ISSN 1978-2071 (Print); ISSN 2580-5967 (Online)
Jurnal Ilmiah Kedokteran Wijaya Kusuma 9(1): 97-111, Maret 2020

Meta-Analisis Efek Sel Punca Mesenkimal pada Model Tumor Hewan Coba

Pratika Yuhyi Hernanda
Department of Biomedicine, Medical Faculty, Wijaya Kusuma University Surabaya
e-mail: yuhyi_h@yahoo.com

Abstrak

Beberapa penelitian melaporkan bahwa Sel Punca Mesenkimal (SPM) dapat memicu ataupun menghambat pertumbuhan tumor. Oleh karena itu kami melakukan tinjauan sistematis dan meta-analisis studi eksperimental yang mengevaluasi efek SPM pada tumor. Metode: Kami mengumpulkan studi yang relevan dengan mencari dari ProQuest, PubMed Publisher, dan GoogleScholar. Sebuah meta-analisis dilakukan untuk ukuran hasil: volume tumor dan berat tumor. Pencarian menghasilkan 440 referensi, namun hanya 22 di antaranya yang dapat dimasukkan dalam meta-analisis. Dari 22 eksperimen ini, 16 eksperimen (72,7%) menunjukkan penurunan pertumbuhan tumor yang signifikan dan 6 eksperimen (27,3%) menunjukkan peningkatan pertumbuhan tumor yang signifikan. SPM yang direkayasa secara genetik dan SPM yang diinjeksikan pada fase akhir memiliki kontribusi yang signifikan terhadap efek penghambatan tumor. Meta-analisis menunjukkan bahwa tidak ada efek yang signifikan dari terapi SPM terhadap volume hewan tumor (SMD-0,23 [-0,55, 0,09]; n = 15), dan terhadap berat hewan tumor (SMD -0,19 [-0,77] , 0,39]; n = 7). Kesimpulan: Efek SPM pada model tumor hewan coba tampaknya relatif tergantung terhadap beberapa faktor yang menyertai kondisi eksperimennya.

Kata Kunci: sel punca mesenkimal, model tumor hewan coba

A Meta-Analysis of the Ultimate Effect of Mesenchymal Stem/ Stromal Cell in Tumor Animal Models

Abstract

Several studies have reported the Mesenchymal Stem Cell (MSC) triggered and inhibited tumor growth. We therefore performed a systematic review and meta-analysis of experimental studies evaluating the effects of MSC on tumors. Method: We collected the relevant studies by searching ProQuest, PubMed Publisher, and GoogleScholar. A meta-analysis was performed for the outcome measure: tumor volume and tumor weight. The search resulted in 440 references, of which 22 could be included in the meta-analysis. Of these 22 experiments, 16 articles (72,7%) showed a significant decrease of tumor growth and 6 articles (27,3%) experiments showed a significant increase of tumor growth. The engineered MSC and the late phase of MSC injection have a significant contribution to tumor inhibition effect. The meta-analysis showed that there are no significant effect of mesenchymal stem cell therapy to the tumor animal volume (SMD-0.23[-0.55, 0.09]; n=15), and to the tumor animal weight (SMD -0.19 [-0.77,0.39]; n=7). Conclusion: MSC appears to have a relative dependent effect in animal models.

***Keywords**: mesenchymal stem cell, tumor animal model*

INTRODUCTION

Study on MSC has been widely published which suggesting that the reciprocal relationship of stromal tumors will affect the growth and spread of cancer cells (Hanahan and Weinberg, 2011). Evidence showed MSC accumulation on tumor microenvironment both in primary cancers (Hernanda *et al,* 2013b, Huang *et al,* 2014b) and metastases (Hernanda *et al,* 2013a, Li *et al,* 2014, Song *et al,* 2014) has also been widely reported. Furthermore, several studies reported MSC effects triggered tumor growth (Karnoub *et al,* 2007, Zhang *et al,* 2013, Beckermann *et al* 2008), and several other studies reported evidence of anti-tumor role in MSC (Li *et al,* 2010b, Ryu *et al,* 2014, Zhao *et al,* 2012, Takahara *et al,* 2014). Although the infiltration of mesenchymal stem (stromal) cells (MSCs) into different tumors is widely recognized in animal models, the question whether these MSCs have a positive or negative effect on disease progression remains unanswered. This is reflected in the results obtained in experimental tumor models which show that depending on the exact experimental conditions MSCs can either exert tumor promoting effects and/or enhance metastasis but can also limit Hepatocellular Carcinoma (HCC) growth.

METHODS

We collected the relevant studies by searching ProQuest, PubMed Publisher, and GoogleScholar. Studies were included according to the following inclusion criteria: Mesenchymal Stem/Stromal Cell, tumor, and xenograft /animal study. The search resulted in 440 references. The study characteristics of the included studies varied considerably. The meta analysis was done using software Review Manager (RevMan) software Version 5.3.

LITERATURE SEARCH

A systematic search (conducted on March 2019), without any restrictions on publication data or language) was conducted in ProQuest. Additional references were retrieved from Google Scholar, and unindexed references from PubMed. The search strategy consisted of two main components: mesenchymal stem cell and tumor, and results were limited to animal studies.

