REVIEW ARTICLE

Therapeutic Application of Multipotent Stem Cells†

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Abstract

Cell therapy is an emerging fields in the treatment of various diseases such as cardiovascular, pulmonary, hepatic and neoplastic diseases. Stem cells are an integral tool for cell therapy. Multipotent stem cells are an important class of stem cells which have the ability to self-renew through dividing and developing into multiple specific cell types in a specific tissue or organ. These cells are capable to activate or inhibit a sequence of cellular and molecular pathways leading to anti-inflammatory and anti-apoptotic effects which might contribute to the treatment of various diseases. It has been showed that multipotent stem cells exert their therapeutic effects via inhibition/activation of a sequence of cellular and molecular pathways. Although the advantages of multipotent stem cells are numerous, further investigation is still necessary to clarify the biology and safety of these cells before they could be considered as a potential treatment for different types of diseases. This review summarizes different features of multipotent stem cells including isolation, differentiation and therapeutic applications.

Key words: Multipotent stem cells; Therapy; Differentiation

Introduction

Cell therapy has emerged as an effective tool in the treatment of various diseases such as cardiovascular diseases, cancer, lung and liver diseases (Mirzaei et al., 2016c; Mirzaei et al., 2016f). Various types of cells could be used to repair tissues damage. Multiple lines of evidences have indicated that a variety of cells including stem cells, T cells, and NK cells could be applied as suitable tools for the treatment of various diseases (Mirzaei et al., 2016c; Mirzaei et al., 2016f). It has been shown that the utilization of various cells alone or in combination with therapeutic agents could be associated with favorable effects. However, some studies have reported that the use of cells as therapeutic agents might be associated with adverse outcomes such as disease progression in cancer (Mirzaei et al., 2016c; Mirzaei et al., 2016f).

Stem cells are an integral part of cell therapy (Mirzaei et al., 2016f; Mohammadi et al., 2016b). Multipotent stem cells are one of main classes of stem cells which have the same basic properties of all stem cells (Mirzaei et al., 2016f; Mohammadi et al., 2016b). Stem cells are self-renewing and undifferentiated cells that have the potential to differentiate into various functional cell types (Alison et al., 2002; Bongso and Fong, 2009; Dai et al.; Gargett, 2006). Self-renewal, the capacity to generate identical daughter cells without any differentiation, is necessary to preserve stem cell pools in different tissues (Gargett, 2006; Smith, 2005). It has been shown that stem cells have specific properties (Jiang et al., 2002). These properties have led to the use of stem cells as therapeutic agents (Mirzaei et al., 2016f; Mohammadi et al., 2016b). Multiple lines of evidence have indicated that stem cells could be used for the treatment of a large number of diseases such as liver diseases, lung diseases, cardiovascular diseases and cancer (Mirzaei et al., 2016f; Mohammadi et al., 2016b). It has been showed that these cells are able to activate and/or inhibit a number of cellular and molecular pathways involved in various diseases. However, some reports have revealed that

these cells might activate some cellular and molecular pathways which could contribute to the development of various diseases.

The utilization of stem cells in particular multipotent stem cells could be associated with some disadvantages. For examples, various side effects of stem cell therapy are still unclear. Hence, stem cell therapy is still under extensive research. A number of issues should be clarified before stem cells could be widely employed as a reliable treatment for human diseases. Here, we highlight various aspects of multipotent stem cells such as characterization, identification and their medical applications.

Multipotent stem cells

Multipotent stem cells are known as one of important classes of stem cells (Trounson et al., 2011). It has been showed that these cells show some similar properties with other types of stem cells. For example, multipotent stem cells are undifferentiated cells and have the ability of self-renewing. These cells are able to extend into a variety of specific cells which could have particular actions (Clevers, 2015). A wide range of stem cells including skeletal myoblasts, hematopoietic stem cells (HSCs), and endothelial progenitor cells (EPCs), mesenchymal stem cells could be known as multipotent stem cells (Blanpain and Fuchs, 2014; Clevers, 2015; Trounson and McDonald, 2015; Wuidart et al., 2016). These cells could be differentiated in various tissues such as bone, cartilage, fat, muscle, and other related tissues (Trounson and McDonald, 2015). Numerous studies indicated that multipotent stem cells could be used as attractive tools for a variety of clinical applications in various diseases such as cardiovascular, lung diseases, inflammatory diseases, and cancer (Kim et al., 2006b; Kuo et al., 2008; Pittenger et al., 1999; Segers and Lee, 2008). These cells have suitable properties including stable cell phenotype, low immunologic, low metabolic status, which lead to be them as interesting approaches for transplantation and drug targeted therapy (Liao

and Tse, 2013). Moreover, these properties could lead to decreasing of rejection risk, tumor risk and increasing of survival (Liao and Tse, 2013). In spite of various advantages (e.g. easily accessible, simple isolation, and bio-preserved with minimal loss of potency) associated with multipotent stem cell therapy, several reports indicated that some risks could be related with these cells (Liao and Tse, 2013; Sobhani et al., 2017). For examples, some studies indicated that injection of stem cells could be related with emerging of some cancers such as brain tumors (Sobhani et al., 2017). Table 1 shows some risks related with multipotent stem cells as therapeutic agents.

