Tzu Chi Medical Journal 2023; 35 (1): 24-30

Review Article

Role of cancer-associated mesenchymal stem cells in the tumor microenvironment: A review

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Submission : 10-May-2022
Revision : 09-Jun-2022
Acceptance : 14-Jun-2022
Web Publication : 01-Aug-2022

Abstract

Mesenchymal stem cells (MSCs) were applied to the therapy for degenerative diseases, immune, and inflammation. In tumor microenvironments (TME), different sources of MSCs showed that tumor-promoting and -inhibiting effects were mediated by different signaling pathways. Cancer-associated MSCs (CaMSCs) could be recruited from bone marrow or local tissues and mainly showed tumor-promoting and immunosuppressive effects. The transformed CaMSCs preserve the characteristics of stem cells, but the properties of regulating TME are different. Hence, we specifically focus on CaMSCs and discuss the detailed mechanisms of regulating the development of cancer cells and immune cells. CaMSCs could be a potential therapeutic target in various types of cancer. However, the detailed mechanisms of CaMSCs in the TME are relatively less known and need further study.

Keywords: *Cancer, Immunosuppression, Mesenchymal stem cells, Microenvironment*

Introduction

The tumor microenvironments (TME) are complex and regulate tumor progression. TME includes stroma/fibroblasts cells, vascular/endothelial cells, mesenchymal stem cells (MSCs), immune cells, and secreted factors, such as cytokines [1]. Among the cell components in TME, MSCs play critical roles in enhancing the malignancies by direct interacting with cancer cells or affecting the other cell components, such as immune cells. Cancer-associated MSCs (CaMSCs) are unique MSCs and are educated by cancer cells. The studies of CaMSCs were focused on primary culture of cancer-associated MSC from cancer tissues, and indirectly (by conditioned medium of CaMSCs) or directly interact with cancer cells as well as immune cells. Only a few studies surveyed the CaMSCs in clinical specimens. In this review, we will discuss the roles of CaMSCs affecting cancer cells and immune cells and the mechanisms in various types of cancer.

Characterization of mesenchymal stem cells

MSCs could be derived from bone marrow (BM-MSCs), adipose tissue (MSCs), umbilical cord, or its blood (UC/UCB-MSCs), and other adult tissues. The minimal criteria for defining MSCs include (i) MSCs must be plastic-adhering and spindle-shaped morphology, (ii) MSCs must express CD73, CD90, CD105, and lack CD34, CD45, CD19, CD14, and HLA-DR, (iii) MSC must have the ability to differentiate to adipocytes, osteoblasts, and chondrocytes [2]. Due to the potential for therapy, MSCs were applied to the clinical trials in many areas, including immune rejection (34.32%), degenerative diseases (18.65%), orthopedics (15.79%), autoimmunity (10.53%), severe inflammation (8.35%), and others (12.36%) [3]. Briefly, MSCs obtain genetic stability, poor immunogenicity, tissue repair property, and immunomodulation ability. However, not all of MSCs have benefits for diseases, there are some unhealthy MSCs or educated-MSCs, especially cancer-associated MSCs (CaMSCs), which may contribute to the progression of diseases. Compared to normal MSCs, the role and function of CaMSCs were studied much less.

The role of normal mesenchymal stem cells and cancer-associated mesenchymal stem cells in cancer development

The functions of normal MSCs in cancer are controversial. In general, most of the BM-MSCs and AT-MSCs obtained tumor-promoting effects, but UCB-MSCs inhibited tumor progression, however, all of those MSCs showed

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Access this article online

Quick Response Code:

Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_138_22

How to cite this article: Wang KH, Ding DC. Role of cancer-associated mesenchymal stem cells in the tumor microenvironment: A review. Tzu Chi Med J 2023;35(1):24-30.

immunosuppressive effects. Tumor-promoting MSCs could enhance tumor growth, angiogenesis, metastasis, cancer stemness, and drug resistance by secreting different cytokines and growth factors [4-7]. CaMSCs obtained the same or similar properties to enhance the development of cancer itself. Besides, MSCs could differentiate into cancer-associated fibroblasts (cancer-associated fibroblasts [CAFs]) to contribute to the tumor microenvironment (TME) favored tumor progression [8]. The sources of CaMSCs may be recruited from bone-marrow or tissue-specific normal MSCs [8,9] and educated by cancer cells. CaMSCs displayed intermediate and slow cell cycle behavior and increased number in the G0-G1 phase compared with BM-MSCs, supporting a role for quiescent CaMSCs in tumor dormancy regulation [10]. In summary, CaMSCs, regardless of their sources, show tumor-promoting effects by regulating cancer cells and the TME as shown in Table 1.

Cancer-associated mesenchymal stem cells in brain tumor

Gliomas CaMSCs increased the proliferation and stemness of glioma stem Cells through the interleukin (IL)-6/gp130/STAT3 pathway [11]. In the GL261 syngeneic glioma mouse model, CaMSCs expressed C-X-C chemokine receptor type 4 (CXCR4) and CXCR6. These CaMSCs were accumulated at a later stage of brain tumor from 2 weeks (0.5 ± 0.1%) after tumor inoculation to 3 weeks (31 ± 3.2%) grown tumors. The CaMSCs, which were identified as CD44, CD9, and CD166 triple-positive populations, were also shown in glioblastoma multiforme (GBM) specimens [12]. The Korean group first identified mesenchymal stem-like cells (MSLCs, CD90+, and CD31-) in glioma specimens [13]. Mesenchymal stem-like cells (MSLCs) promoted the invasion of GBM cells into parenchymal brain tissue through complement component C5a/p38/ZEB1 axis. Intriguingly, the survival time was significantly shorter in the 4-step-MSLCs-isolatable-MSLCs GBM patients than in the nonisolatable-MSLCs patients. The MSLCs isolatable GBM patients also showed higher CD44, YKL40, and C5a expression [14]. However, the specimen amount was not related to MSLC isolation and detection [15]. These results revealed that the CaMSCs from brain tumors may differ from other tissues, but play the same role: promoting cancer development.

