REVIEW ARTICLE

MSCs: Is This the Future Therapeutic for Cancer?

Andrea Kakouri
Post Graduate Student, Cell and Gene Therapy, University College, London, UK.

ABSTRACT
Cancer is nowadays one of the main causes of death worldwide. The numbers have shown that one in three people will develop cancer at some point in their lives. Cancer is a major issue for the whole humanity, and therefore a lot of research has been running for the past years in order to understand the mechanisms that underlie tumorigenesis and eventually cancer formation, with the perspective to discover new approaches for effective treatment. Gene therapy strategies that intended to tackle cancer systemically are often impaired by inefficient delivery of the vector to the tumor site. Several studies have shown the possibility of using mesenchymal stem cells (MSCs) as a future therapeutic mechanism against cancer, since they possess important features such as the ability to home to and target cancer cells. The engineering of MSCs to produce and deliver an apoptotic factor, calledtumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has been studied excessively. TRAIL is a transmembrane protein that causes selective apoptosis of tumor cells but does not have any harmful effects on the normal neighboring cells. Experiments have shown that this approach has significant results in mouse models and has now proceeded for clinical trials.

Keywords: Cancer, Mesenchymal stem cells (MSCS), Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)

INTRODUCTION

Cancer remains one of the leading causes of death in the world with more than 10 million cases occurring globally each year.[1-3] Despite the great improvements in medicine and healthcare, the current treatments have often limited results and are often accompanied by severe side effects, while metastatic cancer remains poorly responsive to conventional therapy.[2] The emerging of mesenchymal stem cells (MSCs) as a tool against several diseases, gives a new perspective for cancer therapy which may also be beneficial against metastatic cancer. The use of MSCs has number of advantages, including their ability to home to damaged tissue sites, their facile isolation from various parts of the body and subsequently expansionin vitro, as well as their ability to be genetically modified with viral and non-viral vectors. They are described as migratory molecules which home to sites of inflammation including tumors and interact with lymphocytes exerting potent immunosuppressive and anti-inflammatory effects.[4] The isolation of MSCs is convenient and accessible from a number of tissues, with the commonest being the bone marrow.[4] As true stem cells, MSCs can self-renew and differentiate into multiple cell lineages of the mesoderm and are hence promising candidates for clinical use either as delivery particles or for regenerative medicine.[5-7]

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a type II transmembrane death ligand that causes apoptosis of target cells through the extrinsic apoptosis pathway. TRAIL belongs in the tumor necrosis factor superfamily, similarly with tumor necrosis factor and Fas ligand.[2,8] The extracellular region of TRAIL forms a soluble molecule on cleavage and both membrane-bound and soluble TRAIL can interact with the death receptors DR4/TRAIL-R1 and DR5/TRAIL-R2 and result in apoptosis of transformed cells.[8-12] The capability of TRAIL to be expressed constitutively in many normal tissues without having toxic effects on them is what makes it an attractive and ideal molecule for clinical application, while it also suggests that normal cells have mechanisms which protect them from TRAIL-induced apoptosis.[8,9,13-15] Reports have concluded that TRAIL can specifically kill malignant cells, leaving the normal neighboring cells unaffected,[9] whereas tumor necrosis factor and Fas ligand seem to be toxic towards both malignant and normal tissues.[2,16,17] Although the extracellular region of TRAIL is sufficient to induce apoptosis of tumor cells, the homotrimerization is needed in order for TRAIL to retain its activity, be expressed and capable of interaction with the death receptors DR4/TRAIL-R1 and DR5/TRAIL-R2.[9,13,14,18] Several studies have reported anti-tumor activity of TRAIL

Access this article online	
Website: www.actamedicainternational.com	Quick Response code
DOI: 10.5530/ami.2015.4.9	

Corresponding Author:
Andrea Kakouri, Post Graduate Student, Cell and Gene Therapy, University College, London, UK. +44 7719100402.
E-mail: andrea_kak29@hotmail.com

against a range of different cancers, although the levels of sensitivity of each type towards TRAIL vary.[9] However, its intravenous delivery has presented problems including a short pharmacokinetic half-life.[2,13,14] thus requiring frequent and high doses in order to cause an efficient therapeutic effect.[2] Here we review that the use of MSCs as a delivery vector promises to provide a specifically targeted, as well as prolonged delivery of the TRAIL death ligand.[2]