STUDY SELECTION AND INCLUSION CRITERIA

The selection procedure was performed by the author. The exclusion criteria for the title and abstract screening phase include: 1). not primary study; 2). not animal study; 3). not disease of interest (tumor/ cancer), 4). not intervention of interest

(mesenchymal stem cell). The following additional criteria were used for full-text screening: 1). full-text not available; 2). duplication; 3). conference abstracts.

STUDY CHARACTERISTICS AND DATA EXTRACTION

Data was extracted from the full-text papers of the studies. The following items were extracted: author, year, type of tumor, species/strain, source of MSC, MSC intervention, timing or phase of MSC administration, and outcome measures (Table 1). The outcome measure were tumor weight or volume. Mean value, standard deviation (SD) and the number of animals per group were extracted. If relevant data were not available in the text but only presented in graphic form, obtaining the data by measuring the graphs using desktop ruler.

DATA SYNTHESIS AND STATISTICAL ANALYSIS

For the outcome measures, the standardized mean difference (SMD) was used as the effect measure. I2 was used as a measure of heterogeneity. Forest Plots were established with assistance of RevMan5.3 (Cochrane Library) software. Visual inspection of funnel plots was used to detect publication bias.

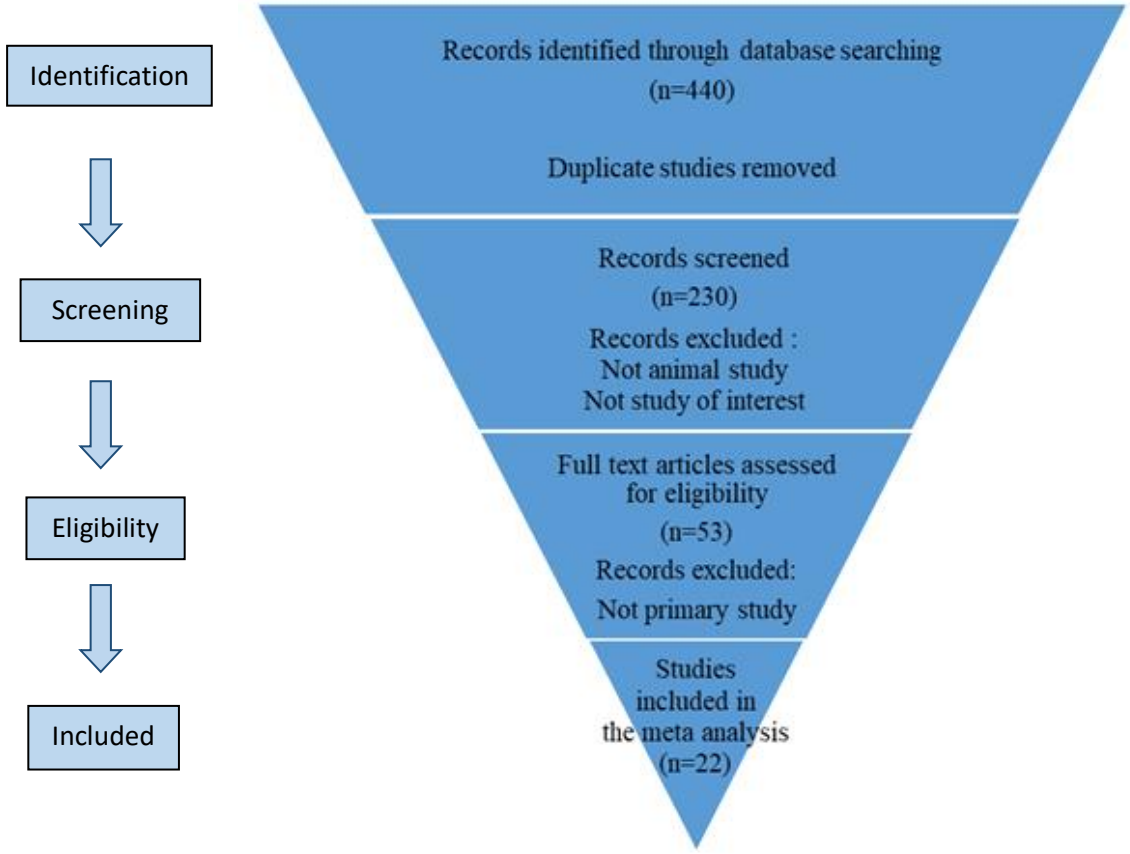

Figure 1. Flow diagram showing literature search and selection results.

RESULTS

The comprehensive search strategy on the effects of MSC in tumor animal models resulted in 440 records. After duplicates were removed, 230 studies were left. Duplicates were there because of the input keywords. After title and abstract screening, 53 studies were screened for full text. Ultimately, 22 studies were included in our analysis.

From the descriptive analysis, it was shown 6 articles (27.3%) reported MSC promotes tumor growth and 16 articles (72.7%) reported MSC inhibits tumor growth. Most of them (18 articles, 63.6%) injected at a late phase after the tumor were inoculated and developed. The type of tumor animal model that author used mostly was hepatic cancer (26.1%) (Xie *et al,* 2013, Cavallari *et al,* 2013, Hernanda *et al,* 2013c, Li *et al,* 2010a, Li *et al,* 2013b, Liu *et al,* 2013, Qiao *et al,* 2008, Yan *et al,* 2013a). Apparently, all the analyzed articles that used engineered MSC or injected at a late phase had a tumor inhibition final effect (p value <0.05), Figure 2)

Table 1. Characteristics of the included MSC tumor animal studies.

