	Iliac crest	[62,118,121,123]
	Not indicated	[90,91,97,103,116,124,125]
CD146	Femur	[20,110]
	Hip	[73]
	Iliac crest	[20,41,45,48,49,62,122]
	Not described	[83,84,87,90,94,97,103]
CD271	Femur	[110,126]
	Hip	[73]
	Iliac crest	[122]
	Not described	[90]

Table 3

Cell surface markers assessed from *in vitro* studies in cells isolated from cartilage in femur, hip, iliac crest, vertebra and knee. Negative cell surface markers were not included, such as CD45, CD34, CD14, CD11b, CD79a, CD19 and HLA-DR.

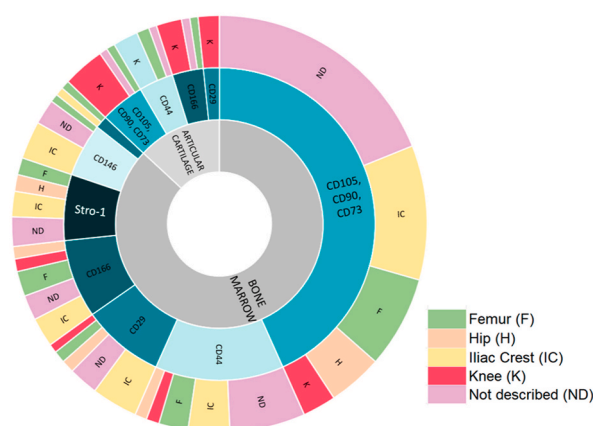| Cell Surface markers	Anatomical site	Reference
CD105, CD90 and CD73	Femur	[127]
	Hip	[71]
	Knee	[38,81,117,127–133]
	Not described	[71,134–136]
CD44	Knee	[81,128–130,132]
	Not described	[135,136]
CD166	Femur	[127]
	Hip	[71]
	Knee	[127–130,132,133,137]
	Not described	[28,135,138]
CD29	Knee	[81,128,129,131,136,137]
STRO-1	Knee	[129]
	Not described	[134,136]
CD146	Knee	[128,132]

Fig. 3. Summary of cell surface markers in bone marrow and cartilage. Percentage of articles evaluating cell surface markers *in vitro*. Inner circle: bone marrow (BM) and articular cartilage (AC). Middle circle describes cell surface markers for BM and AC. Outer circle describes anatomical sites where markers were identified to characterize possible MSCs. Abbreviations: BM: Bone marrow, AC: Articular cartilage, ND: Not described, IC: Iliac crest, F: Femur, H: Hip, K: Knee.

3.3. In situ evaluated cell surface markers

From our search, only 4% of the publications evaluated cell surface markers *in situ* from the following anatomical sites: vertebrae, femur and iliac crest. The most frequent ones identified by IHC were CD105, CD90 and CD73 [136,139,140]. Additionally, CD271 expression was observed in histological MSCs studies in femoral heads of osteoarthritic patients [55,139,140]. Last, perivascular endothelial cells surrounding endothelial capillaries were identified by immunofluorescence and IHC and were positive for CD146 and CD271 [45].

4. Discussion

This is an original work set out to validate which cell surface markers have been identified in the literature for hMSCs related to the skeletal system, as there is a need to determine the true surface markers of these stem cells; thus a scoping review was performed. Based on our search, it was evidenced the most common cell surface markers for MSCs characterization were those proposed by the ISCT in 2006: CD105 (82.9%), CD90 (75.0%), CD73 (52.0%); yet other markers were identified: CD44 (42.1), CD166 (30.9%), CD29 (27.7%), STRO-1 (17.8%), CD146 (15.1%) and CD271 (7.9%) in cells cultured *in vitro* derived from different locations of the skeletal system, such as bone marrow and cartilage. Our search included articles from 1994 to 2021 in PubMed, Scopus and Web of Science, where most reports were performed in studies with cells isolated from human adult bone marrow, followed by cartilage obtained from surgical procedures and last non-reported site of isolation. 96% of the studies identified cell surface markers from cells cultured *in vitro*, and only six articles (4%) carried out *in situ* evaluations using IHC. To date it remains to be determined if these proteins correspond to true stemness markers, as contradictory results have been reported in the literature. Therefore, it is important to establish the function of

each surface marker according to the niche that characterizes skeletal tissues, where MSCs have been identified.

