Case of malignant transformation of mesenchymal stem cell engineered tissue in a rat heart in vivo

C. Spath¹, F. Schlegel¹, S. Leontyev², M. Nichtitz¹, R. Schmiedel¹, F.W. Mohr², S. Dhein¹

Abstract

Aim:
To find an alternative treatment option for heart failure we produced engineered tissue from mesenchymal stem cells (MSC) to enhance the immunological compatibility after implantation in rat heart.

Methods:
We used a rat bone marrow derived mesenchymal stem cell line (MSC, Gibco) to produce engineered tissues (MSC-ET). Low-passage (P6) MSCs were analyzed for phenotype characteristics by flow cytometry and adipogenic differentiation.

Cultured MSCs were mixed with matrigel, collagen and serum containing media and were casted into a circular structure for creating MSC-ETs. After 5 days of consolidation time the MSC-ETs were electrically stimulated (1Hz, 1mV and 0,1mA) for further 6 days. Subsequently MSC-ETs (n=3) were implanted around the beating heart of immunosupressed adult rats. After 1 month the rat hearts were surgically excised.

In vitro and in vivo MSC-ETs were histologically examined for collagen and elastic-fibers. By immunohistochemical investigation we measured expression of cardiac connexins (Cx40, Cx43 and Cx45), vessel associated von Willebrandt factor and mesenchymal stem cell-marker CD90.

Results:
At day 14 in vitro MSC-ETs (n=4) did not exhibit any contractions. Histological analysis showed rings containing 64.57±2.04% collagen tissue, but no elastic fibres. Furthermore we exhibited 19.7±8.1 micro vessels / 1mm².

In vivo 2 of 3 MSC-ETs were clearly distinguishable from the native heart. Our investigation showed that MSC-ETs in vivo consisted of less collagen (27.43±9.56%) than in vitro, but developed elastic fibers (0.93±0.18%). The number of micro vessels showed an increase up to 39.3± vessels /1mm². We also found CD90 and Cx43 expressing cells in vivo and in vitro.

Surprisingly, in 1 of 3 MSC-ET-transplanted rats the heart was completely surrounded by a huge, undifferentiated, pleomorphic sarcoma. Histological investigations of the growth and location of the tumour indicated that the tumour was part of the MSC-ET. Analysing the grade of the sarcoma by using the FNCLCC-grading system revealed, that the neoplasm was a high grade malignant sarcoma (total score= 7/8).

Dedifferentiated sarcoma cells lost the CD90 expression utterly, which certainly might indicate the malignant transformation.

Additionally, the majority of sarcoma cells were positive for the cardiac connexins (Cx40, Cx43, Cx45), but at the tumour-heart border their expression was left. Therefore, we hypothesize that the tumour was not able to communicate with the heart, which gives the sarcoma cells the opportunity to infiltrate healthy tissue.

Conclusion:
Low passage MSCs of a MSC-ET can dedifferentiate into a high grade malignant sarcoma in vivo. However, it remains unclear whether the transformation might be inborn to these cells or whether it might be caused by the treatment of these cells during the process of ET formation.

¹Herzzentrum Leipzig, Forschung und Lehre/Chirurgie, Leipzig, Germany, ²Herzzentrum Leipzig, Chirurgie, Leipzig, Germany

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