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INTRA-ARTICULAR DEXAMETHASONE TO INHIBIT THE DEVELOPMENT OF POST-TRAUMATIC OSTEOARTHRITIS

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Abstract

Injury to the joint provokes a number of local pathophysiological changes, including synthesis of inflammatory cytokines, death of chondrocytes, breakdown of the extra-cellular matrix of cartilage and reduced synthesis of matrix macromolecules. These processes combine to engender the subsequent development of post-traumatic osteoarthritis (PTOA). To prevent this from happening, it is necessary to inhibit these disparate responses to injury; given their heterogeneity, this is challenging. However, dexamethasone has the necessary pleiotropic properties required of a drug for this purpose. Using in vitro models, we have shown that low doses of dexamethasone sustain the synthesis of cartilage proteoglycans while inhibiting their breakdown after injurious compression in the presence or absence of inflammatory cytokines. Under these conditions, dexamethasone is non-toxic and maintains the viability of chondrocytes exposed chronically to such cytokines as interleukin (IL)-1, IL-6 and tumor necrosis factor-α. Moreover, the anti-inflammatory properties of dexamethasone have been appreciated for decades. In view of this information, we have initiated a pilot clinical study to determine whether a single, intra-articular injection of dexamethasone into the wrist shows promise in preventing PTOA after intra-articular fracture of the distal radius.

Introduction

Because post-traumatic osteoarthritis (PTOA) follows an obvious injury to the joint, it offers the opportunity for early therapeutic, even prophylactic, intervention. Recent advances in our understanding of the pathophysiological sequelae triggered by acute injuries to joints have generated a plausible general etiologic schema for PTOA[1,2].

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Author Contributions

All authors contributed to the writing and editing of this manuscript

The initial injury leads to disruption of the cartilaginous matrix and the rapid death of chondrocytes in the impacted area. Acutely, this may occur via necrosis[3] with subsequent apoptotic death of additional cells[4]. During the next several days, the zone of chondrocyte death expands. Moreover, the surviving chondrocytes further damage their surrounding cartilaginous matrix both by reducing the synthesis of matrix macromolecules and by increasing their degradation[5]. Osseous disturbances also occur during this period[6]. These changes occur in response to mechanical insult and are exacerbated by the inflammatory environment of injured joints. Since the work of Cameron et al.[7], subsequently confirmed in several additional studies[8–12], we know that the expression of several major inflammatory cytokines, including interleukins- (IL-) -1, 6 and -8, tumor necrosis factor-α (TNF-α), interferon-γ and granulocyte-macrophage colony stimulating factor, is elevated soon after injury to the human knee joint. The inflammatory response may be amplified by wear particles[13] and various damage-associated molecular pattern molecules (DAMPs) created as a result of injury[14]. Collectively, these inflammatory mediators contribute to the synovitis, effusion, pain, cartilage degeneration and osseous changes that occur soon after injury. If these imbalances are allowed to persist, cartilage is irreversibly lost and the symptoms of OA ensue, despite a delayed anabolic phase that attempts to restore the cartilaginous matrix.

In this context, it should be noted that although living chondrocytes are able to replenish proteoglycan lost from their extracellular matrix, damage to the type II collagen of cartilage is generally thought to be irreversible[15]. Moreover, while human articular cartilage is now reported to contain a progenitor cell sub-population[16], these cells are unlikely to be capable of replacing the extensive population of dead chondrocytes caused by injury, especially if these progenitors, too, are damaged. Extensive death of chondrocytes and destruction of the collagenous matrix of cartilage may thus determine the point at which degeneration of the cartilage becomes irreversible and PTOA inevitable, rendering futile any subsequent attempt at prophylaxis or restorative therapy[17].

Cartilage matrix degradation and suppression of cartilage matrix synthesis, chondrocyte death and inflammation thus feature among the major, early, deleterious events that follow trauma to the joint. Any intervention to prevent the development of PTOA after injury must inhibit as many of these responses as possible, without suppressing endogenous reparative responses or triggering additional adverse events. This article summarizes pre-clinical evidence supporting the use of low-dose, intra-articular dexamethasone in this regard, and describes a consequent clinical trial.