No	Author	Type of tumor	Source of MSC	MSC Intervention	Animal	MSC's Phase	Final Effect
1	Ahn *et al*	Melanoma	AT-MSC	IFN-b	BALB/c nude mice	late - it	tumor inhibition
2	Balyasnikova *et al*	Glioma	AT-MSC	EGFRvIII	athymic nu/nu mice	early-it	tumor inhibition
3	Bianchi *et al*	Neuroblastoma	BM-MSC	no	Athymic nude mice	late -iv	tumor inhibition
4	Xie *et al*	HCC	BM-MSC	IFN-b	NOD/SCID mice	late - iv	tumor inhibition
5	Cavallary *et al*	Hepatoma	T-MSC	Sh-Lefty A	SCID mice	late - it	tumor inhibition
6	Cousin *et al*	Pancreatic ca	AT-MSC	no	athymic mice	late - it	tumor inhibition
7	de Melo *et al*	Glioblastoma	AT-MSC	no	nude mice	late - it	tumor inhibition
8	Du *et al*	Renal ca	AT-MSC	no	BALB/c nu/nu mice	early -sc	tumor promotion
9	Galie *et al*	Breast ca	Mu-MSC	no	FVB mice	early- sc	tumor promotion
10	Gao P *et al*	Renal ca	BM-MSC	IL-12	Athymic nude mice	late - iv	tumor inhibition
11	Gao Y *et al*	HCC	BM-MSC	PEDF	nude mice	late - iv	tumor inhibition
12	Hernanda *et al*	HCC	T-MSC	no	NOD/SCID mice	early- sc	tumor promotion
13	Huang F *et al*	Gastric cancer	T-MSC	no	BALB/c nu/nu mice	early- sc	tumor promotion
14	Kang *et al*	Breast cancer	AF-MSC	AF2.CD-TK	BALB/c nude mice	late- it	tumor inhibition
15	Li T *et al*	HCC	AT-MSC	no	BALB/c nude mice	late - iv	tumor inhibition
16	Li L *et al*	Lung ca	AF-MSC	CXCR4	BALB/c nude mice	late - it	tumor inhibition
17	Li GC *et al*	HCC	BM-MSC	no	nude mice	late -iv	tumor inhibition
18	Ma *et al*	Breast ca	UC-MSC	no	SCID mice	late - it	tumor inhibition
19	Pessina *et al*	Prostate ca	AT-MSC	Paclitaxel	NOD/SCID mice	early -sc	tumor inhibition
20	Rhodes *et al*	Breast ca	BM-MSC	no	SCID mice	early- sc	tumor promotion
21	Secchiero *et al*	NH Lymphoma	BM-MSC	no	SCID mice	late - ip	tumor inhibition
22	Spaeth *et al*	Ovarian ca	AT-MSC	no	SCID mice	early- sc	tumor promotion

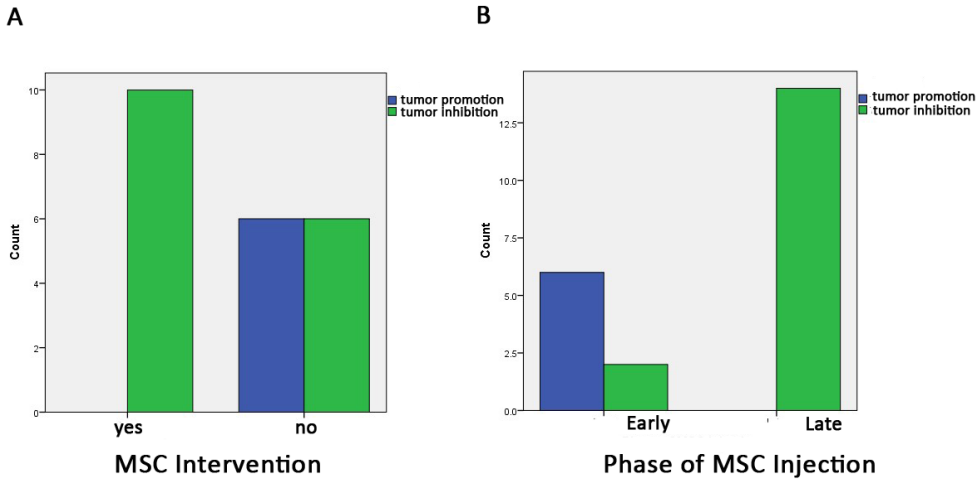

Figure 2. A) Diagram of MSC intervention affecting the final effect of MSC in the tumor animal model with fisher exact test p-value of 0.015. B) Late phase of MSC injection affecting the final effect of MSC and gave the tumor inhibition effect with p value of 0.000

Effect of MSC on tumor weight in tumor animal model

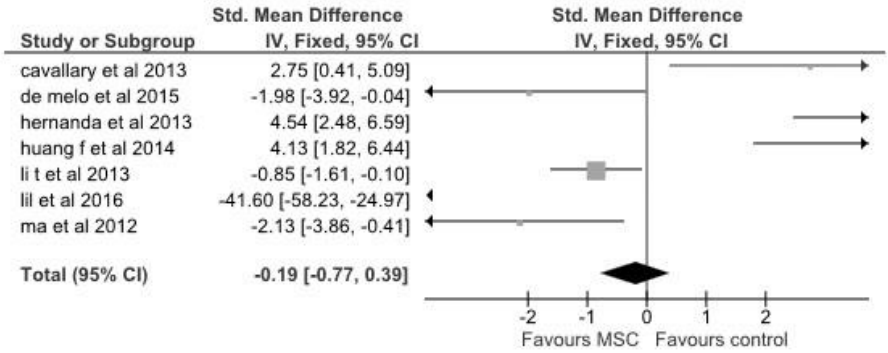

Figure 3. Effect of MSC on tumor weight in tumor animal model.

