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BONE MARROW CELL THERAPY AMELIORATE LIVER DISEASE IN MOUSE MODEL OF FIBROSIS AND ALPHA1-ANTITRYPSIN DEFICIENCY

Prakash Baligar[1] & Asok Mukhopadhyay[2]

[1]Amity University, India
[2]Scientific Mind, India

Alpha1-antitrypsin deficiency (AATD) is a genetic disease, causes by mutation of AAT gene. Accumulation of mutated AAT protein aggregates in hepatocytes leads to endoplasmic reticulum (ER) stress resulting in impairment of liver functions and in some cases hepatocellular carcinoma, whereas decline of AAT level in sera is responsible for pulmonary emphysema. In critical cases of liver ailment the only treatment option is liver transplantation, whereas AAT replacement therapy is followed for the treatment of emphysema. As hepatocytes are the primary affected cells in AATD, we investigated whether transplantation of bone marrow-derived stem cells in transgenic mice expressing human AATZ (Z variant of AAT) confers any competitive advantages relative to host cells for pathological improvement, if any. Mouse bone marrow (BM) progenitors- and human mesenchymal stem cells (MSCs)-derived hepatic cells replaced 40% and 13% host hepatocytes, respectively in compatible hosts. Transplantation of cells was associated with decline of globule-containing hepatocytes, improvement in proliferation of globule-devoid host and donor hepatocytes as compared to AATZ globule containing hepatocytes. Further analyses revealed that transplantation leads to partial improvement of liver pathology in terms of inflammatory response, fibrosis and apoptotic death of hepatocytes. Cell therapy was also found to improve liver glycogen storage and sera glucose level in the PiZ mice. These overall improvements in liver pathology was not restricted to the transplantation of mouse BM cells; preliminary results showed that in case of human BM-derived MSCs also the globule-containing hepatocytes were declined and the donor cells converted into hepatocyte-like cells and expressed human AAT protein. These results suggest that bone marrow stem cell transplantation may be a promising therapy in the future for AATD related liver disease.

academicrm2016@gmail.com