Journal of Cell Signaling
ISSN: 2576-1471

Neshati et al., J Cell Signal 2018, 3:3
DOI: 10.4172/2576-1471.1000188

Commentary Open Access

Transduced Mesenchymal Stem Cells and Cardiomyogenic Differentiation

Vajiheh Neshati[1*], Bibi Sedigheh Fazly Bazzaz[1,2*], Majid Mojarrad[3,4], Zeinab Neshati[5] and Mohammad Amin Kerachian[3,4]

[1]*Biotechnology Research Center, Faculty of medicine, Institute of Pharmaceutical Technology, Mashhad University of Medical Sciences, Mashhad, Iran*

[2]*School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran*

[3]*Medical Genetics Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*

[4]*Department of Medical Genetics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*

[5]*Department of Biology, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, Iran*

[*]**Corresponding author:** Fazly Bazzaz BS, Biotechnology Research Center, Institute of Pharmaceutical Technology, Mashhad University of Medical Sciences, Mashhad, Iran, Tel: +985138823251; E-mail: fazlis@mums.ac.ir

Received date: July 23, 2018; **Accepted date:** August 16, 2018; **Published date:** September 5, 2018

Commentary

This commentary aims to discuss the findings of our recent published article in which we showed the overexpression of Tbx20 induced cardiomyogenic differentiation in adipose-derived mesenchymal stem cells (ADMSCs) [1].

Myocardial infarction (MI), a main reason of mortality in the world, occurs due to death of cardiac cells following cardiac ischemic diseases. Since the adult mammalian cardiomyocytes are unable to regenerate and repair damaged tissues, constant cell loss leads to failure of contractile tissue, which reduces cardiac output and function [2]. Producing new cardiomyocytes to improve the function of the infarcted heart is the main purpose of cardiac regenerative medicine. In this regard, stem cells therapy has been determined as one of the most potential therapeutic options by replacing the damaged heart cells with new cardiomyocytes [3]. Mesenchymal stem cells (MSCs) with several specific features are one of the most favourable candidates for regenerative cardiac therapies. They are multipotent stromal cells with self-renewal capacity that can differentiate into a variety of cells. Human MSCs can be obtained in large amounts and are significantly expanded *in vitro* without losing their normal karyotype and undergoing senility [4,5]. Among MSCs, ADMSCs are seemingly the proper candidates for tissue regeneration and organ repair due to the ease of isolation and development in *ex vivo* [6-8]. There is substantial data supporting the fact that ADMSCs have the ability to differentiate into cardiomyocytes [8-12] and exhibit greater cardiomyogenic potential than other sources of MSCs [13]. Improving the myoregenerative potential of MSCs depends on the recognition of molecular mediators and transcription factors that regulate cardiac lineage-specific genes during heart development and cardiomyogenic differentiation. Many researchers have attempted to introduce and overexpress cardiomyogenic factors into stem cells. Overexpression of cardiomyogenic transcription factors have been used for differentiation of several types of MSCs into cardiomyocytes [14-18]. Despite the constant progress and innovation in gene transfer to target cells, there are some limitations in clinical success of gene therapy that is due to the lack of a safe and highly efficient gene delivery system, off-target transduction and genotoxicity.

Lentiviral vectors (LVs) are relatively suitable candidates for gene delivery into MSCs [19,20], since they have the capability to induce constant expression of transgene into target cells, with low cytotoxicity and limited immunogenicity [21,22]. In our recent study, cardiomyogenic effects of Tbx20 overexpression in ADMSCs were evaluated. To this end, ADMSCs were transduced with lentiviral vectors encoding Tbx20 and cardiomyogenic differentiation was investigated 7 and 14 days post-transduction. The transduced cells adopted a myocyte-like shape and increased the expression of the cardiomyogenic differentiation markers. These findings elucidated that targeted efficient expression of Tbx20 in ADMSCs can generate cardiomyocyte-like cells [1].