Table 1: The roles and signaling pathways of cancer-associated mesenchymal stem cells s in promoting cancer progression

Cancer types	Study subjects/issues	Signaling pathway	*In vivo* experiments
Breast	Proliferation, stemness	EGF/EGFR/Akt	Ca: MSC=2:1
	Chemoresistance	IL-6/STAT3	No *in vivo* experiments
Colon	Proliferatio, migration, invasion, tumorigenesis, metastasis	IL-6/Notch-1/CD44	Ca: MSC=1:1
	Proliferation, migration, invasion, tumorigenesis	miR-30a+miR-222/MIA3	Without coinjection
Colorectal	EMT, migration, stemness, angiogenesis, tumorigenesis	IL-6/JAK2/STAT3	Ca: MSC=1:1
Gastric	Proliferation, migration, tumorigenesis	PDGF-DD	Ca+MSC-CM
	Migration, invasion, tumorigenesis	NF-κB p65	Ca+MSC-CM
	Angiogenesis, tumorigenesis	NF-κB/VEGF	Ca+MSC-CM
	Proliferation, migration, angiogenesis	IL-8	No *in vivo* experiments
	Migration, tumorigenesis	exsosomal miR-221	Ca: MSC=3.3:1
	Migration, EMT, Metastasis	Wnt/β-catenin	Ca+MSC-CM
	Proliferation, migration, Invasion, EMT, stemness, angiogenesis, tumorigenesis	YAP	Ca+MSC-CM
	Proliferation, metastasis, metabolism	G6PD-NF-κB-HGF	Ca+MSC-CM
	Escape from senescence	p53, p21	Ca+MSC-CM
GBM	Invasion	C5a/p38/ZEB1	Ca: MSC=1:1
Glioma	Proliferation, stemness	IL-6/gp130/STAT3	Ca: MSC=1:1
Head and neck	Tumorigenesis	No data	Ca: MSC=1:1
	EMT, metastasis	IL-8/CPNE7/NF-κB	Ca: MSC=1:1
Liver	Proliferation, migration, invasion, tumorigenesis, metastasis	DNM3OS/KDM6B/TIAM1	Without coinjection
	EMT, stemness, tumorigenesis	lncRNA-MUF/ANXA2	Ca: MSC=1:10 to 1:10000
Lung	Migration, invasion, partial EMT, stemness, tumorigenesis, metastasis	No data	Ca: MSC=1:1 Ca: MSC=1:5
Melanoma	Tumorigenesis	NF-κB	Ca: MSC=2.5:1
Osteosarcoma	Stemness	IL-6	No *in vivo* experiments
	Stemness	NF-κB	No *in vivo* experiments
Ovarian	Stemness	BMP2/SMAD	Ca: MSC=1:1
	Stemness and chemoresistance	HH/BMP4	Ca: MSC=1:1
	Stemness, chemoresistance, EMT	PDGF-BB/PDGFR-β	CSC: MSC=1:3
	Migration, invasion, metastasis	EZH2/WT1	Ca: MSC=1:1
Prostate	Migration, invasion, vascular mimicry	TGF-β1	No *in vivo* experiments

EMT: Epithelial mesenchymal transition, GBM: Glioblastoma multiforme, Ca: Cancer cells, MSC: Mesenchymal stem cells, CM: Conditioned medium, IL: Interleukin, miR: MicroRNA, PDGF: Platelet-derived growth factor, lncRNA: Long noncoding RNA, TGF: Transforming growth factor, BMP: Bone morphogenetic proteins, G6PD: Glucose-6-phosphate dehydrogenase, HGF: Hepatic growth factor, NF-κB: Nuclear factor-κB, HH: Hedgehog, BMP: Bone morphogenetic protein

Cancer-associated mesenchymal stem cells in breast cancer

CaMSCs promoted breast cancer cell proliferation and increased mammosphere formation through EGF/EGFR/Akt pathway [16]. Furthermore, CaMSCs promote the proliferation and migration of the MCF-7 cell line *in vitro* [17]. Most important, CaMSCs enhanced chemoresistance by secreting IL-6 and activating the downstream STAT3 signaling pathway [18]. Those *in vitro* and *in vivo* studies suggested that breast CaMSCs promote tumor progression and may result in poor prognosis.

Cancer-associated mesenchymal stem cells in the colon and colorectal cancer

Colon CaMSCs increased tumor progression of colon cancer cells through the IL-6/NOTCH-1/CD44 axis [19]. Besides, the exosomal microRNA (miR)-30a and miR-222 derived from colon CaMSCs promoted proliferation, migration, invasion, and tumorigenesis through downstream target MIA3 [20]. Colorectal CaMSCs promote epithelial-mesenchymal transition (EMT), migration, stemness, angiogenesis, and tumorigenesis through IL-6/JAK2/STAT3 signaling [21]. The CaMSC-conditioned medium (CM) could promote colorectal cancer cells' escape from senescence through p53/p21 pathway [22]. The mechanisms of how colorectal CaMSCs regulate tumor progression are still lacking and need further study.

