

Therapeutic Potential of Human Mesenchymal Stromal Cells Secretome

Luigi Balducci^{1*} and Gianluca Accogli²

¹Laboratory of Cell Culture and Molecular Biology, CARSO Consortium, Valenzano, Bari, Italy

²Veterinary Clinics and Animal Productions Unit, Department of Emergency and Organ transplantation (DETO), University of Bari "Aldo Moro", Bari, Italy

Human multipotent mesenchymal stromal cells (hMSCs) have been isolated and expanded from several tissues. Bone marrow [1], adipose tissue [2], umbilical cord [3], skeletal muscle [4] and skin [5] are only a small example of hMSCs origin. Due to the heterogeneity deriving from the different cell source and isolation methods, three minimal criteria have been proposed to define hMSCs: plastic-adherence, phenotypic profile (positive expression of CD105, CD73 and CD90 and lack expression of CD45, CD34 and HLA-II), and trilineage mesenchymal differentiation potential [6]. From a functional point of view, many *in vitro* and *in vivo* studies have showed that hMSCs possess immune-modulatory, pro-angiogenic, pro-survival, anti-apoptotic, anti-oxidant, anti-fibrotic, anti-bacterial and neuro-protective properties. As a consequence, hMSCs have become a very interesting tool for cell therapy and regenerative medicine, and they still continue to be studied for this purpose.

Several findings have elucidated that hMSCs release a plethora of cytokines, interleukins, prostaglandins and growth factors. More recently, it has also been demonstrated that hMSCs secrete exosomes and microvesicles [7,8]. The main differences between these subcellular particles are essentially their size (40 to 100 nm for exosomes and 100 to 1000 nm for microvesicles) and origin (exosomes by exocytosis of multivesicular bodies, microvesicles by budding of plasma membranes). In contrast, the common feature of both particles is their content, consisting of proteins, lipids, mRNAs, and microRNAs (miRNAs) [9]. All together, the above mentioned factors and the subcellular particles containing the active bio-molecules represent the hMSCs secretome.

Many studies have ascertained and still continue to clarify that the hMSCs therapeutic potential is linked to their secretory abilities. Skin aging [10], myocardial ischemia/reperfusion injury [11], stroke [12], and wound healing [13] are representative examples of pre-clinical investigations evaluating the effectiveness of hMSCs secretome. Of note, also some clinical studies have been conducted to assess the regenerative properties of hMSCs secretome [14,15].

Compared to direct hMSCs administration, the employment of cell secretome for therapeutic scopes could have at least three advantages. The first benefit relates to the possibility to avoid potential problems such as tumorigenicity, pathogens transfer and donor-recipient mismatch when cells are administered. From a practical point of view, the hMSCs secretome could be managed and manufactured in an easier way compared to cell suspensions, specifically in terms of storage, availability, delivery and quality testing. Moreover, such biological material may represent a ready-to-use therapeutic device, particularly important when used for acute pathologies where the time required to expand cells could be unfavorable.

Undoubtedly, several concerns about hMSCs secretome as a therapeutic tool remain to be solved. Thus, future challenges should address fundamental aspects regarding the production, safety, and characterization of hMSCs secretome. The first point principally aims to manufacture large quantities (scale-up) of hMSCs secretome in accordance to GMP-procedures. We have recently proposed a possible strategy to obtain large amounts of hMSCs secretome [16]. However, it

is mandatory to analyze more extensively this hypothesis by performing *in vitro* and *in vivo* studies.

The second aspect is particularly urgent in order to avoid detrimental side effects deriving from hMSCs secretome administration. Indeed, it was recently reported that exosomes could be involved in cancer and neurodegenerative disorders [17,18].

Finally, a deeper molecular characterization would allow a better definition of the hMSCs secretome content. New methodologies such as NGS (Next Generation Sequencing) and glycome-profiling will be very valuable to understand the molecular composition and the related functions of the hMSCs secretome biomolecules and subcellular particles.

In conclusion, the characterization and therapeutic application of hMSCs secretome may represent a new and exciting field of research for the scientific community.

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*Corresponding author: Luigi Balducci, Laboratory of Cell Culture and Molecular Biology, CARSO Consortium, Strada Prov.le Valenzano-Casamassima km.3, 70010 Valenzano, Bari, Italy, Tel: +39-080-4602121; E-mail: luigi.balducci.lb@gmail.com

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