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REVIEW ARTICLE

Comparison of the Characteristics of Breast Milk-derived Stem Cells with the Stem Cells Derived from the Other Sources: A Comparative Review

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Abstract: Breast milk (BrM) is not only a nutrition supply but also contains a diverse population of cells. It has been estimated that up to 6% of the cells in human milk possess the characteristics of mesenchymal stem cells (MSC). Available data also indicate that these cells are multipotent and capable of self-renewal and differentiation to other cells. In this review, we have compared different characteristics such as CD markers, differentiation capacity, and morphology of stem cells derived from human breast milk (hBr-MSC) with human bone marrow (hBMSC), Wharton's jelly (WJMSC), and human adipose tissue (hADMSC). The literature review revealed that human breast milk-derived stem cells specifically express a group of cell surface markers, including CD14, CD31, CD45, and CD86. Importantly, a group of markers, CD13, CD29, CD44, CD105, CD106, CD146, and CD166, were identified which were common in the four sources of stem cells. WJMSC, hBMSC, hADMSC, and hBr-MSC are potently able to differentiate into the mesoderm, ectoderm, and endoderm cell lineages. The ability of hBr-MSCs in differentiation into the neural stem cells, neurons, adipocyte, hepatocyte, chondrocyte, osteocyte, and cardiomyocytes has made these cells a promising source of stem cells in regenerative medicine, while isolation of stem cells from the commonly used sources, such as bone marrow, requires invasive procedures. Although autologous breast milk-derived stem cells are an accessible source for women who are in the lactation period, breast milk can be considered a source of stem cells with high differentiation potential without any ethical concern.

Keywords: Mesenchymal stem cell, breast milk, bone marrow, Wharton's jelly, adipose tissue, differentiation.

1. INTRODUCTION

Breast milk (BrM) is not just a nutrition supply, it also contain a wide range of bioactive molecules, such as hormones, growth factors, cytokines, and antioxidants, involved in the normal development of the offspring. BrM also contains a diverse population of cells such as lactocytes, myoepithelial cells, progenitor cells, and stem cells [1-3]. The cellular composition of human milk is dynamic, and the proportion of different cell types can be changed by many factors, such as the stage of lactation, health, and infant feeding. Cells in the BrM include probiotic bacteria, immune cells, desquamated epithelial cells as well as stem cells [2]. Generally, BrM cells are categorized as blood-derived and breast-derived cells, and in both of these sources, a small subpopulation of progenitor or stem cells has been identified. Interestingly, some of these cells are able to pass through the infant's gastrointestinal tract and populate in some tissues such as the brain, spleen, liver, and lymph nodes [1, 3]. Although extensive research has been carried out on the field of breast milk stem cells, the source and origin of multipotent cells found in breast milk are still not completely addressed.

Several studies have shown that BrM contains a group of cells expressing typical features of stem cells. For example, it has been shown that some of them express mammary stem cell and epithelial progenitor markers such as α6 integrin (CD49f) and p63 [4, 5]. Evidence also indicates that these cells are multipotent [5]. These cells have the capability of self-renewal, and under certain conditions, can undergo differentiation towards at least two types of epithelial lineages, milk proteins-producing CK18+ luminal cells and CK14+ myoepithelial cells [6].

Evidence indicates that a mesenchymal stem cell-like population exists in BrM. It has been estimated that up to 6% of the cells in human milk have the characteristics of MSCs [7]. MSCs are self-renewing, highly proliferative, and potentially differentiating cells with adherent growing features [8]. This population was positive for MSC surface markers such as CD44, CD29, SCA-1 and negative for

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CD33, CD34, CD45, CD73, confirming their identity as MSCs. Interestingly, the finding revealed the presence of an MSC-like population in human milk with multi-lineage differentiation potential [9]. Our research group has previously shown that isolated stem cells from human breast milk are able to differentiate into hepatocytes [10], neural cells [11], adipocytes as well as osteoblast. Based on our studies, human breast milk contains a group of cells expressing endodermal markers such as albumin. Besides, we have demonstrated that a subpopulation of these cells expresses some embryonic stem cell markers such as TRA-60-1, Oct4, Sox2, and Nanog, indicating high pluripotency of these cells. We have also reported that a small population of breast milk-derived stem cells express embryonic cell markers such as Nanog, OCT4, Sox2, SEEA4, and TRA 1–60/81 [12]. The presence of multipotent stem cells in human milk suggests that breast milk could be an alternative source of stem cells for autologous stem cell therapy, although the application of these cells in regenerative medicine needs to be more clarified.

Taking all together, breast milk is a valuable source of cell population displaying many of the properties typical of stem cells. In this review, we made an attempt to compare different characteristics such as CD markers, differentiation capacity, and morphology of stem cells derived from breast milk with bone marrow, Wharton jelly, and adipose tissue. This review outlines unique features of progenitor cells from breast milk.