It has been revealed that various multipotent stem cells via secreting a variety of growth factors, chemokines mitogenic proteins (e.g. TGF-a, TGF-b, EGF, and IGF-1) which could induce cell proliferation and angiogenesis (Caplan and Bruder, 2001; Doorn et al., 2011; Haynesworth et al., 1996).

Immunomodulatory and anti-inflammatory properties of multipotent stem cells are main properties which are led to using of them in wide ranges of clinical applications. Multipotent stem cells could secret various types of growth factors and anti-inflammatory proteins against inflammatory molecules (e.g. IL-1, IL-2, IL-12, TNF, and INF-g) (Aggarwal and Pittenger, 2005). Moreover, it has been showed that these cells show anti-apoptotic properties via affecting on sequences cellular and molecular targets such as IGF-1, Akt and nuclear factor kappa-light-chain-enhancer of activated B cells (Gnecchi et al., 2006; Murphy et al., 2013).

These findings suggested that these cells might be applied as therapeutic candidates for treatment of various diseases such as cardiovascular diseases and cancer.

Isolation and identification of multipotent stem cells

Multipotent stem cells are known as undifferentiated and unspecialized cells which are able to differentiate into specialized cells with particular actions (Liao and Tse, 2013). It has been

showed that there are various sources for multipotent stem cell isolation (Liao and Tse, 2013; Sobhani et al., 2017). The important accessible sources of autologous adult stem cells are adipose tissue, bone marrow, and blood. It has been showed that various tissues including nervous tissues, skin, adipose tissue, tendons, and synovial membranes could be suitable sources for multipotent stem cells (Sobhani et al., 2017). It has been showed that a variety of markers could be used for identification and isolation of multipotent stem cells (Sobhani et al., 2017)(Table 2).

Bone marrow stem cells are one of important population of multipotent stem cells which are attractive option for using as therapeutic tools for treatment of various diseases (Chamberlain et al., 2007).

It has been showed that marrow stromal cells do not express the hematopoietic markers such as CD34, CD14, CD45, and CD11. Various studies indicated that some markers including CD105, CD73 , CD44, CD90 , CD71, and Stro-1 expressed on marrow stromal cells (Chamberlain et al., 2007).

Adipose tissue is other source for isolation multipotent stem cells. It has been revealed that adipose stem cells have not specific marker (Gronthos et al., 2001). Some studies indicated that adipose stem cells could be isolated (CD34-positive cells/CD31-negative cells) by using magnetic beads. Flow cytometry and immunocytochemistry analysis indicated that adipose stem cells could express a variety of markers including CD9, CD10, CD13, CD29, CD34, CD44, CD 49d, CD 49e, CD54, CD55, CD59, CD105, CD106, CD146, and CD166 (Gronthos et al., 2001; Schäffler and Büchler, 2007).

Applications of multipotent stem cells in different diseases

Cell therapy is one important therapeutic approach which is associated with significant results in pre-clinical and clinical studies (Assinck et al., 2017; Nadig, 2009). Stem cell therapy is known as one of attractive cell therapy approaches which show various benefits (Nadig, 2009; Trounson and McDonald, 2015). It has been showed that this approach could be used for patients suffering a wide range of diseases such as cardiovascular, cancer, Infammatory diseases, and lung diseases (Trounson and McDonald, 2015). Among of various types of stem cells, adult stem cells (multipotent stem cells) have been emerged as attractive tools for treatment of various diseases (Trounson and McDonald, 2015). It has been showed that multipotent stem cells could be used as suitable option for transplantation and targeted therapy in various diseases. In the following parts, we will present recent clinical and preclinical uses of multipotent stem cells (Tuan, 2006).