MSCS: ATTRACTIVE CANDIDATES FOR CLINICAL APPLICATIONS

MSCs are multipotent progenitor cells with the potential to self-renew and differentiate into multiple cell types of the mesoderm, including the adipocytes, osteocytes, and chondrocytes.MSCs have also been describeto differentiate beyond those cell lineages, and particularly to cells originating from the ectoderm and endoderm, such as hepatocytes, neurons, and cardiomyocytes.[4,19-24] This multipotent nature of MSCs facilitates their use in regenerative medicine and tissue repair.[4] MSCs have been reported to migrate to tumors when injected systemically, although the mechanisms by which MSCs are guided towards specific in vivo targets are poorly understood.[7,25,26] They can also be isolated from a number of tissues with commonest being the bone marrow, while they can be expanded and manipulated in vitro with the potential to be re-implanted in the patient's organism. The fact that MSCs are immunoprivileged facilitates the re-implantation, since they can suppress immune system, reintegrate into tissue architecture and give rise to progeny consisting of both stem cells and lineage restricted daughter cell types without the need of prior immunomodulation.[2,27,28] MSCs can also be isolated from the adipose tissue, the placenta, the amniotic fluid and the umbilical cord blood.[4,18,29-34] Apart from that, the ability to be genetically modified, gives the choice of using MSCs for overexpression of anti-tumor genes as an approach for cancer therapy.[4]

The commonest source of MSCs is bone marrow, since MSCs isolated from there have been described to possess the highest degree of lineage plasticity. Particularly, MSCs isolated from this tissue site can differentiate to virtually all cell types following implantation into early blastocysts and are relatively easy to handle in vitro.[28,35,36] However, the procedure of isolating MSCs from the bone marrow is invasive, and results in insufficient numbers of MSCs and a limited differentiation potential.[28,37-39] This limitation shows that other more practical sources must be used in the clinical setting. The adipose tissue can be used; this isolation site can give abundant numbers of MSCs. In addition to the simple techniques used for the adipose tissue MSCs isolation, this tissue site gives a sufficient expansion potential for MSCs, as well as differentiation capacity and immunophenotype that resembles that of bone-marrow MSCs.[28,38] Another important source of MSCs is the umbilical cord blood, obtained after removal of the placenta. This rich source of hematopoietic stem cells (HSCs) has also been shown to be rich in MSCs.[28,40,41] Compared to bone marrow-derived MSCs, the MSCs that are isolated from the umbilical cord blood have a higher expansion rate, while they also maintain a great differentiation potential without being affected from ageing, whereas bone marrow MSCs lose this ability through time.[28,38,42] The high levels of expansion of umbilical cord blood MSCs have been explained to be partly caused by the high telomerase activity.[28,43]

In regards to cancer therapy, MSCs seem to bring important features, such as the secretion of soluble factors that induce an immunomodulatory environment. MSCs were shown that can naturally have anti-tumor effects in both in vitro and in vivo studies. Apart from their advantage of being genetically altered with anti-tumor factors, the unmodified MSCs have also the advantage of secreting factors with anti-tumor properties and consequently result in the reduction of proliferation of cancer cells and tumor growth. Studies have shown evidence of the anti-tumor capacity of MSCs in several cancer models, including glioma, melanoma, lung cancer, hepatoma and breast cancer, as well as Kaposi's sarcoma when MSCs were injected intravenously.[28,44-47] MSCs also interact with chemokine and receptor interactions, such as stromal cell-derived factor 1 (SDF-1)/C-X-C chemokine receptor type 4 (CXCR4)stem cell factor/c-kit, HGF/c-Met, vascular endothelial growth factor (VEGF)/VEGF receptor, platelet-derived growth factor (PDGF)/PDGF receptor, monocyte chemoattractant protein-1 (MCP-1)/C-C chemokine receptor type 2, and high mobility group box 1/receptor for advanced glycation end-products as well as other cell adhesion molecules, which facilitate their migration towards tumor sites.[4,13,48-54] The role of these cytokine-chemokine receptor pairs is major, since they are required for leukocytes or HSC responses to injury and inflammation and are thought to function similarly in MSCs. This in addition to the fact that the tumor microenvironment resembles that of an unhealed wound, by continuously producing inflammatory signaling molecules, such as cytokines, chemokines, and other chemoattractant molecules make the MSCs ideal for a treatment approach against cancer, since they tend to migrate towards these stimulatory molecules.[4,55] The SDF-1 and CXCR4 is the most important chemokine receptor pair for stem cell recruitment to tumor sites.[4,51] The homing of MSCs towards tumor sites also includes the action of hypoxia-induced transcription factor, HIF-1a, which when found in a hypoxic environment such as that of the tumor, it results in the transcription of genes such as VEGF, macrophage migration inhibitor factor, TNF and other cytokines which in turn lead to the expression of chemokines and the migration of MSCs.[4,56,57]

