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Can Synovium-derived Stem Cells Deposit Matrix with Chondrogenic Lineage-specific Determinants?

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Recent reviews of consecutive knee arthroscopies have demonstrated the occurrence of chondral defects ranging from 60% to 65%, irrespective of the surgical indication [1]. Osteoarthritis, trauma, and disorders of the subchondral bone – such as osteochondritis dissecans or osteonecrosis, which secondarily affect articular cartilage – may cause defects in cartilage. Based on current trends, osteoarthritis is predicted to be the fourth leading cause of disability worldwide by the year 2020 [2]. Articular cartilage is a unique, hypocellular, avascular tissue mostly made of extracellular collagens and proteoglycans; it has a limited ability to self heal after trauma and degenerative disease [3]. Current clinical practice usually involves a bone marrow stimulation technique in which subchondral bone is broken to facilitate cartilage repair from bone marrow stromal cells (BMSCs) and cytokines. However, with this procedure, cartilage defects are most often repaired with fibrocartilage, which is known to be biochemically and biomechanically different from native hyaline cartilage; this tissue subsequently undergoes degeneration [4]. Autologous chondrocyte transplantation (ACT) is currently used clinically; however, it has not proven to be as successful as originally predicted [5]. Obtaining vital and differentiated chondrocytes presents one of the major challenges for successful ACT. Each biopsy presents an additional trauma to already damaged joint cartilage and may cause postoperative pain and increase the long-term risk of developing osteoarthritis [4]. Furthermore, the expansion phase the chondrocytes have to undergo *in vitro* leads to rapid cell de-differentiation with a loss of chondrogenic potential [6]. Additionally, isolation of cells from the cartilage matrix by enzymatic digestion diminishes cartilage-specific mRNA levels and changes are exaggerated during expansion [7]. The *ex vivo* expansion of articular chondrocytes leads to a telomere erosion comparable to 30 years of aging *in vivo* [8]. Although re-differentiation of these cells has been shown *in vitro* [9], only partial gene expression was restored [7] and a progressive loss of cell ability to form stable ectopic cartilage *in vivo* became evident [10]. Thus, newly synthesized cartilage often consists of more fibrous tissue than hyaline cartilage [11].

It becomes important to find an alternative, easily obtainable cell source with stable chondrogenic potential [12]. Mesenchymal stem cells (MSCs) are a promising cell source for cartilage regeneration because, compared to articular chondrocytes, they are easily obtainable in high numbers, expand *in vitro* without losing their differentiation potential [13], and have more pronounced expansion ability with no higher risk for replicative aging [14]. Due to an 'age phenotype' of chondrocytes but not MSCs from patients of advanced age, MSCs were found to be more attractive for cartilage repair in older individuals. One possible source of MSCs is adipose tissue, which is easily accessible in large quantities. Apart from a similar osteogenic and adipogenic differentiation potential, however, adipose-derived MSCs showed a reduced chondrogenic differentiation capacity under standard induction conditions [15]. In addition to adipose tissue, bone marrow is a particularly attractive source for MSCs. Some recent reports indicated that BMSC-based repairs perform better than chondrocyte-based ones [16,17], despite one report suggesting that BMSC transplantation showed comparable results with ACT in the repair of articular cartilage defects [18]. Compared to the ACT approach having a greater effect in younger patients, transplantation with BMSCs did not show any difference in ages older or younger than 45 [18]. A major hurdle in cartilage tissue engineering with BMSCs is their differentiation toward endochondral ossification [19]. During *in vitro* chondrogenesis, BMSCs up-regulate not only hyaline cartilage-specific markers such as collagen II and aggrecan, but also markers typical for hypertrophic chondrocytes such as collagen X and alkaline phosphatase (ALP) [20-22]. Collagen X makes up 45% of the collagen produced in hypertrophic chondrocytes and is therefore considered an important marker of enchondral ossification [23]. In contrast, collagen X is almost negligible in healthy mature chondrocytes and engineered cartilage [24,25].

One of the challenges that need to be solved for the advancement of regenerative cartilage medicine is to find a tissue-specific stem cell that generates articular cartilage-like chondrocytes and does not undergo hypertrophy as a terminal differentiation stage. Under chondrogenic induction, BMSCs showed a 5- to 10-fold increase in osteocalcin and ALP compared to synovium-derived stem cells (SDSCs) [26]; in contrast, SDSCs have fewer tendencies to become hypertrophic when incubated in a chondrogenic induction medium [27-33]. Figure 1 shows the different lineage tendencies of both human stem cells. There is increasing evidence demonstrating that SDSCs are a tissue-specific stem cell for chondrogenesis [34]. Synovium is the closest tissue to articular cartilage, not only in development but also in function; synovial cells share properties with chondrocytes, such as cartilage oligomeric matrix, link protein, and sulfated glycosaminoglycans (GAGs). Synovium is also the only tissue that can produce hyaline cartilage in benign conditions; under appropriate stimulatory conditions, synovial cells are able to migrate into articular cartilage defects and subsequently undergo chondrogenic differentiation. It was demonstrated that SDSCs match more closely with articular chondrocytes in gene profile than BMSCs and are better at chondrogenic differentiation than stem cells from bone marrow, periosteum, adipose tissue, and muscle. Both chondrocytes and synovial cells bordering the joint cavity could also synthesize superficial zone protein (SZP) that provides a protective microenvironment for cartilage progenitor cells at the surface of articular cartilage.

