

PLENARY PRESENTATIONS

HUMAN CELLS AND THEIR SECRETOME AS A TOOL FOR REGENERATIVE PHARMACOLOGY

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The maintenance and preservation of tissue cellular composition directly depend on the balance between cell death and formation, which is largely ensured by tissue-specific stem cells and their specialised microenvironment – the niches. Disruption of stem cell niche regulation underlies the pathogenesis of oncological, fibrosis-associated and neurodegenerative diseases, and also accelerates ageing and the development of age-related disorders. In recent decades, regenerative medicine has been actively developing approaches to restore damaged tissues, with cell therapy occupying a central place among them. However, classical cell therapy faces challenges such as low survival of transplanted cells, difficulties in controlling their differentiation, and unpredictable biodistribution. Increasing attention is therefore being drawn to the paracrine mechanism of action of cell-based products, one of the most studied and promising sources of which are mesenchymal stromal cells (MSCs). It has been shown that the main effector arm of MSC therapy is their secretome – a complex mixture of bioactive molecules, including growth factors, cytokines, extracellular matrix components, and biomolecules carried within extracellular vesicles, primarily regulatory RNAs. This opens the way for the development of cell-free regenerative preparations that possess multi-targeted action, advantages in pharmaceutical development, and a more favourable safety profile.

This report presents the results of studies on the fundamental mechanisms of stem cell niche restoration under the influence of MSCs and their secretome. The spermatogonial stem cell (SSC) niche was used as a model in two experimental injury settings – abdominal cryptorchidism in rats and doxorubicin-induced toxicity in mice. After injury, an increase in the number of tissue-specific MSCs in the testicular interstitium was observed, indicating their recruitment to the damage site. Local administration of both MSCs themselves and their secretome under the tunica albuginea led to restoration of both the structure and function of the SSC niche: the number of atrophic and fibrotic seminiferous tubules decreased, the blood-testis barrier was restored, total sperm count and motility increased, and partial recovery of fertility was noted at later time points. The cellular mechanisms included stimulation of spermatogenic cell proliferation, enhanced migration of Sertoli cells, and normalisation of Leydig cell secretory activity with a return of testosterone levels to physiological values. Using inhibitory analysis, vascular endothelial growth factor (VEGF) and microRNA-21 were identified as key secretome components mediating the regenerative effects of MSCs: their blockade significantly reduced the stimulatory effect on testosterone production by Leydig cells. In addition, the MSC secretome exerted pronounced anti-fibrotic effects, suppressing fibroblast-to-myofibroblast differentiation and reducing collagen deposition, which was mediated, in part, by microRNA-29c and -129 transported within extracellular vesicles.

The fundamental data obtained formed the basis for a technological platform for the development of innovative biological drugs aimed at stimulating tissue regeneration.

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This platform comprises a set of technological solutions for producing preparations based on human MSC secretome components to address a wide range of clinical challenges. As the first biological drug developed on this platform, the original product "MediReg®" (based on human MSC secretome) was created for the treatment of moderate and severe spermatogenesis disorders leading to non-obstructive male infertility. An original biological potency assay was developed, based on the dose-dependent ability of the secretome to stimulate testosterone secretion by Leydig cells isolated from healthy rodent testes, and VEGF was substantiated as a pharmacodynamic marker for standardisation. Preclinical studies confirmed the safety of the drug, including the absence of immunogenicity, local irritant effects, and systemic absorption upon local administration, while a long-term carcinogenicity study (2.5 years) revealed no signs of tumour transformation.

In 2024, an open-label, single-centre phase I/II clinical trial (NCT06869863) of MediReg® was initiated in 80 patients with severe spermatogenesis disorders. Preliminary results demonstrated a favourable safety profile. In more than one third of patients with initial azoospermia, spermatozoa appeared in the semen after drug administration, and inhibin B levels increased by 76–81%, indicating restoration of the reproductive reserve and activation of spermatogenesis.

Thus, the human MSC secretome is an effective multi-targeted regulator of stem cell niche restoration, acting primarily on the cellular components of the niche and triggering a complex of reparative processes – stimulation of proliferation, migration, angiogenesis, as well as anti-inflammatory and anti-fibrotic effects. Importantly, these effects are reproduced when not the cells themselves but their secretome is administered, which overcomes the limitations of classical cell therapy and provides a platform for developing standardised, safe, and long-term storable biological drugs. The MediReg® product has already passed the full cycle of preclinical studies and is currently in clinical testing, showing encouraging efficacy and safety results in patients with severe male infertility. The developed concept can be extended to other pathologies associated with stem cell niche damage, opening new horizons for regenerative pharmacology.

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