Review Article

Mesenchymal Stem Cells: A New Platform for Targeting Suicide Genes in Cancer†

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†This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1002/jcp.26094]

Received 15 June 2017; Revised 10 July 2017; Accepted 11 July 2017

Journal of Medical Virology

DOI 10.1002/jcp.26094

Abstract

One of the important strategies for the treatment of cancer is gene therapy which has the potential to exclusively eradicate malignant cells, without any damage to the normal tissues. Gene-directed enzyme prodrug therapy (GDEPT) is a two-step gene therapy approach, where a suicide gene is directed to tumor cells. The gene encodes an enzyme that expressed intracellularly where it is able to convert a prodrug into cytotoxic metabolites. Various delivery systems have been developed to achieve the appropriate levels of tumor restricted expression of chemotherapeutic drugs. Nowadays, mesenchymal stem cells (MSCs) have been drawing great attention as cellular vehicles for gene delivery systems. Inherent characteristics of MSCs make them particularly attractive gene therapy tools in cell therapy. They have been used largely for their remarkable homing property towards tumor sites and availability from many different adult tissues and show anti-inflammatory actions in some cases. They do not stimulate proliferative responses of lymphocytes, suggests that MSCs have low immunogenicity and could avoid immune rejection. This review summarizes the current state of knowledge about genetically modified MSCs that enable to co-transduce a variety of therapeutic agents including suicide genes (i.e. cytosine deaminase, thymidine kinase) in order to exert potent anti-carcinogenesis against various tumors growth. Moreover, we highlighted the role of exosomes released from MSCs as new therapeutic platform for targeting various therapeutic agents.

Key word: Mesenchymal stem cells, Suicide Gene, Therapy, Cancer

Introduction

Based on World Health Organization (WHO), Cancer is the second leading cause of death globally which was responsible for 8.8 million mortality in 2015. Nearly 1 in 6 deaths is due to cancer and the number of new cases is expected to rise by about 70% over the next 2 decades worldwide (Siegel et al., 2015; Torre et al., 2015). There are many types of cancer treatment including surgery, chemotherapy and radiotherapy (Amer, 2014). Cancerous patients had no survival benefits from current insufficient treatments and in most cases relapse and metastasis occurred (Nowakowski et al., 2016; Zhang et al., 2014). Such poor prognosis seems to be linked to: detrimental effects on vital noncancerous bodily tissues, deficient drug concentrations in tumors also problems of accessing tumor sites principally in metastatic cancers and systemic toxicity demonstrates the urgency to explore more effective anti-tumor therapy (Kim and Tannock, 2005; Liu et al., 2015; Pessino and Sobrero, 2006). Targeted therapy is emerging as a supplement or alternative to chemotherapy and/or radiation for various malignant diseases (Mirzaei et al., 2016c; Mirzaei et al., 2016g; Mirzaei et al., 2016j). In the field of targeted therapy, gene therapy appears as a good substitute method for cancer treatment(Wu et al., 2006). There are different approaches for cancer gene therapy including immunotherapy, oncolytic viruses and gene transfer (Cross and Burmester, 2006; Lin and Nemunaitis, 2004; McCormick, 2001; Mirzaei et al., 2016c; Mirzaei et al., 2016h). Immunotherapy employ for immune system stimulation to destroy cancer cells (Blattman and Greenberg, 2004). Oncolytic viruses, that replicates within the cancer cell and cause cell destruction (Chiocca and Rabkin, 2014; Dwyer et al., 2010; Singh et al., 2012). Gene transfer serves as a new treatment approach that introduces foreign genes into cancerous cells to promote cell death or slow the progression of the cancer. Gene transfer represents the best way for cancer gene therapy. In this path, we could introduce multiple genes with completely different function to malignant cell such as pro-apoptotic genes, anti-angiogenesis genes and

suicide genes (Cao et al., 1998; Cross and Burmester, 2006; Persano et al., 2007). Failure to distinguish between normal and tumor cells will probably remain a limiting factor for chemotherapy drugs but Suicide genes form the basis of a strategy for making cancer cells more vulnerable and susceptible to chemotherapy (Karjoo et al., 2016b). Suicide gene therapy system is based on gene transfer into tumor cells, which leads to the exclusive expression of an enzyme able to convert a non-toxic prodrug into a lethal drug (Freeman, 2002; Izmirli et al., 2016; Touati et al., 2014). Achieving the specified purpose requires vehicles that encapsulate the gene and deliver it particularly to cancer cell and cancer local environment of the tumor. In gene therapy and especially cancer gene therapy at first we need to utilize vehicle so called vector that includes a set of criteria; having tumor tropism (specificity for tumor microenvironments), don't able to elicit an immune response and safety (Hacein-Bey-Abina et al., 2002; Rajab et al., 2013). From the first reports of gene therapy in 1960 -1970 to present, there are three types of gene delivery systems into the target cell (Collins and Thrasher, 2015). Through to their high transduction efficiency, viral vectors are the most frequently used gene delivery strategies. Retrovirus, lentivirus and adenovirus are common viral vectors. In the field of gene therapy with viral vectors there are two major obstacles in terms of the safety and toxicity of these vectors that limit the clinical potential of this approach (i.e. insertional mutagenesis of retroviral vectors and intensive immune reaction of adenoviral vectors) (Collins et al., 2008; Nayerossadat et al., 2012; Rajab et al., 2013; Waehler et al., 2007). Molecular vectors including, naked DNA and application of cationic polymers such as polyethylenimine or poly-L-lysine, cationic peptides, and cationic liposomes. The major drawbacks of this approach are non-specific uptake of the DNA by cancer cells and toxicity of some cationic polymers such as lipoplexes (Dani, 1999; Miller and Vile, 1995; Nayerossadat et al., 2012; Simões et al., 2005; Zhang et al., 2014). Cellular vectors are promising vehicles to deliver various anticancer agents, including small molecule

