**Supplementary**

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| Reference | Source | Model | Main findings |
| Endothelial Dysfunction | | | |
| Salvolini et al [1] | Human skin-MSC | In vitro human aortic endothelial cells | Skin-derived MSCs increased NO production |
| Lin et al [2] | Human BM-MSC | 1. In vitro human umbilical vein endothelial cells  2. Intravenous delivery of allogeneic MSCs in atherosclerosis mice model | 1. MSCs prevent ox-LDL-mediated inhibition of eNOS activity through the phosphorylation and restoration of Akt/eNOS activity  2. MSCs restored endothelium-dependant relaxation via an increase in phosphorylated Akt/eNOS via anti-interleukin-8 antibodies |
| Hyperlipidaemia | | | |
| Frodermann V et al[3] | Mice BM-MSC | Intravenous delivery of MSCs in atherosclerosis mice model | MSCs significantly reduced circulating cholesterol and lipoprotein lipase |
| Hong et al [4] | Human gingival-MSC | Intravenous delivery of MSCs in ApoE−/− mice | MSCs decreased circulating total cholesterol and LDLs whilst increasing HDLs |
| Li et al [5] | Human umbilical cord-MSC | Intravenous delivery to leptin deficient mice | Decreased circulating cholesterol via an increase in PPAR-α and reduction in fatty acid synthase |
| Inflammation | | | |
| Nicola M Di et al[6] | Human BM-SC | In vitro human cell culture | SCs suppress CD4+/CD8+ T cells; even without direct cell to cell contact |
| Frodermann V et al[3] | Mice BM-MSC | Pre-treatment with MSC in atherosclerosis mice model | MSCs suppress CD3+ T cells via cell to cell contact |
| Frodermann V et al[3] | Mice BM-MSC | Pre-treatment with MSC in atherosclerosis mice model | Initial 51% increase in Tregs and progression to 10% decrease from baseline |
| Wang ZX et al[7] | Mice BM-MSC | MSC post-treatment in chronic atherosclerosis mice model | MSCs promote an anti-inflammatory environment. MSCs increase number and activity of CD4+CD25+FOXP3+ Treg subpopulation and decrease effector T cell populations |
| Cahill EF et al[8] | Mice BM-MSC | In vitro cell culture | MSCs augment Treg induction via ligand Jagged-1 activation of Notch signalling |
| Rashedi I et al[9] | Human BM-MSC | In vitro human cell culture | MSCs augment Treg induction via TLR3 and 4 increasing Notch signalling |
| Adutler-Lieber S et al [10] | A-MSC | In vitro human cell culture | A-MSCs can polarise macrophages into anti-inflammatory phenotype |
| Li Q. et al[11] | S-MSC | MSC post-treatment in chronic atherosclerosis mice model | S-MSCs decrease plaque size. S-MSCs promote a NFKB dependant anti-inflammatory cytokine profile |
| Zhang X. et al[12] | Human G-MSC | MSC post-treatment in chronic atherosclerosis mice model and in vitro human macrophage culture | G-MSCs decreased plaque area and spleen/blood/lymph node macrophage numbers. G-MSCs can polarise macrophages into anti-inflammatory phenotype |
| Wang ZX et al[7] | Mice BM-MSC | In vitro macrophages cultured with ox-LDL | Decrease in foam cell formation by decrease in scavenger receptors: CD36 and SRA |
| Plaque Stability | | | |
| Shi et al [13] | Human induced pluripotent stem cell-MSCs | Intravenous delivery of MSCs in ApoE−/− mice | Reduced size of atherosclerotic plaque |
| Wang et al [14] | Rabbit BM-MSCs | Intravenous delivery of MSCs into rabbit atherosclerosis model | MSCs increased fibrous cap thickness, with increased vascular smooth muscle cell numbers and collagen content |
| Regeneration | | | |
| Iwase et al [15] | Rat BM-MSCs | Intravenous delivery of MSCs into rat model of hind limb ischaemia | MSCs differentiated into ELCs and VSMCs improving hind limb ischaemia |
| Lu et al [16] | Human BM-MSCs | Intravenous delivery into diabetic patients with critical limb ischaemia | MSCs improved healing time of ulcers via increased perfusion |
| Wang et al [17] | Human BM-MSCs | Intravenous delivery of MSCs into model of vascular injury | MSCs homed to site of injury and differentiated into ELCs, contributing to vascular reendothelialization  MSCs can also contribute to intimal hyperplasia |

Table 1: A table summarising the key studies cited in the review. MSC = Mesenchymal Stem Cell; A-MSCs = Adipose-derived mesenchymal stem cells; BM-MSCs= Bone marrow-derived MSCs; ELC = Endothelial-like cell; PPARα = Peroxisome proliferator-activated receptor-alpha.