Cancer-associated mesenchymal stem cells in gastric cancer

GC-MSCs were first isolated from gastric cancer tissues (13 out of 20) in 2009 [23]. GC-MSC conditioned medium (GC-MSCs-CM) promoted gastric cancer cell proliferation, migration, and tumor growth through secreted platelet-derived growth factor (PDGF)-DD [24]. They also enhanced angiogenesis and tumorigenesis by a nuclear factor (NF)-κB and vascular endothelial growth factor (VEGF) and could be inhibited by Curcumin, a bioactive compound [25,26]. GC-MSC-CM treatment enhanced the proliferation, migration, and angiogenesis of gastric cancer cells, which was more potent than adjacent noncancerous tissues (GCN-MSCs) or BM-MSCs. IL-8 secretion is strikingly high in the GC-MSCs-CM and anti-IL-8 antibodies could attenuate the gastric cancer-promoting effects [27]. GC-MSCs-CM also contained YAP and contributed to cancer progression, including proliferation, migration, invasion, EMT, angiogenesis, and tumorigenesis [28]. Resveratrol (RES) pretreated GC-MSCs reduced the production of IL-6, IL-8, MCP-1, and VEGF from CM, resulting in reduced migration, EMT, and metastasis by attenuating Wnt/β-catenin signaling [29]. Other than cytokines and growth factors, GC-MSCs could enhance the migration and tumorigenesis of gastric cancer cells through the exosomal miR-221 [30]. Besides, downregulation of miR-155-5p induced BM-MSC to acquire a GC-MSC-like phenotype and function depending on NF-κB p65 activation. NF-kappa B p65 (NF-κB p65) and inhibitor of NF-kappa B kinase subunit epsilon (IKBKE/IKKε) were identified as targets of miR-155-5p. GC-MSCs enhanced the migration and invasion of cancer cells *in vitro*, and GC-MSCs-CM enhanced tumor growth *in vivo* [31]. Moreover, GC-MSCs highly expressed glucose-6-phosphate dehydrogenase (G6PD) and facilitated the proliferation and metastasis of gastric cancer through the metabolic G6PD-NF-κB-HGF (hepatic growth factor)-HK2 (Hexokinase 2) axis coordinates [32]. In summary, the GC-MSCs were studied more, and not only cytokines and growth factors but miRNAs and exosomal miRNAs from GC-MSCs-CM could promote tumor progression.

Cancer-associated mesenchymal stem cells in head and neck cancer

The frequency of CD90-positive cells, representing CaMSCs, is significantly higher in tumors than in control specimens [33]. Head-and-neck squamous cell carcinoma (HNSCC) could enhance the expression of IL-8 in CaMSCs, on contrary, CaMSCs further promoted tumorigenesis of HNSCC [34]. CaMSCs derived from oral squamous cell carcinoma (OSCC) promoted the EMT and metastasis of OSCC cells by IL-8/CPNE7/NF-κB axis [35]. The studies of CaMSCs in HNSCC are relative few, and detailed mechanisms are needed to further elucidate.

Cancer-associated mesenchymal stem cells in liver cancer

Hepatocellular carcinoma (HCC)-associated MSCs promoted HCC proliferation, migration, invasion, tumorigenesis, and metastasis via a long non-coding (lnc) RNA, DNM3OS, and downstream KDM6B and TIAM1 axis [36] and enhanced EMT, stemness, and liver tumorigenesis through a novel lncRNA, *lncRNA-MUF*, and downstream Annexin A2 and Wnt/β-catenin signaling. Besides, *lncRNA-MUF* targets miR-34a, resulting in the activation of EMT genes [37]. The studies of CaMSCs in HCC are few but novel, suggesting that the mechanisms of how CaMSCs regulate cancer cells are multiple and complex.

Cancer-associated mesenchymal stem cells in lung cancer

Lung CaMSCs were highly expressed α-smooth muscle actin, hypoxic inducing factor-1α, matrix metalloproteinase 11, VEGF, CXCL12, transforming growth factor (TGF)-β1, TGF-βRII, IL6, and tumor necrosis factor (TNF) α, the markers referred to CAFs, suggesting that differentiation of CaMSCs were toward to CAF-related phenotype [38]. Besides, CaMSCs derived from lung cancer enhanced migration, invasion, partial EMT, stemness, tumorigenesis, and metastasis of A549 cells [39]. Primary lung cancer cells secreted C-C motif chemokine ligand 3 (CCL3) and further stimulated IL-6, CCL2, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1 expression in CaMSCs. The coculture of cancer cells and CaMSCs facilitated those

gene expressions and could be disrupted by the lipid-lowering drug simvastatin [40]. These data suggested that the cytokines secreted from CaMSCs play important roles in cancer cells and possibly in immune cells.

Cancer-associated mesenchymal stem cells in melanoma

IL-17 and interferon (IFN)γ could transform BM-MSCs into CaMSCs and further promote tumor progression in B16F0 syngeneic melanoma mouse model. The expression of CCL2, CCL5, CCL7, and CCL20 was increased after the transformation of CaMSCs, resulting in the activation of the NF-κB signaling pathway. These phenomena could be arrested by retinoic acid treatment [41]. The syngeneic melanoma mouse model is beneficial to the studies of TME, especially for immune cells.

Cancer-associated mesenchymal stem cells in osteosarcoma

CaMSCs of osteosarcoma promoted the proliferation, migration, and stemness of osteosarcoma cells via IL-6 [42] and NF-κB signaling pathway [43]. Detailed mechanisms are needed to further elucidate. Exosomes in the osteosarcoma microenvironment are also discussed for their role in tumor growth, metastasis, chemoresistance, therapy, and diagnosis [44]. BM-MSC-derived extracellular vesicles can promote cell migration, proliferation, and invasion of osteosarcoma via autophagy or the Wnt/beta-catenin signaling pathway [45,46]. Osteosarcoma tumor cells can educate CaMSC to promote tumor progression. Tumor secreting TGF-beta affected CaMSC secreting IL-6 to promote tumor progression [47]. Osteosarcoma tumor cells can secret exosomes to resist chemo drugs [48], which are mediated by a number of miRNAs [49]. Conversely, exosomes also can harbor anti-tumor capabilities [50]. The miR150 derived in MSC-exosomes can target IGF2BP1 to reduce cancer cell proliferation and migration [51]. For diagnosis, osteosarcoma patients-derived exosomes-specific repetitive element DNA sequence can be used [52]. In summary, the use of exosomes for the therapy and diagnosis of osteosarcoma still needs further exploration.