drugs, proteins, suicide genes, nanoparticles, and viruses. Cellular vectors have several advantages such as low immunogenicity, practically unlimited genetic material packaging capacity, simple and low-cost construction which makes them appropriate for large-scale production and most likely safe for clinical gene therapy (Link et al., 2000; Ohlfest et al., 2005).

Cell therapy is an effective therapeutic approach for treatment of various diseases such as cancer (Goradel et al., 2017; Mirzaei et al., 2016h). Among of various cells which could be used for cell therapy, MSC are known as powerful tools for treatment of various diseases such as cancer. MSC can be utilized for targeted-gene delivery (Goradel et al., 2017; Mirzaei et al., 2016e). MSCs have a low immunogenic potential besides the capacity to home and integrate in to the injured and inflamed sites. MSCs have indicated preferential tropism for tumor, so could transferred suicide genes and their products just in tumor local and reduce side effects about systemic toxicity and could achieve more efficient gene delivery to the target (Desmoulière, 2008; Nauta and Fibbe, 2007; Uchibori et al., 2014). The aim of the present review is to discuss about; 1; Suicide genes, known as good killers in cancer therapy 2; Characteristics and application of MSCs in cancer therapy, 3; investigating previous research studies about MSCs in role of a vehicle for suicide genes.

1. Suicide Genes as a Good Killer

The term of gene directed enzyme prodrug therapy (GDEPT) is one of the promising alternatives to conventional chemotherapy because it minimizes the systemic toxicities of conventional chemotherapy drugs and refer to expression of a suicide gene in tumor cells for the in situ conversion of a pro-drug into cytotoxic metabolites (Greco and Dachs, 2001; Springer and Niculescu-Duvaz, 2000). The first attempt to use of suicide genes against cancer was in 1986 by Moolten et al (Rajab et al., 2013). These points must consider in selection of

suicide genes; Intended gene must encodes an enzyme that didn't exist in normal cells or there is no enzyme with similar function in cells; Minimal toxicity of prodrug before activation in body and maximum toxicity after converting to active drug in tumor location; high kinetic enzyme activity or high affinity to target prodrug and finally active drug must diffuse in whole tumor mass by Bystander effects (Both, 2009; Rajab et al., 2013; Zarogoulidis et al., 2013). This mentions to the demolition of tumor cells that are not directly expressing the suicide gene. In this effect, gap junctions play substantial role via local diffusion of the active drug. Previous studies revealed that this approach could abolish tumors even if 10% of tumor cells expressed suicide genes, this efficiency is about bystander effects (Freeman et al., 1993; Mesnil and Yamasaki, 2000). There are several mechanisms for Bystander affect; intercellular communication via gap junctions, diffuse through the cell membrane, endocytosis of apoptotic vesicles and stimulation of the immune system against tumor. The gap junctional intercellular communication (GJIC) capacity varied among cancer cell lines and was dependent on the connexin 43 (cx43) expressions (Duarte et al., 2012; Huber et al., 1994; Pierrefite-Carle et al., 1999). The overexpression of Cx43 in glioma cells leading to the increase in the number of gap junctions and enhanced the bystander effect of HSV-TK as a suicide gene, reverse situation is in esophageal cancer (Huang et al., 2010; Matono et al., 2003). So evaluation of degree of GJIC has predictive value for determination of response to suicide genes that dependent on GJIC such as HSV-TK. Also studies reported that radiation could induce bystander effect, so suicide cancer therapy juxtaposed with the irradiation could increase tumor eradiation (Azzam and Little, 2004). In the following, we discussed two most applicable suicide genes in cancer gene therapy.