The Injurious Compression of Cartilage, Inflammation and Dexamethasone

A variety of in vitro loading systems have been developed to induce mechanical damage in a manner relevant to in vivo joint injury; these systems have been recently codified and reviewed[18]. Of these various approaches, we have established a reliable, well-characterized *in vitro* model with which to investigate the combined effects of injurious mechanical compression in an inflammatory environment on the metabolism of articular cartilage[5,19–23]. Using this system, it has been confirmed that injurious loading alone leads to degradation of both proteoglycan and collagen by chondrocytes, with suppression of compensatory matrix synthesis. This is accompanied by cell death and leads to loss of the structural and

mechanical integrity of cartilage. These effects are dramatically exacerbated in the presence of inflammatory cytokines known to be upregulated in traumatized joints, particularly TNF-α and IL-6 in association with its soluble receptor (sIL-6R)[24]. This system has enabled an approach to in vitro screening of potential chondro-protective agents[21,24–26] as well as intra-articular nano-particle drug delivery methods[27].

The multiplicity of mediators generated in response to injury constitutes a major challenge to preventing degenerative responses of cartilage to trauma, and the onset of PTOA in the damaged joint. A partial list of mediators includes the inflammatory cytokines mentioned in the previous section, as well as a variety of proteinases (matrix metalloproteinases (MMPs), a disintegrin and a metalloproteinase with thrombospondin motifs (ADAMTS), serine proteinases), reactive oxygen species, nitric oxide, prostanoids and numerous DAMPs. In the face of such a large and varied cocktail of mediators, an agent that selectively neutralizes a single mediator, or even a class of mediators, is unlikely to provide comprehensive protection from PTOA.

In this context, dexamethasone emerges as an attractive candidate because of its pleiotropic protective properties. In various cell types and animal models it inhibits the induction of MMPs[28], prostaglandins[29], inflammatory cytokines[30], nitric oxide[31] and other oxygen-derived radicals[32]. The literature is inconsistent on whether dexamethasone inhibits or promotes apoptosis in different types of cells[33,34] but, as described below, it protects the viability of chondrocytes exposed to IL-1.

Collectively, these properties make dexamethasone a potential prophylactic agent for preventing degenerative responses in cartilage and the onset of PTOA in joints after injury. Moreover, translation is facilitated by its widespread use in routine clinical practice, including intra-articular injection for established OA, with a good understanding of its pharmacology and safety profile.

Dexamethasone is a synthetic member of the glucocorticoid class of steroid drugs, with a potency about 20–30 times that of the naturally occurring hydrocortisone and 4–5 times that of another widely used synthetic analog, prednisolone[35]. Over seventy years after the first chemical synthesis of cortisone[36], corticosteroids remain among the top ten most commonly used drugs. Because they have been widely used to treat a variety of autoimmune diseases much is known about their pharmacology, pharmacokinetics and toxicology[37,38]. Systemically administered corticosteroids are very effective in controlling inflammatory conditions, but their use is constrained by adverse side effects, the main ones being loss of bone mineral density, avascular necrosis, increased body weight, increased cardiac risk, increased risk of infection and glucose intolerance. Intra-articular administration minimizes these systemic risks[39,40].

Although intra-articular steroids are effective in providing symptomatic relief in established OA, there are concerns that repeated use damages the articular cartilage[41]. For this reason, orthopaedists are reluctant to administer repeated intra-articular steroid injections. However, when used to prevent the development of PTOA, we propose that a limited number of intra-articular injections – possibly as few as one[27] – should be effective. This should maintain

chondrocyte viability and restore metabolic equilibrium, while suppressing inflammation. From this point onwards, joint homeostasis will have been recovered and, in the absence of further injury, it should not be necessary to inject additional dexamethasone or, indeed, any other agent. Moreover our preliminary data, described below, strongly suggest that even very high doses of dexamethasone have no adverse effects on chondrocyte metabolism during periods of time relevant to a single, intra-articular application. From the surgical perspective, a single, intra-articular injection of dexamethasone would not interfere with any subsequent necessary adjunctive surgery to restore the mechanical integrity and alignment of the joint once the metabolic response to injury has been addressed.