Cancer-associated mesenchymal stem cells in ovarian cancer

Ovarian CaMSCs was arisen from the normal stroma of local tissue but not from BM, and they could be further enhanced by hypoxia condition [9]. These CaMSCs highly expressed bone morphogenetic protein (BMP) proteins, especially BMP2, and could enhance the population of cancer stem cells (CSCs) and increase tumorigenesis [53]. Ovarian cancer cells secreted Hedgehog (HH) and further activated the production of BMP4 from CaMSCs, resulting in the increase of CSCs and chemoresistances [54]. CaMSCs cocultured with CSCs could enhance the stemness, chemoresistances, and EMT by PDGF-BB/PDGFR-β signaling [55]. A recent study proved that ovarian cancer cells induced mesenchymal-epithelial-transition (MET) of host stromal cells by epigenetic alterations, such as DNA hypermethylation, chromatin accessibility, and differential histone modifications. These educated stromal cells were transformed to CaMSCs and further enhanced the migration, invasion, and metastasis of ovarian cancer cells, which were mediated by EZH2 and WT1 [56]. These results suggested that ovarian CaMSCs were arisen from local stromal tissues, not from BM, and majorly enhanced chemoresistances of ovarian cancer cells through BMP signaling and epigenetic modifications.

Cancer-associated mesenchymal stem cells in prostate cancer

TGF-β1 is a crucial molecule to attract BM-MSC recruitment both to prostate cancer cells as well as to tumor stroma components. Moreover, cancer cells and CaMSCs secreted TGF-β1 is important to induce MSC transdifferentiation into CAF-like cells. CaMSCs enhanced the invasiveness of prostate cancer and acquired vascular mimicry ability compared to noneducated MSCs. In addition, differing from normal MSC, CAF-like MSC performs vascular mimicry and recruits monocytes, which can be further polarized to M2 macrophages within the PCa environment [8]. The percentage of CaMSCs, identified by CD73, CD90, and CD105 triple-positive cells, in prostate cancer tissues was around 1%, and these primary CaMSCs highly expressed programmed death-ligand 1 (PD-L1) and PD-L2. The CaMSCs could be further licensed by treating IFN-γ and TNF-α, resulting in the increases in PD-L1 and PD-L2 [57]. These data suggested that prostate CaMSCs could differentiate into CAFs and may obtain immunosuppressive effects.

The interaction between cancer-associated mesenchymal stem cells and immune cells

Different sources of CaMSCs all showed immunosuppressive effects, and the targets include macrophages, T-cells, and natural killer (NK) cells. Breast CaMSCs highly expressed FAPα and increased pulmonary metastasis by recruitment of M2 tumor-associated macrophages (TAM), which were identified by F4/80 and CCR2-positive population [58]. GC-MSC-primed M2 macrophages promoted the migration, invasion, and EMT of gastric cancer cells through secretion of IL-6 and IL-8, and the JAK2/STAT3 signaling pathway [59].

Neuroblastoma CaMSCs exhibited greater immunosuppressive capacity on activated T-lymphocytes at a 1:2 (MSC: PBMC [peripheral blood mononuclear cells]) ratio compared with BM-MSCs [60]. CaMSCs derived from HNSCC inhibited CD4+ and CD8+ T-cell proliferation via indoleamine 2,3 dioxygenase activity [33]. GC-MSCs derived IL-8 induced PD-L1 expression in gastric cancer cells via STAT3/mTOR-c-Myc signal axis, resulting in resistance to CD8+ T cells cytotoxicity [61]. Increased PD-L1 could further enhance CSC properties and tumorigenesis by interacting with the CCCTC-binding factor [62]. CD4+ T cell primed GC-MSCs facilitated the tumor growth of gastric cancer cells through mTOR signaling [63]. IL-15 derived from GC-MSCs enhanced stemness, EMT, and migration of gastric cancer cells

as well as increased regulatory T-cells (Treg) ratio through STAT3 and STAT5, respectively [63].

PBMCs pretreated with GC-MSCs-CM significantly enhanced the migration, EMT, and liver metastases of gastric cancer. The proportion of Treg cells was increased and the T-helper (Th) 17 cells were reduced in PBMCs pretreated with GC-MSCs-CM, resulting in the immunosuppressive TME [64]. CaMSCs coculture with cervical cancer cells induced CD73 expression and adenosine production in an MSC ratio-dependent manner, and could be reversed by anti-hTGF-β1 neutralizing antibodies [65]. Adenosine could suppress the proliferation and activation of CD8+ T cells [66].

Ovarian CaMSCs are inversely correlated with the intratumoral CD8+ T cells but positively correlated with TAMs, resulting in decreases in the response to anti-PD-L1 immune checkpoint inhibitor treatment. Furthermore, these immunosuppressive immune cells expressed high levels of transforming growth factor β-induced protein, which suppresses NK cell activity and HH inhibitor therapy could reverse CaMSC effects [67].