2. MESENCHYMAL STROMAL/STEM CELL MARKERS

A group of cell surface molecules has been suggested as markers for Human Breast Milk MSC (hBr-MSC), as presented in Table **1**. As shown in the Table, the expression patterns of the CD markers are categorized into four levels, highly expressed (>75%), low expressed (<25%), non-expressed, and expressed (positive), that refer to data from studies where the frequency of the positive cells was not reported. The markers which are reported to be highly expressed in hBr-MSC include CD13 [13], CD14 [13, 14], CD94d [13], CD54 [13], CD86 [13], CD140b [13, 15], CD166 [13] and CD271 [12, 16]. However, we found contradictory reports about the expression level of CD29 [7, 13, 17-20], CD34 [7, 12, 13, 16-19], CD44 [7, 11-17, 19, 21, 22], CD45 [7, 12-14, 18, 19], CD49f [18, 20, 23-25], CD73 [7, 12-14, 16, 19, 25], CD105 [11-16, 19, 22], CD117 [13, 15, 18, 19] and CD133 [11-13, 16, 18, 25]; some reports claimed these are highly expressed in hBr-MSC, while the others indicate low expression or lack of expression of the mentioned markers. This contradiction may be due to isolating the cells by different methods or from different stages of lactation (Table **2**). As CD marker expression pattern is different in situ and isolated mesenchymal stem cells cultured *in vitro* [26], fresh *versus* cultured hBr-MSC may also show some differences in CD marker profile. In most of the studies that reported the CD marker expression pattern,

Table 1. Comparison of the CD marker expression in WJMSC, hBMSC, hADMSC, and hBr-MSC. CD makers are expressed at least in one of the four sources of stem cells.

CD Marker	Warton Jelly MSC (WjMSC)	Human Bone Marrow MSC (hBMSC)	Human Adipose MSC (hADMSC)	Human Breast Milk MSC (hBr-MSC)	References
CD4	+	-	-	Non-Reported	WjMSC: [27] hBMSC: [28] hADMSC: [28-31]
CD7	+	-	-	Non-Reported	WjMSC:[32] hBMSC [33] hADMSC:[34]
CD9	+	+	+ (>75%) High expression	Non-Reported	WjMSC:[35] hBMSC:[36] hADMSC: [31, 37-40]
CD10	+ (>75%) High expression	+	+ (>75%) High expression	-	WjMSC: [35, 41-47] hBMSC: [36, 48-50] hADMSC: [29, 34, 38, 51-53] hBr-MSC:[18]
CD13	+ (>75%) High expression	+ (>75%) High expression	+ (>75%) High expression	+ (>75%) High expression	WjMSC: [35, 41-45, 47, 54-63] hBMSC: [28, 31, 36, 48-50, 57, 64-71] hADMSC: [28, 29, 31, 34, 38, 51, 53, 65, 67, 72-77] hBr-MSC:[13]
CD14	-	-	-	+ (>75%) High expression	WjMSC: [32, 41, 45-47, 57, 59, 60, 63, 78-88] hBMSC: [28, 31, 33, 48, 49, 57, 64-66, 68, 69, 81, 86, 88-109] hADMSC: [28, 29, 31, 34, 38, 65, 73, 75, 76, 110-117] hBr-MSC: [13, 14]
CD24	+	-	+	+ 25%)>) Low expression	WjMSC: [118] hBMSC: [49] hADMSC: [119] hBr-MSC: [18, 20]
CD25	+	-	-	Non-Reported	WjMSC: [120] hBMSC: [104] hADMSC: [31, 34]

(Table 1) contd….

