



## In Focus

# Mesenchymal Stem Cells and their Potential for Microengineering the Chondrocyte Niche

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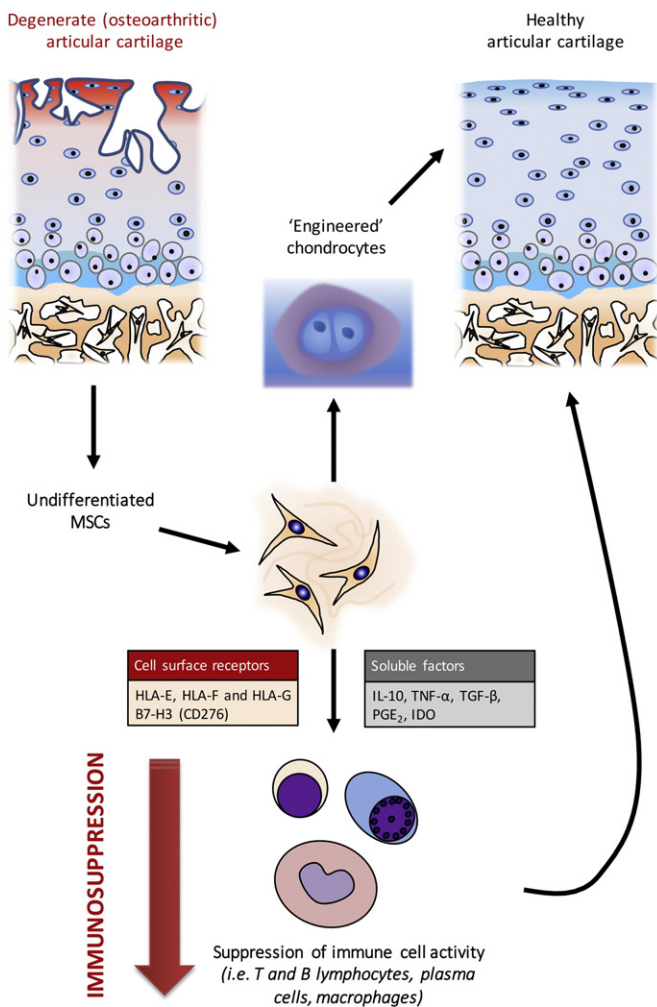
Musculoskeletal disorders including osteoarthritis (OA) represent a major cause of disability and morbidity, and cause an enormous burden for health and social care systems globally. In the Global Burden of Disease 2010 study, hip and knee OA was ranked as the 11th highest contributor to global disability (Cross et al., 2014), and its prevalence is set to increase in parallel with the number of people aged 60 years and older. Articular cartilage within synovial joints has limited self-repair capacity because of its avascular nature and the low proliferation rate of chondrocytes, the main cell type responsible for its maintenance. Chondrocytes reside in a unique niche of cartilage extracellular matrix (ECM) that consists of collagen type II, large aggregating proteoglycans (e.g. aggrecan), glycosaminoglycans, hyaluronan, other non-collagenous proteins (e.g. COMP), and a large amount of water and mobile cations (i.e. Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>); this composition allows cartilage to resist biomechanical forces (Jahr et al., 2015). Cell-based therapies are rapidly being developed in a number of diseases including bone and joint disorders.

As OA is currently incurable, novel biological and cell-based therapies that can effectively treat joint degeneration are high priorities in regenerative medicine.

