GENE THERAPY

Shielded vectors improve liver gene therapy

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The main treatment for hemophilia, a bleeding disorder caused by congenital deficiency of coagulation factor VIII or IX (FIX), is protein replacement therapy (PRT). PRT requires lifelong and frequent injections of recombinant clotting factor, which is a burden for the patients. Gene therapy might provide a lasting cure for hemophilia: recent clinical trials have shown that liver-directed delivery of coagulation factors to the patients via adeno-associated virus (AAV) vectors gene transfer is safe and can correct the disease. But given the potential limitations of AAV vectors, several preclinical studies are also investigating lentiviral vector (LV)-mediated gene therapies. A study now shows that LVs modified to avoid phagocytosis enhance hepatocyte gene transfer of FIX in nonhuman primates (NHPs) compared with unmodified vectors. These results might lead to the development of clinical trials to assess the efficacy of this new LV-mediated gene therapy in patients with hemophilia.

Lead investigator Alessio Cantore and his team from San Raffaele Telethon Institute in Milan had previously shown that intravenous administration of LV can efficiently transfer genes encoding clotting factors to the liver and allow dose-dependent phenotypic correction of hemophilia in mouse and dog models. "However, therapeutic efficacy in dogs was low at the administered LV dose and we observed some acute inflammation. Thus we set out to improve the potency of the LV-mediated gene therapy," he explains. Hypothesizing that LV capture by professional phagocytes might reduce the efficacy of gene therapy, the investigators engineered LVs with high surface content of Leukocyte surface antigen CD47 (CD47hiLVs), a natural phagocytosis inhibitor. When injected in mice, CD47hiLVs showed a higher circulating half-life and a lower uptake by Kupffer cells (KC) than unmodified LVs, which supported that CD47 protects LVs from phagocytosis in vivo.

Next, the investigators injected LVs and CD47hiLVs bearing a human FIX cassette in *Macaca nemestrina*. Blood analysis of the NHPs showed that concentration of human FIX antigen and human FIX activity were higher in the plasma of CD47hiLV-treated animals than in LV-treated animals. "We describe efficient liver gene transfer in NHPs, which is further and substantially increased by CD47hiLVs, likely because of skewed vector biodistribution within the liver, favoring transduction of hepatocytes at the expense of KCs," explain the investigators. The team also showed that overexpression of CD47 on LVs prevented the increase in acute cytokines and chemokines release observed with unmodified LVs.

"These results prompt us to pursue further pre-clinical development and possible clinical testing of LV-mediated gene therapy for hemophilia and potentially inherited metabolic diseases affecting the liver," concludes Cantore.

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