STUDIES ON CANCER TREATMENT USING TRAIL

TRAIL Delivery by an Adenoviral Vector

The appearance of TRAIL for delivery via MSCs is a new method which has now stepped into the clinical trials after several pre-clinical studies on mouse models.[28] In 2001, the study of Kagawa et al., examined the delivery of TRAIL into malignant cells in vitro and tumors in vivoby a construction of adenoviral vectors. Systemic delivery of TRAIL was shown to induce cancer cell apoptosis without having toxic effects to the rest of the cultured normal fibroblasts or mouse hepatocytes. In contrast, Bax which is an apoptosis regulator, has hazardous effects on normal cells.It was also observed that apoptosis was not only induced in TRAIL-expressing cells, but also in the neighboring GFP-expressing cancer cells which were co-cultured with the TRAIL-expressing ones. In contrast, Bax-expressing cells did not allow the apoptosis of GFP-expressing cancer cells, suggesting that the use of TRAIL as an anticancer agent has bystander effects.[28] The study of Kagawa et al. (2001) showed that the delivery of TRAIL by an adenoviral vector resulted into cell death, bystander effects and suppressed growth in vitro and in vivo without any significant effects on normal cells. The experiment ran with TRAIL delivered via an adenoviral vector without transfer via medium, suggesting that the properties of TRAIL against cancer cells are induced through membrane-bound TRAIL.[9] The significant property of TRAIL being non-toxic to normal cells was also confirmed after the TRAIL gene was shown to not causing any effects in vitro cultured normal human cells and in vivo animal models.[14,15,34] The use of TRAIL against cancer can also be applied in cooperation with a chemotherapeutic agent with the potential to result into a more efficient cancer cell death. This suggestion was confirmed in this study where results showed that TRAIL could work synergistically with chemotherapeutic drugs and result into reduction of tumor proliferation and growth, and in some cases tumor ablation.[9,13,14,58-59]

TRAIL-EXPRESSING MSCS DELIVERED BY A LENTIVIRAL VECTOR

Despite the very promising conclusions of Kagawa et al. (2001), it has been reported that normal cells could in some cases be susceptible to apoptosis induced by TRAIL and that a treatment combining TRAIL and chemotherapeutic drugs could lead to toxic effects on human cells.[9,59] To minimize the possibility of normal cells being affected by such a treatment, further studies have focused on the targeting of TRAIL towards cancer cells specifically via stem cell delivery.[9] There has been a number of studies examining the delivery of TRAIL using the MSCs as a delivery vector. The paper of Loebinger et al. in 2009, has proposed that genetically modified MSCs delivered by a lentiviral vector can be proven importantly beneficial against lung cancer and it indeed showed that there's a significant reduction in the number of cancer and metastatic cancer cells in a mouse lung metastatic cancer model. The activation of TRAIL was conditionally activated by the Tet-On system, which allows the turn on and off of TRAIL expression, through addition or withdrawal of doxycycline or other tetracycline derivatives.[2] It was shown that MSCs can be infected at high efficiency using a lentiviral vector and that the delivery of TRAIL causes apoptosis of cancer cells through the extrinsic death pathway. What is more, in vivo mouse models presented significant reduction in metastasis number and complete clearance in 38% of mice compared to the controls, making MSCs a promising therapeutic against cancer.[2] The study of Loebinger et al. (2009) using bone-marrow derived MSCs reported that transduction with TRAIL and the IRES-eGFP reporter gene under the control of a tetracycline promoter using a lentiviral vector induces cancer cell apoptosis in various cancer types, including lung, breast, squamous and cervical cancer. In addition, subcutaneous xenograft experiments confirmed that directly delivered TRAIL-expressing MSCs were able to reduce tumor growth, while in a pulmonary metastasis model delivery of MSCs completely cleared the metastatic disease in 38% of mice compared with 0% of controls.

A more recent study has also described the delivery of TRAIL-transduced MSCs by a lentiviral vector, as a possible therapy to treat malignant pleural mesothelioma (MPM).[59] MPM is a devastating type of cancer, occurring in the pleural lining.[59] Although rare, it is one of the most lethal types of cancer, related to asbestos exposure, and no effective treatment has been identified so far.[59,60] MPM shows high resistance to the intrinsic-mediated apoptosis and hence, as most chemotherapeutic drugs act through that particular pathway, they cannot result into efficient cancer cell apoptosis in the MPM cases. Because of this limitation, interest has turned to activation of the extrinsic apoptotic pathway for MPM targeted therapy.[61] The study of Sage et al., in 2014, has focused on the use of TRAIL, which as described earlier binds via the transmembrane death receptors DR4/TRAIL-R1 and DR5/TRAIL-R2, causing apoptosis via caspase cascade activation. The benefit of inducing cancer cell apoptosis via the extrinsic pathway has been demonstrated in the experiments of Sage et al. (2014), where MSCs were transduced with TRAIL and delivered via a lentiviral vector to the cancer cell lines in vitro as well as cancer sites of mouse models in vivo. MSCs were transduced with TRAIL-IRES-eGFP and the expression of the proteins was controlled via the Tet-On system and specifically via the addition or withdrawal of doxycycline.TRAIL-transduced MSCs or recombinant TRAIL (rTRAIL) were co-cultured in vitro with MPM. 49 hours later a significant increase in apoptosis was observed in cancer cells when co-cultured with transduced