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Another challenge is preventing dedifferentiation and enhancing proliferation and chondrogenic capacity during *in vitro* cell expansion. A recent study indicated that a functional stem cell niche exists in adult knee joint synovium *in vivo* [35]. Extracellular matrix (ECM) can be used to imitate the features of an *in vivo* environment [36]. Our reports demonstrated that, for the first time, decellularized stem cell matrix (DSCM) deposited by SDSCs is a promising and novel cell expansion system for cartilage tissue engineering, not only enhancing cell proliferation but also promoting expanded cell chondrogenic potential instead of (or even against) hypertrophy [37-44]. DSCM could be deposited by either SDSCs [37,41] or BMSCs [45]; the former enhanced SDSC chondrogenic potential while preventing hypertrophy and the latter enhanced BMSC chondrogenic capacity with up-regulated hypertrophic markers. These results suggest that DSCM deposited by SDSCs or BMSCs may provide a tissue-specific microenvironment for lineage-specific differentiation.

Not only for stem cells [37,38,40-42,45], our findings suggest that this cell expansion system also works for primary cells, such as chondrocytes [42,43] and nucleus pulposus cells [39,44]; the results have been summarized in our recent review paper [46]. Figure 2 shows porcine chondrocyte morphology and polarity when expanded on either plastic flasks or DSCM. DSCM may also provide an excellent model for other specific lineage tissue engineering and regeneration, which needs further investigation. The DSCM approach combined with SDSCs may provide a novel and promising approach to overcome replicative senescence [47] and chondrogenic hypertrophy, which are two significant hurdles for cell-based cartilage engineering and regeneration. DSCM will be significant not only in advancing the development of new generations of stem cell-based approaches for cartilage engineering and regeneration, but also will provide fundamental new knowledge regarding the interaction between stem cell and matrix microenvironment as well as the potential mechanisms underlying stem cell rejuvenation or reprogramming by surrounding stem cell matrix.

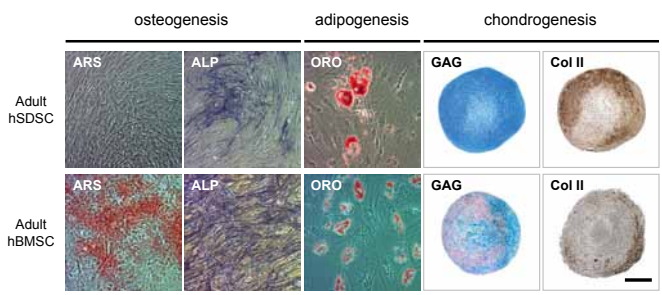

Figure 1: Human adult synovial fibroblasts (Asterand plc, Detroit, MI, USA) and BMSCs (Lonza Group Ltd., Switzerland) were characterized for their multi-lineage differentiation capacities. Human synovial fibroblasts were positively stained for alkaline phosphatase (ALP), adipose drops [Oil Red O (ORO) staining], GAG (Alcian blue staining) and collagen II (immunostaining), indicating they are hSDSCs. After incubation in osteogenic medium for two weeks, hBMSCs were intensively stained with calcium matrix [stained by Alizarin Red S (ARS)] and ALP, indicating that, compared to hSDSCs, hBMSCs are tissue-specific stem cells for osteogenesis. There was non-detectable ARS staining and comparable ALP staining in hSDSCs, suggesting that there was less osteogenic potential for the hSDSC group. After incubation in chondrogenic medium for two weeks, hSDSCs exhibited intensive staining of GAG and collagen II compared to hBMSCs, suggesting that hSDSCs had more chondrogenic differentiation capacity than hBMSCs. The scale bar is 800 μm.

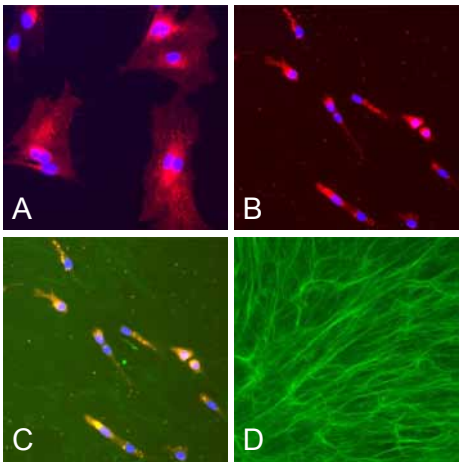

Figure 2: Dil-stained chondrocytes (red) with DAPI as a nuclear counterstain (blue) were expanded on either Plastic (A) or DSCM deposited by SDSCs (B). DSCM plated with (C) or without the stained porcine chondrocytes (D) were immunostained with collagen I antibody (green). See reference 43 for details.

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