Editorial

Gene therapy and rheumatic diseases: Back to the future

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Gene therapy has become a major field in modern biotechnology, especially in the area of human health. Fascinating developments achieved in the past decades are impressive examples of an interdisciplinary interplay between medicine, biology and engineering. Gene therapy opens up challenging new areas[1]. The consequences of wealth in genetic knowledge for the practice of medicine are profound with the most significant impact being the enhancement of our understanding of disease etiology and pathogenesis. However, genetics is rapidly playing a more prominent role in the diagnosis, prevention and treatment of disease[2].

Gene therapy concepts have been extensively developed and tested in clinical trials in many diseases[3] including cancer and Rheumatoid Arthritis (RA)[1]. In a broader sense, gene therapy can be considered not only the replacement of a defective endogenous gene, but can also incorporate the addition of foreign or modified genes to alter a biological function[4]. It is noteworthy that the ability to transfer genes efficiently and safely to target cells is central to any successful gene therapy[5].

It consists of repairing or replacing mutated genes. Gene therapy also regulates the expression of genes, affects the immune system and directs the cell to be destroyed. With it, the basics of the disease can also be learnt, the diagnosis improved or a form of therapy established, plus the results of treatment can be tracked. It gives great hope for an effective fight against many diseases[1]. Over time and with proper oversight, gene therapy might become an effective weapon in modern medicine's arsenal to help fight diseases such as AIDS, diabetes, high blood pressure, coronary heart disease, peripheral vascular disease, neurodegenerative diseases, hemophilia and other genetic disorders[6] as well as many rheumatic and connective tissue diseases.

Gene therapy is performed *ex vivo*, when a gene is introduced into the cells outside the body. These cells are then introduced into the host, where the desired protein is subjected to expression. The *in vivo* method is the direct injection of the gene into the body. A gene vector is used and its type depends on the delivered gene or its destination. The recombinant vector, with a new piece of DNA, is inserted into the patient or directly into tissue or cells. Most of the vectors used in gene therapy are viruses, and these are both those with DNA, as well as those with RNA. The viruses used as gene therapy vectors include retroviruses, AAV (adenoassociated virus), adenoviruses, HSV (herpes simplex virus), other lentiviruses, the cytomegalovirus (CMV) and influenza virus. Viruses were the first to be used in gene therapy because of their ability in introducing DNA into the targeted cells. However, for this method they have been changed so that they do not have the ability to replicate. The genes responsible for the expression of proteins harmful to the host are also removed, and the fragments meant for therapeutic use are implemented. Thus prepared, the virus is a safe vector[1].

Gene transfer using a viral vector is known as *transduction*[7]. In viral delivery systems, nonpathogenic attenuated viruses can be used as delivery systems for genes/DNA molecules; especially plasmids[6]. Because of their ability to

sneak into cells, viruses appear to be efficient delivery vehicles for replacing mutant genes. The viral genes for infection are taken out and then the therapeutic gene is inserted into the viral chromosome. The hybrid is then mixed with purified viral capsid proteins[8]. Viruses have the capacity to carry foreign genes and efficiently deliver them with competent gene expression. Because these vector systems have unique advantages and limitations, each has applications for which it is best suited[9]. Gene expression using viral vectors has been achieved with high transfection efficiencies in tissues such as kidney, heart muscle, eye and ovary[6].

Due to extra safety concerns, immunogenicity and production issues associated with viral vectors, non viral delivery systems were developed by complexing of genes (DNA) to various chemical formulations. Non viral gene transfer is known as *transfection*[7]. The need for safer alternatives has led to the development of liposomes, cationic polyplexes, micro and nanoparticles. Although these alternative vectors have shown promise, degradable nanoparticles are the only non-viral vectors that can provide a targeted intracellular delivery with controlled release properties[1,10].