MSCs compared to those which were co-cultured with rTRAIL, suggesting that MSCs can target cancer cells more efficiently by homing to tumor sites and expressing TRAIL.[58] The deliveryfor the in vivo experiments was succeeded via intrapleural and intravenous injections, with the results showing that the transduced MSCs caused a significant reduction in the tumor growth when injected intravenously, but not intrapleurally. Immunofluorescent microscopy was used to confirm that the MSCs were signaling within the tumor stroma after they were delivered intrapleurlly and intravenously, while no signal was observed outside the lungs, confirming that MSCs did not migrate to other tissues and that no toxicity was detected. The experiments carried in vivo on mouse models showed a significant reduction in tumor growth and lung weight in the transduced-MSC group of mice compared to the untransduced-MSC and PBS groups. The study of Sage et al. (2014) concludes that even though both delivery routes, the intrapleural and intravenous, lead to MSC migration to the tumor sites, there is a specific advantage in the level of accumulation when the injection is intravenous. Consequently, this massive accumulation of cells after intravenous injection could be the reason why the level of apoptosis was higher in the group of mice where TRAIL-transduced MSCs were delivered via the intravenous route than in the group which were injected intrapleurally. The mechanism by which MSC were suggested to accumulate in tumor sites is suggested to be via adhesion to vascular endothelial cells and cooperation of other factors which facilitate this adhesion.[59,62,63] Hence, in intravenous injection, where the cells are directly delivered to endothelial cells, it is more likely that adhesion will occur compared to intrapleural delivery where the cells are delivered to areas that are poorly vascularized and hypoxic, thus leading to MSC death.[59,64]

TRAIL-EXPRESSING MSCS IN ADDITION TO A CHEMOTHERAPEUTIC AGENT

A later study of Loebinger et al., in 2010, has focused on the synergistic cooperation of TRAIL and a chemotherapeutic agent against side and non-side populations of squamous and lung cancer cell lines. Side populations (SP) of tumors are described those parts of tumors which contain stem-like populations that show increased potential towards tumorigenesis, as well as resistance to traditional therapies. TRAIL was delivered to tumor cell lines via transduction of MSCs with a lentiviral vector expressing the TRAIL gene. The TRAIL expression was conditionally activated with the Tet-On system, as described earlier, using doxycycline. Under GFP-expression, the delivery and activation of TRAIL via MSCs, was shown to significantly reduce the colony formation.[34] Numbers have concluded in 57.3±10.0% of apoptotic cells when doxycycline was added, whereas when TRAIL was not activated with doxycycline, the number of apoptotic cells reached only the 33.9±2.4%. The SP of tumors is characterized by its resistance to chemotherapeutic drugs and other cancer treatments. The study of Loebinger et al., (2010), tested whether a chemotherapeutic agent, such as mitoxantrone, could result in a significant reduction of cancer cells in SP when combined with TRAIL-expressing MSCs. This method can also be applied with other chemotherapeutic or radiotherapeutic drugs. The study of Sasportas et al., in 2009, has published significant results of CD133-positive glioma cell apoptosis by TRAIL, while other studies have also shown that the application of a TRAIL therapy could result in an increased sensitivity of SP colon cancer cells and oesophageal cancer cells to apoptosis, whereas they are resistant to radiotherapy.[34,64] Similarly Loebinger et al. (2010), demonstrated that a therapy combining both TRAIL with MSCs and a chemotherapeutic agent can have synergistic effect on cancer cells of both SP and non-SP lines, and consequently lead to apoptosis.

CLINICAL TRIALS

A number of phase I/II clinical trials have been running to this new approach of delivering TRAIL to tumor cells as a possible treatment against cancer. Specifically, a phase I/II trial with the agonistic TRAIL-R1 antibody, called Mapatumumab, in combination with a chemotherapeutic agent, called cisplatin and radiotherapy showed safe and efficient results in patients with cervical cancer. Other chemotherapeutic drugs were also tested in combination with TRAIL, such as Bevacizumab, which was used for treatment of non-small cell lung cancer. The use of TRAIL was also described as a synergistic tool for T-cells against metastatic renal cancer.[65] The potential delivery of TRAIL-transduced MSCs via a lentiviral vector was also proceeded into phase I/II clinical trials with promising results for the treatment of malignant pleural mesothelioma and eventually other types of cancer.[59] As described previously, TRAIL has the advantage of targeting only the tumor cells for apoptosis, leaving the neighboring normal cells unaffected. This property of TRAIL facilitates its use in clinical trials, since it is non-toxic to the patients, in contrast with chemotherapeutic and radiotherapeutic agents which damage the normal tissue. As a result, the application of TRAIL in phase I/II clinical trials is approved and promises a possible treatment for cancer.