In this study it was evidenced BM was the preferred site of isolation, obtained from pelvic gridle comprised of femur, iliac crest, and hip. However, many studies did not define site of isolation (Fig. 3, ND), which might be important. Moreover, to a lesser extent knee was used as a structure to attain MSCs. Last, vertebra was also employed to obtain bone marrow MSCs, yet very few studies used this bone (one to three publications), thus they do not appear in Fig. 3. It remains to be determined if anatomical location influences surface marker expression. The pelvic gridle originates during embryological development for the somatopleure, and the vertebra from somites. On the other hand, knee cartilage was the other important element to obtain MSCs. This tissue also develops from the somatopleure, yet the process is different compared with endochondral ossification [141]. Therefore, we hypothesize anatomical site, and embryological origin could be key in characterizing surface marker expression, which remains to be established. Another issue to consider is overall, many studies use remnants of bone or cartilage tissue from surgeries in patients with skeletal pathologies, and these cells might be affected by inflammatory cytokines [142].

Multipotent mesenchymal stromal cells were first identified from BM; however, the acronym MSC has been widely used to describe cells from different tissues, as a case in point, cells from non-skeletal sources such as placenta, umbilical cord and adipose tissue [7]. In those studies, multipotent stromal cell surface marker from BM were employed to characterize their phenotype (mainly CD90, CD105, CD73), highlighting their low specificity to determine stemness in skeletal tissues [8,143,144]. Hence, researchers have opted to use other epitopes. Among surface markers proposed to identify MSCs are those suggested by Robey in 2014 [10], including CD105$^+$, CD90$^+$, CD146$^+$ and CD271$^+$. In their work, they highlight the importance of verifying the characteristics of a stem cell, first by demonstrating clonicity and also by transplanting cells into a mouse to verify their differentiation capacity to form bone, stroma and adipocytes *in vivo* [10].

Regarding these proteins CD105 (endoglin) corresponds to a glycoprotein of the cell membrane, which is a receptor for transforming growth factor beta-1 and beta-3. It is mainly expressed in vascular endothelial cells, the syncytiumtrophoblast, and to a lesser extent in monocytes, fibroblasts and chondrocytes [145]. Additionally, CD90 (Thy-1 cell surface antigen THY1) is a protein that is bound to glycophosphatidylinositol, present in intercellular interactions [146]. It has been identified in various cell types, such as hematopoietic stem cells HSC [147] and fibroblasts [148]. Furthermore, CD146 (melanoma cell adhesion molecule MCAM) is present in vascular endothelial cells, where MCAM is a cell adhesion protein key in angiogenesis processes. Cells characterized as possible MSCs that express CD146 have been described to be multipotent, a feature required by a stem cell [149]. In addition, they have a greater capacity to support hematopoiesis, as demonstrated by Sorrentino et al. in hBM, where CD146$^+$ MSCs secreted growth factors capable of controlling HSC function [150]. Hence, CD146 becomes an important candidate to identify possible MSCs [151]. Last, CD271 (nerve growth factor receptor, NGFR) is not expressed as a universal marker in MSCs, as the name describes it has been observed ubiquitously in brain and more specific in meninges, but has been recognized in human adult bone marrow [152].

On the other hand, in 2018 Chan et al. reported the identification of MSCs related to the skeletal system in humans with the capacity of self-renewal and multipotential, characterized by the following cell surface markers: PDPN$^+$, CD146$^-$, CD73$^+$, CD164$^+$ [11]. These
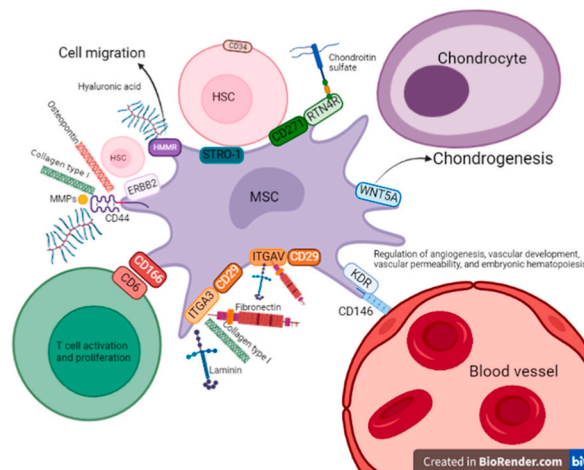

