Editorial

Connecting the Dots: The Promises of Wharton's Jelly Mesenchymal Stem Cells for Tissue Repair and Regeneration

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Mesenchymal stem cells (MSC) constitute a variety of cellular populations which were described first about 35 years ago in the bone marrow (BM) stroma [1]. These years have foreseen an exponential increase of reports pointing out features, stemness, markers, tissue sources and clinical applications of these cells. Cells with MSC features can be isolated from virtually every adult organ in the body, as well from a group of fetus-associated sources (cells derived from the latter tissues are collectively known as perinatal stem cells) [2]. In recent years, the umbilical cord arose as a promising source of mesenchymal stem cells, which can be isolated in relatively high numbers (compared to BM) and should be further cultured and cryopreserved. Wharton's jelly (WJ) is the main constituent of the umbilical cord. This mature mucous tissue extends from the amniotic epithelium to the perivascular zone of the cord, and contains an abundant extracellular matrix with fibroblast-like or myofibroblast-like cells inside. The high interest for new stem cell sources for the most diverse clinical applications and the amount of data accumulating on WJ-MSC, pushed for the development of this special issue [3].

The plethora of cellular sub-sources and populations that can be derived from umbilical cord is well described in the review proposed by Conconi *et al.,* [4], who clearly describe the key properties of cellular populations obtained by different preparations of umbilical cord tissue. This is an important point since to date no standardized methods are widely accepted to derive MSC from the cord, with the concurrent application of enzyme-mediated and enzyme-free methods, as reported in a number of reports and patented applications [5].

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This topic is further analyzed in the review by Jeschke and co-workers [6] who compare the literature evidences on the isolation process and features of MSC isolated from the umbilical cord lining (derived from the amniotic epithelium) with respect to cells isolated from the other zones of the umbilical cord.

One key property of MSC, which is strikingly enhanced in WJ-derived cells, is their ability to interact with immune cells *in vitro* and *in vivo*. Prasanna and Jahnavi [7] review this point in their paper, providing an updated view of the immunomodulatory molecules which have been demonstrated to be expressed by WJ-MSC. The authors also analyze the *in vitro* and *in vivo* data on their immune-modulating activities, and the perspectives for cellular therapy. There are a number of diseases which could clearly benefit from administration of cells capable to evade or modulate the host immune response, independently from immunosuppressive therapy [8]. Further efforts are needed, to characterize the immunomodulatory molecules expressed by differentiated WJ-MSC, with respect to undifferentiated ones, a still controversial and poorly defined process.

Another key application of WJC is their possible use as anti-cancer agents, and the relevant literature is reviewed by Tamura and co-workers in their review [9]. This is a striking point in MSC biology, since these cells show a clear *in vivo* tropism for organs which are site of a damage or wound. In addition, the classical definition applied to (solid) tumors as "wounds which do not heal" [10], further highlights the importance of this phenomenon. In addition, the authors discuss the evidences pointing out that MSC derived from adult tissues (e.g. bone marrow), differently from WJ-MSC, may promote tumor growth and metastasis by different mechanisms.

WJC are stem cells which are capable to differentiate towards a growing number of mature tissues. While MSC were first characterized for their ability to form mesoderm-

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derived mesenchymal tissues (as bone, adipose, cartilage), it is now widely recognized their ability to differentiate towards mature cell types belonging also to the endodermal or ectodermal lineages [11, 12]. To this regard, Scheers and co-workers reviewed the umbilical cord cell sources for the treatment of metabolic liver diseases [13], discussing the outcome of the differentiation experiments performed so far, the *in vivo* models, and the prospects for therapy. The shortage of donor livers and the lack of a reliable intra- or extra-hepatic cellular source to derive mature hepatocytes, are key elements which push ahead the research on this topic.

In a further paper, Dezawa and co-workers [14] analyze the literature reports on the ability of WJC to differentiate towards Schwann cells. Given the intrinsic ability of activated Schwann cells to promote axonal regeneration *in vivo*, umbilical cord-derived MSC can be used to successfully derive mature Schwann cells for the regeneration of peripheral nerve.