1.1. Cytosine deaminase (CD) / 5-fluorocytosine (5-FC)

Although 5-flourouracil (5-FU) has been widely used in the past decades for the treatment of multiple cancers especially colorectal and breast cancers, but this drug failed to treat efficiently due to some limits: insufficient delivery of drug to cancer mass and adverse effect on body. High systemic toxicity made it unpleasant choice for patients (Cheung et al., 2008; Longley et al., 2003). Serious side effects could be reduced by gene-directed enzyme prodrug therapy depending on the bacterial and/or yeast cytosine deaminase (CD) enzyme activity with no equivalent in mammalian cells. CD gene codes cytosine deaminase, an enzyme express in a variety of bacteria, fungi and yeast that convert nontoxic prodrug 5-FC to its toxic metabolite 5-fluorouracil (5-FU) (Kucerova et al., 2007; Kuriyama et al., 1999). 5-FU metabolites direct the formation of fraudulent 5FU-RNA and 5FU-DNA and inhibit RNA and DNA synthesis by thymidylate synthase blockage and finally apoptosis. Although there is no DNA synthesis in non-dividing cancer cells but high concentration of 5-FU could decrease mRNA level and subsequently protein starvation and cell death. 5-FU could exert toxic effects on neighboring cells through freely diffusion across the cellular membrane without GJIC mediation, owing to its small size and suitable charge (Gopinath and Ghosh, 2008; Karjoo et al., 2016a). 5-FC, but not 5-FU crosses the blood brain barrier (Karjoo et al., 2016a; Ostertag et al., 2012). This capability seems to be another advantage of this gene, since it makes 5-FC appropriate for treatment of tumors in brain with difficult accessibility. Several reports revealed that CD/5FU system accompanied with radiotherapy will be more effective in tumor suppression (Kaliberov and Buchsbaum, 2012). Comparative studies showed that yeast CD produces 15 fold higher amount of 5-FU than bacterial CD (Kievit et al., 2000). Also results demonstrated that bifunctional yeast fusion gene CD::UPRT (cytosine deaminase::uracil phosphoribosy ltransferase) could produce 100 - 10,000-higher amount of 5-FU compared with CD enzyme alone, in vitro and in vivo (Kanai et al., 1998; Tiraby et al.,

1998). The ABC transporters are trans-membrane proteins that can facilitate the export of substrates through cellular membranes. ABC transporters participate in chemo-resistance of cultured cells. Actually multidrug resistance protein 5 (MRP5) and MRP8 confer resistance to 5-FU by increase the permeability of cellular membrane to monophosphate metabolites (Nambaru et al., 2011; Oguri et al., 2007). Matuskova et al., shown that silencing of the ABCC11 by RNA interference significantly sensitized breast carcinoma cell line (MDA-MB-231) to the CD::UPRT system (Matuskova et al., 2012).

1.2. Herpes simplex thymidine kinase (HSV-TK) / ganciclovir (GCV)

HSV-TK gene codes for a thymidine kinase that able to convert GCV to GCV monophosphate which is then turned into GCV-di and triphosphate by endogenous kinases. Insertion of GCV triphosphate to double stranded DNA leads to termination of DNA synthesis and finally continued with apoptosis as a result of maintenance of cell in S phase (Abate-Daga et al., 2010; Tomicic et al., 2002). Since HSV-TK has greater affinity for GCV in compare to endogenous kinases enzymes, the primary steps of GCV phosphorylation occurs mainly by viral TK. But GCV required very high dose rate to fully occupy the active site (Gallois-Montbrun et al., 2004; Karjoo et al., 2016a). This creates nonspecific toxicity such as immune suppression, acute depression of the bone-marrow and finally insufficient tumor killing ability. Manipulation of enzyme gene to create a mutant HSV-TK that provide the same effect of wild type enzyme at lower levels of prodrug, can greatly reduce this obstacle (Balzarini et al., 2006; Black et al., 2001). HSV-TK/GCV system similar to CD/5-FC system has been shown bystander effect. The difference is that GCV trafficking is depending on the presence of gap junctions, which enable the exchange of toxic products between transduced and untransduced cells (Li Bi et al., 1993; Mesnil et al., 1996). As it seems CD/5-FC system has better performance because it is freely diffusible across the cellular membrane and independent of GJIC and connexins expression. Rainov NG et al.,

reported that Temozolomide enhances the efficiency of TK/GCV against malignant glioma (Rainov et al., 2001). On the other hand, some ABC transporters such as ABCC4 and ABCG2 enhanced resistancy of transgene-expressing and bystander cells against TK/GCV system (Adachi et al., 2002). Also, based on previous studies, the origins of mutations are distinct in different tumor types so they show differences in sensitivity to various enzyme/prodrug systems (Huang et al., 2009; Jiang et al., 2014). This situation is seen more in single suicide gene therapy. Some results suggested that double suicide gene therapy with this genes had severer deadly effects than either one used alone (Aghi et al., 1998; Freytag et al., 1998; Uckert et al., 1998). On the other hand some reports shown that anticancer effect and survival rate were not significantly different between one and double suicide gene delivery, even single suicide gene systems may be preferable than combinations of the two systems (Chang et al., 2000; Moriuchi et al., 2002).

