

SHORT COMMUNICATION

GENE THERAPY FOR LETHAL MURINE HYPOPHOSPHATASIA

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Hypophosphatasia (HPP) is an inherited systemic skeletal disease caused by a deficiency in tissue-nonspecific alkaline phosphatase (TNALP). The major symptom is hypomineralization, rickets or osteomalacia, but the clinical severity is variable ranging from a lethal perinatal form to mild dental abnormality. Recently, it was demonstrated that enzyme replacement following systemic injection of bone targeted soluble TNALP with a decapartate tag was effective to treat HPP patients. A limitation of enzyme replacement therapy is the short half-life of the TNALP protein. Repeated administration of large amounts of the costly enzyme is required for long-term correction. Gene therapy may be an alternative and more practical approach for treatment of HPP. We are examining the feasibility of gene therapy using lentiviral vector¹ or adeno-associated viral (AAV) vector². TNALP null mice (Akp2^{-/-}) phenotypically mimic the severe infantile HPP; they appear normal at birth

but develop growth failure, epileptic seizures and hypomineralization, and die by 2 weeks of age. When the neonates of these model mice were treated by a single injection of viral vector expressing bone targeted TNALP, alkaline phosphatase activity in plasma was increased and remained at high levels for throughout the life. Treated animals showed normal growth, normal activity and seizure-free survival more than 10 months. Improved mineralization was confirmed by X-ray examination. We also found that systemic injection of AAV vector in utero can rescue lethal HPP mice³. These results suggest that viral vector mediated gene therapy is an important option for the treatment of HPP.

¹Yamamoto, et al., J. Bone Min. Res. 26: 135-142, 2011

²Matsumoto, et al., Hum. Gene Ther. 22: 1355-1364, 2011

³Sugano, et al., Hum. Gene Ther. 23: 399-406, 2012