CD Marker	Warton Jelly MSC (WjMSC)	Human Bone Marrow MSC (hBMSC)	Human Adipose MSC (hADMSC)	Human Breast Milk MSC (hBr-MSC)	References
CD26	Non-Reported	+	+ (>75%) High expression	Non-Reported	hBMSC: [121] hADMSC: [53]
CD29	+ (>75%) High expression	+ (>75%) High expression	+ (>75%) High expression	+ (>75%) High expression [7, 13] 25%)>) Low expression [18, 19]	WjMSC: [32, 35, 41, 42, 45-47, 54-60, 63, 78, 81, 85, 88, 122-132] hBMSC: [28, 31, 33, 49, 57, 64-66, 68, 71, 81, 88-90, 92, 94, 98, 99, 101, 102, 105, 108, 133-139] hADMSC: [30, 31, 38, 40, 51, 53, 65, 72-75, 77, 111, 113, 140-153] hBr-MSC: [7, 13, 17-20]
CD31	-	-	-	+	WjMSC: [41, 43, 45, 47, 54, 57, 59, 60, 81, 84, 85, 154, 155] hBM-SC: [28, 48-50, 57, 65, 81, 89, 92, 99, 103-105, 108, 136, 156] hADMSC: [31, 37-39, 65, 67, 72, 73, 75, 77, 103, 111, 141, 142, 157-165] hBr-MSC: [13, 25]
CD34	-	-	+ [29, 38, 157-160, 166] - [31, 34, 37, 39, 65, 72-74, 76, 77, 110-113, 116, 117, 140-142, 145, 149, 163-165, 167, 168]	+ 25%)>) Low expression [13, 18, 19] - [7, 12, 16]	WjMSC: [32, 41, 43-47, 54-57, 59, 60, 63, 78-80, 82-86, 88, 122-130, 169-180] hBMSC: [31, 33, 48-50, 57, 65, 66, 68-70, 86, 88-109, 133, 134, 136-139, 181-191] hADMSC: [29, 31, 34, 37-39, 65, 72-74, 76, 77, 110-113, 116, 117, 140-142, 145, 149, 157-160, 163-168] hBr-M-SC: [7, 12, 13, 16, 18, 19]
CD36	+	-	+ (>75%) High expression	Non-Reported	WjMSC: [192] hBMSC: [49, 50, 98] hADMSC: [29, 31, 53]
CD40	-	-	+	+	WjMSC: [32, 193, 194] hBMSC: [104] hADMSC: [53] hBr-MSC: [195]
CD41a	Non-Reported	+	-	Non-Reported	hBMSC: [196] hADMSC:[30]
CD44	+ (>75%) High expression	+ (>75%) High expression	+ (>75%) High expression	+ [7, 11-17, 19, 21, 22] (>75%) High expression [7, 11, 13, 15, 16] 25%)>) Low expression [19]	WjMSC:[32, 35, 41-43, 45-47, 57-60, 63, 78, 81, 85, 88, 122-125, 127, 128, 130, 169-173, 175, 176, 180, 197, 198] hBMSC: [28, 31, 33, 48, 49, 57, 64-69, 71, 81, 88-90, 92, 94, 98-106, 108, 109, 133, 134, 136-139, 156, 182, 185, 186, 188, 191] hADMSC: [31, 34, 37-39, 51, 53, 65, 67, 72-75, 77, 111, 113, 114, 140-142, 144, 145, 151, 153, 160, 162, 164, 167, 199-204] hBr-M-SC: [7, 11-17, 19, 21, 22]
CD45	-	-	-	+ [12-14, 19] - [7, 18]	WjMSC:[32, 41, 43-47, 54-57, 59, 60, 63, 78-86, 88, 122, 125-128, 130, 171, 173-175, 177-180, 197] hBMSC: [28, 31, 33, 48-50, 57, 65, 66, 68-70, 81, 86, 88-109, 134, 137-139, 156, 181-183, 185, 186, 188-191] hADMSC: [28, 31, 34, 37-39, 51, 65, 67, 72-77, 110-114, 116, 117, 141, 142, 144, 145, 157, 164, 167, 168, 199, 201-203, 205-207] hBr-MSC:[7, 12-14, 18, 19]

(Table 1) contd….

CD Marker	Warton Jelly MSC (WjMSC)	Human Bone Marrow MSC (hBMSC)	Human Adipose MSC (hADMSC)	Human Breast Milk MSC (hBr-MSC)	References
CD47	Non-Reported	+ (>75%) High expression	+ (>75%) High expression	Non-Reported	hBMSC:[208] hADMSC:[53]
CD49	+	+	+	Non-Reported	WjMSC:[209] hBMSC: [98] hADMSC: [72]
CD49a	+	+	+ (>75%) High expression	Non-Reported	WjMSC:[35] hBMSC: [210] hADMSC: [31, 53]
CD49b	+ (>75%) High expression	+ (>75%) High expression	+ (>75%) High expression	Non-Reported	WjMSC: [32, 35, 41, 45] hBM-SC: [33, 50] hADMSC: [30, 31]
CD49c	+	+ (>75%) High expression	+	Non-Reported	WjMSC:[41] hBMSC: [98] hADMSC: [31]
CD49d	+ [41] - [32, 45]	+ 25%)>) Low expression [33, 211] - [49, 104]	+ (>75%) High expression [30, 205] 25%)>) Low expression [38, 73, 145, 164]	+ (>75%) High expression	WjMSC: [32, 41, 45] hBMSC: [33, 49, 98, 104, 211] hADMSC: [30, 31, 38, 73, 142, 145, 164, 205] hBr-MSC: [13]
CD49e	+	+ (>75%) High expression	+ (>75%) High expression	Non-Reported	WjMSC: [41, 63, 126] hBMSC: [48, 66, 104] hADMSC: [30, 31, 38, 51, 53]
CD49f	+	+ (>75%) High expression	-	+ (>75%) High expression [20] 25%)>) Low expression [18]	WjMSC:[212] hADMSC: [30] hBMSC: [48, 98] hBr-MSC: [18, 20, 23-25]
CD50	Non-Reported	-	+[31] -[38]	Non-Reported	hBMSC: [33, 50, 69, 104, 106] hADMSC: [31, 38]
CD51	+ High expression	+	+ (>75%) High expression	Non-Reported	WjMSC:[122] hBMSC: [33] hADMSC: [30, 31, 53]
CD54	+ (>75%) High expression	+	+	+ High expression	WjMSC: [35, 46, 63, 174] hBM-SC: [33, 48, 104, 213] hADMSC: [38, 53, 77, 142, 152] hBr-MSC: [13]
CD56	+ [35, 58] - [41, 45]	-	-	Non-Reported	WjMSC: [35, 41, 45, 58] hBM-SC: [28, 100] hADMSC: [28, 34, 38, 73]
CD58	+	+	+ (>75%) High expression	Non-Reported	WjMSC:[32] hBMSC:[104] [28, 33] hADMSC: [28, 31, 53]
CD59	+	+ (>75%) High expression	+ (>75%) High expression	+	WjMSC:[58] hBMSC: [98, 133] hADMSC: [29, 38, 51, 53] hBr-MSC: [214]
CD61	+	+	+ [30, 53] - [31, 73]	Non-Reported	WjMSC:[58] hBMSC: [33] hADMSC: [30, 31, 53, 73]
CD62e	+ (>75%) High expression	Non-Reported	-	Non-Reported	WjMSC:[35] hADMSC: [31, 38, 73]
CD62P	+ 25%)>) Low expression	-	-	Non-Reported	WjMSC: [215] hBMSC: [28, 33, 104] hADMSC: [30, 31]

(Table 1) contd….

