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Review

Cartilage regeneration and ageing: Targeting cellular plasticity in osteoarthritis

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ABSTRACT

Ageing processes play a major contributing role for the development of Osteoarthritis (OA). This prototypic degenerative condition of ageing is the most common form of arthritis and is accompanied by a general decline, chronic pain and mobility deficits. The disease is primarily characterized by articular cartilage degradation, followed by subchondral bone thickening, osteophyte formation, synovial inflammation and joint degeneration. In the early stages, osteoarthritic chondrocytes undergo phenotypic changes that increase cell proliferation and cluster formation and enhance the production of matrix-remodelling enzymes. In fact, chondrocytes exhibit differentiation plasticity and undergo phenotypic changes during the healing process. Current studies are focusing on unravelling whether OA is a consequence of an abnormal wound healing response. Recent investigations suggest that alterations in different proteins, such as TGF-ß/BMPs, NF-Kß, Wnt, and Cx43, or SASP factors involved in signalling pathways in wound healing response, could be directly implicated in the initiation of OA. Several findings suggest that osteoarthritic chondrocytes remain in an immature state expressing stemness-associated cell surface markers. In fact, the efficacy of new disease-modifying OA drugs that promote chondrogenic differentiation in animal models indicates that this may be a drug-sensible state. In this review, we highlight the current knowledge regarding cellular plasticity in chondrocytes and OA. A better comprehension of the mechanisms involved in these processes may enable us to understand the molecular pathways that promote abnormal repair and cartilage degradation in OA. This understanding would be advantageous in identifying novel targets and designing therapies to promote effective cartilage repair and successful joint ageing by preventing functional limitations and disability.

Abbreviations: ALP, alkaline phosphatase; BMPs, bone morphogenetic proteins; C/EBPß, CCAAT/enhancer binding protein beta; CIA, collagen II induced arthritis; CTD, C-terminal domain; Cx43, connexin43; Cxs, connexins; DMOADs, disease-modifying osteoarthritis drugs; ECM, extracellular matrix; EMT, epithelial to mesenchymal transition; ES cells, embryonic stem cells; FLNA, filamin A; FLSs, fibroblast-like synoviocytes; GAGs, glycosaminoglycans; GDF5, growth and differentiation factor 5; GJIC, gap junction intercellular communication; IL, interleukin; KGN, kartogenin; MAPK, mitogen-activated protein kinase; MET, mesenchymal to epithelial transition; MMPs, matrix metalloproteinases; mRNA, messenger RNA; MSCs, mesenchymal stem cells; NFATs, nuclear factor of activated T-cells; NF-Kß, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; OA, osteoarthritis; OCT4, octamer-binding transcription factor 4; OlAG, oleuropein aglycone; OP-1, osteogenic protein-1; PARP, poly ADP ribose polymerase; RA, rheumatoid arthritis; RNAi, RNA interference; ROS, reactive oxygen species; Runxs, runt-related transcription factors; SAbGal, senescence-associated beta-galactosidase; SASP, senescence-associated secretory phenotype; SCID, severe combined immune deficient; sIL-6R, soluble form of IL-6 receptor; SOX, Sry-related HMG box; TGF-ß, transforming growth factor-beta; TNFα, tumour necrosis factor alpha; VCAM, vascular cell adhesion protein-1; Wnt, wingless-related integration site; ZIP8, zinc-transporting protein

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1. Introduction

1.1. Osteoarthritis (OA)

OA is the most common joint disorder worldwide. Pain and loss function are the main clinical features that lead to treatment, including surgical approaches. The prevalence of OA varies according to the definition of the disease, the specific joint(s) under study and the characteristics of the study population. However a standardized prevalence of radiographic knee OA in USA indicated that more than 19% of population age ≥ 45 had radiographic knee OA (Helmick et al., 2008). This joint disorder is associated with an increasing socioeconomic impact affecting one or several synovial joints. The knee, hip and hand are most affected by this disease. The Global Burden of Disease (GBD) 2010 and 2014 studies ranked hip and knee OA as the 11th highest contributor to global disability and one of the highest contributors to disability-adjusted life years (DALYs) among 291 conditions (Cross et al., 2014; Storheim and Zwart, 2014). OA is expected to continue to rise with an increasingly aged population, with higher incidence in females (Cross et al., 2014; Storheim and Zwart, 2014). Unfortunately, the underlying pathogenic mechanisms are not yet fully understood, and there are no currently disease-modifying drugs that could slow or stop the disease progression in patients.

Although OA has been mainly characterized by a failure of the repair process of damaged cartilage, it is considered a disease of the whole joint, where all surrounded tissues are affected because of their physical and functional association (Loeser et al., 2012). There is evidence that muscle sensorimotor dysfunction contributes to the development and progression of OA (Hurley, 1999; Kemnitz et al., 2017; Oiestad et al., 2015; Sims et al., 2002; Turkiewicz et al., 2017). One contribution from the muscle dysfunction to OA could be that the neuromuscular protective mechanisms that prevent abnormal joint movements or damage could be impaired. Skeletal development is also influenced by the mechanical forces generated by muscles. Also, the muscles release biochemical molecules that affect cartilage homeostasis and repair (Cairns et al., 2010a; Cairns et al., 2010b; Rainbow et al., 2013). Certainly, the understanding of the interactions of cartilage and its surrounding tissues through paracrine or endocrine signalling (secretome or small vesicles) will bring new knowledge about OA pathogenesis.