Tbx20 is initially expressed in cardiac progenitor cells and has a key regulatory role during heart development and maturation [23-26]. The main question that arises here is that, by which mechanism(s) Tbx20 overexpression can result in cardiomyogenic differentiation of ADMSCs? It is known that Tbx20 interacts with various cardiac transcription factors such as Nkx2-5, GATA4 and GATA5 and promotes the expression of genes like connexin 40, connexin 43, Mef2c and Nkx2.5 which are crucial for cardiomyocyte differentiation [23,27-31]. Our findings are the initial steps of cardiomyogenesis using Tbx20-transduced ADMSCs. To achieve a complete cardiomyogenic reprogramming, combination of several cardiac factors is required. In addition to the genetic modification, pre-conditioning and exposing the ADMSCs to additional cardiomyogenic stimuli such as growth factors, extracellular matrix components, electrical stimulation and co-cultures with cardiomyocytes can be useful. The future plan would be preclinical efficacy studies, to aim efficiency and safety concerns prior to clinical trials.

References

1. Neshati V, Mollazadeh S, Fazly Bazzaz BS, deVries AAF, Mojarrad M, et al. (2018) Cardiomyogenic differentiation of human adipose-derived mesenchymal stem cells transduced with Tbx20 -encoding lentiviral vectors. J Cell Biochem 119: 6146-6153.
2. Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, et al. (2015) The global burden of ischemic heart disease in 1990 and 2010: The global burden of disease 2010 study. Circulation 129: 1493-1501.
3. Passier R, Van Laake LW, Mummery CL (2008) Stem-cell-based therapy and lessons from the heart. Stem-cell-based therapy and lessons from the heart. Stem cell 453: 322-329.
4. Phinney DG, Prockop DJ (2007) Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair current views 25: 2896-2902.
5. Roobrouck VD, Ulloa-Montoya F, Verfaillie CM (2008) Self-renewal and differentiation capacity of young and aged stem cells. Exp Cell Res 314: 1937-1944.
6. Nakagami H, Morishita R, Maeda K, Kikuchi Y, Ogihara T, et al. (2006) Adipose tissue-derived stromal cells as a novel option for regenerative cell therapy. J Atheroscler Thromb 13: 77-81.