CD Marker	Warton Jelly MSC (WjMSC)	Human Bone Marrow MSC (hBMSC)	Human Adipose MSC (hADMSC)	Human Breast Milk MSC (hBr-MSC)	References
CD62L	+ 25%)>) Low expression	-	+ 25%)>) Low expression	Non-Reported	WjMSC: [215] hBMSC: [33, 48, 104] hADMSC: [216]
CD63	+	+	+	Non-Reported	WjMSC:[54] hBMSC: [217] hADMSC: [31, 218]
CD68	+	-	+	+	WjMSC:[35, 179] hBMSC: [105] hADMSC: [111, 219] hBr-MSC:[17]
CD71	+ [130] - [123]	+ 25%)>) Low expression	+	Non-Reported	WjMC:[123, 130] hBMSC: [94, 104] hADMSC: [31, 53, 73, 164]
CD 73	+	+ (>75%) High expression	+ (>75%) High expression	+ 25%)>) Low expression [14, 19, 25] - [7, 12, 13, 16]	WjMSC:[32, 35, 43, 45-47, 54-60, 63, 79-85, 88, 124-128, 130, 171, 172, 175, 177, 178, 180] hBMSC: [28, 36, 48, 49, 57, 65-67, 70, 81, 88-92, 95-97, 99, 100, 102, 103, 106, 107, 134, 139, 156, 181, 183, 185-191, 211] hADMSC: [31, 37, 39, 52, 53, 65, 75, 103, 110-112, 114, 116, 117, 141, 143, 160, 162, 166, 168, 200, 202, 204-207, 220-223] hBr-MSC: [7, 12-14, 16, 19, 25]
CD 83	Non-Reported	-	+	-	hBMSC: [106] hADMSC: [224, 225] hBr-MSC:[13]
CD86	-	-	-	+	WjMSC: [32, 79, 193, 194] hBM-SC: [104, 106] hADMSC: [116] hBr-MSC: [13]
CD 90	+ (>75%) High expression	+ (>75%) High expression	+ (>75%) High expression	+ 25%)>) Low expression	WjMSC: [35, 41-43, 45-47, 54-60, 63, 78-80, 83-86, 88, 124-128, 171-178, 180, 197] hBMSC: [28, 31, 33, 48, 49, 65-71, 86, 88-92, 94-104, 106, 107, 109, 134, 136, 137, 139, 156, 181-183, 185-191, 211] hADMSC: [28, 30, 31, 34, 37, 39, 51-53, 65, 72, 73, 75, 103, 110-114, 116, 117, 140, 142, 153, 157, 159, 160, 163, 166, 168, 200, 201, 204-207, 220-223, 226] hBr-MSC: [11-14, 16, 19, 25]
CD95	+	Non-Reported	+ (>75%) High expression	Non-Reported	WjMSC:[123] hADMSC: [53]
CD102	+ Low expression	Non-Reported	+	Non-Reported	WjMSC: [215] hADMSC: [31]
CD105	+	+ (>75%) High expression	+ (>75%) High expression 25%)>) Low expression [73, 157]	+ (<25%) Low expression [11, 13-16, 19, 22] - [12, 16]	WjMSC: [32, 35, 42, 45-47, 54-60, 63, 79-86, 88, 122-130, 169-178, 180, 197, 198] hBMSC: [28, 31, 36, 48, 49, 57, 64-68, 70, 71, 81, 86, 88-92, 95-105, 107-109, 134, 136, 138, 139, 156, 181-183, 185-191, 211, 213] hADMSC: [28, 31, 38, 52, 53, 65, 72-76, 103, 110-114, 117, 140-144, 148, 153, 157, 159, 160, 166, 168, 199-201, 204-207, 220, 222, 223, 226, 227] hBr-MSC: [11-16, 19, 22]

(Table 1) contd….

