Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Intra-articular drug delivery systems for joint diseases

Muhammad Farooq Rai[1,2] and Christine TN Pham[3]

Intra-articular (IA) injections directly deliver high concentrations of therapeutics to the joint space and are routinely used in various musculoskeletal conditions such as osteoarthritis (OA) and rheumatoid arthritis (RA). However, current IA-injected drugs are rapidly cleared and do not significantly affect the course of joint disease. In this review, we highlight recent developments in IA therapy, with a special emphasis on current and emerging therapeutic carriers and their potential to deliver disease-modifying treatment modalities for arthritis. Recent IA approaches concentrate on platforms that are safe with efficient tissue penetration, and readily translatable for controlled and sustained delivery of therapeutic agents. Gene therapy delivered by viral or non-viral vectors and cell-based therapy for cartilage preservation and regeneration are being intensively explored.

Addresses
[1] Department of Orthopedic Surgery, Musculoskeletal Research Center, Washington University School of Medicine, 660 South Euclid Avenue, Box 8233, Saint Louis, MO 63110, USA
[2] Department of Cell Biology and Physiology, Washington University School of Medicine, 660 South Euclid Avenue, Box 8233, Saint Louis, MO 63110, USA
[3] Department of Medicine, Division of Rheumatology, 660 South Euclid Avenue, Box 8045, Saint Louis, MO 63110, USA

Corresponding authors: Rai, Muhammad Farooq (rai.m@wustl.edu), Pham, Christine TN (cpham@wustl.edu)

Current Opinion in Pharmacology 2018, **40**:67–73

This review comes from a themed issue on **Musculoskeletal**

Edited by **S Jeffrey Dixon** and **Peter Chidiac**

https://doi.org/10.1016/j.coph.2018.03.013

Introduction

Intra-articular (IA) drug delivery presents many advantages as it offers direct access to the joint space, thus increasing the bioavailability of therapeutic agents at the affected site while reducing systemic exposure, potential side effects and overall cost. Although IA injections are generally considered safe, their therapeutic effectiveness remains severely limited due to rapid clearance of the drugs. IA injections are routinely used for various rheumatic diseases, especially osteoarthritis (OA), the most common form of arthritis that usually affects a few large joints but can result in severe disability, often requiring costly joint replacement [1].

The focus of current research is to move OA from a disease requiring joint replacement to one that can be managed with early detection and medical intervention. While the pathogenesis of OA remains poorly understood, post-traumatic OA (PTOA) offers a model to study early changes and provides an opportunity for intervention as the time and nature of the initial trauma are generally known [2,3]. As depicted in Figure 1, a joint trauma can set off a series of molecular-level events beginning immediately with disturbance in joint homeostasis [4,5] and, over time, leading to end-stage OA characterized by structural changes [6]. Arthroscopic strategies for meniscus and/or ligament repair do not alter the course of disease [7]. Currently, pain management and physical therapy offer short-term benefits, but they cannot prevent surgical joint replacement [8,9]. Unless, new therapeutic interventions targeting pre-OA at the onset of disease become available, OA will remain a non-curable disease resulting in higher number of joint replacement surgeries at younger age.

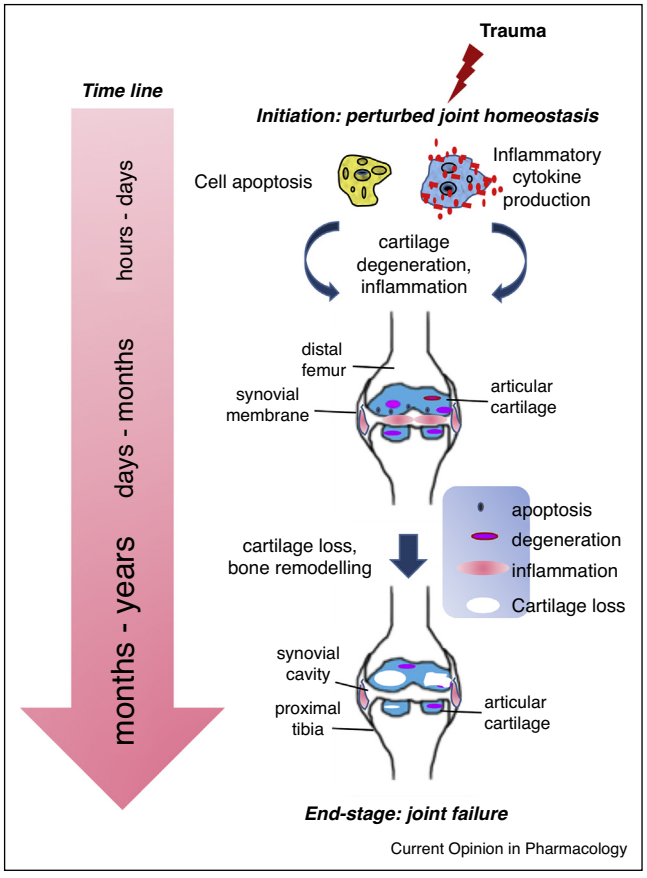
Currently few options exist for IA treatment. Corticosteroids are often administered IA to treat pain and resolve the joint effusion associated with rheumatoid arthritis (RA) and OA. Their effect, however, is short-lived and does not modify disease progression [10,11]. Likewise, hyaluronic acid (HA), a viscosupplementation approved by the U.S. Food & Drug Administration (FDA), is commonly used to treat OA. However, there is no conclusive evidence that HA, in its original formulation, delays or prevents the need for joint replacement [12,13]. Ideal IA drug delivery platforms should offer controlled release of the therapeutic agent with extended bioavailability and joint retention, have no or minimal safety concerns, promise a disease-modifying effect and/or cartilage regeneration, and be readily translatable. Despite recent advances, no single IA drug delivery platform fulfills all these properties.