1.3. Other important suicide genes

The other gene/prodrugs that commonly used as suicide genes including CYP2B6/ cyclophosphamide (CPA), nitroreductase/CB1954 (NTR/CB1954), carboxylesterase (CE)/ CPT-11 (irinotecan) and Inducible caspase-9 (iC9) /chemical inducer of dimerization (CID). Primary studies demonstrate that efficiency of CYP2B6 for cancer therapy is low; the poor results may be explained by low affinity of CYP2B6 to CPA. This can be solved by insertion mutations in CYP2B6 (CYP2B6TM; CYP2B6 triple mutant) and fusion with NADPH cytochrome P450 reductase (RED) (CYP2B6TM-RED) (Argos, 1990; Braybrooke et al., 2002; Nguyen et al., 2008; Touati et al., 2014). NfsB nitroreductase (NTR) isolated from Escherichia coli can convert CB 1954 (5-(aziridin-1-yl)-2, 4-dinitrobenzamide) to a potent cytotoxic DNA chelating agent which can freely diffuse across the cell membrane and

trigger extensive DNA damage and apoptosis in cancer cells. However, low activation rate of this non-natural substrate, CB1954, appears to restrict the impact of this enzyme. In addition CB1954 induced dose-dependent hepatotoxicity (Chung-Faye et al., 2001; Greco and Dachs, 2001; Green et al., 2013). Gene-directed enzyme prodrug therapy (GEPT) is another approach for chemotherapeutics selectivity improvement. One of such gene/prodrug to drug systems is carboxylesterase (CE)/campothecin (CPT-11) to SN-38 (7-ethyl-10-hydroxycamptothecin). CPT-11 could inhibit mammalian DNA topoisomerase I, while SN-38 Inhibits this enzyme activity approximately 1000 times more effectively than CPT-11 (Pommier, 2006; SATOH et al., 1994; Wierdl et al., 2001). iC9 is another suicide context refer to an inducible caspase-9 actually a pro-apoptotic protein caspase9 that bind to a modified human FK-binding protein. AP1903, as chemical inducer of dimerization (CID) can activate iC9 and dimerized caspase-9 resulting in apoptosis (Ando et al., 2014; Boatright et al., 2003).

2. Talent of MSCs in Cancer Gene Therapy

Adult stem (AS) cells are a potentially valuable source in regenerative medicine .they are dividing to neural stem cells (NSCs) (ectoderm), hematopoietic stem cells (HSCs) (mesoderm), and MSCs (mesoderm) (Robinton and Daley, 2012; Weissman, 2000). In vitro expansion of NSCs is limited to the nervous system; they couldn't survive outside the nervous system. HSCs have been utilized in allogeneic cell therapy. Although bone marrow (BM) has been the principal source for the isolation of these cells, the harvesting of bone marrow entailed a highly invasive procedure with low cell yields (Prockop, 1997; Sylvester and Longaker, 2004). It is easier to work with MSCs, due to their less invasive and free of ethical issues harvest in compare with other sources (Amara et al., 2014; Cavarretta et al., 2010; Compte et al., 2009). MSCs were first obtained from bone marrow and defined as

fibroblast-like multipotent stem cells by Friedenstein and coworkers in 1974 (Friedenstein et al., 1970).

International Society for Cell Therapy (ISCT) proposed minimal criteria to describe human MSCs; adhere to plastic, ability to differentiate into adipocytes, osteoblasts, and chondrocytes, fibroblastoid phenotype and expression of cell surface markers CD105, CD73, CD271, CD90 and ganglioside GD2 in more than 95% of cells and absence of CD45, CD79a or CD19, CD34, CD14 or CD11b, CD40, CD80, CD86 and the MHC II class cellular receptor HLA-DR (Baird, 2015; Dominici et al., 2006; Goradel et al., 2017; Horwitz et al., 2005; Mirzaei et al., 2016d; Mirzaei et al., 2017d; Mohammadi et al., 2016b). But it should be noted that there is no unique key determinant factor to distinguish MSCs, also the relative expression levels for these markers could be varied according to the species diversity, tissue sample and culture conditions. At first MSCs isolated from bone marrow (BM) but subsequently found in other source such as adipose tissue (AT), umbilical cord blood (UCB), peripheral blood, surrounding blood vessels, synovium, the circulatory system, dental pulp and amniotic fluid (Morizono et al., 2003; Phinney and Prockop, 2007; Uchibori et al., 2014). In spite of the fact that MSCs only represent a small percentage of the total number of BM populating cells 0.01-0.001%), they extensively used by many researchers (Li et al., 2015). Since MSC isolation from BM recognized as an unpleasant experience, adipose tissue another valuable source of MSCs, has drown great attention in recent years (Kucerova et al., 2008).

Adipose tissue mostly isolated from subcutaneous tissue, we can get ~ 40-fold higher yield of MSC from adipose tissue compared with the bone marrow. The rate of isolation of MSC from human AT is 100%. Great interest has developed in AT-MSC, which is free of ethical concerns and invasiveness (Kern et al., 2006). Moreover it was reported that AT-MSC can be expanded long term without the loss of their phenotype. In contrary, BM-MSCs should be

used during early cell passages (below P8) to prevent potential differentiation (Lee et al., 2006). UCB-derived MSC has significantly higher rate of expansion in compared with BM-MSC. Since these cells are obtained from placenta that discarded after birth, so the collection procedure is totally noninvasive and free from ethical considerations (Li et al., 2015). MSCs also have been exploited as tumor specific delivery vehicles for cancer gene therapy by multiple reasons; immunoprivileged status (due to lack of major histocompatibility complex MHC-II and only minimal MHC-I expression) and natural tropism for tumors and their metastases. MSCs do not motivate the host immune response and escape immunological rejection in allogeneic injection (Desmoulière, 2008; Kidd et al., 2008; Zhang et al., 2014).