In a B16F10 syngeneic melanoma mice model, tumor conditioning licenses MSCs inhibited T-cell proliferation by blocking cysteine export from dendritic cells through IL-10-STAT3 signaling [68], which could be blocked by nontoxic neem leaf glycoprotein [69]. GC-MSCs inhibited the degranulation capacity, perforin production, and cytotoxicity of NK cells by upregulating the expression of fructose-bisphosphatase 1 [70]. Lung CaMSCs inhibited the cytotoxicity of NK cells by expression of IL6 and prostaglandin E2 [71]. In general, CaMSCs enhanced M2 macrophages and Treg and reduced CD4+, CD8+ T cells, and NK cells, resulting in an immunosuppressive TME, thus promoting carcinogenesis and inhibiting the effects of immunotherapy [Table 2].

Perspective

CaMSCs enhance tumor progression through the same signaling, such as IL-6 and NF-κB, as BM-MSCs or other sources of local tissues. Besides, there are more novel mechanisms, such as lncRNAs and miRNAs that were discovered and may have stronger effects on cancer cells as well as immune cells. However, the mechanisms are relatively less known, especially in endometrial cancer, pancreatic cancer, renal cell carcinoma, and other cancers which were not mentioned in this review. CaMSCs were shown in the specimens with low proportion and maintained high similarity with normal MSCs; thus, it is important for potential therapies to selectively target CaMSCs or CaMSC-dependent signaling pathways. Furthermore, there are some MSCs, such as UCB-MSCs, function as anti-tumor progression, which may generate the issues that how to transform CaMSCs into anti-tumor MSCs by modifications.

Table 2: The immunosuppressive effects of cancer mesenchymal stem cells

Cancer types	Target immune cells	Signaling pathway
Breast	M2 macrophages	No data
Cervical	CD8+ T cells	Adenosine
Gastric	M2 macrophages	IL-6/IL-8/JAK2/STAT3
	CD8+ T cells	STAT3/mTOR-c-Myc
	Regulatory T cells	IL-15/STAT5
	Treg and Th17 cells	No data
	NK cells	FBP1
Head and neck	CD4+ and CD8+ T cells	IDO
Lung	NK cells	IL6 and PGE2
Ovarian	M2 macrophages, CD8+ T cells	HH
Melanoma	T cell proliferation	IL-10-STAT3

NK: Natural killer cells, IL: Interleukin, FBP1: Fructose-bisphosphatase 1, IDO: Indoleamine 2,3-dioxygenase, PGE2: Prostaglandin E2, HH: Hedgehog

Conclusion

From these data of CaMSCs studies, the primary CaMSCs need to examine before senescence (usually before passage 8 [P8]). In most of the studies, the authors finished the experiments around P5 to P7. CaMSCs were shown in the cancer specimens with a relatively low percentage, which is around 1% to 5% defined by CD73, CD90, and CD105 triple-positive cells. However, the *in vivo* studies may take them as CAFs and mixed with cancer cells at high ratios, such as 1:1 or more [Table 1]. On the contrary, in most studies of GC-MSCs, CaMSCs-CM had shown significant results, representing that CaMSCs could regulate cancer cells through direct interaction or paracrine effects.

CaMSCs play a pivotal role in TME, including differentiating into CAFs and affecting cancer cells as well as immune cells through various signaling pathways. Besides, cancer cells and immune cells may feedback regulation of CaMSCs to facilitate tumor progression. CaMSCs could be a direct therapeutic target or by modification as drug-delivery vehicles [72]. In conclusion, further investigations of CaMSCs are needed to accumulate to fully understand the mechanisms of CaMSCs regulating TME for reaching the purpose of therapy in various cancers.

Financial support and sponsorship

This work was supported by Hualien Tzu Chi Hospital (TCRD-111-80) and the Buddhist Tzu Chi Medical Foundation (TCMF-CP 111-05).

Conflict of interest

Dr. Dah-Ching Ding, an editorial board member at *Tzu Chi Medical Journal*, had no role in the peer review process of or decision to publish this article. The other author declared no conflicts of interest in writing this paper.

References

1. Casey SC, Amedei A, Aquilano K, Azmi AS, Benencia F, Bhakta D, et al. Cancer prevention and therapy through the modulation of the tumor microenvironment. Semin Cancer Biol 2015;35 (Suppl):S199-223.
2. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006;8:315-7.
3. Naji A, Eitoku M, Favier B, Deschaseaux F, Rouas-Freiss N, Suganuma N. Biological functions of mesenchymal stem cells and

