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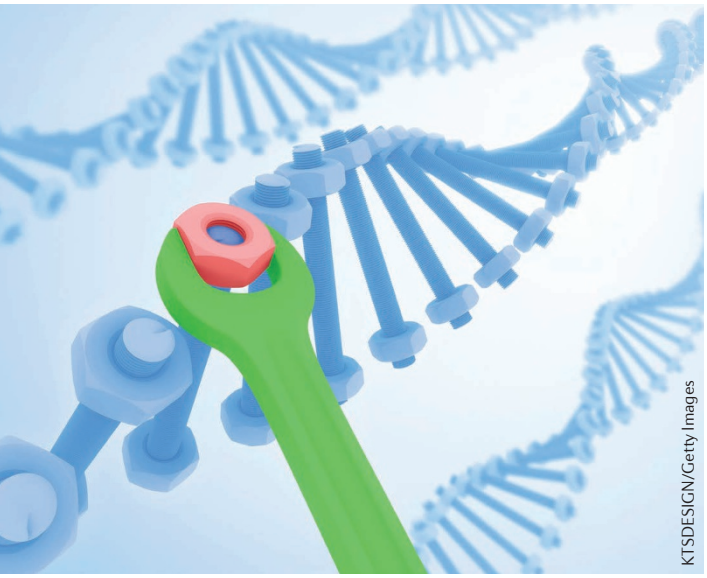
REGENERATIVE MEDICINE

Engineered iPSCs for cartilage repair

> Stem cell therapies hold great promise for tissue repair in inflammatory arthritis

Murine induced pluripotent stem cells (iPSCs) lacking IL-1 receptor type 1 (IL-1R1), engineered using the CRISPR/Cas9 system, are able to form cartilaginous tissue that is resistant to IL-1α-mediated inflammation, a new study shows. "We were able to effectively and efficiently create a new line of stem cells that did not previously exist in nature and were immune to the effects of cytokine-induced inflammation, but had no other detectable changes in their properties," explains Farshid Guilak, one of the corresponding authors of the study.



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Stem cell therapies hold great promise for tissue repair in inflammatory arthritis. However, the inflammatory microenvironment within arthritic or injured tissues remains a major problem, as it inhibits the differentiation capacity of stem cells and can degrade newly regenerated tissue. "Our goal was to apply the newly developed CRISPR/Cas9 method for gene editing to create a stem cell that does not respond to inflammatory cytokines," says Guilak.

The researchers obtained 41 iPSC clones, four of which had a homozygous deletion of *Il1r1* (*Il1r1*$^{-/-}$), and three that had a heterozygous *Il1r1*$^{+/-}$ genotype. Reduced or absent transcriptional activity of nuclear factor-κB (NF-κB) following stimulation with IL-1α confirmed the effective deletion of IL-1R1 in these clones.

In cartilage pellets derived from wild-type and *Il1r1*$^{+/-}$ iPSCs, treatment with IL-1α increased the expression of proinflammatory cytokines such as CC-chemokine ligand (CCL) 2 and IL-6, as well as extracellular matrix proteolytic enzymes such as ADAMTS4 and MMP9. By constrast, no significant differences were found in the expression of these inflammatory markers in cartilage derived from *Il1r1*$^{-/-}$ iPSCs. The investigators also found that IL-1α considerably reduced the levels of sulfated glycosaminoglycan in cartilage derived from wild-type and *Il1r1*$^{+/-}$ cells, whereas no such effect was seen in cartilage derived from *Il1r1*$^{-/-}$ cells.

These data suggest that CRISPR/Cas9 gene editing could be successfully used in iPSCs to generate cartilage that is resistant to cytokine-induced inflammation and degradation. "More advanced strategies could be developed that build on this proof-of-principle work, such as engineering the dynamic, autonomous control of cell responses to environmental stimuli or reprogramming epigenetic states," remarks Charles Gersbach, co-corresponding author of the study.

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