Helper-dependent adenoviral liver gene therapy protects against induced attacks and corrects protein folding stress in acute intermittent porphyria mice

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Acute intermittent porphyria (AIP) is a hepatic metabolic disease that results from haplo-insufficient activity of porphobilinogen deaminase (PBGD). The dominant clinical feature is acute intermittent attacks when hepatic heme synthesis is activated by endocrine or exogenous factors. Gene therapy vectors over-expressing PBGD protein in the liver offers potential as a cure for AIP. Here, we developed a helper-dependent adenovirus (HDA) encoding human PBGD (hPBGD) and assessed its therapeutic efficacy in a murine model of AIP. Intravenous or intrahepatic administration of HDA-hPBGD to AIP mice resulted in a sustained hepatic hPBGD expression in a dose-dependent manner. Intrahepatic administration conveyed full protection against induced porphyria attacks at a significantly lower viral dose than intravenous injection. Transgenic hPBGD accumulated only in the cytosol of hepatocytes as the endogenous protein. Characterization of PBGD-deficient mouse strains revealed that a strong PBGD deficiency causes the chronic disturbance of cytosolic and endoplasmic reticulum folding machineries. This disturbance was completely restored over time by the over-expression of hPBGD. HDA-hPBGD is a promising vector that protects against porphyria attacks and resolves the chronic folding stress associated with low levels of PBGD activity.

INTRODUCTION

Acute intermittent porphyria (AIP, OMIM 176000) is a rare inborn error of the heme synthesis pathway caused by half-normal activity of the third enzyme of the route, porphobilinogen deaminase (EC 4.3.1.8; PBGD). AIP is clinically characterized by acute attacks when hepatic heme synthesis is activated by endocrine and environmental factors, caloric restriction or intercurrent infections (1–4). Severe and recurrent attacks are associated with motor neuropathy (5). Recurrent attacks are a life-threatening condition that can be cured only by allogenic liver transplantation (6,7). Nevertheless, transplantation suffers from limited availability of donors; requires life-long immunosuppression and is associated with mortality and morbidity and high rate of hepatic artery thrombosis (8). The observation that liver transplantation cannot reverse the effect of previous neuronal damage supports the need to implement therapeutic procedures before severe neurological symptoms appear or become irreversible.

Liver gene therapy mediated by recombinant adeno-associated viral (rAAV) vectors has demonstrated long-term protection against biochemical induced acute attacks in a predictive mouse model for AIP (9,10). After rAAV administration, most transgene expression results from extrachromosomal vector genomes that persist as concatemeric structures (11). This rate of integration into the genome of the host cell reduces the risk of insertional mutagenesis but entails the dilution of the vector and its therapeutic effect with the natural division of hepatocytes. As a consequence, maintenance of the therapeutic effect throughout the life of the patient would require successive re-administration of the vector. However, host immunity against viral vector precludes re-administration (12–14). Thus, one option to circumvent anti-vector immunity could be alternating administration of

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