Various types of stem cells could employ a variety of cellular and molecular mechanisms and targets (e.g. microRNA, exosome, various proteins and transcription factors) which exert their therapeutic effects. For example, exosomes released from stem cells have critical roles in various biological functions associated with stem cells in body (Ong and Wu; Tsao et al., 2014). It has been showed that exosomes and microRNAs (miRNAs) are one of main players in pathogenesis of various diseases (Mirzaei et al., 2016d; Saadatpour et al., 2016a). MiRNAs are known as one of important cellular regulators which could regulate a variety of cellular and molecular pathways (Hoseini et al., 2017; Keshavarzi et al., 2017b; Mirzaei et al., 2017; Mirzaei et al., 2016g; Moridikia et al., 2017; Rashidi et al., 2017). Deregulation of these molecules could be associated with various diseases such as cancer, cardiovascular, and stroke (Fathullahzadeh et al., 2016; Keshavarzi et al., 2017a; Mirzaei et al., 2016a; Mohammadi et al., 2016a; Rashidi et al., 2016; Salarinia et al., 2016a). It has been revealed

that stem cells therapy via alteration of miRNA expression could contribute to obtaining better therapeutic results (Mathieu and Ruohola-Baker, 2013; Tyagi et al., 2011).

Cardiovascular diseases such as myocardial infarction and heart failure are diseases which multipotent stem cell therapy could contribute to treat them (Liao and Tse, 2013). Cardiovascular diseases are known as one of important leading cause of mortality and morbidity worldwide. It has been showed that the utilization of interventional therapies can only decrease the loss of cardiomyocytes during myocardial infarction but are not associated with loss of cardiomyocytes after MI (Liao and Tse, 2013). A large number studies indicated that multipotent cell therapy could restore cardiac function in heart failure (Liao and Tse, 2013).

Numerous studies have assessed the therapeutic effects of autologous and allogeneic mesenchymal stem cells for acute MI. In a study, Hare et al., assessed of injection of allogeneic mesenchymal stem cells for 53 patients 7 to 10 days after MI and in different doses (Hare et al., 2009). Their result indicated that there were fewer arrhythmic events, improved EF and .improvement in overall clinical status 6 months after infusion (Hare et al., 2009). Telukuntla et al indicated that intravenous infusion of allogeneic mesenchymal stem cells within 7 days of an acute MI could be associated with therapeutic effects in patients with MI. They showed that injection of allogeneic mesenchymal stem cells could significantly decrease cardiac hypertrophy, heart failure, stress-induced ventricular arrhythmia, and rehospitalizations for cardiac complications (Telukuntla et al., 2013).

It has been revealed that multipotent stem cells via a variety of mechanisms (e.g. Decreasing of fibrosis, increasing of angiogenesis, and restoration of contractile function) exert their cardio-protective effects (Kim et al., 2015).

Neurological disorders are other diseases which stem cell therapy could be used as an attractive therapeutic approach for treatment of them. Pre-clinical and clinical studies indicated that utilization of various types of stem cells is associated with significant results.

In a study, Karussis et al., assessed therapeutic effects of mesenchymal stem cells in patients with multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS)(Karussis et al., 2010). They showed that injection of autologous mesenchymal stem cells isolated from bone marrow into spinal cord cerebrospinal fluid could be used as safe therapeutic approach for treatment patients with multiple sclerosis and ALS (Karussis et al., 2010). They indicated that mesenchymal stem cells show some immunomodulatory effects within 24 hours of injection. Immunological analysis indicated that there were an increase in the proportion of CD4(+)CD25(+) regulatory T cells, and a decrease in the proliferative responses of lymphocytes, CD83(+), CD86(+),HLA-DR and CD40(+) expression on myeloid dendritic cells at 24 hours after mesenchymal stem cells injection (Karussis et al., 2010). Table 1 illustrates various clinical and animal studies that have been done on this landscape.

Multipotent stem cells as a biological vehicle for cancer treatment

Cancer is known as one of the main public health problems worldwide (Loda et al., 2016; Penney, 2017). Numerous studies have focused on the identification and finding new therapies for cancer treatment (Mirzaei et al., 2016b; Mirzaei et al., 2016f; Saadatpour et al., 2016b). It has been shown that present therapies could not provide satisfactory effects for patients with cancer (Mirzaei et al., 2016e; Saadatpour et al., 2016a; Saadatpour et al., 2016c; Salarinia et al., 2016b). Hence, new therapies to overcome the limitations of conventional therapies are necessary (Mirzaei et al., 2016c). Indeed, multipotent stem cells have already been utilized as a novel delivery system for the treatment of various diseases such as neurodegenerative diseases and cancer (Mohammadi et al., 2016b). Multiple lines of evidence have shown that multipotent stem cells could be used as a suitable source for

