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Editorial

Moving Forward: Gene Therapy for Intervertebral Disc Degeneration

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See the article "Gene Therapy Approach for Intervertebral Disc Degeneration: An Update" via https://doi.org/10.14245/ns.2040042.021.

Intervertebral disc (IVD) degeneration is a multifactorial process including the progressive loss of disc cells, leading to further loss of extracellular matrix (ECM) such as proteoglycan and type 2 collagen. Degenerated disc shows an imbalance of anabolic and catabolic factors that leads to ECM degradation and chronic neck or back pain.[1] To modify decreased anabolism and increased anabolism in IVD degeneration, biological approaches including growth factor injection and cell and gene therapy began to receive considerably more attention over the past 20 years due to limitation of current treatments.[2]

Over the past 2 decades, there has been a decisive shift towards large molecules, or biopharmaceuticals, and away from chemically synthesized small molecular weight drugs. The first generation of biopharmaceuticals include vaccines and therapeutic proteins (copies of naturally occurring growth factors, hormones, or cytokines) such as insulin and interferon. The second-generation biopharmaceuticals are monoclonal antibodies (e.g., golimumab for ankylosing spondylitis and rheumatoid arthritis) with increased bioavailability and improved therapeutic index. Now, the range of biopharmaceuticals available is steadily increasing and third-generation biopharmaceuticals including cell therapy and gene therapy are available.

Gene therapy is designed to introduce genetic material into cells to compensate for abnormal genes or to make a beneficial protein. The U.S. Food and Drug Administration has approved a limited number of gene therapy products (e.g., Imlygic [drug name], Amgen [company], 2015 [approval]; Kymriah, Novartis, 2017; Yescarta, Gilead, 2017; Luxturna, Spark, 2017) for the treatment of recessive inherited diseases and cancer. In addition, hundreds of clinical trials are underway to test gene therapy for genetic diseases, cancer, and acquired immunodeficiency syndrome. Currently, the focus of gene therapy has moved to approaches designed to ameliorate acquired musculoskeletal disease processes. Chronic neck or back pain from IVD degeneration is an example of a disease process affecting a large proportion of the population for which effective long-term treatments have remained elusive. Recent studies of the mechanisms that underlie the development of chronic pain from IVD degeneration have created a base of physiological and genetic information that identify multiple points of intervention to treat chronic pain.[3-5] On the basis of these insights, gene therapy may be used to produce products that block catabolism in degenerated disc, enhance anabolism, or reverse the degenerated disc state.

In the review article provided by Dr. Yurube, the development of gene therapy for treatment of IVD degeneration are well described and his excellent review strongly supports gene therapy as a potentially practical approach suitable for intervening in the treatment of chronic pain from IVD degeneration.[6] Gene therapy for IVD degeneration is based on the premise that focal delivery of genetic materials targeting well-known and understood elements of the pathways contributing to IVD degeneration might be used to improve anabol-

ic and catabolic balance. There are 2 important aspects of his review that bear our attention. The first is RNA interference that has been developed for downregulating harmful gene expression in the degenerated disc, leading to decelerated disc degeneration. The second aspect is the emergence of the mammalian target of rapamycin (mTOR) signaling as a target of gene therapy. Autophagy is an important component of the metabolic stress responses that promotes cell survival and prevent the accumulation of damaged organelles, cell membranes, and proteins during metabolic stress.[7] The mTOR plays a negative role in autophagy by regulating autophagy-related proteins and lysosome biosynthesis.[8] The author proposes selective interference of mTORC1 (mTOR complex 1)/RAPTOR (regulatory-associated protein of mTOR) to protect disc cells from inflammation-induced apoptosis, senescence, and prevent ECM catabolism.

Chronic neck or back pain from IVD degeneration is complex, and there are significant limitations of available treatments and there has been a growing interest in the biological repair of degenerated disc, including cell and gene therapy. One major obstacle facing effective gene therapy involves finding the best targets for gene therapy. Dr. Yurube's review in this special issue will take us one step further toward the development of gene therapy for chronic pain from IVD degeneration.

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Title: Great Still Life on Pedestal
Artist: Pablo Picasso
Year: 1931

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