Fig. 4. Possible MSCs-cell/extracellular matrix interactions based on cell surface markers. Using STRING database interactions among cell surface markers and cells expressing them were established. CD44 is a receptor that associates with bone extracellular matrix proteins (osteopontin and collagen Type I, hyaluronic acid). In association with ERB-B2 it plays a function in hematopoiesis. CD166: expressed by stromal cells it interacts with CD6 in T cells to sustain their proliferation and activation. CD29: Receptor in association with ITG-alpha-3 binds to fibronectin, laminin and collagen type I. In association with ITGAV binds to fibronectin and laminin. CD146: Plays a role in cell adhesion to vascular endothelium when co-expressed with KDR. WNT5A is co-expressed with CD146 that could be associated with chondrogenesis. CD271: Stromal cells expressing CD271 are in direct contact with CD34 positive HSCs. CD271 can be associated with RTN4R, whose function is to bind to chondroitin sulfate. STRO-1: Is a protein that binds to CD34 HSCs cells. Abbreviations: ERBB2: Receptor tyrosine-protein kinase erbB-2; HMMR: Hyaluronan mediated motility receptor; MMPs: matrix metalloproteinases, ITG-alpha-3: Integrin alpha-3; ITGAV: Integrin alpha-V; KDR: Vascular endothelial growth factor receptor 2; WNT-5A: Wingless Protein Wnt-5a, RTN4R: (Reticulon-4 receptor) chondroitin sulfate receptor; HSC: Hematopoietic stem cell.

cells isolated from the growth plate generated progenitors for bone, cartilage and stroma, but not adipose tissue. However, this report has not echoed in the community, as it was not found in our scoping review. Additionally, according to Chan et al. CD146⁻ characterizes a stem cell, whereas CD146$^+$ identifies a progenitor cell. In contrast, Robey et al. point out CD146$^+$ defines one of the cell surface markers associated with possible skeletal stem cells [10]. Collectively, Robey et al. and Chan et al. make clear a unique cell surface marker to determine self-renewal capacities and differentiation does not exist for skeletal tissue.

The present scoping review identified other markers used to determine MSCs: CD44$^+$, CD166$^+$, CD29$^+$ and STRO-1$^+$ in BM, and cartilage. CD44 corresponds to hyaluronic acid receptor, which mediates cell-cell and cell-matrix interactions, with affinity for ligands such as osteopontin, collagens and metalloproteases (MMPs). Additionally, it participates in hematopoietic processes and is associated with receptor tyrosine-protein kinase (ERBB2) and Hyaluronan mediated motility receptor (HMMR). CD166 (Activated Leukocyte Cell Adhesion Molecule, ALCAM) is expressed on osteoblasts and HSC residing in the hematopoietic niche and may be key in regulatory processes in bone formation [153]. On the other hand, CD29 (integrin beta 1) are heterodimers that bind ligands which are components of the extracellular matrix proteins, such as fibronectin, laminin, collagen and thrombospondin. In addition, they regulate processes, such as cell proliferation, differentiation, cell adhesion, and cell migration in the context of mineralization, bone development and angiogenesis [154]. Last, STRO-1 first identified in 1991 was described to bind to BM stromal elements [155], yet its identity has not been totally described [156]. These markers are not exclusive of the skeletal system, they are found in other tissues, such as: CD44 in cervix [157], CD166 in epithelium of the Fallopian tubes, CD29 in liver, particularly in bile ducts (preliminary results).

Collectively, our results established MSCs surface markers reported in the literature related to the skeletal system remain to be determined. Therefore, we hypothesize MSCs surface antigen can change according to anatomical location based on their niche. For example, the periosteum contains and outer fibrous layer and an inner layer where skeletal stem cells must reside to differentiate into osteoblasts and promote cortical bone maintenance [158]. The growth plate is the main site of longitudinal bone growth and stem cells are found in this tissue [159]. Stromal cells in the BM make part of the niche that supports hematopoiesis, regulating proliferation, self-renewal, differentiation and HSC migration [160]. On the other hand, articular cartilage antagonizes vascular invasion and prevents friction between two skeletal elements. During development, it derives from the interzone, an anatomical location where mesenchymal stem cells migrated [161]. However, in adult tissues it does not house stem cells [162]. Based on surface antigen markers not including those by the ISCT, we propose the following niche and possible cell-cell and cell-extracellular matrix interaction. In adult BM CD146 associated with Vascular endothelial growth factor receptor 2 (KDR) has been suggested as a stem cell marker candidate related with vessel endothelium (pericyte phenotype); and CD271 stromal cell epitope related to CD34 HSCs, hence hematopoiesis [163] (Fig. 4). In conclusion, through surface markers we can suggest a niche and thus cell function, as aforementioned. Moreover, it is likely more than one epitope can to be expressed by the same cell.