In addition MSCs can be efficiently transduced with viral or non-viral vectors containing a target gene. For example, in separate studies JIANG and Bak et al., demonstrated that hUCB-MSCs and hBM-MSCs can be simply infected by the lentivector and baculovirus respectively at a high efficiency of over 80% (Bak et al., 2010; Jiang et al., 2014). MSCs mostly transduced through viral vectors including lentiviruses, retroviruses, baculovirus and adenoviruses. All of these viral vehicles produce stable expression, while the later create transient expression of therapeutic genes. Non-viral vectors have been exploited in limited number of studies. The examples are nucleofection, spermine-pullulan (SP), PEIcyclodextrin and cationic liposomes and cationic polymers (Gao et al., 2010; Uchibori et al., 2009; Zhang et al., 2014). Results revealed that in healthy animal models MSCs mostly migrate to lung, liver and bone but also MSCs have high migration potential to the tissue injury and inflammation (Hu et al., 2010; Kidd et al., 2008). For example, inflammation has long been associated with the development of cancer, MSCs exhibit strong tropism toward tumors and their metastases by expression of receptors such as CCR1, CCR4, CCR7, CCR9, CCR10, CXCR4, CXCR5, CXCR6, RAGE, CX3CR1, VEGFR, c-Kit and c-Met for Infammatory chemokines and growth factors including SDF-1(CXCL12), MCP-1, HGF, IL-8, NT3, TGF-

b, GCSF, VEGF, IL-8, IL-6, CCL2, HMGB1 and SCF (Honczarenko et al., 2006; Reagan and Kaplan, 2011; Ringe et al., 2007). CXCR4 is the most important chemokine receptor implicated in targeted homing of MSCs. MSCs expression profiling demonstrates that overexpression of CXCR4 and down regulation of MMP-2 have greater role in migration capability in to tumor sites, whereas knockdown of SDF-1 plays a negative role in stem cell recruitment to tumors (Menon et al., 2007; Song and Li, 2011). Sato et al demonstrated that epidermal growth factor receptor gene transfection conferred enhanced migratory activity towards GL261 gliomas or B16 melanoma in vivo (Sato et al., 2005). Moreover adhesion molecules, such as b1- and b2-integrins and L-selectin, are involved in MSC migration and homing to tumor site (Hu et al., 2010). A recent report on MSC behavior have highlighted the great impact of irradiation on MSC tropism and engraftment to tumor location, mediated at least in part by apoptosis and subsequent enhanced local release of inflammatory signals such as CCL2 and CCR8. For example UCB-MSCs-based TRAIL gene delivery to irradiated glioma tumors enhanced apoptosis in glioma cells. Besides radiotherapy could increase MSC localization in LoVo, HT-29 (colon) and MDA-231 breast cancer cells (Kim et al., 2010; Klopp et al., 2007; Zielske et al., 2009). Every safe cell-based therapy will require the capability to harness the unwanted growth of cells. Local injection of MSC developed some side effects i.e. ectopic ossification and calcification foci in mouse and rat models of myocardial infarction. Moreover bilateral diffuse pulmonary arises after bone marrow transplant in a dog. In a distinct study spontaneous osteosarcoma formation in culture has been reported in murine-derived MSCs (Breitbach et al., 2007; Sale and Storb, 1983; Yoon et al., 2004). Albeit MSCs have been utilized for treatment of many patients without major undesirable effects but some results, both in vitro and in vivo models suggest that must be cautions in this regard. MSCs exhibit pro-tumorigenic or tumor-supporting roles through inhibition of immune system and apoptosis, stimulation of EMT (epithelial– mesenchymal

transition) and enhancement of angiogenesis, proliferation, migration and metastasis (Djouad et al., 2003; Martin et al., 2010; Ramasamy et al., 2007). Unmodified MSC have antitumor properties in leukemias, glioma, and melanoma, and breast, hepatoma and lung cancer cells (Ramasamy et al., 2007; Sun et al., 2009). In this regards Ma et al observed the growth inhibition of breast CSCs by hUCMSC both in vitro and in vivo. Ohlsson L et al., showed that mesenchymal progenitor (immortalized MSCs) are effective at inhibiting the in vivo proliferation of rat colon carcinoma cells (Ma et al., 2012; Ohlsson et al., 2003). The underlying mechanism about antitumor effect of MSCs is likely related to down-regulation of Wnt, Akt, PI3K and NF-kB signaling pathways by factors released from MSC in tumor position (Dai et al., 2011; Ma et al., 2012). Some studies in order to increase the innate antitumor effects of MSCs carried out gene modification with oncogenes or other genes promoting cell proliferation but these modifications are associated with higher risk of tumorigenicity (Miletic et al., 2007). Engineered MSCs was first use for direct delivery of interferon ß (IFN-ß) gene to melanoma xenografts mice (Studeny et al., 2002). Considerable reduced in tumor growth rate and significant prolongation of survival of tumor-bearing mice motivated more researches to study therapeutic efficacy of genetically modified MSCs as cellular vehicles for several cancer treatments. MSCs explored for local secretion of therapeutic cytokine proteins such as; IFN-ß, IL-12, IL-24 and IL-2, delivery of prodrug activator genes (i.e. actually suicide genes) that will be explained in the following, amplifying and deliver of oncolytic viruses such as conditionally replicating oncolytic adenoviruses (CRAd), ICOVIR-5 and measles virus (MV), secretion of pro-apoptotic proteins such as TRAIL, TNF-related apoptosis ligand, anti-angiogenic agents such as TSP1 and endostatin and growth factor antagonists i.e. NK4 (antagonist of hepatocyte growth factor (HGF)) (Fig 1) (Dwyer et al., 2010; Li et al., 2016; Shah, 2012). MSCs loaded with nanoparticles