targeted therapy in cancer (Mirzaei et al., 2016f; Mohammadi et al., 2016b). These cells express a variety of factors and receptors which could help their homing to cancerous locations (Mirzaei et al., 2016f; Mohammadi et al., 2016b). Hence, multipotent stem cells could be employed as therapeutic biological vehicles for targeting especial genes or proteins. Utilization of multipotent stem cells is associated with various advantages such as easy and fast isolation, immunosuppression, tumor tropism, and targeted delivery of a variety of therapeutic agents (Mirzaei et al., 2016f; Mohammadi et al., 2016b). Various studies have shown that multipotent stem cells could deliver a variety of biological agents such as IL-2, IL-18, NK4, IFN-β, IFN γ, CX3CL1, PE-cytotoxins, TRAIL and sFlt-1 (Table 4) (Mirzaei et al., 2016f; Mohammadi et al., 2016b). Hence, the utilization of multipotent stem cells as a biological vehicle might open a new horizon in cancer therapy.

Conclusion

Multipotent stem cells are one of the main cell types which have therapeutic potential for the treatment of a range of diseases. Multiple lines of evidence have indicated that various types of multipotent stem cells including stem cells derived from plancenta, adipose and neural tissues could be employed for treating a variety of diseases such as cardiovascular diseases, neurological diseases and cancer. These cells could exert their function *via* different cellular and molecular pathways such as anti-inflammatory, anti-apoptotic and neurotrophic factors. Obviously, there are numerous debates about the ways to overcome the challenges against safe use of multipotent stem cells; the advantages of these cells are abundant, so they have been considered as a potential treatment for a variety of diseases. The use of multipotent stem cells does not have the ethical problems of pluripotent and totipotent stem cells. However, widespread application of these cells in the clinic for research and therapeutic applications still requires more investigations.

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Table 1. A variety of factors which are involved in the adverse effects of multipotent stem cell therapy.

Factor (s)		**Risk (s)**	**Reference**
Intrinsic	Origin of cells	Rejection of cells	
Characteristics	Tumourigenic	Unwanted biological effect	(Li et al., 2006a)
	Proliferation capacity	Toxicity	(Herberts et al., 2011)
	Life span	neoplasm formation	(Li et al., 2006a)
	Long term viability		(Herberts et al., 2011)
	Differentiation status		
Extrinsic	Starting and raw materials	Reactivation of latent viruses	(Herberts et al., 2011)
	Plasma derived materials	Cell line contamination	
	Contamination by adventitious agents	Mix-up of autologous patient material	
	Pooling of allogenic cell populations		
	Transport conditions		

Clinical characteristics	Therapeutic use	Undesired immune response	(Nussbaum et al., 2007)
	Indication	Unintended physiological and anatomical consequences	(Breitbach et al., 2007)
	Administration route	Engraftment at unwanted location	(Breitbach et al., 2007)
	Initiation of immune responses	Toxicity	(Breitbach et al., 2007)
	Use of immune supressives	Lack of efficacy	(Breitbach et al., 2007)
	Exposure duration		(Breitbach et al., 2007)
	Underlying disease	neoplasm formation	(Werbowetski-Ogilvie et al., 2009)

Table 2. A variety of markers for isolation and identification of multipotent stem cells

Type of multipotent stem cell	Negative marker(s)	Positive marker(s)
Keratinocyte	CD24 and 34	CD73, 44 and 90
Dental pulp	CD14, 45, 34	Stro-1, SH2, 3 and 4, CD29, 44, 166
Adipose	CD31 and Stro-1	P75NTR,CD9, 10, 13, 29, 34, 44, 49d, 49e, 54, 55, 59, 105, 106, 146
VSELs	CD45	SSEA-1, Oct-4, Nanog, Rex-1, Sca-1, CXCR4, Stella and Fragilis
Human marrow stromal cells	CD45, 34, 14, 11, 80, 86, 40 , 31, 18 , and 56	CD105 (SH2), 73 (SH3/4), 44, 90 (Thy-1), 71+, 106, 166, 29, Stro-1
Neural	CD271 , CD44	CD184, CD24
Placenta	CD 11b, 34, and 45	CD29, 73, 166,

Table 3. Various clinical and *in vivo* studies on multipotent stem cells.