Effects of Dexamethasone on Cartilage exposed to Injurious Compression and Inflammatory Mediators

Lu et al[42] were the first to examine the effects of dexamethasone on the metabolism of cartilage after injurious compression in the presence or absence of inflammatory cytokines. They showed that dexamethasone normalized the release of glycosaminoglycans (GAG) from articular cartilage in response to TNF-α (figure 1). This occurred across an exceptionally wide range of dexamethasone concentrations (1–10^5 nM) and could not be explained by toxicity because the same doses of dexamethasone restored GAG synthesis to control levels (figure 1).

Injurious compression of cartilage exposed to TNF-α exacerbated GAG loss, while the addition of IL-6/IL-6sR to this combination provoked even higher GAG release. In every case, GAG synthesis remained at very low levels. Under all conditions, 10 nM dexamethasone normalized GAG synthesis and release rates (figure 2). Of practical clinical relevance, the effects of dexamethasone were still apparent when its administration was delayed until 4 days after injury and the addition of cytokines.

As noted, damage to the collagenous component of the cartilaginous matrix places the joint at particular risk of PTOA because such damage is irreversible. The data shown in figure 3 show that, in this *in vitro* model, loss of collagen from damaged cartilage in response to IL-1 begins at about day 12, after depletion of proteoglycans. Addition of dexamethasone at this time almost completely blocked the subsequent loss of collagen (figure 3).

Death of articular chondrocytes further compromises the integrity of articular cartilage and eliminates any possibility of successful endogenous repair. As shown in figure 4, low dose dexamethasone maintained the viability of chondrocytes within cartilage incubated for an extended period of time with IL-1.

Thus, under these in vitro conditions, low dose dexamethasone reduces the loss of proteoglycan and collagen from the extra-cellular matrix, maintains matrix synthesis and preserves chondrocyte viability. Based on this, it has the properties required of a drug for protecting cartilage in the traumatized joint. Its wide dose-response range and lack of toxicity are particular advantages.

The anti-inflammatory properties of dexamethasone have been appreciated for decades, and it has been widely administered by intra-articular injection to treat inflammation of joints. Its safety in this application is well established. Heard et al[43] recently reported data from a rabbit study that addressed the effects of dexamethasone on the inflammatory aspects of PTOA in the absence of blunt trauma. Using a drill-hole model that induced inflammation without mechanical injury to the knee joint, these investigators reported a dramatic effect of a single, intra-articular injection of dexamethasone. Expression of IL-1, IL-6 and IL-8 was reduced and cartilage integrity was maintained.

The First Clinical Trial

Based upon the foregoing information, we have initiated a clinical study to determine whether a single, intra-articular injection of dexamethasone soon after injury can reduce the incidence or severity of PTOA (ClinicalTrials.gov Identifier: NCT02318433). Because we lack the data necessary for a comprehensive power analysis, this is a pilot study designed to provide the quantitative information required for a subsequent interventional trial with adequate statistical strength.

For a feasibility and pilot study of this nature, it was necessary to identify an indication where the incidence of PTOA was high and its development rapid. PTOA following intra-articular fractures of the distal radius seems to satisfy this requirement, where, according to Knirk et al[44], there can be radiologic evidence of PTOA in 65% of patients at a mean follow-up of 6.7 years.