Multipotent mesenchymal stem cells (MSCs) derived from bone marrow, adipose tissue and umbilical cord (UC) show considerable promise for use in cartilage repair. Under appropriate micro-environmental conditions they can proliferate and give rise to chondrocytes and other related mesenchymal cell phenotypes, allowing them to act as key players in regenerating injured tissue following injury and trauma (Richardson et al., 2015). Another key feature of MSCs is their capacity to modulate immune responses *in vitro* and *in vivo*, making them well-suited for the treatment of systemic inflammatory and autoimmune conditions that affect synovial joints. Their immunosuppressive nature extends to both the innate and adaptive immune system through interactions with dendritic cells, natural killer cells, macrophages and B and T lymphocytes by means of cell–cell contacts or soluble mediators (Burr et al., 2013). Given the avascular and alymphatic characteristics of articular cartilage and the specific features of the ECM that can shield the MHC molecules from recognition by host cells, an immune response against allogeneic chondrocytes or osteochondral constructs in the host has not been reported. However, the immunomodulatory effects of MSCs may have critical outcomes in diseases of the musculoskeletal system where an inflammatory or autoimmune process is at the core of the main disease. The molecular mechanisms underlying the effects of MSCs on the immune system are diverse and employ the release of soluble factors such as interleukin-10, tumour necrosis factor- $\alpha$ , transforming growth factor- $\beta$ , prostaglandin-E<sub>2</sub> and indoleamine-2,3-dioxygenase by MSCs. UC-MSCs express the HLA-E, HLA-F and HLA-G non-canonical type I MHC receptors. In addition, the fact that B7-H3 (CD276), a co-stimulatory molecule that inhibits T cell activation, was demonstrated to be expressed not only in undifferentiated UC-MSCs but persisted following differentiation towards the chondrogenic lineage indicate that differentiated UC-MSCs continue to have immunosuppressive characteristics, which is an added advantage with potentially important clinical implications (La Rocca et al., 2013).

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**Fig. 1.** In addition to their regenerative properties, the immunoregulatory potential of MSCs make them ideal for use as therapeutic agents as they are uniquely positioned to suppress local inflammation and at the same time participate in tissue repair. MSCs isolated from the bone marrow (as shown here) or elsewhere employ diverse molecular mechanisms to modulate the immune system including expression of cell surface receptors (HLA-E, HLA-F and HLA-G non-canonical type I MHC receptors, as well as the co-stimulatory molecule B7-H3 (CD276) that inhibits T cell activation) and the secretion of soluble mediators (IL-10, interleukin-10; TNF- $\alpha$ , tumour necrosis factor- $\alpha$ ; TGF- $\beta$ , transforming growth factor- $\beta$ ; PGE<sub>2</sub>, prostaglandin-E<sub>2</sub>; IDO, indoleamine-2,3-dioxygenase). Please note that this list is not exhaustive.

The immunoregulatory and regenerative properties of MSCs make them ideal for use as therapeutic agents *in vivo* as they are uniquely positioned to suppress local inflammation and at the same time initiate tissue repair (Fig. 1). However, directing stem cell fate decisions towards a specific lineage is influenced by a variety of external and internal factors (Kobolak et al., 2015), which are still not completely elucidated. To successfully microengineer the native microenvironment of the cartilage ECM and the chondrocyte niche, it is critical to fully understand, and if needed, precisely modulate the molecular steps involved in chondrogenesis. This approach could be facilitated by using biomaterials that mimic the native ECM in combination with the necessary biophysical cues required for cellular remodelling (Jahr et al., 2015). Depending on the specific properties of the biomaterial under investigation, a variety of biophysical parameters such as swelling or porosity can be engineered to induce changes in cell spreading, migration and differentiation.

New biomimetic biomaterials are now being developed for micro-engineering the unique niche in articular cartilage, taking advantage of

the integration of mechanical and topographical properties of materials in scaffold design, and incorporation of biochemical cues such as cytokines in tethered, soluble, or time-released forms (Edalat et al., 2012; Zorlutuna et al., 2013). For example, fibrous poly(glycerol sebacate):poly(caprolactone) (PGS:PCL) scaffolds containing aligned fibres are able to direct the growth of primary human valvular interstitial cells along the scaffold axis (Masoumi et al., 2014). A similar approach could be used to mimic the zonal structure and mechanical properties of native articular cartilage.

