

## Abstract

Cell therapies are increasingly considered in preclinical studies and in the future of medicine. The main cell type investigated in this manner is mesenchymal stem cells (MSCs), because of their strong immunomodulatory properties. The efficacy of the therapy depends on various aspects, such as the viability and source of MSCs, the purity of the cell suspension and many more. There is a need for more tailored therapy and the use of cell type better fitting for the specific pathology. Sertoli cells (SCs) are deemed by some authors to be a kind of MSCs, namely because of their similar immunomodulatory properties. Because they reside in the seminiferous tubules in the testes, they are a promising candidate for the treatment of inflammatory pathologies of testicular tissue, such as bacterial infection-induced infertility. *In vitro* comparison of the ability of MSCs and SCs to differentiate into mesenchymal cell lineages such as osteocyte, chondrocyte, and adipocyte showed success in the case of SCs, providing evidence for their mesenchymal origin. The effect of MSCs or SCs on activated immune cells *in vitro* showed immunosuppression in both cases with distinct features. MSCs suppressed Th17 cell activation and IL-17 production by CD4<sup>+</sup> T cells and SCs down-regulated TNF $\alpha$  and IL-2 production by these cells, pointing more towards overall inflammation induction. SCs promoted the M2 macrophage induction, as shown by stronger up-regulation of CD206 molecule when compared to M $\phi$  co-cultured with MSCs. SCs were also shown for the first time to be capable of mitochondrial transfer to immune cells, one of the mechanisms of immune modulation employed by MSCs. For *in vivo* examination of SCs ability to suppress inflammation and maintain sperm production, a model of LPS-induced acute testicular inflammation and subsequent SCs transplantation was used. Presence of SCs in the organism alleviated the inflammatory burden in the testes, accompanied by lower relative number of Ly6G<sup>+</sup> cells within the testes. The peritubular and interstitial macrophage phenotype was changed in the LPS-only injected cohort, and SC application brought the phenotype closer to healthy controls. Lastly, both sperm count and motility were preserved in animals treated with LPS and SC, compared to subjects treated with LPS only. Taken together, SCs and MSCs have similar but distinct immunomodulatory properties, which are manifested mainly by suppressing a different type of inflammatory response. In the setting of LPS-induced inflammation, SCs transplantation has a beneficial effect on the preservation of spermatogenesis and

sperm function, also mirrored also by the lower infiltration of Ly6G<sup>+</sup> granulocytes in the testicular tissue and the induction of MerTK immunoregulatory molecule on the surface of MHCII<sup>+</sup>CD206<sup>-</sup> peritubular macrophages. Because of all these abilities, SCs have better potential than MSCs to be used in clinics, especially in the cases of male genital tract pathologies accompanied by inflammation.

**Keywords:** Mesenchymal stem cell, Sertoli cell, inflammation, spermatogenesis, immunomodulation, transplantation