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REVIEWS

Review

Genome Engineering for Personalized Arthritis Therapeutics

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Arthritis represents a family of complex joint pathologies responsible for the majority of musculoskeletal conditions. Nearly all diseases within this family, including osteoarthritis, rheumatoid arthritis, and juvenile idiopathic arthritis, are chronic conditions with few or no disease-modifying therapeutics available. Advances in genome engineering technology, most recently with CRISPR-Cas9, have revolutionized our ability to interrogate and validate genetic and epigenetic elements associated with chronic diseases such as arthritis. These technologies, together with cell reprogramming methods, including the use of induced pluripotent stem cells, provide a platform for human disease modeling. We summarize new evidence from genome-wide association studies and genomics that substantiates a genetic basis for arthritis pathogenesis. We also review the potential contributions of genome engineering in the development of new arthritis therapeutics.

Arthritis: A Family of Complex Diseases of the Joints

Arthritis represents a family of the most prevalent musculoskeletal diseases, collectively forming the greatest source of disability in the USA, and affecting over 54 million Americans[i]. In particular, **osteoarthritis (OA), rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA)**, and **psoriatic arthritis** (see Glossary) are the most common arthritides, characterized by pain and loss of joint function due to inflammation, bone erosion, and remodeling, and the progressive degeneration of articular cartilage and other joint tissues [1–4]. Traditionally, disparate disease paradigms have been applied to RA and OA: RA has been defined as an autoimmune systemic condition, while OA has been described as a mechanically-driven, wear-and-tear arthropathy [5,6]. However, growing evidence indicates that OA consists of a large family of diseases with a similar endpoint, but potentially different pathological mechanisms; in many cases, these may involve dysregulated systemic metabolic or inflammatory cascades [7,8]. For example, multiplex immunoassays have detected inflammatory cytokines in OA patient synovial fluid, supporting the notion that OA might also arise from long-term low-level chronic inflammation, either driven by resident cell types or by systemic **metabolic syndromes** (e.g., associated with diabetes or obesity), rather than by flares of high inflammation, typically seen in rheumatic conditions [7,9].

Pharmacological recommendations from the American College of Rheumatology for rheumatic conditions include synthetic and biologic **disease-modifying antirheumatic drugs (DMARDs)** [10–12]. Synthetic DMARDS, such as methotrexate and leflunomide, are lymphotoxic therapeutics used to treat RA and a range of systemic inflammatory conditions

Trends

Arthritis represents the most prevalent cause of disability in the USA, but the genetic basis of disease etiology remains poorly understood.

Recent GWAS and candidate association studies have identified several loci associated with arthritis. These studies suggest that unique loci may play distinct roles in the development of various types of arthritis.

Advances in genome editing technologies enable the precise modification of candidate causal loci and functional validation in disease pathogenesis. Recently, epigenome editing has been used to uncover the function of regulatory elements near disease susceptibility loci.

Concurrent advances in tissue engineering from pluripotent stem cells have facilitated arthritis disease modeling.

Gene-editing tools have been used in other fields for both regenerative medicine and disease modeling. Given the wealth of data ascribing genetic variation to arthritis, at this time, there is significant potential for using gene editing in conjunction with tissue engineering, to discover mechanisms underlying genetic drivers of arthritis.

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(e.g., Crohn's disease, ulcerative colitis) through their immunosuppressive effects. Biologic DMARDs, such as tumor necrosis factor (TNF) inhibitors (e.g., adalimumab and etanercept) and interleukin (e.g., IL-1 and IL-6) antagonists have also been used to treat RA patients refractory to synthetic DMARDS, and more recently, have been used for patients presenting with moderate to severe RA [10–12]. Although these drugs are aimed at targeting specific inflammatory pathways and cell types, and have shown great promise, they have also led to clinical remission in only approximately 50% of patients with RA or JIA, with highly variable outcomes between individual patients [13]. Furthermore, up to 20% of patients satisfying the American College of Rheumatology (ACR) criteria for remission continue to exhibit radiographic deterioration of the joint space due to sustained low-level inflammation [14,15]. Moreover, systemic delivery of these therapies can lead to the development of significant side effects, such as autoimmune reactions (e.g., vasculitis, psoriasis, or lupus), or increased risk of opportunistic infections through immunosuppressive effects [16–18].

By contrast, attempts to identify clinically effective **disease-modifying osteoarthritis drugs (DMOADs)** have been unsuccessful. The IL-1 receptor antagonist (IL-1Ra, i.e., anakinra), while effective for a subset of individuals with RA and **post-traumatic arthritis (PTA)**, has not demonstrated efficacy in treating OA in the clinical setting [19–22]. Therefore, pharmacological treatment options for OA continue to be palliative, consisting of administration of nonsteroidal anti-inflammatory drugs (NSAIDs) to reduce pain, glucocorticoids to decrease production of inflammatory cytokines, and hyaluronic acid injections to lubricate eroded joints [23]. However, recent studies beyond the scope of this review suggest that even these treatments do not provide beneficial effects and may in fact lead to increased cartilage loss in OA patients [24]. Consequently, it is becoming increasingly clear that patients with unique disease etiologies will require distinct, personalized therapeutics [2].

Indeed, the future of new arthritis therapies might need to involve combinatorial approaches that seek to restore metabolic balance systemically as well as locally in joint tissues exhibiting strong degradative responses to inflammatory cytokines. We envision therapeutics tailored to patients that consider both their genetic susceptibility [e.g., combinations of deleterious **single nucleotide polymorphisms (SNPs)**] as well as environmental risk factors (e.g., injury) [25,26]. This might be accomplished only through a better and updated understanding of distinct pathomolecular mechanisms and alterations leading to various forms of arthritis. Here, we review the growing body of evidence on the contribution of genetic variation to arthritis susceptibility. We also discuss recent advances that highlight our ability to precisely rewrite the genome and epigenome to interrogate the role of genetic variation in arthritic diseases, as well as the application of tissue and genome engineering to human disease modeling platforms. Together, these fields are opening promising avenues toward tailored therapeutics through the interrogation and manipulation of genomic coding, and through the modulation of regulatory genetic elements that might confer arthritis susceptibility [27,28].

Understanding the Genetic Determinants of Arthritis to Effectively Tailor Therapeutics

A variety of **polygenic inheritance** modalities have been implicated in the pathogenesis of RA, JIA, and OA, and development of novel therapies might be enhanced by achieving an improved understanding of specific genetic factors able to modulate varying disease states [29,30]. Until recently, genetic studies investigating the role of naturally occurring arthritis were limited to gene mapping in animal models of arthritis [31]. While these studies have improved our understanding of genetic variation in RA – particularly the role of variants at **major histocompatibility complex (MHC) loci** – their relevance to human disease has remained poorly defined. Based on these data, candidate association studies have further elucidated the effect of various mutations on arthritis pathogenesis in human patients. For example, the first study

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