clinical implications. Cell Mol Life Sci 2019;76:3323-48.
4. Galland S, Stamenkovic I. Mesenchymal stromal cells in cancer: A review of their immunomodulatory functions and dual effects on tumor progression. J Pathol 2020;250:555-72.
5. Lim SK, Khoo BY. An overview of mesenchymal stem cells and their potential therapeutic benefits in cancer therapy. Oncol Lett 2021;22:785.
6. Hass R. Role of MSC in the tumor microenvironment. Cancers (Basel) 2020;12:2107.
7. Ma Y, Hao X, Zhang S, Zhang J. The *in vitro* and *in vivo* effects of human umbilical cord mesenchymal stem cells on the growth of breast cancer cells. Breast Cancer Res Treat 2012;133:473-85.
8. Barcellos-de-Souza P, Comito G, Pons-Segura C, Taddei ML, Gori V, Becherucci V, et al. Mesenchymal stem cells are recruited and activated into carcinoma-associated fibroblasts by prostate cancer microenvironment-derived TGF-β1. Stem Cells 2016;34:2536-47.
9. Coffman LG, Pearson AT, Frisbie LG, Freeman Z, Christie E, Bowtell DD, et al. Ovarian carcinoma-associated mesenchymal stem cells arise from tissue-specific normal stroma. Stem Cells 2019;37:257-69.
10. Pelizzo G, Riva F, Croce S, Avanzini MA, Acquafredda G, de Silvestri A, et al. Proliferation pattern of pediatric tumor-derived mesenchymal stromal cells and role in cancer dormancy: A perspective of study for surgical strategy. Front Pediatr 2021;9:766610.
11. Hossain A, Gumin J, Gao F, Figueroa J, Shinojima N, Takezaki T, et al. Mesenchymal stem cells isolated from human gliomas increase proliferation and maintain stemness of glioma stem cells through the IL-6/gp130/STAT3 pathway. Stem Cells 2015;33:2400-15.
12. Behnan J, Isakson P, Joel M, Cilio C, Langmoen IA, Vik-Mo EO, et al. Recruited brain tumor-derived mesenchymal stem cells contribute to brain tumor progression. Stem Cells 2014;32:1110-23.
13. Kim YG, Jeon S, Sin GY, Shim JK, Kim BK, Shin HJ, et al. Existence of glioma stroma mesenchymal stemlike cells in Korean glioma specimens. Childs Nerv Syst 2013;29:549-63.
14. Lim EJ, Kim S, Oh Y, Suh Y, Kaushik N, Lee JH, et al. Crosstalk between GBM cells and mesenchymal stemlike cells promotes the invasiveness of GBM through the C5a/p38/ZEB1 axis. Neuro Oncol 2020;22:1452-62.
15. Kong SH, Yoo J, Lee D, Moon S, Sung KS, Park SH, et al. Influence of the amount of fresh specimen on the isolation of tumor mesenchymal stem-like cells from high-grade glioma. Yonsei Med J 2021;62:936-42.
16. Yan XL, Fu CJ, Chen L, Qin JH, Zeng Q, Yuan HF, et al. Mesenchymal stem cells from primary breast cancer tissue promote cancer proliferation and enhance mammosphere formation partially via EGF/EGFR/Akt pathway. Breast Cancer Res Treat 2012;132:153-64.
17. Zhang C, Zhai W, Xie Y, Chen Q, Zhu W, Sun X. Mesenchymal stem cells derived from breast cancer tissue promote the proliferation and migration of the MCF-7 cell line *in vitro*. Oncol Lett 2013;6:1577-82.
18. Xu H, Zhou Y, Li W, Zhang B, Zhang H, Zhao S, et al. Tumor-derived mesenchymal-stem-cell-secreted IL-6 enhances resistance to cisplatin via the STAT3 pathway in breast cancer. Oncol Lett 2018;15:9142-50.
19. Lin JT, Wang JY, Chen MK, Chen HC, Chang TH, Su BW, et al. Colon cancer mesenchymal stem cells modulate the tumorigenicity of colon cancer through interleukin 6. Exp Cell Res 2013;319:2216-29.
20. Du Q, Ye X, Lu SR, Li H, Liu HY, Zhai Q, et al. Exosomal miR-30a and miR-222 derived from colon cancer mesenchymal stem cells promote the tumorigenicity of colon cancer through targeting MIA3. J Gastrointest Oncol 2021;12:52-68.
21. Zhang X, Hu F, Li G, Li G, Yang X, Liu L, et al. Human colorectal cancer-derived mesenchymal stem cells promote colorectal cancer progression through IL-6/JAK2/STAT3 signaling. Cell Death Dis 2018;9:25.
22. Li G, Zhang R, Zhang X, Shao S, Hu F, Feng Y. Human colorectal cancer derived-MSCs promote tumor cells escape from senescence via P53/P21 pathway. Clin Transl Oncol 2020;22:503-11.