CD Marker	Warton Jelly MSC (WjMSC)	Human Bone Marrow MSC (hBMSC)	Human Adipose MSC (hADMSC)	Human Breast Milk MSC (hBr-MSC)	References
CD106	+ [57, 59, 60, 85, 169, 170, 197] - [88, 125, 180]	+ [28, 57, 94, 98, 102, 105, 106, 156] - [48, 50, 71, 88, 89, 104, 107, 108, 138, 213]	+ [31, 72, 164] - [30, 73, 77, 142, 145]	+ (<25%) Low expression	WjMSC: [57, 59, 60, 85, 88, 125, 169, 170, 180, 197] hBMSC: [28, 48, 50, 57, 71, 88, 89, 94, 98, 102, 104-108, 138, 156, 213] hADMSC: [30, 31, 72, 73, 77, 142, 145, 164] hBr-MSC: [11, 13, 16]
CD117	+ (>75%) High expression [35, 44, 228] (<25%) Low expression [63, 180, 229] - [32, 43, 45, 61, 88, 118]	-	+ [31, 39, 227] (<25%) Low expression [39] - [30, 37, 72, 77, 111, 151, 226]	+ [13, 15, 19] (>75%) High expression [15] - [18]	WjMSC: [32, 35, 43-45, 61, 63, 88, 118, 180, 228, 229] hBMSC: [48-50, 88, 98, 101, 213] hADMSC: [30, 31, 37, 39, 72, 77, 111, 151, 226, 227] hBr-MSC: [13, 15, 18, 19]
CD120a	Non-Reported	-	+	Non-Reported	hBMSC: [33, 104] hADMSC: [31]
CD120b	Non-Reported	-	+	Non-Reported	hBMSC: [104] hADMSC: [31]
CD123	-	+ (<25%) Low expression	-	-	WjMSC: [180] hBMSC: [104] hADMSC: [31] hBr-MSC: [12, 16]
CD124	Non-Reported	+	-	Non-Reported	hBMSC: [94] hADMSC: [31]
CD133	+ [35] - [32, 54, 56, 125]	-	-	+ [11, 13, 18, 25] - [12, 16]	WjMSC: [32, 35, 54, 56, 125] hBMSC: [33, 49, 70, 102, 188] hADMSC: [30, 31] hBr-MSC: [11-13, 16, 18, 25]
CD140a	-	+	+	Non-Reported	WjMSC:[63] hBMSC: [230] hADMSC: [30, 31]
CD140b	Non-Reported	+	+ (>75%) High expression	+ High expression	hBMSC: [231] hADMSC: [53] hBr-MSC: [13, 15]
CD146	+ [88, 171, 197] - [84, 124, 172]	+	+ [53] - [31]	+	WjMSC: [84, 88, 124, 171, 172, 197] hBMSC: [65, 71, 88, 92, 98, 99, 107, 190, 191, 211] hADMSC: [31, 53] hBr-MSC:[12]
CD147	+	+ (>75%) High expression	+ (>75%) High expression	Non-Reported	WjMSC: [232] hBMSC: [98] hADMSC: [53]
CD163	-	+	Non-Reported	Non-Reported	WjMSC:[179] hBMSC: [233]
CD164	+	Non-Reported	+	Non-Reported	WjMSC:[124] hADMSC: [31, 53]
CD166	+ (>75%) High expression	+ (>75%) High expression	+ (>75%) High expression	+ (>75%) High expression	WjMSC: [32, 35, 45, 47, 57-60, 63, 124, 126, 130, 171, 197] hBMSC: [28, 36, 48, 49, 57, 68, 71, 90, 98, 99, 101, 104, 106, 107, 135, 137, 139, 181, 182, 191] hADMSC: [28, 31, 38, 51, 53, 72, 74-77, 141, 142] hBr-MSC: [13]
CD200	Non-Reported	+ High expression	+	Non-Reported	hBMSC: [211] hADMSC: [75]
CD271	-	+ (>75%) High expression	+ [53] - [31]	+ (>75%) High expression	WjMSC: [54, 124, 198] hBMSC: [98, 190, 191] hADMSC: [31, 53] hBr-MSC: [12, 16]
CD276	Non-Reported	+	+	Non-Reported	hBMSC: [208] hADMSC: [31]

hBr-MSCs were collected from a wide range of times. Therefore, understanding the expression profile of CD markers in different stages of lactation needs more investigation.

On the other hand, we have listed the markers with low expression level in hBr-MSC (Table **1**) including CD24 [18, 20], CD90 [11-14, 16, 19, 25], CD106 [11, 13, 16]. Finally,

Table 2. Diffrerent methods from the isolation of cell of breast milk for charactriztion.

Refrences	Isolation Conditions	Freshly Isolate/Cultured
[7]	Full term, from day 0 until day 5 post-delivery	after culture (2 to 6 passages)
[11]	From various stages of lactation	after culture
[12]	Full term, mother age 22–30 years, from day 1 to 6 months post-delivery	Fresh (without passages)
[13]	Full term, mothers age 21–34 years, from day 3 to day 7 post-delivery	Fresh (without passages)
[14]	From 2 days to 2 months post-delivery	after culture (Three weeks after isolation)
[15]	Every day from 0 to 7 post-delivery day	after culture
[16]	Full term, from day 0 until month 6 post-delivery	Fresh (without passages)
[17]	From various stages of lactation	after culture
[18]	From various stages of lactation	Fresh (without passages)
[19]	Full-term and preterm mothers, from 14 to 49 day post-delivery for preterm, and from 29 to 50 day for full term mothers	Fresh (without passages)
[24]	From various stages of lactation	Fresh (without passages)

it has been reported that CD10, CD83, and CD123 are not expressed in hBr-MSC.