In this review, we have summarized recent developments in IA therapy (Figure 2), with a discussion on how therapeutic delivery systems are being developed to meet the above criteria.

Synthetic, controlled release drug delivery platforms

Rapid clearance of drugs from the joint limits the efficacy of many IA therapeutics such as corticosteroids and HA (reviewed in [14]), prompting the search for safe

Figure 1



Stages of OA after initial trauma. At the molecular level, a joint trauma can set off a series of events immediately beginning with disturbance in joint homeostasis and, over time, leading to end-stage disease. The focus of research is shifting, albeit slowly, from end-stage disease, where total joint replacement is the only solution, to the pre-OA stage where early molecular markers can predict the likelihood of clinical disease. At each stage following trauma, a distinct set of biochemical changes occur.

formulations that, offer sustained and extended drug availability. To this end, numerous natural and synthetic (bio)materials have been employed to achieve ideal properties such as increased articular dwell time with slow and steady (controlled) drug release and safe biodegradation of delivery vehicle. Each type of biomaterials has advantages and disadvantages as summarized in Box 1.

Polymeric micelles are the most studied platforms for IA drug delivery. These nanoscale carriers are composed of amphiphilic polymers that self-assemble into nanostructures [15]. They provide several inherent properties that allow the encapsulation of a wide range of therapeutics, including poorly soluble compounds, for controlled and sustained release as well as protection of the encapsulated drugs from *in vivo* degradation and clearance [16]. These properties make polymeric micelles ideally suited for IA drug delivery to extend drug exposure time and to prevent rapid clearance by synovial phagocytes. Several applications of micelles have been explored for OA and RA treatment. Various hydrophobic, small molecule drugs (e.g. indomethacin, dexamethasone etc.) have been incorporated into micelles and administered either IA or systemically [17]. Polymeric micelles have favorable toxicity profiles and could serve as extended drug delivery platforms [18].

Hydrogels represent another promising mode of IA drug delivery. It is known that HA has a short half-life (1–2 days in the tissue) and the use of unmodified HA is severely limited by high degradation rate, poor mechanical properties, and rapid clearance. To produce mechanically and chemically stable HA while retaining its biocompatibility, aqueous solutions of HA can be cross-linked to form hydrogels, increasing its retention time in the joint space. Combining HA with synthetic materials such as poly(ethylene glycol) (PEG) to form hybrid hydrogels is an alternative approach [19]. PEG is the most prevalent synthetic biomaterial used for developing hydrogels. However, PEG does not support cartilage-specific extracellular matrix synthesis to the same extent as natural biomaterials such as HA. Hybrid hydrogels promise to improve PEG bioactivity while simultaneously enhancing HA stability in the joint space [20]. The potency of HA hydrogels can be further enhanced by integrating kartogenin (KGN) into PEG as these PEG/KGN HA biodegradable hydrogels provide better chondroprotective and cartilage regenerative outcomes than HA hydrogels in experimental OA [21•].

Another way to achieve sustained drug release, in the joint, is to combine natural or synthetic hydrogel materials with injectable drug delivery microspheres. Incorporation of therapeutic agents into the polymeric matrix during microsphere synthesis enables more precise and controlled drug release. For example, the homogeneous nanoporous structure of PEG microgels and the ability to precisely control pore size during microsphere synthesis lead to enhanced drug loading and more sustained release [20].

Synthetic polymeric particles, such as poly(lactic-co-glycolic acid) (PLGA), are other popular delivery platforms due to their unique characteristics such as tunable physiochemical and mechanical properties, and lack of immunogenicity [17]. In fact, they are the most widely used synthetic polymers that are obtained through reproducible industrial processes and the only FDA-approved IA delivery system since they degrade into naturally existing metabolites that are then fully resorbed. PLGA microspheres have been successfully used for IA sustained delivery of therapeutic agents to relieve pain and inflammation [22] but are less successful in targeting chondrocytes unless extremely high doses are used [23].