CONCLUSIONS

The appearance of MSCs in the clinical field holds a promising future for therapies towards a number of diseases, including cancers. Not only MSCs have proven to exhibit anti-apoptotic properties themselves, but they can also be targeted as delivery vehicles to target tumor sites. MSCs have been engineered to express, pro-apoptotic, anti-angiogenic

agents to induce apoptosis in cancer cell lines. This type of stem cells are characterized by their facile isolation from a number of tissue sites, as well as their property of suppressing the immune system, avoiding the need of prior immunomodulation make them ideal candidates for a cell therapy against cancer. As true stem cells, they can also self-renew and differentiate to a number of cell types, thus avoiding the need of repeated injections for a continuous expression of the therapeutic agent, while they can also manipulated in vitro facilitating pre-clinical research.[27,28,66] On the other hand, TRAIL, a pro-apoptotic protein,also member of the TNF ligand family, binds to its death domain and specifically on DR4/TRAIL-R1 and DR5/TRAIL-R2receptors,resulting in caspase-mediated apoptosis in cancer cells while remaining non-toxic most other cell types.[28,67,68] Together with the data referred above, the studies focusing on a TRAIL-expressing MSCs cancer therapy suggest that this protein can show significant results as a potent anticancer agent without causing harm to normal cells.[9] The transfer and expression of TRAIL via viral vectors have been shown to induce cancer cell apoptosis. However, some data have demonstrated a minimum toxicity on normal tissues as well, describing the need of an approach that specifically targets only tumor sites. The application of MSCs as delivery vectors has been proved to be the more efficient and safe way to succeed this.[9] A number of studies have shown that the application of TRAIL-expressing MSCs as delivery vectors in cancer cell lines or mouse models is efficient for treating colorectal carcinoma, gliomas, lung, breast, squamous and cervical cancer, while phase I and II clinical trials are now running to test whether this therapeutic approach can be applied in cancer patients safely and efficiently.[2,28,69-71] The expression of TRAIL is able to cause apoptosis, followed by reduction in tumor growth and proliferation and consequently a decrease in tumor cell viability.[28] However, the level of efficiency in the delivery ofthe TRAIL into as many cancer cells as possible is still an important goal that needs to be targeted for succeeding a cancer treatment.[9] Lastly, the combination of TRAIL gene therapy with a chemotherapeutic or radiotherapeutic agent promises a possible increase in the efficiency of cancer therapy.[9]