Based on Table **1**, the shared markers among the isolated MSc from Warton Jelly (WJMSC), human bone marrow MSC (hBMSC), human adipose MSC (hADMSC) and hBr-MSC are CD13, CD29, CD44, CD105, CD106, CD146 and CD166. Importantly, the markers express just in hBr-MSC, but not in the other MSCs, are CD14 [13, 14], CD31 [13, 25], CD45 [12-14, 19], and CD86 [13].

The review of the literature shows that CD9, CD49, CD49a, CD49b, CD49c, CD49e, CD51, CD 58, CD61, CD63, CD71, and CD147 are expressing in the WJMSC, hBMSC, hADMSC; however, these markers were not reported to be expressed in hBr-MSC. This list could be helpful in future studies for a more precise characterization of these sources of cells.

Also, the literature review revealed that several markers were negatively expressed or not reported to be expressed in four sources of stem cells (Table **3**) [234-239].

3. MORPHOLOGY OF STEM CELS FROM VARIOUS SOURCES

The literature review shows that hBr-MSCs have a similar phenotype to fibroblasts [7, 12]. However, it has been reported that the isolated cells initially contained an epithelial--like cell population, and during the second week of culture, the phenotype changes to typical slender fibroblast-like cells. This morphological change has been suggested as a result of epithelial to mesenchymal transition [7]. Sani *et al*. detected two cell populations in the cultures of isolated hBr-MSCs, fibroblast-like and round cells. After 10±2 days, the fibroblast-like cells were prominent cell types in the cultures [12]. On the other hand, the morphology of most of the WJMSCs and hBMSCs has been recorded as fibroblast-like cells [240]. However, reports show that hADMSCs also contains two cell population based on nucleus size and lectin reactivity [241].

4. DIFFERENTIATION CAPACITY OF STEM CELLS FROM VARIOUS SOURCES

It has been shown that a group of embryonic stem cell (ESC) associated genes, such as Nanog, OCT4, Sox2, SEEA4, and TRA 1–60/81 and KLF4, are expressed in a subpopulation of hBr-MSC [9, 11]. Furthermore, these cells share some similarities in the phenotype, colony morphology, and differentiating capability with ESCs [9, 242]. As multipotent stem cells, hBr-MSCs have been differentiated into all three primary germ layers, ectoderm, mesoderm, and endoderm (Fig. **1**). Furthermore, mesenchymal stem cell markers have also been shown to be expressed in a subpopulation of the cells derived from BrM [243]. Hence, due to embryonic stem cell properties, hBr-MSCs may be greatly able to differentiate toward neural cell lineages [244, 245], including astrocyte [11], neuron [1, 9, 11], and oligodendrocyte [11].

A previous study showed that hBr-MSCs could differentiate into the neural stem cells and neurons [11]. Both mammary gland and nervous system originate from the same origin, ectoderm [246], and they share common regulatory pathways in the development. Besides, a subpopulation of hBr-MSCs express nestin, which is a marker of neural progenitor cells. Therefore, hBr-MSCs may be considered as a reliable source for differentiation to the neural cell lineages [11]. The same differentiation potency toward neurons has been shown in the isolated mesenchymal stem cells from human adipose tissue [247-251], bone marrow [108, 138, 252-254], and Wharton's jelly [255-263]. In the case of bone marrow-originated stem cells, there are also reports indicating that these cells can differentiate into the glial cell [108, 138]. Moreover, Wharton's jelly-originated cells are shown to have the potential to differentiate toward Schwann-cell [256], oligodendrocytes [263], and auditory hair cells [255].

Differentiation of hBr-MSCs into mesoderm-originated cells such as adipocytes [1, 7, 9, 12], chondrocyte [1, 7, 9, 264, 265], osteocyte [1, 7, 12], and cardiomyocytes [9, 266]

Table 3. Comparison of the expression of CD markers which are negative or non-reported in WJMSC, hBMSC, hADMSC, and hBr-MSC.