containing chemotherapy drug, paclitaxel have been shown high efficient tumoricidal effect (Sadhukha et al., 2014).

It has been showed that MSCs could have dual effects on cancerous condition. Anti-cancer and tumorgensis effects of MSCs led to some concerns about utilization of them as therapeutic agents. It has been showed that express of different types of MSCs surface markers play critical roles in the effect of MSCs in various conditions.

Finally, three main points regarding employing of MSCs as vectors remain to be defined: i) MSCs are cells with active physiological process which using of them are not simple delivery platform. They could release a wide array of different molecules (i.e. growth factors, cytokines and chemokines). Hence, they may provide various signals which could lead to enhancing of tumor burden and metastases. ii) Cancerous microenvironments may lead to inducing of malignant transformation in the injected MSCs. iii) How many MSCs need to be given and when and where they should be administrated. Hence, better understanding of MSCs physiology within the tumor sites, and more robust studies characterizing their homing mechanisms could enhance suggested therapies.

MSCs-exosomes as new therapeutic approach for cancer therapy

Among of various signaling and cellular effects of MSCs, exosomes released from MSCs have critical roles for transferring specific signals to host cells. Exosomes are known as nano vesicles which could carry a variety of molecules and markers such as DNAs, mRNAs, microRNAs, and proteins (Banikazemi et al., 2017; Borujeni et al., 2017; Mirzaei et al., 2016e). The cargos are able to change behavior of host cells via targeting various cellular and molecular targets (Mirzaei et al., 2016e; Saadatpour et al., 2016). For example, microRNAs (miRNAs) are one of important cargos which could be carried by exosomes. MiRNAs are small non-coding RNAs which have critical roles in regulating of a variety of vital biological processes such as growth, angiogenesis, and differentiation (Golabchi et al., 2017; Hashemi

Goradel et al., 2017; Keshavarzi et al., 2017b; Mashreghi et al., 2017; Mirzaei et al., 2017b; Mirzaei et al., 2016g; Rashidi et al., 2017; Salarinia et al., 2016). It has been showed that deregulation of them could be associated with imitation and progression of a wide range of diseases such as cardiovascular diseases, stroke, diabetes and cancer (Fathullahzadeh et al., 2016; Gholamin et al., 2017; Hoseini et al., 2017; Keshavarzi et al., 2017a; Mirzaei, 2017; Rabieian et al., 2017; Rashidi et al., 2016; Simonian et al., 2017). These molecules exert their effects via targeting various cellular and molecular pathways involved in various physiological processes (Gholamin et al., 2016; Mirzaei et al., 2017a; Mirzaei et al., 2016b; Mirzaei et al., 2017c; Mirzaei et al., 2016i; Mohammadi et al., 2016a; Moridikia et al., 2017). Hence, targeting of miRNAs by exosomes could lead to change behavior of host cells and could be associated with emerging of diseases condition or therapeutic effects (Mirzaei et al., 2016a; Mirzaei et al., 2016c). Exosomes could be released from various types of cells such as cancer cells, and MSCs. These nano-particles could exert their inflammatory or anti-inflammatory effects on host cells (Rani et al., 2015). It has been showed that MSCs employed exosomes for paracrine functions. Paracrine functions of MSCs are known as one of important mechanisms involved in anti-inflammatory effects of MSCs (Rani et al., 2015). Hence, it seems that utilization of exosomes released from MSCs could be used as effective candidate for treatment of various diseases.

3. MSCs as a Vehicle for Targeting Suicide Genes

Identification of new drug delivery platform is one of the major landscapes in cancer gene therapy (Mohammadi et al., 2016b). Despite a numerous of novel therapeutic approaches have emerged, none has yet confirmed the ability to cure various cancers. In this regard