Even though, all studies used cell epitopes to characterize possible MSCs, an identified weakness of our study was the lack of possibility to evaluate the quality of the publications data because there is no standardized procedure for cell isolation and culture, therefore, there is high heterogeneity among studies. In addition, the searched databases included basic research and clinical investigations, with a variety of techniques for cell isolation and different research questions, hence no standardized protocol exists for MSCs isolation. Furthermore, most reports did not demonstrate the two criteria a stem cell must comply: self-renewal and differentiation. It has been described isolated cells could be progenitors and not stem cells that under non physiological conditions are submitted to differentiation processes that cannot be confirmed by staining methodologies, since the gold standard to evaluate differentiation capacity is *in vivo* transplantation [10]. Additionally, it was recognized almost all publications were carried out in cultured cells. It has been evidenced that cell surface markers can change according to cell niche (*in situ*) and upon cell manipulation, such as trypsinization procedures for cell sorting [5]. This disparity among cell epitopes for skeletal stem cells in the literature could be generating contradictory results.

To expand on the aforementioned, expression of some epitopes could be forced in an artificial manner when cells are cultured *in vitro*, such as stage-specific embryonic antigen-4 (SSEA-4) [164,165]. Furthermore, it has been evidenced cell culture confluence can diminish the expression of cell surface markers, such as CD49f (integrin α6), as well as induce the expression of CD106, CD49d and CD200 [165]. Moreover, certain illnesses, mainly inflammatory diseases, such as osteoarthritis (OA) can produce growth factors and cytokines, which can modify MSCs phenotype. This is also true for growth factors used in culture [142,166]. It is critical to evaluate expressed markers *in vivo*, as well as to identify their possible anatomical location *in situ*, because their phenotype must be well characterized before they are employed in a clinical setting. Furthermore, pathologists can further characterize skeletal tissue malignancies using these markers.

Although MSCs have been employed for clinical applications, future developments aim at using MSCs in different fields. For example, in cancer treatments to inhibit proliferative cells in myeloid chronic leukemia [167], as demonstrated in an *in vitro* study with MSCs from murine origin characterized by presenting CD 44 and CD90; or cardiomyocyte development [168], by presenting again the same markers CD44 and CD90. However, before thinking of clinical applications the biology of stem cells must be further determined. The field has now advanced with norms for their use in research, such as ISO 24651–2022, which specifies requirements for biobanking in human mesenchymal stromal cells derived from bone marrow (hBM-MSCs) [169]. In this norm, section "hBM-MSCs characterization immunophenotyping by flow cytometry", it is detailed these cells must express CD105, CD90, CD73, CD44, CD146 and CD271, which is in agreement with the CD markers identified in this scoping review. Hence, we propose these proteins must be identified *in situ* in different tissues from the skeletal system with specific origins (somatopleure and somites). Our research group is currently assessing the presence of these markers in bone and cartilage during embryological and fetal development. We hope this future study will shed light on the niche that houses MSCs and their cell surface markers.

Author contribution statement

Luisa Nathalia Fonseca, Maria Lucia Gutierrez: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper. Santiago Bolivar: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data. Tatiana Agudelo, Liz Daniela Beltrán, Daniel Camargo, Nestor Correa, Maria Alexandra Del Castillo, Sebastián Fernández de Castro, Valeria Fula, Gabriela García, Natalia Guarnizo, Valentina Lugo, Liz Mariana Martínez, Verónica Melgar, María Clara Peña, Wilfran Arbey Pérez, Nicolás Rodríguez: Performed the experiments; Analyzed and interpreted the data. Andrés Pinzón, Mercedes Olaya: Analyzed and interpreted the data. Sonia Luz Albarracín: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Funding statement

Dr. Maria Lucia Gutierrez and Luisa Nathalia Fonseca were supported by Pontificia Universidad Javeriana, Bogotá-Colombia [20036, Proposal ID 10340 & Master Student scholarship].

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no competing interests.

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