Initiated in 2014, the present study is recruiting 40 subjects with an intra-articular fracture of the distal radius. Patients are prospectively randomized into two groups of 20 individuals who receive an intra-articular injection of either 4 mg dexamethasone or an equal volume of saline within 2 weeks of injury. Each subject is being followed for 2 years. The primary outcome measure is incidence of PTOA, determined by joint space narrowing as measured radiologically. Secondary outcomes include functional assessment using several patient-rated evaluations including the Disabilities of the Arm Shoulder and Hand (DASH), the Michigan Hand Questionnaire (MHQ) and the Patient-Rated Wrist Evaluation (PRWE).

Conclusions and Perspective

Laboratory data and clinical experience suggest that a single, intra-articular injection of low dose dexamethasone soon after injury to the joint holds considerable promise as a safe means of preventing the development of PTOA. A small clinical study has been initiated to begin to explore this possibility. Repurposing intra-articular dexamethasone for preventing the development of PTOA after injury will be facilitated by its widespread clinical use in similar applications. This obviates the cost and regulatory burden of developing novel drugs for this purpose. Moreover, dexamethasone is inexpensive, costing only a few dollars per injection. While its clinical development is being pursued, laboratory research is exploring complementary avenues of treatment. One of them seeks to deliver dexamethasone to chondrocytes more efficiently, and another seeks to study the potential of a combination therapy involving dexamethasone and IGF-1.

Although the safety and anti-inflammatory properties of intra-articular dexamethasone have been well established clinically, its ability to influence chondrocyte metabolism in the manner noted here under *in vitro* conditions may be compromised by the highly hydrophilic nature of cartilaginous matrix and rapid efflux of dexamethasone from the joint[45]. For these reasons a second-generation product is being developed in which dexamethasone is covalently linked to avidin, a small, highly cationic molecule that rapidly diffuses throughout the whole depth of cartilage and delivers dexamethasone efficiently to chondrocytes[27]. Additional refinements could include the combination of a protective agent, such as dexamethasone, with an anabolic stimulus such as insulin-like growth factor-1[26].

Regardless of the drug of choice, it will important to determine the length of time after injury before the pathological changes induced by injury become irreversible and the window of opportunity for preventing PTOA closes.

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Clinical significance

Suppressing the various etiopathophysiological responses to injury in the joint is an attractive strategy for lowering the clinical burden of PTOA. The intra-articular administration of dexamethasone soon after injury offers a simple and inexpensive means of accomplishing this.

