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Editorial

Commentary on "Gene Therapy Approach for Intervertebral Disc Degeneration: An Update"

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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.

In this paper authored by Takeoka et al.,[1] the authors provide a nice general review of the concepts of gene therapy over the past decade as it applies to the field of intervertebral disc degeneration research. The authors review the historical advancements made in the field of gene therapy, whereby certain therapeutic genes are delivered to native cells using viral or nonviral techniques in order to produce a biologic effect on the host tissue or organ. Because the intervertebral disc degeneration is a chronic condition which is associated with numerous clinical maladies (low back pain, disc herniations, spinal stenosis, instability, and more), it would seemingly be an ideal target for gene therapy. The original supposition in the 1990's when gene therapy was receiving enormous optimism for curing many diseases was that this new molecular approach may one day actually help "regenerate" the disc if the right cocktail of anabolic genes mixed with anticatabolic genes were delivered to the cells within the disc.[2] Many studies investigated this concept and there were major advancements made that confirmed, both *in vitro* and *in vivo*, that the concept was indeed viable. Adenovirus followed by adeno-associated viruses seemed to transfect cells of the disc with the transgene efficiency which would allow a therapeutic gene to be delivered with a sustained effect enough to alter the natural history of disc degeneration (in animal models).

However, this great optimism in gene therapy was tempered when the powers of manipulating the genome were viewed through the lens of patient safety. Viral constructs were known to have immunologic effects by the host, and the issue of transgene production of proteins that are "unchecked" or accidentally misapplied, were issues that needed further investigation prior to human clinical trials. Indeed, when such experiments were carried out,[3] gene therapy seemed to have a potential dark side where over production of certain proteins in tissues other than the disc may have serious clinical consequences and therefore create a potential safety hazard for patients. Therefore, the early wave of enthusiasm was rightfully tempered, and the field turned to look for safer vectors and inducible agents (for controlling the transgene product). In addition, it was seemingly more reasonable and safer to inhibit the catabolic cascade that is associated with disc degeneration rather than trying to ramp up the production of matrix proteins with anabolic growth factor genes.

Takeoka et al.[1] discuss the recent advances made in gene therapy in the past decade. In the spirit of a safer therapeutic application of gene therapy, the authors review the concept of RNA interference which specifically inhibits various biochemical pathways that are now better understood in the pathogenesis of disc degeneration. Specifically, they focus on the autophagy molecular pathways which seem to be ideal candidates for inhibiting certain components of the mammalian target of rapamycin pathways which could affect the cell state of autophagy and indirectly have a clinical effect on the march toward disc aging and

degeneration. Such use of gene therapy is novel and clever, and the authors should be commended on their research on this topic, since it has opened up a new avenue into solving the difficult clinical problem that is disc degeneration. However, this story is still far from being complete, since they do not have any convincing animal models to substantiate the theoretical benefit to this type of therapy.

It would seem logical that a single therapeutic attack on this clinical entity is likely not going to succeed, but a strategy that is multipronged with the introduction of various therapeutic genes that either inhibit or promote certain proteins and also alter cell states to tip it into a more conductive anabolic environment will have the best chance of succeeding in patients.

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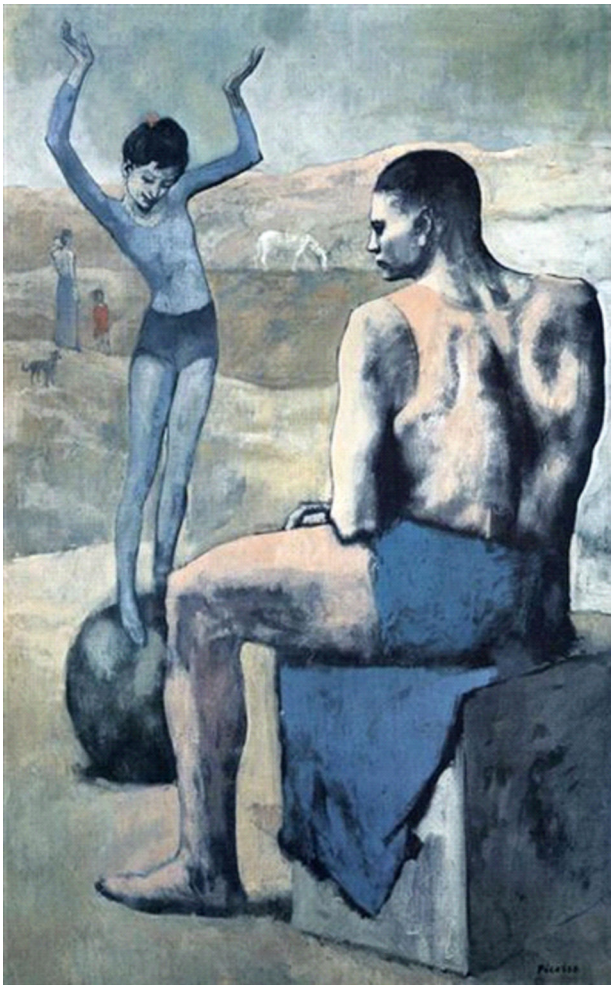

Title: Girl on the ball
Artist: Pablo Picasso
Year: 1923

In this painting, the pinky tones of the Rose Period are apparent, though the chilling grey of the acrobat's bodysuit strangely arrests the young girl's fluid animation. Her lithe, rounded motions, echoing the shape of the ball, are in obvious opposition with the square muscular form of the man, whose shape is interrelated with the solid, cubed seat. Like the Mother and Child (Maternity) (1901), the strong, upward, angular lines are crossed by a series of horizontal blocks, but in this instance they are allowed to undulate to create a further flowing movement that compliments the rolling force of the girl standing on the ball. The whole picture is a study of stasis versus movement, reflecting an interesting evolution in Picasso's own aesthetic advancement as he moves into this new period.
More information: https://www.pablopicasso.org/young-acrobat-on-a-ball.jsp

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