NEWS

Gene therapy dimmer switch may help tailor treatments

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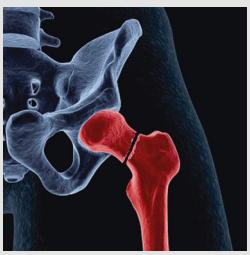
Over the past 20 years, viral and nonviral gene therapy approaches have seen significant advances, especially with regard to the cargo-delivery system. However, the cargo itself, and the controls that regulate cargo expression, have not received the same amount of attention, with some exceptions such as engineered promoters, riboswitches, and 3′ regulatory elements that restrict cell-specific expression. The inability to fine-tune gene therapy expression limits its effectiveness—too much or sustained expression can lead to toxicity, but too little expression may be insufficient to provide the intended benefit to the patient. Monteys and colleagues recently reported in *Nature* (https://doi.org/10.1038/s41586-021-03770-2) that they have developed a technique to finely tune protein expression through a drug-inducible switch dubbed X^{on}. The system capitalizes on alternative splicing to control which exons are included or excluded, thus generating RNA and protein diversity. X^{on} works in combination with a drug, LMI070, that is orally bioavailable and already in later-stage clinical trials for human use. To develop the switch, the researchers performed RNA sequencing in cells treated with LMI070 to find a drug-responsive alternatively spliced pseudo exon in *SF3B3*. They then engineered the exon to contain a Kozak sequence and AUG start codon and removed all downstream start codons to ensure responsiveness only to LMI070 binding. Intravenous administration in mice led to expression in the liver, heart, and skeletal muscles and protein levels correlated directly with LMI070 dose. The researchers then showed that X^{on} works well for controlling erythropoietin (Epo) levels, a common treatment for anemia such as that associated with chronic kidney disease. Intravenous administration of an X^{on} cassette expressing mouse Epo followed by LMI070 treatment resulted in 25- to 62-fold induction of mEpo plasma levels in response to low or high LMI070 dose. In another test, the researchers showed that the approach can also be used for brain-targeted therapies. Altogether, Monteys and colleagues demonstrated that typically unspliced sequences that are found rarely in the transcriptome are spliced in a controlled and dose-dependent manner to control gene therapy protein expression. The authors conclude that the technology offers an unprecedented opportunity for fine-tuning gene therapies. —*V. L. Dengler, News Editor*.

COPB2 haploinsufficiency causes osteoporosis and developmental delay



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Vesicle coat proteins make up the molecular machinery that sorts and transports proteins within the cell. Pathogenic variants in genes encoding coat complex subunits can lead to impaired endoplasmic reticulum (ER) and Golgi function, ER stress, and decreased cell viability, and have been implicated in a number of multisystem disorders known as coatopathies. Coatopathies most frequently impact the central nervous system, manifesting with microcephaly and developmental delay. Skeletal development, bone growth, and bone strength rely on proper biosynthesis, post-translational modification, assembly, and cross-linking of collagen fibrils. In a study recently published in *The American Journal of Human Genetics* (https://doi.org/10.1016/j.ajhg.2021.08.002), Marom and colleagues reported that loss-of-function variants in a component of the COPI coatomer complex, *COPB2*, cause early-onset osteoporosis and variable developmental delay, indicating that *COPB2* and the COPI complex are key regulators of skeletal homeostasis. The researchers identified six individuals from five unrelated families who presented with osteoporosis or osteopenia, and variable developmental delay, as well as microcephaly and spasticity in some individuals. Messenger RNA (mRNA) sequencing from patient blood samples revealed a heterozygous c.1237_1238delAA variant leading to nonsense-mediated mRNA decay. Real-time quantitative polymerase chain reaction confirmed reduced *COPB2* expression, and electron microscopy of patient fibroblasts showed dilated ER, multiple intracellular vacuoles, and prominent cell surface pseudopodia that suggested vesicular traffic disruption. *COPB2* depletion by small interfering RNA treatment resulted in disorganized Golgi marker distribution and ER retention of type I procollagen. Zebrafish depleted of *COPB2* displayed mislocalized and fragmented ER and Golgi, as well as hydrocephaly and kinked notochord. Homozygosity was embryonic lethal within 24 hours in the zebrafish. Micro–computed tomography analysis of bone mass in *COPB2* heterozygous mice revealed up to 20% reduction in spine bone volume/total volume. However, supplementation with ascorbic acid, which acts as a cofactor for procollagen hydroxylases and induces intracellular trafficking and secretion of collagen molecules, rescued defects in zebrafish and mice, including bone mass improvement in rodents fed an ascorbic acid–enriched diet. Altogether, the findings show that loss-of-function variants in *COPB2* cause a coatopathy with variable developmental delay and childhood-onset osteoporosis. The work demonstrates that collagen trafficking is a determinant of bone mass and suggests that early identification of this condition may enable preventative intervention, and that derangement in collagen flux may contribute to other forms of osteoporosis. —*V. L. Dengler, News Editor*.

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