The list of risk factors for OA are still evolving, with an intricate relationship between local and systemic factors (Fig. 1A). Some of these factors include age, obesity, gender, increased biomechanical loading of joints, genetics or low-grade systemic inflammation (Martel-Pelletier et al., 2016; Sellam and Berenbaum, 2013). Age is one of the major risk factor for OA in all joints (Lawrence et al., 2008), probably as a consequence of biological changes within joint tissues. Aged mice have a higher senescence burden and develop more severe OA (cartilage degeneration) after injury (Jeon et al., 2017). Other joint tissues, such as muscle (Sousa-Victor et al., 2014) and bone (Busse et al., 2010), have also shown functional decline and similar molecular changes to those found in cartilage, including accumulation of senescent cells, loss of cellularity or disruption of the extracellular matrix (ECM) (Hasegawa et al., 2012; Pauli et al., 2011). Accumulation of senescence cells in the bone microenvironment contributes to bone loss (Farr et al., 2016; Farr et al., 2017). These authors have recently demonstrated that targeting senescence cells or eliminating their proinflammatory secretome prevent age-related bone loss in mice by decreasing bone resorption and improving bone formation (Farr et al., 2017). Further, senescence of muscle stem cells during ageing limits their regenerative capacity (Garcia-Prat et al., 2016). Moreover, increased expression levels of the senescence-related gene p16 (INK4a), in muscle stem cells in aged mice, made these cells more likely to undergo senesce after injury (Sousa-Victor et al., 2014). Therefore, targeting senescence-associated tissue damage seems a promising strategy for preventing joint degeneration (Farr et al., 2017; Jeon et al., 2017).

1.2. Chondrocyte behaviour in OA

The articular cartilage is composed of water and ECM mainly composed of type II collagen, aggrecan and other proteoglycans together with several non-collagenous proteins and other collagen subtypes. The chondrocytes are cells responsible for the synthesis and turnover of ECM. These cells are located in the lacunae and have low mitotic activity. OA includes multiple phenotypes and subgroups (Fig. 1A). For example, the microscopic analysis of cartilage from patients shows different patterns of damage (Fig. 1B). The degeneration of cartilage can be observed in the superficial zone with the loss of ECM components such as acidic proteoglycans detected by safranin O and fast green staining. However, it is also common to observe cartilage ulceration and damage at the intermediate zone and/or the deepest zones of the cartilage in contact with the subchondral bone (Fig. 1B). These areas do not always exhibit the loss of proteoglycans. During OA, alterations in the structure and function of cartilage are accompanied by changes in the ligaments, muscles, subchondral bone and synovial tissue (Fig. 1B). The disease is characterized by cartilage destruction, synovial inflammation, muscle weakness, osteophyte formation and subchondral bone sclerosis (Burr and Gallant, 2012; Loeser et al., 2012; Sellam and Berenbaum, 2010). In the early stages, chondrocytes exhibit increased synthetic activity, reflecting attempts to repair the damage. However, the disruption of the pericellular matrix of the chondrocytes expose the cells to factors and components, which ultimately affect chondrocyte phenotype and behaviour. The complexity of the disease is in part due to the different types of cells (chondrocytes) coexisting in the osteoarthritic cartilage. For example, it has been reported that some of these chondrocytes assume a senescence-associated secretory phenotype (SASP) that deregulates chondrocyte function (Gao et al., 2016; Jeon et al., 2017; Philipot et al., 2014; Xu et al., 2017). On the other hand, several reports have highlighted different molecular hallmarks that demonstrate the presence of cells expressing immature markers in the osteoarthritic cartilage (Alsalameh et al., 2004; Hiraoka et al., 2006; Jiang et al., 2016; Jiang and Tuan, 2015; Pretzel et al., 2011).

2. Cellular plasticity

In the last decades, it has been demonstrated that certain signalling pathways can restore pluripotency in fully differentiated cells (reprogramming), induce proliferation (dedifferentiation) or even promote switching to another cell type (transdifferentiation) (Jopling et al., 2011) (see Fig. 2). Certain biological conditions associated with senescence, such as tissue injury or ageing, favour cellular reprogramming *in vivo* by provoking cellular plasticity conducive to tissue repair (Jessen et al., 2015; Mosteiro et al., 2016). There are several transcription factors that play pivotal roles in those reprogramming-like cellular plasticity mechanisms. In particular, the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kß), STAT3 or Smad2, with interleukin-6 (IL-6) being of particular relevance, have been suggested to play relevant roles in the mechanisms involved in cellular plasticity under biological conditions characterized by high levels of senescence such as the case of tissue injury (Mosteiro et al., 2016). This review covers several factors described in OA that contribute to reprogramming and dedifferentiation processes in the cartilage. Dedifferentiation of mature cells is a process by which a terminally differentiated cell reverts back to a less-differentiated state within its own lineage. The cell regains the capacity to proliferate, which means that a postmitotic cell such as a chondrocyte can re-enter the cell cycle and replace the cells that have been lost before redifferentiation (Fig. 3A). This mechanism is associated with natural regeneration, but it also leads to pathological processes (Cai et al., 2007; Fassina et al., 2012; Iwano et al., 2002; Kim et al., 2006; Wicki et al., 2006). Although not all differentiated cell types can dedifferentiate and proliferate, there is a growing number of studies indicating that when exposed to appropriate signals, different mammalian cell types can be induced to