Modeling Osteoarthritis Using Three-Dimensional Culture

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Abstract Osteoarthritis (OA) is characterized by the degradation of cartilage caused by dysregulated and inappropriate anabolic and catabolic responses. To study this degeneration in vitro, three-dimensional (3D) culture provides a better model of the in vivo environment compared to the 2D culture along with a multitude of other benefits, providing greater insight into the progression of OA. These 3D cultures can be used in inflammation modeling of OA, demonstrating the effect of inflammatory agents such as cytokines or macrophages. In 3D damage modeling of OA, a wide variety of factors are used to cause damage, and researchers may observe repair and the progression of damage. Therapeutic modeling of OA using 3D culture allows researchers to test possible therapeutic modalities. This review highlights the benefits of 3D culture, and how, when used in inflammation, damage, and therapeutic models, brings a deeper understanding of OA.

Keywords: osteoarthritis, three-dimensional culture, inflammation, degeneration, therapeutics


1. Introduction

Chondrocytes and other cell types are cultured and studied in 3D due to the advantages it provides over 2D culture [1,2,3,4,5]. One key factor in culturing chondrocytes in 3D is that the culture environment closely mimics the in vivo environment [1]. The three-dimensional aspects of the in vivo environment, including cell-cell interactions and cell-ECM interactions, can be recapitulated in a 3D culture [6,7]. Chondrocytes in 3D culture maintain their phenotypic characteristics, such as cell shape and morphology [2,6,8]. De-differentiation is inhibited while re-differentiation is supported [1,2,9,10]. The study of OA using 3D culture is not limited to chondrocytes; a variety of cell types are used, including stem cells, stromal cells, macrophages, and other chondrogenic progenitors, to investigate chondrogenesis and other processes related its progression [1,4,8,11,12,13,14,15,16]. To study OA, 3D culture has been used to develop models that simulate inflammation, damage, and even therapeutic effects.

2. Discussion

2.1. Inflammation Models

Studies using 3D cultures to focus on the assessment of inflammatory agents in OA can be considered inflammatory models. Inflammatory agents involved in the progression of OA include IL-1β, IL-6, IL-8, TNF-α, and NO [11,17,18]. Inflammation models are used in a variety of ways. For example, chondrocytes derived from both osteoarthritic and normal cartilage can be co-cultured with macrophages expressing different phenotypes, activated or naive, to better understand the paracrine interactions between the two cell types [11]. Transcript and protein expression levels of inflammatory markers such as IL-1β, IL-6, TNF-α, and NOS-2 can subsequently be measured. Results from these studies not only confirm other researchers’ in vitro culture results, they expand current knowledge of paracrine interactions, a benefit of using 3D culture [11]. Another study found that an osmolarity of 380 mOsm in osteoarthritic chondrocytes lowers IL-6 levels, and cytokine levels in general were lower in 3D culture compared to 2D culture [18]. The implementation of 3D culture in inflammation models strengthens results and provides new insights into OA [11,17,18].

2.2. Damage Models

Chondrocytes grown in 3D cultures that investigate the cause of damage or degradation of cartilage in OA can be considered damage models. Damage models may incorporate inflammatory agents (ex. IL-1β, TNF-α) to induce inflammation and therefore damage, [1,12] may induce mechanical stress, enzymatic degradation, or lesions [19,20]. In co-cultures macrophage activation/ deactivation can also cause damage [11,16]. As discussed above, macrophages are used in 3D co-culture as inflammatory agents to study paracrine interactions [11]. Similarly, activated macrophages can be used in 3D hydrogel


cultures to study damage and hypertrophic responses. Peck and Wang found that activated macrophages induce greater hypertrophic responses than non-activated macrophages, as well as cause degradation of collagen II [16]. Inflammatory cytokines such as IL-1β and TNF-α are also used to induce damage in an in vitro OA model using scaffold-free 3D cartilage transplants [12]. Evans et al. (2020) are working to develop a 3D model using mesenchymal stem cells differentiated in a hyaluron matrix. Once chondrogenesis has been induced, the pellets are subjected to hyaluronidase to induce damage and the effects of stress hormones on degradation after damage are examined [personal communication]. Compared to other studies, no other studies used hyaluronidase to induce damage in a mesenchymal stem cell differentiation model to determine the effect of stress hormones on chondrogenic phenotype, giving hope for new insights on osteoarthritis. Damage models provide important information concerning the pathology of OA and preliminary models for future studies [1,11,12,16,19,20].

2.3. Therapeutic Models

Studies using 3D cultures involving the experimentation of new or potential therapeutic advances in OA are considered therapeutic models. Therapeutic models can range from testing potassium treatments, [21] possible gene therapy, [22] testing different types of 3D culture and expansion/maintenance methods, [4,13,14,15,19,23] to using different compounds, chemicals or drugs to assess chondrogenesis or chondrogenic repair [6,10,14,15,23]. A recent study found that osteoarthritic chondrocytes, grown in 3D hydrogel and treated with hyperosmolar potassium (80 mM K+ gluconate) increased transcription of anabolic chondrogenic markers, such as aggrecan, collagen II, and SOX-9 demonstrating the therapeutic potential of this treatment [21]. The potential for gene therapy has also been demonstrated using 3D culture. Transfection of a vector carrying the sequence for SOX-9 induced increased collagen II and proteoglycan transcription and reduced the hypertrophic phenotype in a 3D model of OA [22].

Using a 3D model, it is also possible to examine the efficacy of therapeutic compounds. For example, the phytoestrogen, Daidzein, has been studied in 3D culture. Transfection of a vector carrying the sequence for SOX-9 induced increased collagen II and proteoglycan transcription and reduced the hypertrophic phenotype in a 3D model of OA [22].

3. Conclusion

The use of 3D culture for modeling can provide a vast amount of information about many diseases, particularly OA, due to its versatility and applicability. It can be used to create inflammation, damage, and therapeutic models to emulate the in vivo environment more accurately when compared to 2D culture. It is important to continue developing new models of OA using 3D culture. One group, Evans et al. (2020) as highlighted above, is developing a damage model using chondrocytes derived from mesenchymal stem cell differentiation. Most work with mesenchymal stem cells has the goal of using them as a therapeutic or in repair. Using them in a new way, such as in a damage model, may provide new insights into the complex pathophysiology of OA. Overall, 3D modeling allows for advances in our understanding of the pathogenesis of OA and provides a defined in vitro system for testing the efficacy of potential therapeutics.

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References


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