1. Salvolini E, Orciani M, Vignini A, Mattioli-Belmonte M, Mazzanti L, Di Primio R. Skin-derived mesenchymal stem cells (S-MSCs) induce endothelial cell activation by paracrine mechanisms. Exp. Dermatol. (2010).

2. Lin Y-L, Yet S-F, Hsu Y-T, Wang G-J, Hung S-C. Mesenchymal Stem Cells Ameliorate Atherosclerotic Lesions via Restoring Endothelial Function. *Stem Cells Transl. Med.* (2015).

3. Frodermann V, Van Duijn J, Van Pel M, *et al.* Mesenchymal Stem Cells Reduce Murine Atherosclerosis Development. *Sci. Rep.* (2015).

4. Hong R, Wang Z, Sui A, *et al.* Gingival mesenchymal stem cells attenuate pro-inflammatory macrophages stimulated with oxidized low-density lipoprotein and modulate lipid metabolism. *Arch. Oral Biol.* (2019).

5. Li B, Cheng Y, Yu S, *et al.* Human Umbilical Cord-Derived Mesenchymal Stem Cell Therapy Ameliorates Nonalcoholic Fatty Liver Disease in Obese Type 2 Diabetic Mice. *Stem Cells Int.* (2019).

6. Nicola M Di, Carlo-Stella C, Magni M, *et al.* Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. *Blood*. (2002).

7. Wang ZX, Wang CQ, Li XY, *et al.* Mesenchymal stem cells alleviate atherosclerosis by elevating number and function of CD4+CD25+FOXP3+ regulatory T-cells and inhibiting macrophage foam cell formation. *Mol. Cell. Biochem.* (2014).

8. Cahill EF, Tobin LM, Carty F, Mahon BP, English K. Jagged-1 is required for the expansion of CD4+ CD25+ FoxP3+ regulatory T cells and tolerogenic dendritic cells by murine mesenchymal stromal cells. *Stem Cell Res. Ther.* (2015).

9. Rashedi I, Gómez-Aristizábal A, Wang XH, Viswanathan S, Keating A. TLR3 or TLR4 Activation Enhances Mesenchymal Stromal Cell-Mediated Treg Induction via Notch Signaling. *Stem Cells*. (2017).

10. Adutler-Lieber S, Ben-Mordechai T, Naftali-Shani N, *et al.* Human macrophage regulation via interaction with cardiac adipose tissue-derived mesenchymal stromal cells. *J. Cardiovasc. Pharmacol. Ther.* (2013).

11. Li Q, Sun W, Wang X, Zhang K, Xi W, Gao P. Skin-Derived Mesenchymal Stem Cells Alleviate Atherosclerosis via Modulating Macrophage Function. *Stem Cells Transl. Med.* (2015).

12. Zhang X, Huang F, Li W, *et al.* Human gingiva-derived mesenchymal stem cells modulate monocytes/macrophages and alleviate atherosclerosis. *Front. Immunol.* (2018).

13. Shi H, Liang M, Chen W, *et al.* Human induced pluripotent stem cell-derived mesenchymal stem cells alleviate atherosclerosis by modulating inflammatory responses. *Mol. Med. Rep.* (2018).

14. Wang SS, Hu SW, Zhang QH, Xia AX, Jiang ZX, Chen XM. Mesenchymal stem cells stabilize atherosclerotic vulnerable plaque by anti-inflammatory properties. *PLoS One*. (2015).

15. Iwase T, Nagaya N, Fujii T, *et al.* Comparison of angiogenic potency between mesenchymal stem cells and mononuclear cells in a rat model of hindlimb ischemia. *Cardiovasc. Res.* (2005).

16. Lu D, Chen B, Liang Z, *et al.* Comparison of bone marrow mesenchymal stem cells with bone marrow-derived mononuclear cells for treatment of diabetic critical limb ischemia and foot ulcer: A double-blind, randomized, controlled trial. *Diabetes Res. Clin. Pract.* (2011).

17. Wang CH, Cherng WJ, Yang NI, *et al.* Late-outgrowth endothelial cells attenuate intimal hyperplasia contributed by mesenchymal stem cells after vascular injury. *Arterioscler. Thromb. Vasc. Biol.* (2008).