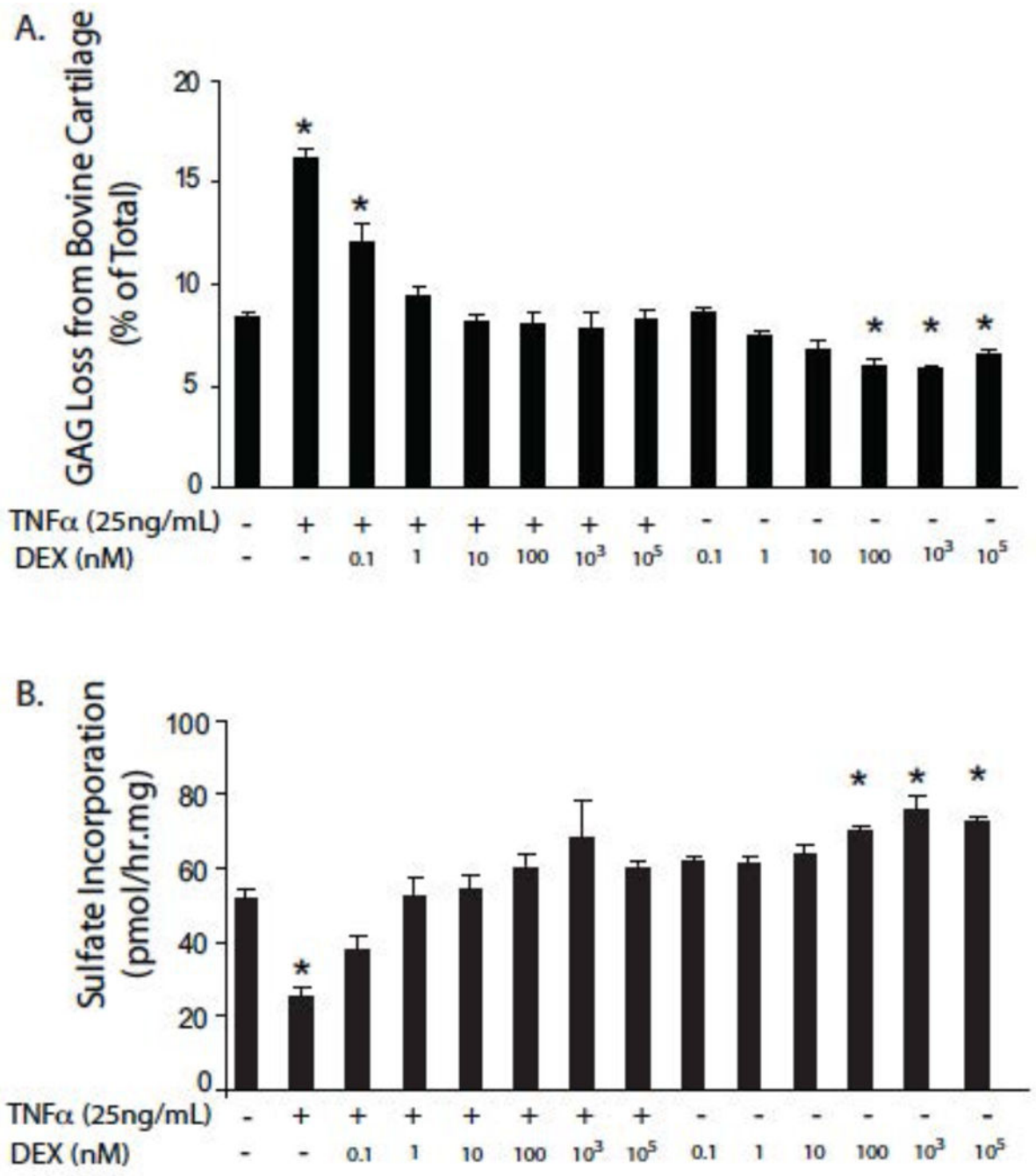

Figure 1. Dose-dependent effects of dexamethasone on GAG loss and GAG synthesis in cartilage explants exposed to TNF-α

Cartilage samples were maintained in serum-free medium containing low-glucose DMEM, 10 mM HEPES buffer supplemented with 1% ITS: insulin (10 μg)-transferrin (5.5 μg/ml) – selenium (5 ng/ml). Dexamethasone and TNF-α were added at the indicated concentrations, for six days.

Panel A: Effects on GAG loss. Panel B: Effects on GAG synthesis. Values given are means ± SEM, n=5. * = $p<0.05$ difference from untreated cells.