7. Choi YS, Dusting GJ, Stubbs S, Arunothayaraj S, Han XL, et al. (2010) Differentiation of human adipose-derived stem cells into beating cardiomyocytes. J Cell Mol Med 14: 878-889.
8. Mazo M, Gavira JJ, Pelacho B, Prosper F (2011) Adipose-derived stem cells for myocardial infarction. J Cardiovasc Transl Res 4: 145-153.
9. Planat-Bénard V, Menard C, André M, Puceat M, Perez A, et al (2004) Spontaneous Cardiomyocyte Differentiation from Adipose Tissue Stroma Cells 94: 223-229.
10. Song K, Wang Z, Li W (2013) In Vitro Culture, Determination and Directed Differentiation of Adult Adipose-Derived Stem Cells Towards Cardiomyocyte-Like Cells Induced by Angiotensin II. Appl Biochem Biotechnol 170: 459-470.
11. Zhu Y, Liu T, Song K, Ning R, Ma X, et al. (2009) ADSCs differentiated into cardiomyocytes in cardiac microenvironment. Mol Cell Biochem 324: 117-129.
12. Neshati V, Mollazadeh S, Fazly Bazzaz BS, Iranshahi M, Mojarrad M, et al. (2018) Cardiogenic effects of characterized Geum urbanum extracts on adipose-derived human mesenchymal stem cells. Biochem Cell Biol 10: 313.
13. Roura S , Gálvez-Montón1 C, Mirabe C, Vives J, Bayes-Genis A (2017) Mesenchymal stem cells for cardiac repair: are the actors ready for the clinical scenario? Stem Cell Research & Therapy 8: 238-249.
14. Li P, Zhang L (2015) Exogenous Nkx2.5- or GATA-4-transfected rabbit bone marrow mesenchymal stem cells and myocardial cell co-culture on the treatment of myocardial infarction in rabbits. Mol Med Rep 12: 2607-2621.
15. Xu M, Millard RW, Ashraf M (2012) Chapter 10 - Role of GATA-4 in Differentiation and Survival of Bone Marrow Mesenchymal Stem Cells, G Prog Mol Biol Transl Sci 111: 217-241.
16. Ruan Z, Zhu L, Yin Y, Chen G (2016) Overexpressing NKx2.5 increases the differentiation of human umbilical cord drived mesenchymal stem cells into cardiomyocyte-like cells. Biomed Pharmacother 78: 110-115.
17. Van Tuyn J, Knaän-Shanzer S, Van De Watering MJM, De Graaf M, Van Der Laarse A, et al. (2005) Activation of cardiac and smooth muscle-specific genes in primary human cells after forced expression of human myocardin. Cardiovasc Res 67: 245-255.
18. Neshati V, Mollazadeh S, Fazly Bazzaz BS, de Vries AAF, Mojarrad M, et al. (2018) MicroRNA-499a-5p Promotes Differentiation of Human Bone Marrow- Derived Mesenchymal Stem Cells to Cardiomyocytes. Appl Biochem Biotechnol 18: 2734-27422.
19. Zhang X, Russa VF La, Reiser J (2004) Transduction of Bone-Marrow-Derived Mesenchymal Stem Cells by Using Lentivirus Vectors Pseudotyped with Modified RD114 Envelope Glycoproteins. J Virol 78: 1219-1229.
20. Lin P, Lin Y, Lennon DP, Correa D, Schluchter M, et al. (2012) Efficient Lentiviral Transduction of Human Mesenchymal Stem Cells That Preserves Proliferation and Differentiation Capabilities. Stem Cells Transl Med 1: 886-897.
21. Barth AS, Kizana E, Smith RR, Terrovitis J, Dong P, et al. (2008) Lentiviral vectors bearing the cardiac promoter of the Na+-Ca2+ exchanger report cardiogenic differentiation in stem cells. Mol Ther 16: 957-964.
22. Allahverdi A, Abroun S, Jafarian A, Soleimani M, Taghikhani M, et al. (2015) Differentiation of Human Mesenchymal Stem Cells into Insulin Producing Cells by Using A Lentiviral Vector Carrying PDX1. Cell Journal 17: 231-242.
23. Stennard FA, Costa MW, Elliott DA, Rankin S, Haast SJP, et al. (2003) Cardiac T-box factor Tbx20 directly interacts with Nkx2-5, GATA4, and GATA5 in regulation of gene expression in the developing heart. Dev Biol 262: 206-224.
24. Greulich F, Rudat C, Kispert A (2011) Mechanisms of T-box gene function in the developing heart. Cardiovasc Res 91: 212-222.
25. Kraus F, Haenig B, Kispert A (2001) Cloning and expression analysis of the mouse T-box gene Tbx18. Mech Dev 100: 83-86.
26. Singh MK, Christoffels VM, Dias JM, Trowe M-O, Petry M, et al. (2005) Tbx20 is essential for cardiac chamber differentiation and repression of Tbx2. Development 132: 2697-2707.
27. Shen T, Aneas I, Sakabe N, Dirschinger RJ, Wang G, et al. (2011) Tbx20 regulates a genetic program essential to adult mouse cardiomyocyte function. J Clin Invest 121: 4640-4654.
28. Hoogaars WMH, Barnett P, Moorman AFM, Christoffels VM (2007) Cardiovascular development: Towards biomedical applicability-T-box factors determine cardiac design. Cell Mol Life Sci 64: 646-660.
29. Chakraborty S, Yutzey KE (2012) Tbx20 regulation of cardiac cell proliferation and lineage specialization during embryonic and fetal development in vivo. Dev Biol 363: 234-246.
30. Paige SL, Plonowska K, Xu A, Wu SM (2015) Molecular regulation of cardiomyocyte differentiation. Circ Res 116: 341-353.
31. Takeuchi JK, Mileikovskaia M, Koshiba-Takeuchi K, Heidt AB, Mori AD, et al. (2005) Tbx20 dose-dependently regulates transcription factor networks required for mouse heart and motoneuron development. Development 2132: 2463-2474.