MSCs emerge to be promising new therapeutic option. The natural tropism of MSCs for tumor sites makes them excellent vehicles for tumor-targeted therapies (Mohammadi et al., 2016b). Also, it has been showed that use of genetically-modified MSCs may overcome limitations related with systemic administration of some cytokines and anti-neoplastic agents with a short half-life and high toxicity (Mohammadi et al., 2016b). Viral vectors for directed enzyme prodrug therapy (GDEPT) or suicide gene therapy have been utilized by multiple studies. This approach has some limitations due to its low specificity for tumor cells and systemic toxicity. Utilization of viral vectors for targeting various genes such as suicide gene are associated with various limitations such as high immunogenicity (Mirzaei et al., 2016f). Hence, several studies applied improved viral vectors for overcoming to various limitations. Moreover, it has been showed that other vectors such as Piggybac could be used for targeting various genes and be associated with same or better results than viral vectors (Mirzaei et al., 2016f). Hence, utilization of Piggybac or improved viral vectors could be employed as new delivery system with high potential for targeting various genes such as suicide genes. Genetically engineered MSCs using a GDEPT strategy could be a good resolve for these obstructions. MSC-targeted gene therapy is a two-step procedure. In the first step, the gene for the foreign enzyme (bacterial, yeast or viral) is targeted to the tumor by transduction of MSCs. In the second step, transcription of the gene encoding the prodrug-drug converting enzyme could generate a lethal substance at the tumor site. With looking to previous studies we found that the retroviral suicide gene construct is often used for MSC transduction and most frequent transduced suicide genes are CD and HSV-TK. A large number of approaches have been applied using AT-MSCs and BM-MSCs as a delivery system for anti-neoplastic agents (Amara et al., 2014). A key characteristic of manipulated MSCs is that they have no difference with naïve MSCs in terms of proliferation, differentiation and tumor homing potentials as well as surface antigenicity (Park et al., 2013). Until now many in vitro and in

vivo studies carried out using MSCs in cancer therapy. A brief report of studies within this research area is embedded in Table 1. Due to this fact that MSCs express very low levels of receptors, like most healthy tissues, are unaffected by TRAIL-induced apoptosis. As a result recruitment of MSCs secreting TRAIL brings brilliant results in cancer treatment (Grisendi et al., 2010; Kim et al., 2008; Loebinger et al., 2009; Mohr et al., 2008). Moreover co-transfection of the TRAIL gene with some cases of double suicide gene approaches (i.e. HSV-TK) that confront with some difficulties including antagonistic antitumor activity, could improve the efficiency of tumoricidal effect (Kim et al., 2013; Martinez-Quintanilla et al., 2013). In order to achieve efficient homing of MSCs to the tumor site, the median amount of administered therapeutic cells recommended to be less than 10% of the tumor mass (Hung et al., 2005). Therefore, it is logical to use multiple injections of the therapeutic cells at a low dose rather than single injection at high dose. For example, Kim W et al., reported that mouse with metastatic renal cell carcinoma (RCC) after 2 and 3 injections of small-divided doses of MSC/TRAIL-TK represents 50% and 100% survival respectively (Kim et al., 2013). The potency of consecutive suicide gene therapy was also evaluated in another study in which repeated intracerebral injection of CDy:UPRT-AT-MSC lead to 88% increase in the survival time of rat with glioblastoma (Altanerova et al., 2012). Some studies employed combined therapeutic modalities for malignant disease treatment. Combination of suicide gene- MSCs with chemotherapy drug shows satisfying results in some cases. Ando M et al revealed that NSCLC progression prevents following proteasome inhibitor bortezomib administration, together with MSC- Ad.iC9. While, this drug is ineffective for the treatment of NSCLC, alone (Ando et al., 2014). In another study MSCs-TK and Valproic acid (VPA) has been used for treatment of glioma-bearing mice (Ryu et al., 2012). The combined treatment had dramatic inhibitory effects on tumor growth and prolonged the survival rate in mice.

Future perspective

Current data indicate that cancer incidence is steadily increasing in the World. There is high mortality statistic available in current decades. All of these highlighted the urgent need for more safer and more effective therapies. One of the principal challenges along cancer treatment is how to destroy malignant tumors without damaging healthy cells. A new approach that shows great promise in this area is employment of a suicide gene. In this way we need an appropriate carrier for therapeutic gene delivery specific to cancer site. The application of anti-cancer gene-expressing MSCs for targeted cancer therapy is a novel and promising strategy. MSCs with important characteristic such as strong tumor tropism, unlimited packaging capacity and unique immunologic tolerance, could overcome current obstacles and successfully deliver these suicide genes. Although MSCs have anticancer capacity but based on some reports could have positive role in tumor progression. Eventually more researches required to find novel insights into MSCs biology, potential clinical application and molecular mechanism for homing to tumor site.