There are still many technical challenges associated with the clinical use of MSCs for the regeneration of degenerate joints. However, we are starting to overcome some of the practical and conceptual difficulties. Interdisciplinary approaches based on the combination of new generation biomaterials and cell-based therapies are more likely to lead to breakthroughs in regenerating musculoskeletal tissues in the future.

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## References

- Burr, S.P., Dazzi, F., Garden, O.A., 2013. Mesenchymal stromal cells and regulatory T cells: the Yin and Yang of peripheral tolerance? *Immunol. Cell Biol.* 91 (1), 12–18. <http://dx.doi.org/10.1038/icb.2012.60> (Jan).
- Cross, M., Smith, E., Hoy, D., Nolte, S., Ackerman, I., Fransen, M., Bridgett, L., Williams, S., Guillemin, F., Hill, C.L., Laslett, L.L., Jones, G., Cicuttini, F., Osborne, R., Vos, T., Buchbinder, R., Woolf, A., March, L., 2014. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann. Rheum. Dis.* 73 (7), 1323–1330. <http://dx.doi.org/10.1136/annrheumdis-2013-204763> (Jul).
- Edalat, F., Sheu, L., Manoucheri, S., Khademhosseini, A., 2012. Material strategies for creating artificial cell-instructive niches. *Curr. Opin. Biotechnol.* 23 (5), 820–825. <http://dx.doi.org/10.1016/j.copbio.2012.05.007> (Oct).
- Jahr, H., Matta, C., Mobasheri, A., 2015. Physicochemical and biomechanical stimuli in cell-based articular cartilage repair. *Curr. Rheumatol. Rep.* 17 (3), 22. <http://dx.doi.org/10.1007/s11926-014-0493-9> (Mar).
- Kobolak, J., Dinnyes, A., Memic, A., Khademhosseini, A., Mobasheri, A., 2015. Mesenchymal stem cells: identification, phenotypic characterization, biological properties and potential for regenerative medicine through biomaterial micro engineering of their niche. *Methods* <http://dx.doi.org/10.1016/j.jymeth.2015.09.016> (Sep 15. pii: S1046-2023(15)30092-X).
- La Rocca, G., Lo Iacono, M., Corsello, T., Corrao, S., Farina, F., Anzalone, R., 2013. Human Wharton's jelly mesenchymal stem cells maintain the expression of key immunomodulatory molecules when subjected to osteogenic, adipogenic and chondrogenic differentiation in vitro: new perspectives for cellular therapy. *Curr. Stem Cell Res. Ther.* 8 (1), 100–113 (Jan, PMID: 23317435).
- Masoumi, N., Larson, B.L., Annabi, N., Kharaziha, M., Zamanian, B., Shaper, K.S., Cubberley, A.T., Camci-Unal, G., Manning, K.B., Mayer Jr., J.E., Khademhosseini, A., 2014. Electrospun PGS:PCL microfibrils align human valvular interstitial cells and provide tunable scaffold anisotropy. *Adv. Healthc. Mater.* 3 (6), 929–939. <http://dx.doi.org/10.1002/adhm.201300505> (Jun).
- Richardson, S.M., Kalamegam, G., Pushparaj, P.N., Matta, C., Memic, A., Khademhosseini, A., Mobasheri, R., Poletti, F.L., Hoyland, J.A., Mobasheri, A., 2015. Mesenchymal stem cells in regenerative medicine: focus on articular cartilage and intervertebral disc regeneration. *Methods* <http://dx.doi.org/10.1016/j.jymeth.2015.09.015> (Sep 15. pii: S1046-2023(15)30091-8).
- Zorlutuna, P., Vrana, N.E., Khademhosseini, A., 2013. The expanding world of tissue engineering: the building blocks and new applications of tissue engineered constructs. *IEEE Rev. Biomed. Eng.* 6, 47–62. <http://dx.doi.org/10.1109/RBME.2012.2233468>.