From reference [42], with permission

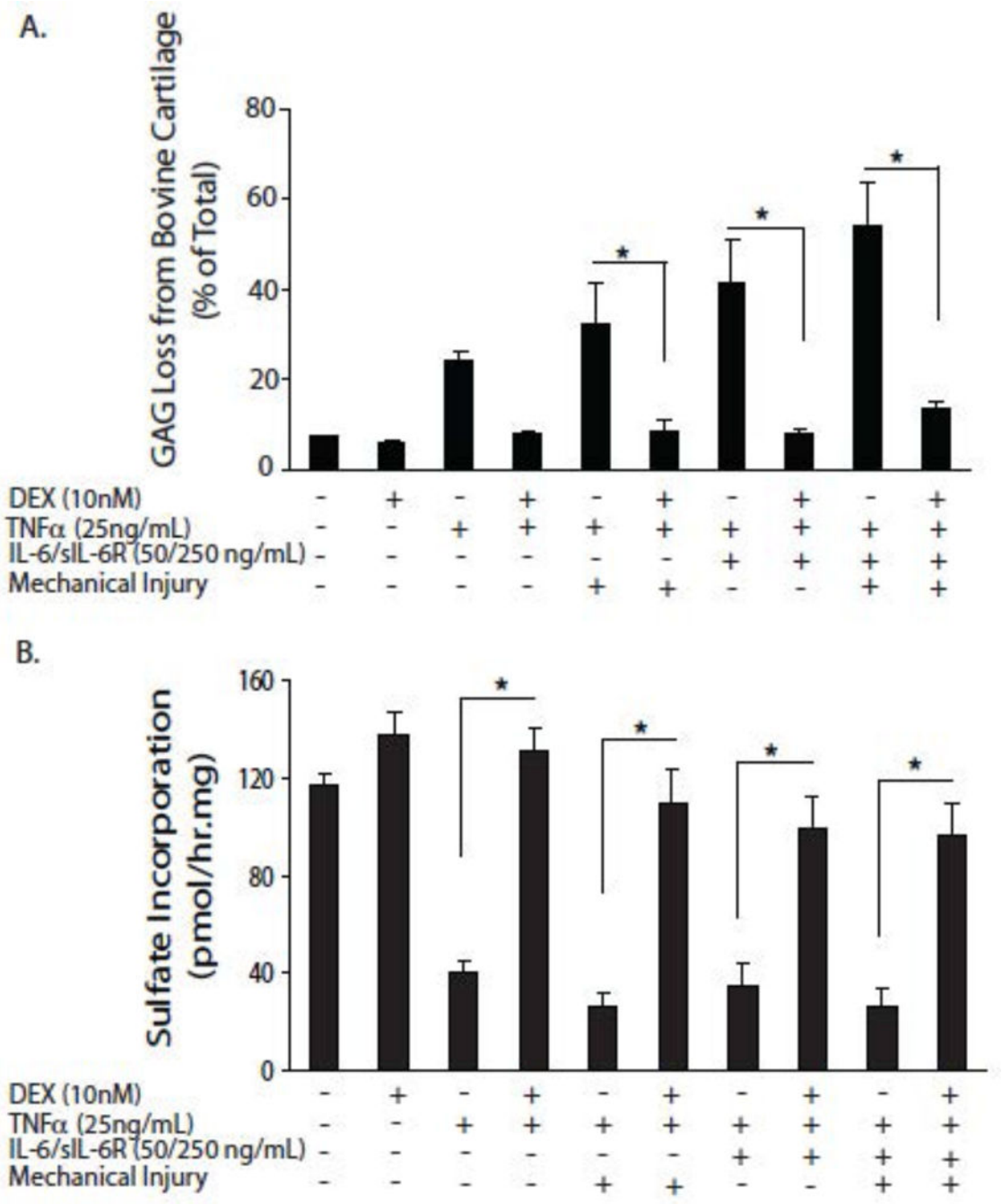

Figure 2. Effect of dexamethasone on GAG loss and GAG synthesis in cartilage explants exposed to combinations of mechanical injury and cytokines

Cartilage samples were maintained in serum-free medium containing low-glucose DMEM, 10 mM HEPES buffer supplemented with 1% ITS: insulin (10 μg)-transferrin (5.5 μg/ml) – selenium (5 ng/ml). Dexamethasone and TNF-α were added at the indicated concentrations, for six days.

Panel A: Effects on GAG loss. Panel B: Effects on GAG synthesis. Values given are means ± SEM, n=5. * = $p<0.05$.