REFERENCES

1. 1. Jemal, A., Siegel, R., Ward, E., Murray, T., Xu, J., Thun, M.J., Cancer statistics. CA: A Cancer Journal for Clinicians. 2007; 57: 43-66.
2. Loebinger, M.R., Eddaoudi, A., Davies, D., Janes, S.M., Mesenchymal stem cell delivery of TRAIL can eliminate metastatic cancer. Cancer Research. 2009; 69: 4134–42.
3. Yuan, Z., Kolluri, K.K., Sage, E.K., Gowers, K.H.C., Janes, S.M.,Mesenchymal stromal cell delivery of full-length tumor necrosis factor-related apoptosis-inducing ligand is superior to soluble type for cancer therapy. Cytotherapy. 2015; 0:1-12.
4. Nayoun, K. & Cho, S.G., Clinical applications of mesenchymal stem cells, The Korean Journal of Internal Medicine: KJIM. 2013; 28: 387-402.
5. Gregory, C.A., Prockop, D.J., Spees, J.L., Non-hematopoietic bone marrow stem cells: Molecular control of expansion and differentiation. Experimental Cell Research. 2005; 306: 330–335.
6. Laflamme, M.A., Murry, C.E., Regenerating the heart. Nature Biotechnology. 2005; 23:845–856.
7. Menon, L.G., Picinich, S., Koneru, R., et al. Differential gene expression associated with migration of mesenchymal stem cells to conditioned medium from tumor cells or bone marrow cells. Stem Cells. 2007; 25: 520-8.
8. Wiley, S.R., Schooley, K., Smolak, P.J., et al. Identification and characterization of a new member of the TNF family that induces apoptosis. Immunity.1995; 3: 673–682.
9. Kagawa, S., He, C., Gu, J., et al. Antitumor activity and bystander effects of the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) gene. Cancer Research. 2001; 61: 3330-8.
10. Pan, G., O'Rourke, K., Chinnaiyan, A.M., Gentz, R., Ebner, R., Ni, J., Dixit, V.M., The receptor for the cytotoxic ligand TRAIL. Science. 1997; 276: 111–113.
11. Pitti, R.M., Marsters, S.A., Ruppert, S., Donahue, C.J., Moore, A., Ashkenazi, A.,Induction of apoptosis by Apo-2 ligand, a new member of the tumor necrosis factor cytokine family. The Journal of Biological Chemistry. 1996; 271: 12687–90.
12. Walczak, H., Degli-Esposti, M.A., Johnson, R.S., et al. TRAIL-R2: A novel apoptosis-mediating receptor for TRAIL. The EMBO Journal. 1997; 16: 5386–97.
13. Ashkenazi, A. & Dixit, V.M., Apoptosis control by death and decoy receptors. Current Opinions in Cell Biology.1999; 11: 255–60.
14. Ashkenazi, A., Pai, R.C., Fong, S., et al. Safety and antitumor activity of recombinant soluble Apo2 ligand. The Journal of Clinical Investigation.1999; 104: 155–62.
15. Walczak, H., Miller, R.E., Ariail, K., et al. Tumoricidal activity of tumor necrosis factor-related apoptosis-inducing ligand in vivo. Nature Medicine.1999; 5: 157–63.
16. Nagata, S., Apoptosis by death factor. Cell. 1997; 88: 355–65.
17. Ogasawara, J., Watanabe-Fukunaga, R., Adachi, M., et al. Lethal effect of the anti-Fas antibody in mice. Nature. 1993; 364: 806–9.
18. Zuk, P.A., Zhu, M., Mizuno, H., et al. Multilineage cells from human adipose tissue: Implications for cell-based therapies. Tissue Engineering. 2001; 7: 211-28.
19. Cogle, C.R., Yachnis, A.T., Laywell, E.D., et al. Bone marrow transdifferentiation in brain after transplantation: A retrospective study. Lancet. 2004; 363: 1432-7.
20. Petersen, B.E., Bowen, W.C., Patrene, K.D.,et al. Bone marrow as a potential source of hepatic oval cells. Science. 1999; 284: 1168-70.
21. Pijnappels, D.A., Schalij, M.J., Ramkisoensing, A.A.,et al. Forced alignment of mesenchymal stem cells undergoing cardiomyogenic differentiation affects functional integration with cardiomyocyte cultures. Circulation Research. 2008; 103: 167-76.
22. Rose, R.A., Keating, A., Backx, P.H., Do mesenchymal stromal cells transdifferentiate into functional cardiomyocytes? Circulation Research. 2008; 103: e120.
23. Schwartz, R.E., Reyes, M., Koodie, L.,et al. Multipotent adult progenitor cells from bone marrow differentiate into functional hepatocyte-like cells. Journal of Clinical Investigation. 2002; 109: 1291-1302.
24. Tropel, P., Platet, N., Platel, J.C.,et al.Functional neuronal differentiation of bone marrow-derived mesenchymal stem cells. Stem Cells. 2006; 24: 2868-76.
25. Studeny, M., Marini, F.C., Champlin, R.E., Zompetta, C., Fidler, I.J., Andreeff, M.,Bone marrow-derived mesenchymal stem cells as vehicles for interferon-beta delivery into tumors. Cancer Research, 2002; 62: 3603–08.
26. Studeny, M., Marini, F.C., Dembinski, J.L.,et al. Mesenchymal stem cells: Potential precursors for tumor stroma and targeted-delivery