Breymann and Semonov [15] analyze the literature data on the application of WJ-MSC for cardiovascular regeneration and tissue engineering. This is a point of great interest for heart regenerative medicine, since for many diseases heart transplant remains the final choice for the surgeon and the resident stem cells seem unable to repair the failing heart.

To this regard, in the continued effort to find a suitable cellular population for cardiac tissue engineering and cardiomyoplasty, Holloweck and co-workers [16] compare the efficiency of cardiac differentiation of WJ-MSC subjected to six different published experimental protocols. This work is of great importance since allowed characterizing the response of the same cell population to diverse differentiation protocols, and allowed to determine the better *in vitro* conditions to achieve the expression of myocite mature features.

Lo Iacono and co-workers [17] review the use of perinatal stem cells, and in particular Wharton's jelly ones, for the regeneration of cartilage, showing the potential of this cellular population to be used effectively in cartilage injury therapy.

In an original paper, Weiss and co-workers [18] show the results of experimental protocols to grow WJC plated at different densities in a low-oxygen atmosphere. This innovative approach to culture of WJC gives interesting results in terms of cellular proliferation, cellular yield, CFU-F, markers expression and differentiative capacities of cells. The combination of low seeding density and reduced oxygen concentration seems ideal to obtain the high numbers of cells needed for cellular therapy applications.

In a further original paper, Pierdomenico *et al.,* [19] report the observations on phenotypical variations between WJC extracted from normal cords versus cords from children of diabetes mellitus affected mothers. This research sets important aspects on the possible subjective variations in MSC populations extracted from the same tissue source with the very same protocol. In addition, the authors suggest that diabetes mellitus during pregnancy should cause a "pre-commitment" of the MSC to the adipogenic lineage.

Emrani and Davies [20] propose an experimental protocol for the use of perivascular MSC (HUCPVC) from human umbilical cord to treat tendon injuries in a rat model. The authors demonstrate that the infused cells improve regeneration in the model used via collagen reorganization and tensile properties variation, thus suggesting the utility of such cells for tendon regeneration and repair.

In a further research paper, Lange-Consiglio *et al.,* [21] describe the isolation and characterization of horse WJ-MSC, and their labeling efficiency with magnetic resonance contrast agents. The animal model described should be of importance for the generation of horse stem cells to be used in veterinary medicine applications. Moreover, the authors provide the rationale for the labeling of these cells with paramagnetic trackers to follow their route into the host body after transplantation and their final fate in organ. This is still a debated issue since one of the main limitations of *in vivo* experiments using cellular transplantation is the poor tracking of these cells *in vivo* in the host.

These papers provide a clear vision of the efforts made to better define the biological and therapeutic properties of mesenchymal stem cells isolated form the human umbilical cord matrix. These cells feature promising characteristics as ease of sourcing, *in vitro* expandability, differentiation abilities, immune-evasion and immune-regulation features, which may render them useful as "off the shelf" cellular therapy vehicles even in allogeneic settings. These cells were demonstrated to easily cross the germ layers boundaries to trans-differentiate towards several mature cell types.

What is needed from current and future research in this field is:

1. Unifying the procedures for derivation and subculture of MSC from human umbilical cord matrix, as well as their storage options.

2. Favor the co-banking of WJC alongside cord blood units in both public and private stem cells banks

3. Better detail the immune features of differentiated *versus* undifferentiated WJC when transplanted into an immunocompetent host, with or without concur-rent immunosuppression. This should lead to define their

usefulness not only in tissue regeneration, but also in tissue repair/support of local host progenitors.

4. Favor the formation of a collective conscience that umbilical cord is no more to be considered a special waste of the delivery process, but is a promising tissue source of stem cells for regenerative medicine applications, without the ethical and safety issues which actually limit the sourcing and use of other progenitor populations.

I am glad and thankful that a panel of renowned scientists has joined this special issue on "Wharton's jelly mesenchymal stem cells: tissue regeneration and beyond" contributing reviews on the most recent data on different topics that may have a strong impact on the future of regenerative medicine, as well as original papers which further move on the targets of the use of these cellular populations.

It is my hope that this special issue will contribute to key developments within this field.

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