The effects of MSC on the tumor weight in animal models was evaluated. The evaluation was done comparing the control group and MSC normal group (without MSC intervention). Three studies showed an increase of tumor weight (Cavallari *et al,* 2013, Hernanda *et al,* 2013c, Huang *et al,* 2014a); whereas the others showed a decrease (de Melo *et al,* 2015, Li *et al,* 2013b, Li *et al,* 2016, Ma *et al,* 2012). However, the meta-analysis didn't show a significant effect of MSC on the tumor weight in comparison with control group (SMD -0.19 [-0.77,0.39]; n=7) (Fig 3). The heterogeneity was high (I2 =92%) and the overall Z test was 0.63 (P=0.53).

Effect of MSC on tumor volume in tumor animal model

In addition to the analysis of the effect on tumor weight, we also did

analysis on tumor volume in fifteen animal experiments. Of these experiments, six showed an increase of tumor volume (Balyasnikova *et al,* 2010, Du *et al,* 2014, Galie *et al,* 2008, Li *et al,* 2010a, Rhodes *et al,* 2010, Pessina *et al,* 2011, Spaeth *et al,* 2009) and others showed a significant decrease (ok Ahn *et al,* 2013, Bianchi *et al,* 2012, Cousin *et al,* 2009, Kang *et al,* 2012, Secchiero *et al,* 2010, Xie *et al,* 2013, Gao *et al,* 2010a, Gao *et al,* 2010b). Although most of the studies did not mention the exact as mean ± SE (Bianchi *et al,* 2012, Du *et al,* 2014, Galie *et al,* 2008, Gao *et al,* 2010a, Li *et al,* 2010a, Rhodes *et al,* 2010, Secchiero *et al,* 2010, Spaeth *et al,* 2009), we might concluded it from the presented figure. The meta-analysis result didn't show significant effect on tumor volume by MSC (SMD-0.23[-0.55, 0.09]; n=15) (Fig 4). We found high heterogeneity (I2 =88%).

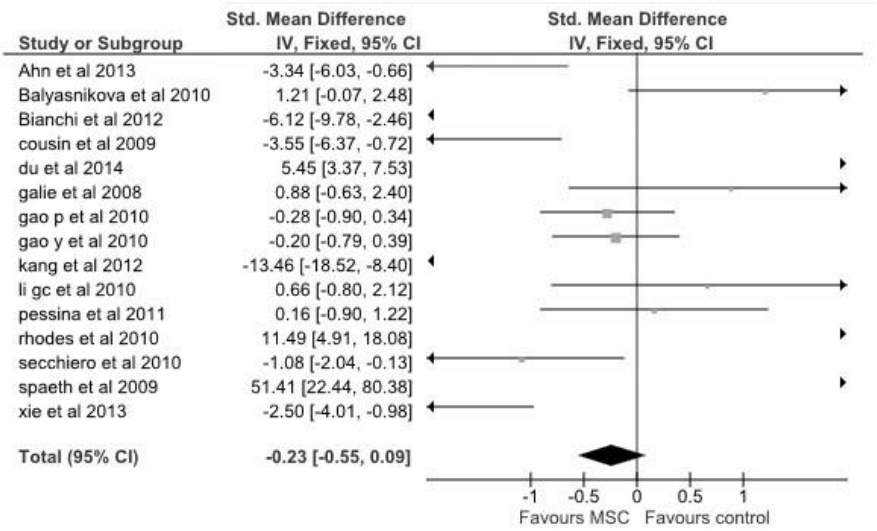

Figure 4. Effect of MSC on tumor volume in tumor animal model.

PUBLICATION BIAS

Publication bias was assessed for the outcome of overall tumor growth, since the analysis of this outcome included the high number of studies. On visual inspection of the funnel plot (Fig 9), only small studies with negative or positive effect seem to be missing. This symmetry might indicate the little presence of publication bias.

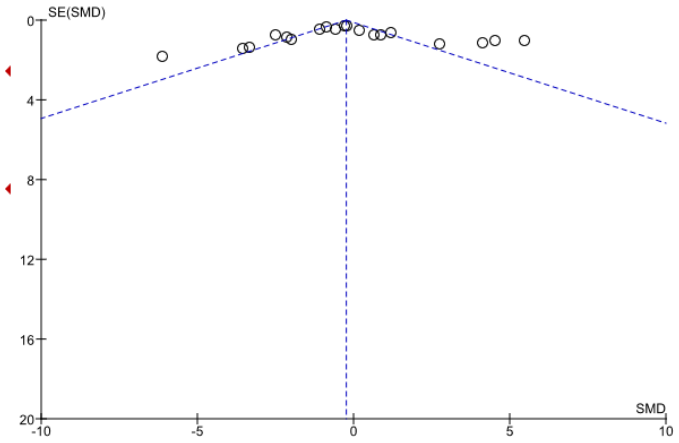

Figure 5. Funnel plot overseeing publication bias in the included study.