CD Marker	Warton Jelly MSC (WjMSC)	Human Bone Marrow MSC (hBMSC)	Human Adipose MSC (hADMSC)	Human Breast Milk MSC (hBr-MSC)	References
CD3	-	-	-	Non-Reported	WjMSC: [32, 45, 84] hBMSC: [28, 48, 98, 183] hADMSC: [28, 29, 34]
CD11a	Non-Reported	-	-	Non-Reported	hBMSC: [104] hADMSC: [30, 31, 38, 201]
CD11b	-	-	-	Non-Reported	WjMSC: [47, 128, 178] hBMSC: [90, 98, 107, 185, 186, 234] hADMSC: [30, 34, 38, 51, 75, 201, 220, 223]
CD15	Non-Reported	-	-	Non-Reported	hBMSC: [28] hADMSC: [28, 29, 31, 158]
CD16	Non-Reported	-	-	Non-Reported	hBMSC: [28] hADMSC: [28, 34, 73, 152]
CD18	-	Non-Reported	-	Non-Reported	WjMSC:[47] hADMSC: [30, 38, 152]
CD19	-	-	-	Non-Reported	WjMSC: [32, 80, 83, 128, 178, 181, 197, 235] hBMSC: [28, 48, 66, 92, 98, 107, 138, 181, 191] hADMSC: [28, 29, 34, 75, 117, 207, 223]
CD33	-	-	-	-	WjMSC: [32, 41, 44, 47] hBMSC: [28] hADMSC: [28, 34] hBr-MSC:[7]
CD38	-	-	-	Non-Reported	WjMSC: [44, 57, 59, 60, 123, 174] hBMSC: [28, 33, 49, 50, 57] hADMSC: [29, 31]
CD79	-	-	Non-Reported	Non-Reported	WjMSC:[44] hBMSC: [90, 98]
CD79A	-	Non-Reported	-	Non-Reported	WjMSC:[83] hADMSC:[236]
CD80	-	-	-	Non-Reported	WjMSC: [32, 79, 193, 194] hBMSC: [103, 104, 106] hADMSC: [103]
CD95L	Non-Reported	-	-	Non-Reported	hBMSC: [48] hADMSC: [151]
CD104	Non-Reported	-	-	Non-Reported	hBMSC: [28] hADMSC: [28, 31, 73]
CD115	-	Non-Reported	-	Non-Reported	WjMSC:[47] hADMSC: [31]
CD126	Non-Reported	-	-	Non-Reported	hBMSC: [237] hADMSC: [31]
CD127	Non-Reported	-	-	Non-Reported	hBMSC: [104] hADMSC: [31]
CD144	-	-	-	-	WjMSC: [169, 170, 172] hBMSC: [28, 49, 102] hADMSC: [28, 67] hBr-MSC: [12]
CD235a	-	-	-	Non-Reported	WjMSC: [180, 238] hBMSC: [238] hADMSC: [238, 239]

is also reported. We did not find any study which compares the potency of the differentiation of hBr-MSCs with three other cell sources. However, it has been shown that osteogenic differentiation in hBMSCs is higher than hADMSCs [65]. Furthermore, quantitative analysis has shown that hBMSCs had better osteogenic and chondrogenic abilities, while urine-derived stem cells (USCs) had superior adipogenic and endothelial cell differentiation abilities than hBMSCs or Placenta Decidua Basalis-derived stem cells (PDB-MSCs) [267]. It has been claimed that hADMSCs have higher adipogenic differentiation potential than hBMSC [268].

WJMSCs are able to differentiate into mesoderm-originated cells. Several studies have reported the differentiation potency of these cells into adipocytes [269, 270], chondrocyte [270-272], osteocytes [270, 273, 274], cardiomyocyte [260, 275-277], Sertoli cell [138, 278], endometrial epithelial cell (EEC), and endometrial stromal cell (ESC) [279]. Similarly, there are reports of the same potency for BMSCs, including adipocyte [108, 138, 254, 280], chondrocyte [108, 138, 280], osteocyte [108, 138, 254, 280], cardiomyocyte [281-283], skeletal myocytes, tendon cell [280], stromal cells [138], and cells of visceral mesoderm [280]. Finally, ADMSCs are able to differentiate toward adipocyte [103, 247, 248, 268, 284, 285], chondrocyte [103, 247, 248, 268, 285-287], osteocyte [103, 247, 248, 268, 284, 285, 287-290], cardiomyocyte [291, 292], and skeletal myocyte [266, 286].

Finally, we also reviewed the potential differentiation of these four sources of stem cells toward endoderm originated cells. In a study, our team evaluated the differentiation potential of Br-MSCs into hepatocyte-like cells [10]. Based on the results, hepatic nuclear factor, albumin, cytokeratin 18 and 19, cytochrome P2B6, glucose-6- phosphatase, and claudin were expressed in the differentiated cells. Furthermore, functional assays showed glycogen storage and omission of indocyanine green; also, cell aggregate formation was observed with the accumulation of the differentiated cells to form spheroids. Differentiation of hBr-MSCs into the beta cell [9] and hepatocyte [1, 9, 10] was also reported. Therefore, hBMSCs are also known as a promising source of beta-cells [133, 293-295] and hepatocyte [296].