23. Cao H, Xu W, Qian H, Zhu W, Yan Y, Zhou H, et al. Mesenchymal stem cell-like cells derived from human gastric cancer tissues. Cancer Lett 2009;274:61-71.
24. Huang F, Wang M, Yang T, Cai J, Zhang Q, Sun Z, et al. Gastric cancer-derived MSC-secreted PDGF-DD promotes gastric cancer progression. J Cancer Res Clin Oncol 2014;140:1835-48.
25. Huang F, Yao Y, Wu J, Liu Q, Zhang J, Pu X, et al. Curcumin inhibits gastric cancer-derived mesenchymal stem cells mediated angiogenesis by regulating NF-κB/VEGF signaling. Am J Transl Res 2017;9:5538-47.
26. Naji M, Soroudi S, Akaberi M, Sahebkar A, Emami SA. Updated review on the role of curcumin in gastrointestinal cancers. Adv Exp Med Biol 2021;1308:55-89.
27. Li W, Zhou Y, Yang J, Zhang X, Zhang H, Zhang T, et al. Gastric cancer-derived mesenchymal stem cells prompt gastric cancer progression through secretion of interleukin-8. J Exp Clin Cancer Res 2015;34:52.
28. Pan Z, Tian Y, Zhang B, Zhang X, Shi H, Liang Z, et al. YAP signaling in gastric cancer-derived mesenchymal stem cells is critical for its promoting role in cancer progression. Int J Oncol 2017;51:1055-66.
29. Yin L, Zhang R, Hu Y, Li W, Wang M, Liang Z, et al. Gastric-cancer-derived mesenchymal stem cells: A promising target for resveratrol in the suppression of gastric cancer metastasis. Hum Cell 2020;33:652-62.
30. Wang M, Zhao C, Shi H, Zhang B, Zhang L, Zhang X, et al. Deregulated microRNAs in gastric cancer tissue-derived mesenchymal stem cells: Novel biomarkers and a mechanism for gastric cancer. Br J Cancer 2014;110:1199-210.
31. Zhu M, Wang M, Yang F, Tian Y, Cai J, Yang H, et al. miR-155-5p inhibition promotes the transition of bone marrow mesenchymal stem cells to gastric cancer tissue derived MSC-like cells via NF-κB p65 activation. Oncotarget 2016;7:16567-80.
32. Chen B, Cai T, Huang C, Zang X, Sun L, Guo S, et al. G6PD-NF-κB-HGF signal in gastric cancer-associated mesenchymal stem cells promotes the proliferation and metastasis of gastric cancer cells by upregulating the expression of HK2. Front Oncol 2021;11:648706.
33. Liotta F, Querci V, Mannelli G, Santarlasci V, Maggi L, Capone M, et al. Mesenchymal stem cells are enriched in head neck squamous cell carcinoma, correlates with tumour size and inhibit T-cell proliferation. Br J Cancer 2015;112:745-54.
34. Kansy BA, Dißmann PA, Hemeda H, Bruderek K, Westerkamp AM, Jagalski V, et al. The bidirectional tumor-mesenchymal stromal cell interaction promotes the progression of head and neck cancer. Stem Cell Res Ther 2014;5:95.
35. Ji X, Sun T, Xie S, Qian H, Song L, Wang L, et al. Upregulation of CPNE7 in mesenchymal stromal cells promotes oral squamous cell carcinoma metastasis through the NF-κB pathway. Cell Death Discov 2021;7:294.
36. Wang W, Wang Q, Huang DB, Sun QK, Wu SS, Zhao YJ, et al. Tumor-associated mesenchymal stem cells promote hepatocellular carcinoma metastasis via a DNM3OS/KDM6B/TIAM1 axis. Cancer Lett 2021;503:19-31.
37. Yan X, Zhang D, Wu W, Wu S, Qian J, Hao Y, et al. Mesenchymal stem cells promote hepatocarcinogenesis via lncRNA-MUF interaction with ANXA2 and miR-34a. Cancer Res 2017;77:6704-16.
38. Arena S, Salati M, Sorgentoni G, Barbisan F, Orciani M. Characterization of tumor-derived mesenchymal stem cells potentially differentiating into cancer-associated fibroblasts in lung cancer. Clin Transl Oncol 2018;20:1582-91.
39. Yan C, Chang J, Song X, Qi Y, Ji Z, Liu T, et al. Lung cancer-associated mesenchymal stem cells promote tumor metastasis and tumorigenesis by induction of epithelial-mesenchymal transition and stem-like reprogram. Aging (Albany NY) 2021;13:9780-800.
40. Galland S, Martin P, Fregni G, Letovanec I, Stamenkovic I. Attenuation of the pro-inflammatory signature of lung cancer-derived mesenchymal stromal cells by statins. Cancer Lett 2020;484:50-64.