DISCUSSION

MSCs is one of the important component within the microenvironment of the tumor and have been shown to have dual roles in the process of malignancy (Hernanda *et al,* 2014). The tumor/ cancer microenvironment is a dynamic environment resulting from tissue remodeling and metabolic changes that include tumor cells and non-tumor cells (stromal cells), tropical factors, transduction signal molecules, extracellular matrices and mechanical signals which can affect the growth and spread of tumor cells and trigger resistance to cancer therapy (3). Various kinds of stromal cells found in the microenvironment include endothelial cells, microglia/ macrophages, astrocyte, fibroblasts, MSC and immune cells. These cells are present in the tumor tissue with different phenotypes and biological functions. Non-immune mesenchymal cells such as fibroblasts, myofibroblasts and adipocytes, have an important role in the tumor/ cancer microenvironment in which they adapt to tumor/ cancer cells.

In experimental tumor models, several studies have reported that MSCs are able to promote tumor progression and metastasis (Zhu *et al,* 2006, Hernanda *et al,* 2013b, Yan *et al,* 2013b, Gong *et al,* 2013, Chen *et al,* 2013, Du *et al,* 2014, Galie *et al,* 2008, Hernanda *et al,* 2013c, Huang *et al,* 2014a, Li *et al,* 2010a, Nowicka *et al,* 2013, Sung *et al,* 2013, Spaeth *et al,* 2009); whereas others reported that MSCs can suppress tumor growth (Zhao *et al,* 2012, Abdel aziz *et al,* 2011, Li *et al,* 2010b, Li *et al,* 2013a, Balyasnikova *et al,* 2010, Bianchi *et al,* 2012, Cavallari *et al,* 2013, Cousin *et al,* 2009, de Melo *et al,* 2015, Gao *et al,* 2010a, Gao *et al,* 2010b, Kang *et al,* 2012, Li *et al,* 2016, Li *et al,* 2013b, Liu *et al,* 2013, Ma *et al,* 2012, Ohta *et al,* 2015, Pessina *et al,* 2011, Qiao *et al,* 2008, Secchiero *et al,* 2010, Xie *et al,* 2013, Wu *et al,* 2013). This discrepancy might be

associated with several issues, including the particular animal models and types of MSCs used and the experimental procedure applied.

Engineered MSCs appears to have more tumor inhibition effect than normal MSCs. This result implies the important of the microenvironment that is favourable for MSC to inhibit tumor growth. One school of thought attributes to an important role for TLRs and subsequent immuno-polarization of MSCs (Waterman *et al,* 2010). MSCs express several TLRs and their capabilities to migrate, invade, and secrete immune modulating factors are tightly regulated by specific TLR-agonist engagement. TLR4-primed MSCs are polarized into pro-inflammatory MSC1 phenotype; whereas TLR3-primed MSCs are polarized into the classical immunosuppressive MSC2 phenotype (Waterman *et al,* 2010). In cancer models, MSC1-based treatment of established tumors in an immune competent model attenuates tumor growth and metastasis but MSC2-treated animals would display increased tumor growth and metastasis (Waterman, Henkle and Betancourt 2012). The priming of all MSCs types with inflammatory cytokines such as IFN-γ and TNF-α in the tumor microenvironment express higher levels of VEGF (Liu *et al,* 2011) and induce inhibition of RUNX2, one of the pivotal factors driving osteoblast differentiation(Lee, Lee and Im 2011) and in turn these MSCs can enhance tumor progression. However, stimulation of MSCs with IFN- α and IFN-β decreased tumor cell proliferation and induced tumor cell apoptosis in mouse model melanoma (Ahn *et al,* 2013, Xu *et al,* 2014). BMP4-differentiated BM-MSCs became less suppressive towards T and NK cell proliferation and switched on their suppressive machinery by activating both IDO and COX-2 and promote the differentiation of neighboring MSCs and trigger the anti-inflammatory effect (Bassi *et al,* 2014) whereas pre conditioning with TGFB1 resulted in pro-invasive MSC in colon cancer progression (De Boeck *et al,* 2013).

Although they were not significantly associated with tumor weight and tumor volume, MSCs appear to promote tumor growth when co-injected with tumor cells, but inhibit tumor progression when administered into established tumors. These results were in line with other researchs by Gupta *et al,* (Klopp *et al,* 2011). Thus, the presence of MSCs during the early phase of tumorigenesis may contribute to angiogenesis that is required for tumor initiation. Indeed, an increase in vessel density was observed when MSCs

were co-injected with tumor cell lines (Gong *et al,* 2013, Beckermann *et al,* 2008).

Limitations

Some methodological issues which might influence the translation of animal results to human trials. There are several different administration routes (intra tumor, subcutaneous, intra venous and intra peritoneal) of MSC injection in the studies. However, MSC is usually an intravenous administrated drug in clinic, raising the question whether administration method could also affect the effect of MSC on tumor. Another limitation is that these animal studies did not study the tumor / cancer stage indicated for MSC. Tumor / cancer stage could be an important factor for the therapeutic efficacy of MSC since the phase of MSC injection also had a significant effect in the final effect of MSC in tumor. As for xenograft animal model, which were used in most of the studies, however, it's hard to define the cancer stage which didn't discuss in the studies.