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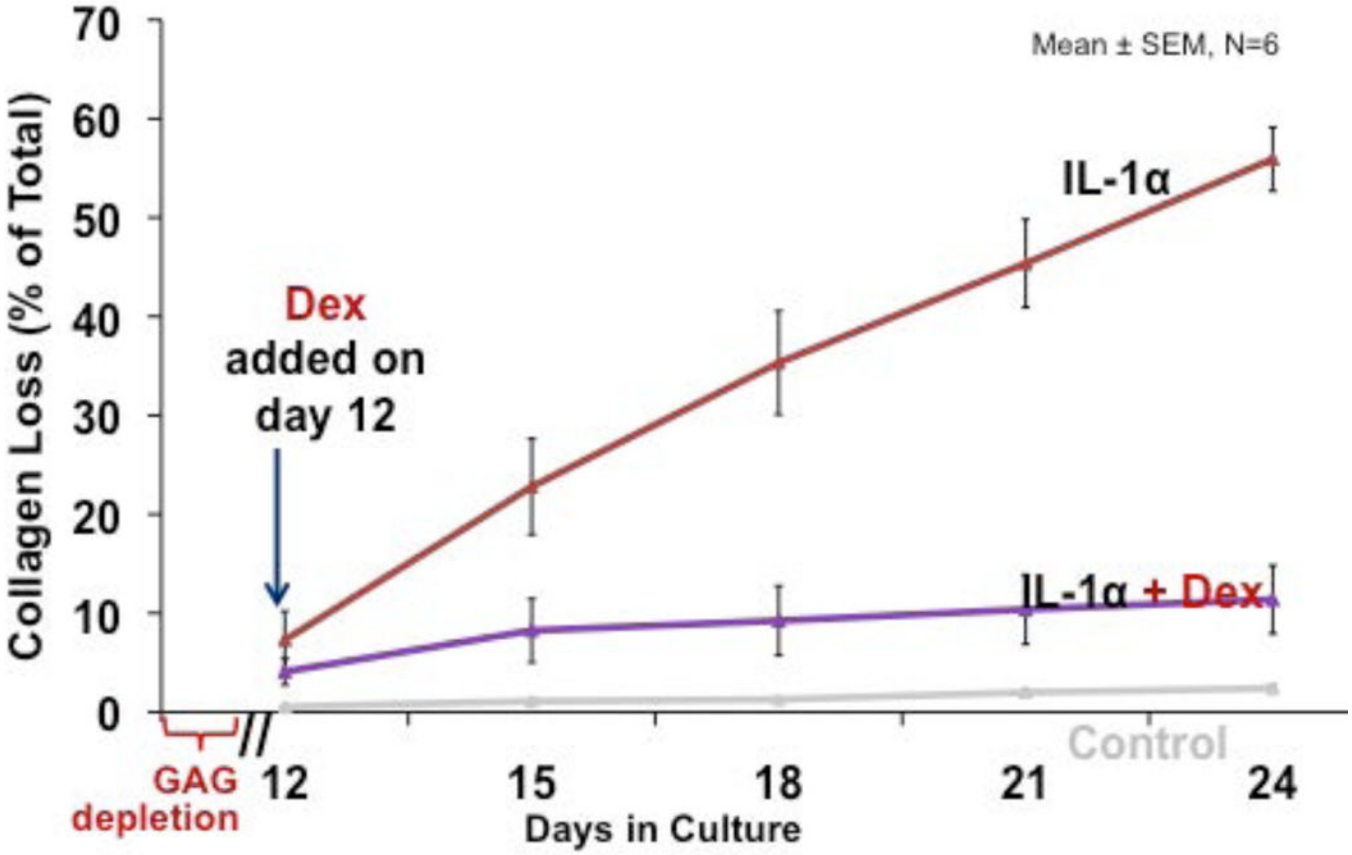

Figure 3. Effect of dexamethasone on loss of collagen from cartilage explants exposed to IL-1

Cartilage samples were maintained in serum-free medium (low-glucose DMEM, 10 mM HEPES) lacking insulin, transferrin, selenium, and in the presence of 1 ng/mL IL-1 throughout culture duration. Dexamethasone was added and maintained at a concentration of 10 nM.