41. Lou Q, Zhao M, Xu Q, Xie S, Liang Y, Chen J, et al. Retinoic acid inhibits tumor-associated mesenchymal stromal cell transformation in melanoma. Front Cell Dev Biol 2021;9:658757.
42. Cortini M, Massa A, Avnet S, Bonuccelli G, Baldini N. Tumor-activated mesenchymal stromal cells promote osteosarcoma stemness and migratory potential via IL-6 secretion. PLoS One 2016;11:e0166500.
43. Avnet S, Di Pompo G, Chano T, Errani C, Ibrahim-Hashim A, Gillies RJ, et al. Cancer-associated mesenchymal stroma fosters the stemness of osteosarcoma cells in response to intratumoral acidosis via NF-κB activation. Int J Cancer 2017;140:1331-45.
44. De Martino V, Rossi M, Battafarano G, Pepe J, Minisola S, Del Fattore A. Extracellular vesicles in osteosarcoma: Antagonists or therapeutic agents? Int J Mol Sci 2021;22:12586.
45. Huang Y, Liu W, He B, Wang L, Zhang F, Shu H, et al. Exosomes derived from bone marrow mesenchymal stem cells promote osteosarcoma development by activating oncogenic autophagy. J Bone Oncol 2020;21:100280.
46. Li F, Chen X, Shang C, Ying Q, Zhou X, Zhu R, et al. Bone marrow mesenchymal stem cells-derived extracellular vesicles promote proliferation, invasion and migration of osteosarcoma cells via the lncRNA MALAT1/miR-143/NRSN2/Wnt/β-catenin axis. Onco Targets Ther 2021;14:737-49.
47. Baglio SR, Lagerweij T, Pérez-Lanzón M, Ho XD, Léveillé N, Melo SA, et al. Blocking tumor-educated MSC paracrine activity halts osteosarcoma progression. Clin Cancer Res 2017;23:3721-33.
48. Torreggiani E, Roncuzzi L, Perut F, Zini N, Baldini N. Multimodal transfer of MDR by exosomes in human osteosarcoma. Int J Oncol 2016;49:189-96.
49. Xu JF, Wang YP, Zhang SJ, Chen Y, Gu HF, Dou XF, et al. Exosomes containing differential expression of microRNA and mRNA in osteosarcoma that can predict response to chemotherapy. Oncotarget 2017;8:75968-78.
50. Lee KM, An JH, Yang SJ, Park SM, Lee JH, Chae HK, et al. Influence of canine macrophage-derived extracellular vesicles on apoptosis in canine melanoma and osteosarcoma cell lines. Anticancer Res 2021;41:719-30.
51. Xu Z, Zhou X, Wu J, Cui X, Wang M, Wang X, et al. Mesenchymal stem cell-derived exosomes carrying microRNA-150 suppresses the proliferation and migration of osteosarcoma cells via targeting IGF2BP1. Transl Cancer Res 2020;9:5323-35.
52. Cambier L, Stachelek K, Triska M, Jubran R, Huang M, Li W, et al. Extracellular vesicle-associated repetitive element DNAs as candidate osteosarcoma biomarkers. Sci Rep 2021;11:94.
53. McLean K, Gong Y, Choi Y, Deng N, Yang K, Bai S, et al. Human ovarian carcinoma-associated mesenchymal stem cells regulate cancer stem cells and tumorigenesis via altered BMP production. J Clin Invest 2011;121:3206-19.
54. Coffman LG, Choi YJ, McLean K, Allen BL, di Magliano MP, Buckanovich RJ. Human carcinoma-associated mesenchymal stem cells promote ovarian cancer chemotherapy resistance via a BMP4/HH signaling loop. Oncotarget 2016;7:6916-32.
55. Raghavan S, Snyder CS, Wang A, McLean K, Zamarin D, Buckanovich RJ, et al. Carcinoma-associated mesenchymal stem cells promote chemoresistance in ovarian cancer stem cells via PDGF signaling. Cancers (Basel) 2020;12:2063.
56. Fan H, Atiya HI, Wang Y, Pisanic TR, Wang TH, Shih IM, et al. Epigenomic reprogramming toward mesenchymal-epithelial transition in ovarian-cancer-associated mesenchymal stem cells drives metastasis. Cell Rep 2020;33:108473.
57. Krueger TE, Thorek DL, Meeker AK, Isaacs JT, Brennen WN. Tumor-infiltrating mesenchymal stem cells: Drivers of the immunosuppressive tumor microenvironment in prostate cancer? Prostate 2019;79:320-30.
58. Li X, Chen M, Lu W, Tang J, Deng L, Wen Q, et al. Targeting FAPα-expressing tumor-associated mesenchymal stromal cells inhibits triple-negative breast cancer pulmonary metastasis. Cancer Lett 2021;503:32-42.
59. Li W, Zhang X, Wu F, Zhou Y, Bao Z, Li H, et al. Gastric cancer-derived mesenchymal stromal cells trigger M2 macrophage polarization that promotes metastasis and EMT in gastric cancer. Cell Death Dis 2019;10:918.
60. Pelizzo G, Veschi V, Mantelli M, Croce S, Di Benedetto V, D'Angelo P, et al. Microenvironment in neuroblastoma: Isolation and characterization of tumor-derived mesenchymal stromal cells. BMC Cancer 2018;18:1176.
61. Sun L, Wang Q, Chen B, Zhao Y, Shen B, Wang H, et al. Gastric cancer mesenchymal stem cells derived IL-8 induces PD-L1 expression in gastric cancer cells via STAT3/mTOR-c-Myc signal axis. Cell Death Dis 2018;9:928.
62. Sun L, Huang C, Zhu M, Guo S, Gao Q, Wang Q, et al. Gastric cancer mesenchymal stem cells regulate PD-L1-CTCF enhancing cancer stem cell-like properties and tumorigenesis. Theranostics 2020;10:11950-62.
63. Sun L, Wang Q, Chen B, Zhao Y, Shen B, Wang X, et al. Human gastric cancer mesenchymal stem cell-derived IL15 contributes to tumor cell epithelial-mesenchymal transition via upregulation tregs ratio and PD-1 expression in $CD4^+$T cell. Stem Cells Dev 2018;27:1203-14.
64. Wang M, Chen B, Sun XX, Zhao XD, Zhao YY, Sun L, et al. Gastric cancer tissue-derived mesenchymal stem cells impact peripheral blood mononuclear cells via disruption of Treg/Th17 balance to promote gastric cancer progression. Exp Cell Res 2017;361:19-29.
65. Ávila-Ibarra LR, Mora-García ML, García-Rocha R, Hernández-Montes J, Weiss-Steider B, Montesinos JJ, et al. Mesenchymal stromal cells derived from normal cervix and cervical cancer tumors increase CD73 expression in cervical cancer cells through TGF-β1 production. Stem Cells Dev 2019;28:477-88.
66. de Lourdes Mora-García M, García-Rocha R, Morales-Ramírez O, Montesinos JJ, Weiss-Steider B, Hernández-Montes J, et al. Mesenchymal stromal cells derived from cervical cancer produce high amounts of adenosine to suppress cytotoxic T lymphocyte functions. J Transl Med 2016;14:302.
67. Cascio S, Chandler C, Zhang L, Sinno S, Gao B, Onkar S, et al. Cancer-associated MSC drive tumor immune exclusion and resistance to immunotherapy, which can be overcome by Hedgehog inhibition. Sci Adv 2021;7:eabi5790.
68. Ghosh T, Barik S, Bhuniya A, Dhar J, Dasgupta S, Ghosh S, et al. Tumor-associated mesenchymal stem cells inhibit naïve T cell expansion by blocking cysteine export from dendritic cells. Int J Cancer 2016;139:2068-81.
69. Ghosh T, Nandi P, Ganguly N, Guha I, Bhuniya A, Ghosh S, et al. NLGP counterbalances the immunosuppressive effect of tumor-associated mesenchymal stem cells to restore effector T cell functions. Stem Cell Res Ther 2019;10:296.
70. Han F, Guo S, Huang C, Cui L, Zhao Y, Ma J, et al. Gastric cancer mesenchymal stem cells inhibit natural killer cell function by up-regulating FBP1. Cent Eur J Immunol 2021;46:427-37.
71. Galland S, Vuille J, Martin P, Letovanec I, Caignard A, Fregni G, et al. Tumor-derived mesenchymal stem cells use distinct mechanisms to block the activity of natural killer cell subsets. Cell Rep 2017;20:2891-905.
72. Vicinanza C, Lombardi E, Da Ros F, Marangon M, Durante C, Mazzucato M, et al. Modified mesenchymal stem cells in cancer therapy: A smart weapon requiring upgrades for wider clinical applications. World J Stem Cells 2022;14:54-75.