vehicles for anticancer agents. Journal of the National Cancer Institute. 2004; 96: 1593–1603.
27. Corsten, M.F. & Shah, K., Therapeutic stem-cells for cancer treatment: Hopes and hurdles in tactical warfare.The Lancet Oncology. 2008; 9: 376–84.
28. Shah, K., Mesenchymal stem cells engineered for cancer therapy. Advanced Drug Delivery Reviews. 2012; 64: 739-48.
29. Bieback, K., Kern, S., Kluter, H., Eichler, H. Critical parameters for the isolation of mesenchymal stem cells from umbilical cord blood. Stem Cells. 2004; 22: 625-34.
30. Erices, A., Conget, P., Minguell, J.J., Mesenchymal progenitor cells in human umbilical cord blood. British Journal of Haematology. 2000; 109: 235-42.
31. Izadpanah, R., Trygg, C., Patel, B., et al. Biologic properties of mesenchymal stem cells derived from bone marrow and adipose tissue. The Journal of Cell Biochemistry. 2006; 99: 1285-97.
32. Pittenger, M.F., Mackay, A.M., Beck, S.C., et al. Multilineage potential of adult human mesenchymal stem cells. Science. 1999; 284: 143-7.
33. Roubelakis, M.G., Pappa, K.I., Bitsika, V.,et al. Molecular and proteomic characterization of human mesenchymal stem cells derived from amniotic fluid: Comparison to bone marrow mesenchymal stem cells. Stem Cells and Development. 2007; 16: 931-52.
34. Zhang, Y., Li, C., Jiang, X., Zhang, S., Wu, Y., Liu, B., Tang, P., Mao, N., Human placenta-derived mesenchymal progenitor cells support culture expansion of long-term culture-initiating cells from cord blood CD34+ cells. Experimental Hematology. 2004; 32: 657-64.
35. Jiang, Y., Jahagirdar, B.N., Reinhardt, R.L., et al. Pluripotency of mesenchymal stem cells derived from adult marrow. Nature. 2002; 418: 41–9.
36. Orlic, D., Kajstura, J., Chimenti, S., et al. Bone marrow cells regenerate infarcted myocardium. Nature.2001; 410: 701– 5.
37. Bentzon, J.F., Stenderup, K., Hansen, F.D., et al. Tissue distribution and engraftment of human mesenchymal stem cells immortalized by human telomerase reverse transcriptase gene. Biochemical and Biophysical Research Communications. 2005; 330: 633–40.
38. Kern, S., Eichler, H., Stoeve, J., Klüter, H., Bieback, K.,Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. Stem Cells. 2006; 24: 1294–1301.
39. Mueller, S.M. & Glowacki, J., Age-related decline in the osteogenic potential of human bone marrow cells cultured in three-dimensional collagen sponges. Journal of Cellular Biochemistry. 2001; 82: 583–90.
40. Prindull, G., Ben-Ishay, Z., Ebell, W., Bergholz, M., Dirk, T., Prindull, B., CFU-F circulating in cord blood. Blut. 1987; 54: 351–9.
41. Wyrsch, A., dale Carbonare, V., Jansen, W., et al.Umbilical cord blood from preterm human fetuses is rich in committed and primitive hematopoietic progenitors with high proliferative and self-renewal capacity. Experimental Haematology. 1999; 27: 1338–45.
42. Goodwin, H.S., Bicknese, A.R., Chien, S.N., Bogucki, B.D., Quinn, C.O., Wall, D.A., Multilineage differentiation activity by cells isolated from umbilical cord blood: Expression of bone, fat, and neural markers. Biology of Blood and Marrow Transplantation. 2001; 7: 581–8.
43. Chang, Y.J., Shih, D.T., Tseng, C.P., Hsieh, T.B., Lee, D.C., Hwang, S.M., Disparate mesenchyme-lineage tendencies in mesenchymal stem cells from human bone marrow and umbilical cord blood. Stem Cells. 2006; 24: 679–685.
44. Maestroni, G.J., Hertens, E., Galli, P., FactoRs) from nonmacrophage bone marrow stromal cells inhibit Lewis lung carcinoma and B16 melanoma growth in mice. Cellular and Molecular Life Sciences. 1999; 55: 663–7.
45. Nakamura, K., Ito, Y., Kawano, Y., et al. Antitumor effect of genetically engineered mesenchymal stem cells in a rat glioma model. Gene Therapy. 2004; 11: 1155–64.
46. Qiao, C., Xu, W., Zhu, W.,et al. Human mesenchymal stem cells isolated from the umbilical cord. Cell Biology International. 2008; 32: 8–15.
47. Qiao, L., Xu, Z., Zhao, T.,et al. Suppression of tumorigenesis by human mesenchymal stem cells in a hepatoma model. Cell Research. 2008; 18: 500–7.
48. Ball, S.G., Shuttleworth, C.A., Kielty, C.M., Vascular endothelial growth factor can signal through platelet-derived growth factor receptors. The Journal of Cell Biology.2007; 177: 489-500.
49. Fiedler, J., Roderer, G., Gunther, K.P., Brenner, R.E., BMP-2, BMP-4, and PDGF-bb stimulate chemotactic migration of primary human mesenchymal progenitor cells. Journal of Cellular Biochemistry. 2002; 87: 305-12.
50. Ip, J.E., Wu, Y., Huang, J., Zhang, L., Pratt, R.E., Dzau, V.J.,Mesenchymal stem cells use integrin beta1 not CXC chemokine receptor 4 for myocardial migration and engraftment. Molecular Biology of Cell. 2007; 18: 2873-82.
51. Nakamizo, A., Marini, F., Amano, T., et al.Human bone marrow-derived mesenchymal stem cells in the treatment of gliomas. Cancer Research. 2005; 65: 3307-18.
52. Palumbo, R. & Bianchi, M.E., High mobility group box 1 protein, a cue for stem cell recruitment. Biochemical Pharmacology. 2004; 68: 1165-70.
53. Palumbo, R., Galvez, B.G., Pusterla, T., et al. Cells migrating to sites of tissue damage in response to the danger signal HMGB1 require NF-kappaB activation. The Journal of Cell Biology. 2007; 179: 33-40.
54. Son, B.R., Marquez-Curtis, L.A., Kucia, M., et al. Migration of bone marrow and cord blood mesenchymal stem cells in vitro is regulated by stromal-derived factor-1-CXCR4 and hepatocyte growth factor-c-met axes and involves matrix metalloproteinases. Stem Cells. 2006; 24: 1254-64.
55. Balkwill, F. Cancer and the chemokine network. Nature Reviews Cancer, 2004; 4: 540-50.
56. Dwyer, R.M., Potter-Beirne, S.M., Harrington, K.A., et al. Monocyte chemotactic protein-1 secreted by primary breast tumors stimulates migration of mesenchymal stem cells. Clinical Cancer Research.2007; 13: 5020-27.
57. Winner, M., Koong, A.C., Rendon, B.E., Zundel, W., Mitchell, R.A.,Amplification of tumor hypoxic responses by macrophage migration inhibitory factor-dependent hypoxia-inducible factor stabilization. Cancer Research. 2007; 67: 186-93.
58. Gliniak, B. & Le, T., Tumor necrosis factor-related apoptosis-inducing ligand's antitumor activity in vivo is enhanced by the chemotherapeutic agent CPT-11. Cancer Research.1999; 59: 6153–58.
59. Sage, E.K., Kolluri, K.K., McNulty, K.,et al. Systemic but not topical TRAIL-expressing mesenchymal stem cells reduce tumor growth in malignant mesothelioma. Thorax. 2014; 69: 638-47.
60. Wagner, J.C., Sleggs, C.A., Marchand, P.,Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. British Journal of Industrial Medicine. 1960; 17: 260–71
61. Fennell, D.A. & Rudd, R.M., Defective core-apoptosis signalling in diffuse malignant pleural mesothelioma: Opportunities for effective drug development. The Lancet Oncology. 2004; 5: 354–62.
62. Hosokawa, Y., Hosokawa, I., Ozaki, K., Nakae, H., Matsuo, T., Cytokines differentially regulate ICAM-1 and VCAM-1 expression on human gingival fibroblasts. Clinical & Experimental Immunology. 2006; 144: 494–502.
63. Uchibori, R., Tsukahara, T., Mizuguchi, H., et al. NF-kappaB activity regulates mesenchymal stem cell accumulation at tumor sites. Cancer Research. 2013; 73: 364–72.