Disease	**Stem cells derived from**	**Effect (s)**	**Model**	**Sample (n)**	**Ref**
Ischemic brain injury	Human placenta	The reducing of cortical lesions and behavioral deficits in adult stroke rats	Rat		(Wu et al., 2015)
MI	Bone marrow	The decreasing of Infarct size	Human	10	(Boonbaichaiyapruck et al., 2010)

Cardiac Injury	Human placenta	The increasing of vascularity, cardiomyogenic differentiation, and antiapoptotic effect	Mouse		(Liu et al., 2015)
Ischemic heart disease	Bone marrow	The loss of cardiomyocytes and viable blood vessels	Animal		(Lee et al., 2005)
Buerger's disease	human umbilical csord blood	Digital capillaries were increased in number and size	Human	4	(Kim et al., 2006a)
Acute ischemic heart	Mouse testis	the improvement in cardiac function	Mouse		(Iwasa et al., 2010)
Chronic Cardiosclerosis	Cardiac **Stem** Cell	The reducing of cicatricial tissue volume and promoted angiogenesis in the damaged zone	Rat		(Chepeleva et al., 2015)
Acute kidney injury	mesenchymal stem cells	The increase of kidney volume and the decrease in renal	Rat		(Ittrich et al., 2007)

		function			
Post ischemic kidney	Bone marrow	the optimal time window for stem cell therapy is during the early phase of the ischemic injury	Rat		(Behr et al., 2007)
Acute renal **injury**	**Human bone marrow**	The reducing of renal cell apoptosis and increase proliferation.	Mouse		(Morigi et al., 2008)
Diabetes	**Bone marrow**	A decreasing in mesangial thickening and a decrease in macrophage infiltration	Mouse		(Lee et al., 2006)
Renal transplantation	**Bone marrow**	down-regulation of immune responses, reduced production of some inflammatory mediators	Rat		(Zhang et al., 2007)
Articular cartilage repair	Bone marrow	more osteogenic potential and high proliferation capacity	Rabbit		(Fu et al., 2014)
Acute-on-chronic	Umbilical cord	The increasing of	Human	19	(Shi et al., 2012)

liver failure		serum albumin, cholinesterase, prothrombin activity; and platelet counts			
Cirrhosis	Bone marrow	The increasing of prothrombin and serum albumin levels, and decreasing of bilirubin	Human	15	(El-Ansary et al., 2012)
Hepatitis B	Bone marrow	The level of alanine aminotransferase, total bilirubin, prothrombin time , and Model for End-Stage Liver Disease are improved	Human	527	(Peng et al., 2011)
Idiopathic pulmonary fibrosis	Bone marrow	The up-regulation of hepatocyte growth factor	Mouse		(Lan et al., 2015)

Chronic obstructive pulmonary disease	Bone marrow	The enhancing of HIF-1α and SDF-1 expression	Rat		(Zhang et al., 2014)
Glioma	Bone marrow	Immune modulatory	Rat		(Nakamura et al., 2004a)
Ewing sarcoma	Bone marrow	Activates T cells and NK cells	Mouse		(Duan et al., 2009a)
Glioma	**Adipose**	Therapeutic effects	Rat		(Choi et al., 2012b)
Fibrosarcoma	Bone marrow	Therapeutic effects	Rat		(Xiang et al., 2009)
Melanoma	**placenta**	Therapeutic effects	Mouse		(Chen et al., 2012)

Table 4. Anti-tumor agents delivered by multipotent stem cells

Cancer	Agent	Citation
Glioma	IL-2	(Nakamura et al., 2004b)
Ewing sarcoma Renal cell carcinoma	IL-12	(Duan et al., 2009b) (Gao et al., 2010)
Glioma	IL-18	(Xu et al., 2009)
Lung tumors	NK4	(Kanehira et al., 2007)
Prostate cancer lung metastasis, Glioma	IFN-β	(Ren et al., 2008; Studeny et al., 2002)
Leukaemia	IFN γ	(Li et al., 2006b)
Multiple lung tumors	CX3CL1	(Xin et al., 2007)
Glioblastoma	PE-cytotoxins	(Stuckey et al., 2014)
lung metastases	sFlt-1	(Hu et al., 2008)
fibrosarcoma	iNOS	(Xiang et al., 2009)
Glioma	HSV-tk	(Uchibori et al., 2009)
Glioma	Nanoparticle	(Li et al., 2011)
Glioma	TRAIL	(Loebinger et al., 2009; Shah et al., 2005)
Breast	Oncolytic viruses	(Stoff-Khalili et al., 2007)
Lung metastasis	rCE	(Choi et al., 2012a)

IL-2: Interleukin-2, IL-12: Interleukin-12, IL-18: Interleukin-18, NH4: HGF-antagonist/angiogenesis inhibitor, PE-cytotoxins : Pseudomonas exotoxin - cytotoxins , HSV-tk: herpes simplex virus thymidine kinase, sFlt-1:

fms-like tyrosine kinase 1, iNOS: *inducible nitric oxide synthase* , TRAIL: TNF-related apoptosis-inducing ligand , rCE: rabbit carboxylesterase .