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Table 1. Characteristic of previous studies in MSC-targeted suicide gene therapy

Type of cancer (cell line)	Source of MSCs	Type of suicide gene	Vector	Administration route	Ref
ovarian carcinoma (SKOV3)	hUCBMSCs	HSV-tk/ CD Combined treatment	lentivirus	Just in vitro	(Jiang et al., 2014)
colon cancer (HT-29)	hAT-MSC	CD::UPRT	retrovirus	systemically administered	(Kucerova et al., 2007)
bone metastatic PC (Du145, PC3, and LNCaP)	hAT-MSC	CD::UPRT	retrovirus	systemically administered	(Cavarretta et al., 2010)
Glioma (9L)	hBM-MSC	Hsv-tk	pcDNA3.1/Hygro(-) plasmid	local injection	(Mori et al., 2010)
Glioma (9L)	RatBM-MSC	HSV-tk	retrovirus	local injection	(Miletic et al., 2007)
Lewis lung carcinoma (LLC cell line)	miceAT-MSC	CD::UPRT & CD::UPRT::VP22 Separately	plasmid	systemically administered	(Krassikova et al., 2016)

Melanoma (A375)	hAT-MSC	CD::UPRT	retrovirus	systemically administered	(Kucerova et al., 2008)
gastric cancer (MKN45)	hBM-MSC	CD	pcDNA-CD plasmid	systemically administered	(You et al., 2009)
non-small cell lung cancer	hBM-MSC	iC9	adenovirus	systemically administered	(Ando et al., 2014)
Breast cancer MDA-MB-231	hAT-MSC	CD::UPRT or HSV-tk Seperatly	retrovirus	systemically administered	(Matuskova et al., 2015)
Renal Cell Carcinoma (RENCA)	RatBM-MSC	TRAIL-tk	adenovirus	systemically administered	(Kim et al., 2013)
Glioma (C6)	hAT-MSC	CD::UPRT	retrovirus	local injection	(Altanerova et al., 2012)
mice bearing TC1-Luc2 tumors	miceBM-MSC	CYP2B6TM-RED	lentivirus	local injection	(Amara et al., 2016)

pulmonary melanoma (B16F10)	RatBM-MSC	CMV-tk	spermine-pullulan (SP)	systemically administered	(Zhang et al., 2014)
ovarian cancer (SKOV3)	hBM-MSC	TK007 & TK SR39 & CD:UPRT & NTR Seperatly	mammalian Expression plasmid vectors	local injection	(Nouri et al., 2015)
Glioma (8-MGBA, 42-MG-BA and U-118 MG)	hAT-MSC	HSV-tk	retrovirus	systemically administered	(Matuskova et al., 2010)
Melanoma (A375) & Glioma (8-MG-BA)	hAT-MSC	HSV-tk & CD::UPRT Seperatly	retrovirus	Just in vitro	(Matuskova et al., 2012)
Prostate cancer (TRAMPC1 & TRAMPC2)	hAT-MSC & miceBM-MSC	CD::UPRT	retrovirus	systemically administered	(Abrate et al., 2014)

Glioma (9L)	RatBM-MSC	HSV-tk	retrovirus	local injection	(Uchibori et al., 2009)
Glioma (U87MG)	hBM-MSC	CD	retrovirus	local injection	(Park et al., 2013)
Hepatocellular Carcinoma (Huh7)	miceBM-MSC	HSV-tk	plasmid	systemically administered	(Niess et al., 2011)
Lung adenocarcinoma (A549)	miceBM-MSC	HSV-tk	retrovirus	Just in vitro	(Yang et al., 2014)
Prostate cancer (DU145 & PC3)	SV40-hfBMSCs *	HSV-tk	lentivirus	systemically administered	(Lee et al., 2013)
Lung metastatic (By B16F10)	RatBM-MSC	HSV-tk	spermine-pullulan (SP)	systemically administered	(Zhang et al., 2015)
Osteosarcoma (Cal72)	hBM-MSC	CD::UPRT	plasmid	systemically administered	(NguyenThai et al., 2015)

Pancreatic carcinoma (Panc02)	miceBM-MSC	HSV-tk	plasmid	systemically administered	(Zischek et al., 2009)
Glioma (TJ899, TJ905, U251, U87 & C6)	RatBM-MSC	HSV-tk	adenovirus	local injection	(Huang et al., 2010)
Glioma (C6)	RatBM-MSC	CD	lentivirus	local injection	(Fei et al., 2012)
Glioma (U-87)	hAT-MSC	HSV-tk	lentivirus	local injection	(de Melo et al., 2015)
Glioma (C6/LacZ7)	hBM-MSC	CD	retrovirus	systemically administered	(Chang et al., 2010)
Glioma (C6)	RatBM-MSC	HSV-tk	retrovirus	local injection	(Gu et al., 2010)
Glioma (9L)	RatBM-MSC	CD	adenovirus	local injection	(Kosaka et al., 2012)
Glioma (U-87)	hBM-MSC	CD	retrovirus	local injection	(Jung et al.,

					2015)
prostate cancer (PC3,DU145) & breast cancer (MCF7) & mouse fibrosarcoma (RIF1)	RatBM-MSC	HSV-tk	lentivirus	systemically administered	(Song et al., 2010)
Glioma (C6)	RatBM-MSC	HSV-tk	retrovirus	local injection	(Amano et al., 2011a)
Glioma (C6)	RatBM-MSC	HSV-tk	retrovirus	local injection	(Amano et al., 2011b)
Glioma (U-87)	hBM-MSC	HSV-tk	adenovirus	local injection	(Ryu et al., 2012)
Glioma (U87MG)	hBM-MSC	HSV-tk	baculovirus	systemically administered	**(Bak et al., 2010)**

* Immortalization of human fetal bone marrow-derived mesenchymal stromal cells by simian virus 40