Implications for practice

Based on the results of this meta-analysis, MSC could potentially have a therapeutic effect on tumor. Although several clinical studies reported that MSC could promote the risk of tumorigenesis, some other sudies showed a very promising result on the effect of MSC in the tumor. Currently, several ongoing clinical trials (www.clinicaltrials.gov) are evaluating the effects of MSC on different cancers (breastcancer, colorectal cancer, pancreatic cancer, etc.). Of note, tumor cells and the tumor microenvironment will in turn affect the ultimate function of these recruited MSCs.

CONCLUSIONS

The effect of MSC has been demonstrated in experimental tumor animal model with the ultimate effect are both MSC inhibit and promote tumor growth. However, the final effect of MSC in tumor animal model is significantly associated with the MSC intervention and the phase of MSCs injection, and NOT associated with the source of MSC used and the type of tumor. Conclusion MSC appears to have a relative dependent effect in animal models since the micro environment play an important role. Although there were intrinsic limitations of the included animal studies, this systematic review and meta analysis could provide an important reference for future preclinical animal trials and may give contribution for management stem cell therapy of in cancer patients.

REFERENCES

Abdel aziz MT, El Asmar MF, Atta HM, Mahfouz S, Fouad HH *et al,* 2011. Efficacy of mesenchymal stem cells in suppression of hepatocarcinorigenesis in rats: possible role of Wnt signaling. *J Exp Clin Cancer Res.* 30(1)**:** 49.

Ahn J, Lee H, Seo K, Kang S, Ra J, Youn H, 2013. Anti-tumor effect of adipose tissue derived-mesenchymal stem cells expressing interferon-beta and treatment with cisplatin in a xenograft mouse model for canine melanoma. *PLoS One.* 8(9): e74897.

Balyasnikova IV, Ferguson SD, Sengupta S, Han Y, Lesniak MS, 2010. Mesenchymal stem cells modified with a single-chain antibody against EGFRvIII successfully inhibit the growth of human xenograft malignant glioma. *PloS one.* 5(3): e9750.

Bassi G, Guilloton F, Menard C, Di Trapani M, Deschaseaux F *et al,* 2014. Effects of a ceramic biomaterial on immune modulatory properties and differentiation potential of human mesenchymal stromal cells of different origin. *Tissue Eng Part A*. 21(3-4): 767-781.

Beckermann BM, Kallifatidis G, Groth A, Frommhold D, Apel A *et al,* 2008. VEGF expression by mesenchymal stem cells contributes to angiogenesis in pancreatic carcinoma. *Br J Cancer.* 99(4)**:** 622-631.

Bianchi G, Morandi F, Cilli M, Daga A, Bocelli-Tyndall C *et al,* 2012. Close interactions between mesenchymal stem cells and neuroblastoma cell lines lead to tumor growth inhibition. *PloS one.* 7**:** e48654.

Cavallari C, Fonsato V, Herrera M, Bruno S, Tetta C, Camussi G, 2013. Role of Lefty in the anti tumor activity of human adult liver stem cells. *Oncogene*. 32**:** 819-826.

Chen X, Liu B, Li Q, Honorio S, Liu X *et al,* 2013. Dissociated primary human prostate cancer cells coinjected with the immortalized Hs5 bone marrow stromal cells generate undifferentiated tumors in NOD/SCID-γ mice. *PloS one.* 8**:** e56903.

Cousin B, Ravet E, Poglio S, De Toni F, Bertuzzi M *et al,* 2009. Adult stromal cells derived from human adipose tissue provoke pancreatic

cancer cell death both in vitro and in vivo. *PloS one.* 4: e6278.

De Boeck A, Hendrix A, Maynard D, Van Bockstal M, Daniels A *et al,* 2013. Differential secretome analysis of cancer-associated fibroblasts and bone marrow-derived precursors to identify microenvironmental regulators of colon cancer progression. *Proteomics.* 13 (2): 379-388.

de Melo SM, Bittencourt S, Ferrazoli EG, da Silva CS, da Cunha FF *et al,* 2015. The anti-tumor effects of adipose tissue mesenchymal stem cell transduced with HSV-Tk gene on U-87-driven brain tumor. *PLoS One.* 10**:** e0128922.

Du T, Ju G, Wu S, Cheng Z, Cheng J *et al,* 2014. Microvesicles derived from human Wharton's jelly mesenchymal stem cells promote human renal cancer cell growth and aggressiveness through induction of hepatocyte growth factor. *PloS one.* 9**:** e96836.

Galie M, Konstantinidou G, Peroni D, Scambi I, Marchini C *et al,* 2008. Mesenchymal stem cells share molecular signature with mesenchymal tumor cells and favor early tumor growth in syngeneic mice. *Oncogene.* 27(18): 2542-2551.

Gao P, Ding Q, Wu Z, Jiang H, Fang Z, 2010a. Therapeutic potential of human mesenchymal stem cells producing IL-12 in a mouse xenograft model of renal cell carcinoma. *Cancer letters.* 290(2)**:** 157-166.