64. Loebinger, M.R., Sage, E.K., Davies, D., Janes, S.M., TRAIL-expressing mesenchymal stem cells kill the putative cancer stem cell psopulation. British Journal of Cancer.2010; 103: 1692-7.
65. Clinicaltrials.gov - A service of the U.S. National Institutes of Health. Available at: https://clinicaltrials.gov/ct2/results?term=TRAIL+cancer&Search=Search
66. Teo, A.K. & Vallier, L.,Emerging use of stem cells in regenerative medicine. Biochemical Journal. 2010; 428: 11–23.
67. Walczak, H. & Krammer, P.H., The CD95 (APO-1/Fas) and the TRAIL (APO-2L) apoptosis systems. Experimental Cell Research. 2000; 256: 58–66.
68. Ehtesham, M., Kabos, P., Gutierrez, M.A.R., et al. Induction of glioblastoma apoptosis using neural stem cell-mediated delivery of tumor necrosis factor-related apoptosis-inducing ligand. Cancer Research. 2002; 62: 7170–74.
69. Ehtesham, M., Kabos, P., Kabosova, A., Neuman, T., Black, K.L., Yu, J.S., The use of interleukin 12-secreting neural stem cells for the treatment of intracranial glioma. Cancer Research. 2002; 62: 5657–63.
70. Kim, S.K., Cargioli, T.G., Machluf, M.,et al. PEX-producing human neural stem cells inhibit tumor growth in a mouse glioma model. Clinical Cancer Research. 2005; 11: 5965–5970.
71. Mueller, L.P., Luetzkendorf, J., Widder, M., Caysa, H., Mueller, T.,TRAIL-transduced multipotent mesenchymal stromal cells (TRAIL-MSC) overcome TRAIL resistance in selected CRC cell lines in vitro and in vivo. Cancer Gene Therapy. 2010; 18: 229-39.

How to cite this article: Kakouri A. MSCs: Is this the future therapeutic for cancer? Acta Medica International. 2015;2(2):161-167.

Source of Support: Nil, **Conflict of Interest:** None declared.

Handling Editor: Rohin Garg India