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Efficacy of umbilical cord lining mesenchymal stem cells for wound healing in diabetic murine model

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Purpose: This study investigates the roles of Cord Lining Mesenchymal Stem Cells (CLMSC) as potential therapeutic agents for diabetic wounds. It aims to investigate the healing potential of CLMSC in full-thickness dermal wounds of db/db induced diabetes mice.

Design: 20 mice were randomly assigned to two arms: (1) Control group received placebo treatment (sham media or cells delivery material) via intra-peritoneal (IP) injection and (2) Active comparator received CLMSC via IP injection.

Methods: Genetically diabetic db/db mice (BKS.Cg-m+/+Leprdb/J) from the Jackson Laboratories (Bar Harbor, ME) were used in this study. Two full-thickness wounds, each sized 10×10 mm were created, one on each side of the midline on the back of the mice. Digital pictures were taken on day 1, 3, 7, 10, 14, 17, 21, 24 and 28. Wound area were analyzed with ImageJ TM software and calculated as percentage of the original wound. Time to time closure was defined as the day the wound bed were completely epithelized and filled with new tissues. Tissue was harvested at point of termination for immune-profiling and histological analysis. Pro-inflammatory cytokines [IFNγ, GM-CSF] and anti-inflammatory cytokines [IL-10] were quantified to determine the immunomodulation properties of the CLMSC. Throughout the entire course of the study, mice overall health behavioral changes and the lifespan of the mice were monitored.

Result: The percentage of wound closure, either treated or not treated, presented with an uptrend pattern starting from day 7; however, the CLMSC-treated wounds, compared with the control group, showed a significant increase in the percentage of wound closure on day 14, day 17 and day 19 and eventually achieved 100% closure of the wound sooner that the control group by an average of 3.7 days. The mice treated with CLMSC have a shorter wound closure time (mean closure day: 19.8 days) as compared to the control group (mean closure day: 23.5 days). Our histology analysis of repair revealed that CLMSC treatment enhanced re-epithelialization compared to control group with a fully differentiated multi-layered epithelium being developed in CLMSC-treated wounds from Day 21 onwards, while the epithelium regenerated in control group was not fully differentiated at the same time points. Our systemic analysis on immunomodulation indicated an up-regulation of pro-inflammatory serum cytokines (GM-CSF and IFN-gamma) in CLMSC treatment group during the first 7 days of injury to allow infiltration of inflammation cells. In contrast, the level of systemic anti-inflammatory serum cytokines (IL-10) decline during the first 7 days of injury to allow pro-inflammatory serum cytokines to kick-start the inflammatory activities. There is up-regulation of anti-inflammatory serum cytokines (IL-10) to halt the inflammatory activity after 7 days of injury.

Conclusion: Our preliminary findings are indicative of the positive effect of CLMSCs on diabetic wound healing. Our findings inferred that CLMSCs treated wound achieved higher percentage of wound closure within a shorter duration of time with an enhanced re-epithelialization potential and potential of CLMSC as an immunoregulatory anti-inflammatory agents.

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