Gao Y, Yao A, Zhang W, Lu S, Yu Y *et al,* 2010b. Human mesenchymal stem cells overexpressing pigment epithelium-derived factor inhibit hepatocellular carcinoma in nude mice. *Oncogene.* 29(19):2784-2794.

Gong P, Wang Y, Wang Y, Jin S, Luo H *et al,* 2013. Effect of bone marrow mesenchymal stem cells on hepatocellular carcinoma in microcirculation. *Tumour Biol.* 34(4): 2161-2168.

Hanahan D and Weinberg RA, 2011. Hallmarks of cancer: the next generation. *Cell.* 144(5): 646-674.

Hernanda PY, Pedroza-Gonzales A, van der Laan LJW, Janssen HLA, Peppelenbosch MP, Pan Q, 2013a. Human Liver Carcinomas Recruit Mesenchymal Stem/ Stromal Cells That Can Promote Tumor Growth Via Paracrine

Signaling. *Journal of Hepatology*. 58**:** S431-S431.

Hernanda PY, Pedroza-Gonzalez A, Sprengers D, Peppelenbosch MP, Pan Q, 2014. Multipotent mesenchymal stromal cells in liver cancer: implications for tumor biology and therapy. *Biochim Biophys Acta.* 1846(2): 439-445.

Hernanda PY, Pedroza-Gonzalez A, van der Laan LJ, Broker ME, Hoogduijn MJ *et al,* 2013b. Tumor promotion through the mesenchymal stem cell compartment in human hepatocellular carcinoma. *Carcinogenesis.* 34: 2330-2340.

Hernanda PY, Pedroza-Gonzalez A, van der Laan LJ, Bröker ME, Hoogduijn MJ *et al,* 2013c. Tumor promotion through the mesenchymal stem cell compartment in human hepatocellular carcinoma. *Carcinogenesis.* 34**:** 2330-2340.

Huang F, Wang M, Yang T, Cai J, Zhang Q *et al,* 2014a. Gastric cancer-derived MSC-secreted PDGF-DD promotes gastric cancer progression. *Journal of cancer research and clinical oncology.* 140**:** 1835-1848.

Huang F, Wang M, Yang T, Cai J, Zhang Q *et al,* 2014b. Gastric cancer-derived MSC-secreted PDGF-DD promotes gastric cancer progression. *J Cancer Res Clin Oncol.* 140**:** 1835-1848.

Kang N, Hwang K, Yi B, Lee H, Jeung E *et al,* 2012. Human amniotic fluid-derived stem cells expressing cytosine deaminase and thymidine kinase inhibits the growth of breast cancer cells in cellular and xenograft mouse models. *Cancer gene therapy*. 19(6): 412-419.

Karnoub AE, Dash AB, Vo AP, Sullivan A, Brooks MW *et al,* 2007. Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. *Nature*. 449(7162): 557-563.

Klopp AH, Gupta A, Spaeth E, Andreeff M, Marini F 3rd, 2011. Concise review: Dissecting a discrepancy in the literature: do mesenchymal stem cells support or suppress tumor growth?. *Stem Cells.* 29(1): 11-9.

Lee JS, Lee JM, Im GI, 2011. Electroporation-mediated transfer of Runx2 and Osterix genes to enhance osteogenesis of adipose stem cells. *Biomaterials,* 32(3): 760-768.

Li GC, Ye QH, Xue YH, Sun HJ, Zhou HJ *et al*, 2010a. Human mesenchymal

stem cells inhibit metastasis of a hepatocellular carcinoma model using the MHCC97-H cell line. *Cancer science.* 101(12): 2546-2553.

Li H, Feng Z, Tsang TC, Tang T, Jia X, He X *et al,* 2014. Fusion of HepG2 cells with mesenchymal stem cells increases cancerassociated and malignant properties: an in vivo metastasis model. *Oncol Rep.* 32**:** 539-547.

Li L, Li S, Cai T, Wang H, Xie X *et al,* 2016. The targeted inhibitory effects of human amniotic fluid stem cells carrying CXCR4 promoter and DAL-1 on non-small cell lung carcinoma growth. *Gene therapy.* 23(2)**:** 214.

Li T, Song B, Du X, Wei Z and Huo T, 2013a. Effect of bone-marrow-derived mesenchymal stem cells on high-potential hepatocellular carcinoma in mouse models: an intervention study. *Eur J Med Res.* 18(1): 34.

Liu J, Han G, Liu H, Qin C, 2013. Suppression of cholangiocarcinoma cell growth by human umbilical cord mesenchymal stem cells: a possible role of Wnt and Akt signaling. *PloS one.* 8**:** e62844.

Liu Y, Han ZP, Zhang SS, Jing YY, Bu XX *et al,* 2011) Effects of inflammatory factors on mesenchymal stem cells and their role in the promotion of tumor angiogenesis in colon cancer. *J Biol Chem.* 286**:** 25007-25015.

Ma Y, Hao X, Zhang S, Zhang J, 2012. The in vitro and in vivo effects of human umbilical cord mesenchymal stem cells on the growth of breast cancer cells. *Breast cancer research and treatment.* 133**:** 473-485.

Nowicka A, Marini FC, Solley TN, Elizondo PB, Zhang Y*e al,* 2013. Human omental-derived adipose stem cells increase ovarian cancer proliferation, migration, and chemoresistance. *PloS one.* 8**:** e81859.