In rheumatic diseases, concerns of using biologically-derived immunomodulating compounds such as TNF-α inhibitors, IL-1 blocking agents and anti-inflammatory cytokines include the re-activation of granulomatous diseases especially tuberculosis, re-activation of chronic hepatitis B if not given concurrently with antiviral therapy and increased lymphoma risk[11]. An alternative approach might be the use of gene transfer to deliver therapeutic genes locally at the site of inflammation[12]. Gene therapy emerged as a novel successful anti arthritis strategy as a part of the wider movement toward biologic therapy[13]. Continuous identification of specific targets and candidate genes together with refined approaches offers new promises for the future of gene therapy design in rheumatic diseases[11].

A number of different types of transgenes have been suggested for local therapy of diseased joints including those encoding cytokine antagonists, immunomodulators, antiangiogenic factors, apoptotic agents, antioxidants, and inhibitors of mitosis as well as molecules that modulate cell signaling and the activities of transcription factors[13]. However, future studies will need to address improving targeted delivery of vectors, regulating and obtaining long-term transgene expression and improving the safety and efficacy of the vectors already in use before being available for arthritis[14].

In previous studies, gene polymorphism in RA[15] and Systemic Lupus Erythematosus (SLE)[16] has been confirmed. Interest in applying gene therapy to the treatment of rheumatic diseases began in the early 1990s with attempts to deliver DNAs to the synovial lining of joints. Because Sjögren syndrome and SLE, unlike RA, do not respond well to present biologics, alternative approaches, such as gene therapy, seem worthwhile. Their success could encourage further investigations in serious intractable rheumatic diseases, such as scleroderma[5]. Amazing advances have been made in our understanding of the genetic basis of human SLE[17] and gene therapy in lupus promises to correct the aberrant immunological response without the numerous side effects of the immunosuppressant medications. However, undesirable side effects such as the impaired response to T-cell-dependant and independent antigens, increased susceptibility for infectious diseases have been indicated. Thus, despite its promise, gene therapy is a young field and a variety of questions must be addressed in lupus[18].

Heritability of serum uric acid concentration is high, suggesting that genetic variation might contribute to determining its concentration through regulation of synthesis, excretion, or reabsorption[19]. Knowledge of genotype could help to identify individuals at risk of developing gout long before the onset of clinical features. In addition to risk prediction, knowledge of an individual's genotype could be used to help guide clinical decisions, especially with respect to selection of drugs that are known to increase uric acid concentration and worsen gout[20]. Acute gout is Monosodium Urate (MSU) crystal–induced acute inflammation that is characterized by a massive influx of neutrophils into the inflamed joints. The deposition of MSU crystals rapidly induces the production of cytokines and chemokines, which then play an important role in the development of acute inflammation in gouty arthritis. IL-10 gene therapy can block the production of cytokines and chemokines by MSU crystal–stimulated macrophages *in vitro* and ameliorate MSU crystal–induced acute inflammation *in vivo*[21].

It is becoming clear that many genes, each with a small effect size, contribute to the risk of developing osteoarthritis (OA). However, the genetics of OA pain are only just starting to be explored[22]. OA was relatively late to enter the Genome-Wide Association Scans (GWAS) era but the returns were substantial[23]. Gene products triggering anti-inflammatory or chondroprotective effects are of obvious therapeutic utility. As OA affects a limited number of weight-bearing joints and has no major extra-articular manifestations, it is well suited to local, intra-articular gene therapy. The efficacy of local gene delivery in OA treatment has been confirmed[5] using interleukin-1 receptor antagonist (IL-1Ra) as the transgene product; thus reflecting the importance of IL-1 as a mediator in the osteoarthritic joint[24]. Many signal transduction pathways involved in joint formation are stimulated by Bone Morphogenetic Proteins (BMPs), Transforming Growth Factors (TGFs) and Wnt family proteins, and components of each of these pathways have been implicated in OA[25].

The future outlook for genetics of rheumatic diseases appears likely to be shaped by larger meta-analytical efforts to identify additional susceptibility loci. Gene therapy is a rapidly growing field of medicine

and actually a sophisticated extension of conventional medical therapy. Rather than treating the patient's disease with drugs or surgery, the patient receives DNA. It may hold the cure for many of the rheumatic diseases.

References

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