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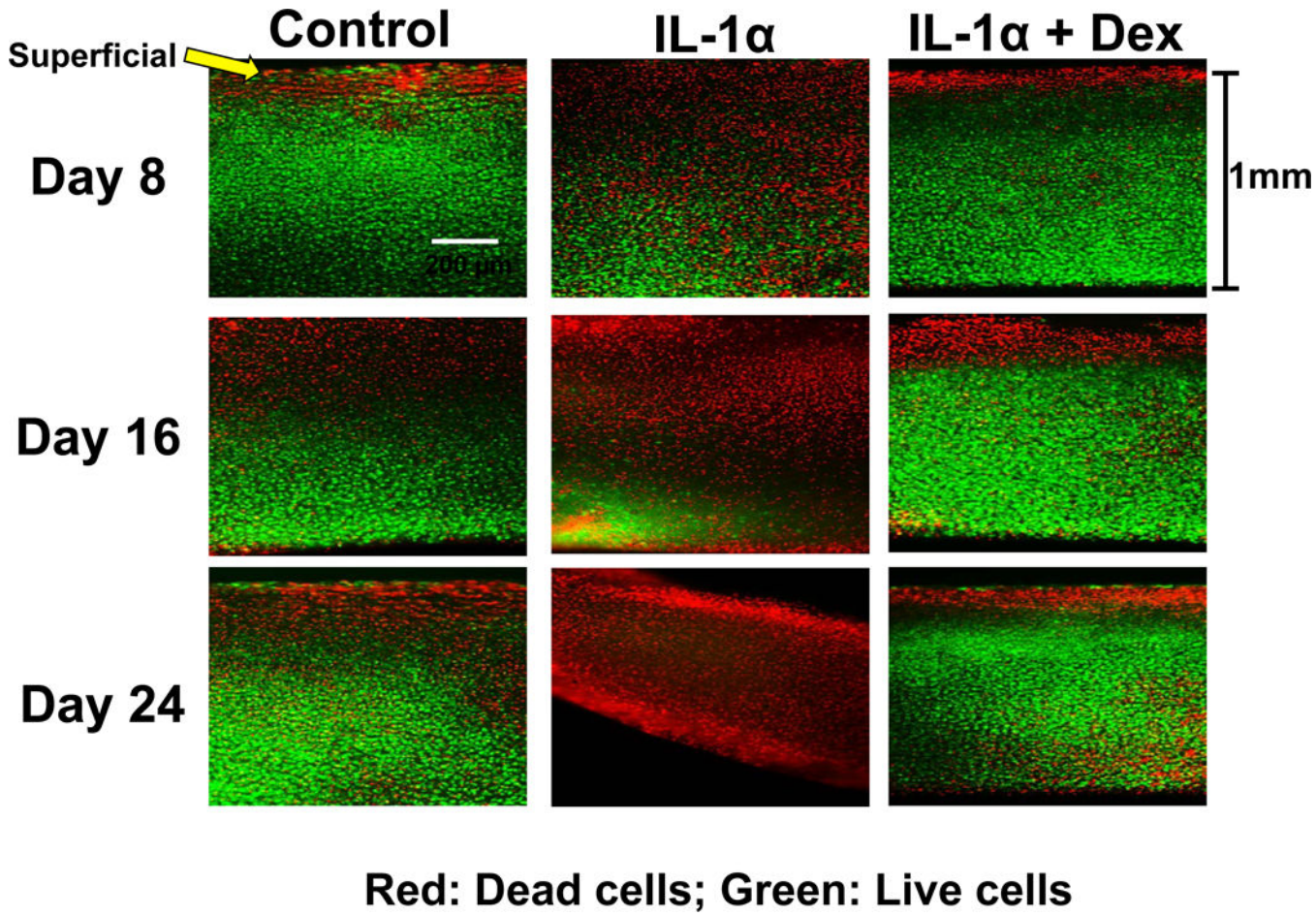

Figure 4. Effect of dexamethasone on the viability of chondrocytes within cartilage explants exposed to IL-1

Cartilage samples were maintained in serum-free medium (low-glucose DMEM, 10 mM HEPES) lacking insulin, transferrin, selenium and in the presence of 1 ng/mL IL-1 throughout culture duration. Dexamethasone was added and maintained at a concentration of 10 nM.

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