Ohta N, Ishiguro S, Kawabata A, Uppalapati D, Pyle M *et al,* 2015. Human umbilical cord matrix mesenchymal stem cells suppress the growth of breast cancer by expression of tumor suppressor genes. *PLoS One.* 10**:** e0123756.

ok Ahn J, woo Lee H, won Seo K, keun Kang S *et al,* 2013. Anti-tumor effect of adipose tissue derived-mesenchymal stem cells expressing interferon-β and

treatment with cisplatin in a xenograft mouse model for canine melanoma. *PLoS One.* 8**:** e74897.

Pessina A, Bonomi A, Coccè V, Invernici G, Navone S *et al,* 2011. Mesenchymal stromal cells primed with paclitaxel provide a new approach for cancer therapy. *PLoS One.* 6**:** e28321.

Qiao L, Xu Z, Zhao T, Zhao Z, Shi M *et al,* 2008. Suppression of tumorigenesis by human mesenchymal stem cells in a hepatoma model. *Cell research.* 18**:** 500.

Rhodes LV, Muir SE, Elliott S, Guillot LM, Antoon JW *et al,* 2010. Adult human mesenchymal stem cells enhance breast tumorigenesis and promote hormone independence. *Breast cancer research and treatment.* 121**:** 293-300.

Ryu H, Oh JE, Rhee KJ, Baik SK, Kim J *et al,* 2014. Adipose tissue-derived mesenchymal stem cells cultured at high density express IFN-beta and suppress the growth of MCF-7 human breast cancer cells. *Cancer Lett*. 352(2): 220-227.

Secchiero P, Zorzet S, Tripodo C, Corallini F, Melloni E *et al,* 2010. Human bone marrow mesenchymal stem cells display anti-cancer activity in SCID mice bearing disseminated non-Hodgkin's lymphoma xenografts. *PloS one.* 5**:** e11140.

Song B, Kim B, Choi SH, Song KY, Chung YG *et al,* 2014. Mesenchymal stromal cells promote tumor progression in fibrosarcoma and gastric cancer cells. *Korean J Pathol.* 48**:** 217-24.

Spaeth EL, Dembinski JL, Sasser AK, Watson K, Klopp A *et al,* 2009. Mesenchymal stem cell transition to tumor-associated fibroblasts contributes to fibrovascular network expansion and tumor progression. *PloS one.* 4**:** e4992.

Sung, SY, Liao CH, Wu HP, Hsiao WC, Wu IH *et al,* 2013. Loss of let-7 microRNA upregulates IL-6 in bone marrow-derived mesenchymal stem cells triggering a reactive stromal response to prostate cancer. *PloS one.* 8(8): e71637.

Takahara K, Ii M, Inamoto T, Komura K, Ibuki N *et al,* 2014. Adipose-derived stromal cells inhibit prostate cancer cell proliferation inducing apoptosis. *Biochem Biophys Res Commun.* 446**:** 1102-1107.

Waterman RS, Henkle SL, Betancourt AM, 2012. Mesenchymal stem cell 1 (MSC1)-based therapy attenuates tumor growth whereas MSC2-treatment promotes tumor growth and metastasis. *PLoS One.* 7**:** e45590.

Waterman RS, Tomchuck SL, Henkle SL, Betancourt AM, 2010. A new mesenchymal stem cell (MSC) paradigm: polarization into a pro-inflammatory MSC1 or an Immunosuppressive MSC2 phenotype. *PLoS One.* 5**:** e10088.

Wu S, Ju GQ, Du J, Zhu YJ, Liu GH, 2013. Microvesicles derived from human umbilical cord Wharton's jelly mesenchymal stem cells attenuate bladder tumor cell growth in vitro and in vivo. *PloS one.* 8**:** e61366.

Xie C, Xie D, Lin B, Zhang G, Wang P *et al,* 2013. Interferon-β gene-modified human bone marrow mesenchymal stem cells attenuate hepatocellular carcinoma through inhibiting AKT/FOXO3a pathway. *British journal of cancer.* 109**:** 1198.

Xu C, Lin L, Cao G, Chen Q, Shou P *et al,* 2014. Interferon-alpha-secreting mesenchymal stem cells exert potent antitumor effect in vivo. *Oncogene.* 33**:** 5047-5052.

Yan XL, Jia YL, Chen L, Zeng Q, Zhou JN *et al,* 2013a. Hepatocellular carcinoma-associated mesenchymal stem cells promote hepatocarcinoma progression: Role of the S100A4-miR155-SOCS1-MMP9 axis. *Hepatology.* 57**:** 2274-2286.

Zhang T, Lee YW, Rui YF, Cheng TY, Jiang XH, Li G, 2013. Bone marrow-derived mesenchymal stem cells promote growth and angiogenesis of breast and prostate tumors. *Stem Cell Res Ther.* 4**:** 70.

Zhao W, Ren G, Zhang L, Zhang Z, Liu J *et al,* 2012. Efficacy of mesenchymal stem cells derived from human adipose tissue in inhibition of hepatocellular carcinoma cells in vitro. *Cancer Biother Radiopharm.* 27**:** 606-613.

Zhu W, Xu W, Jiang R, Qian H, Chen M *et al,* 2006. Mesenchymal stem cells derived from bone marrow favor tumor cell growth in vivo. *Exp Mol Pathol.* 80(3): 267-274.