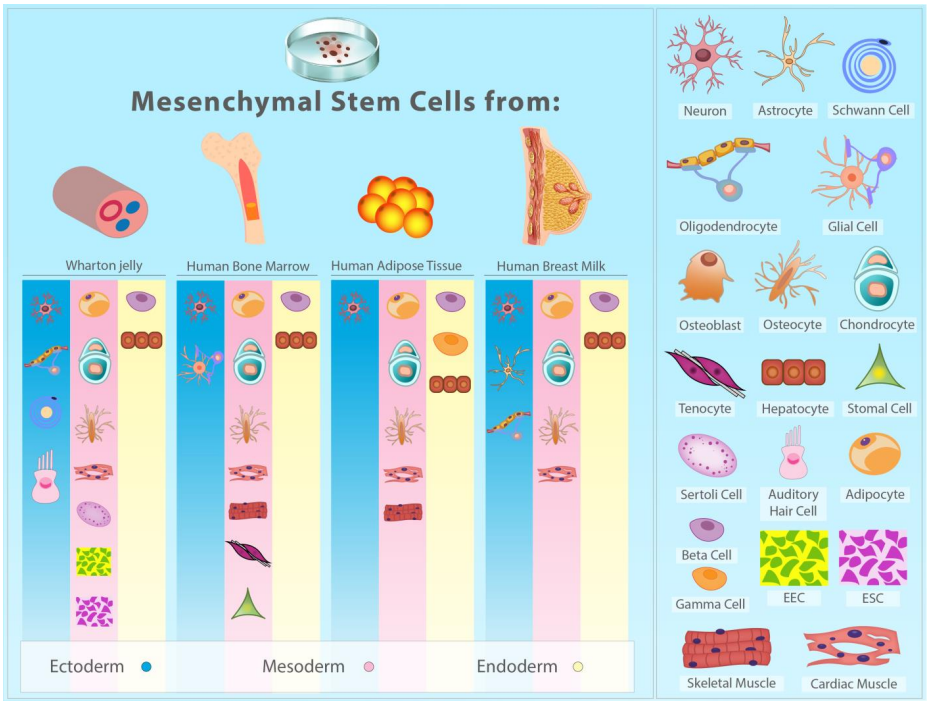

Fig. (1). Comparison of the differentiation capacity in four sources of WJMSC, hBMSC, hADMSC, and hBr-MSC into different cell lineages. All four sources can differentiate into components of all three germ layers (ectoderm, mesoderm, and endoderm). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Differentiation of hADMSCs into various endoderm-originated cells has been reported in several studies, alpha cell [297], beta-cell [295, 297], hepatocyte [249, 284, 296, 298, 299], and gamma cell [297]. The same reports exist about Wharton's Jelly Derived Mesenchymal stem cells, beta cells [133, 295, 300], and hepatocyte [170, 299, 301-307]. It was shown that WJMSC expresses a high level of transcription factors involved in liver development. The production of early hepatic markers has made Wharton's jelly a suitable source of hepatocyte differentiation compared to hBMSC and hADMSC [303].

5. hBr-MSCs APPLICATIONS IN PRECLINICAL AND CLINICAL TRIAL STUDIES

Given the novelty, there are few studies to treat a disease or injury tissue using hBr-MSCs. Borhani-Haghighi *et al*. conducted a preclinical study to investigate the therapeutic effects of the hBr-MSC-conditioned medium in a rat model of spinal cord injury. They showed that intrathecal administration of the hBr-MSC-conditioned medium reduced apoptosis and inflammation at the site of injury and improved sensory, motor, locomotor, and sensorimotor neurons in a rat model of spinal cord injury [308]. This finding displays the therapeutic capacity of hBr-MSC and their potential to reduce inflammation and tissue damage *via* secreted factors.

Also, the literature showed a few ongoing clinical trial studies in this field. In phase 1 clinical trial, fresh breast milk is injected intranasally to cure intraventricular hemorrhage in preterm infants. It has been suggested that fresh breast milk can be considered a safe source of stem cells for preterm patients suffering from intraventricular hemorrhage [309]. In the other ongoing studies, the infants suffering from necrotizing enterocolitis were fed with stem cell-rich breast milk [310]. Not only hBr-MSC can be applied in regenerative medicine, but it can also provide a non-invasive source of stem cells for food engineering as it reduces slaughtering animals and prevents the detrimental influence of livestock production [311].

CONCLUSION

Human breast milk is a remarkable source of stem cells. These cells have multilineage differentiation potential and show mesenchymal and embryonic stem cells properties. This literature review revealed that human breast milk-derived stem cells were expressing specifically a group of cell surface markers, including CD14, CD31, CD45, and CD86. Importantly, a group of markers, CD13, CD29, CD44, CD105, CD106, CD146, and CD166, were retrieved, which are common in the four studied stem cells WJMSC, hBMSC, hADMSC, and hBr-MSC.

The differentiation potential of these cells was also compared. Based on the literature review, hBr-MSCs are potently able to differentiate toward the mesoderm, ectoderm, and endoderm originated cells. The same ability has been reported for the WJMSC, hBMSC, and hADMSC. The ability of hBr-MSCs in differentiation toward the neural stem cells, neurons, adipocyte, hepatocyte, chondrocyte, osteocyte, and cardiomyocytes has made these cells a promising source of

stem cells in regenerative medicine. Often, isolation of stem cells from the commonly used sources, such as bone marrow, requires invasive procedures. Although autologous breast milk-derived stem cells are an accessible source for lactating women, breast milk is a non-invasive and abundant source of stem cells, with high potential cells for differentiation without any ethical concern. Several studies indicate hBr-MSC have the potency to differentiation to a wide variety of cells; however, more studies are needed to further clarify the characteristics of the differentiated cells and their functionality.

LIST OF ABBREVIATIONS

BrM	=	Breast milk
MSC	=	Mesenchymal Stem Cell
hBr-MSC	=	Human Breast Milk MSC
WJMSC	=	Warton Jelly MSC
hBMSC	=	Human Bone Marrow MSC
hADMSC	=	Human Adipose MSC
ESC	=	Embryonic Stem Cell
USC	=	Urine-derived Stem Cells
PDB-MSC	=	Placenta Decidua Basalis-derived Stem Cell
EEC	=	Endometrial Epithelial Cell
ESC	=	Endometrial Stromal Cell

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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