Lentiviral Vectors That Express UGT1A1 in Liver and Contain Mir-142 Target Sequences Normalize Hyperbilirubinemia in Gunn Rats

Submitted by Emmanuel Lemoine on Fri, 07/18/2014 - 09:44

Titre
Lentiviral Vectors That Express UGT1A1 in Liver and Contain Mir-142 Target Sequences Normalize Hyperbilirubinemia in Gunn Rats

Type de publication
Article de revue

Auteur
Schmitt, Françoise [1], Remy, Séverine [2], Dariel, Anne [3], Flageul, Maude [4], Pichard, Virginie [5], Boni, Sébastien [6], Usal, Claire [7], Myara, Anne [8], Laplanche, Sophie [9], Anegon, Ignacio [10], Labrune, Philippe [11], Podevin, Guillaume [12], Ferry, Nicolas [13], Nguyen, Tuan Huy [14]

Editeur
WB Saunders

Type
Article scientifique dans une revue à comité de lecture

Année
2010

Langue
Anglais

Date
2010

Numéro
3

Pagination
999 - 1007

Volume
139

Titre de la revue
Gastroenterology

ISSN
0016-5085
Background & Aims

Crigler–Najjar type 1 (CN-I) is an inherited liver disease caused by an absence of bilirubin–uridine 5′-diphosphate–glucuronosyltransferase (UGT1A1) activity. It results in life-threatening levels of unconjugated bilirubin, and therapeutic options are limited. We used adult Gunn rats (an animal model of the disease) to evaluate the efficiency of lentiviral-based gene therapy to express UGT1A1 in liver.

Methods

Gunn rats were given intraportal injections of VSVG-pseudotyped lentiviral vectors that encode UGT1A1 under the control of a liver-specific transthyretin promoter (mTTR.hUGT1A1); this vector does not contain target sequences for miR-142, a microRNA that is expressed specifically in hematopoietic cells. Rats were also injected with the vector mTTR.hUGT1A1.142T, which contains 4 copies of the miR-142 target sequences; its messenger RNA should be degraded in antigen-presenting cells. Bilirubinemia was monitored, and the presence of transduced hepatocytes was analyzed by quantitative polymerase chain reaction. Vector expression was tested in vitro in rat hematopoietic cells. Results

In Gunn rats, bilirubin levels normalized 2 weeks after administration of mTTR.hUGT1A1. However, hyperbilirubinemia resumed 8 weeks after vector administration, concomitant with the induction of an immune response. In contrast, in rats injected with mTTR-UGT1A1.142T, bilirubin levels normalized for up to 6 months and transduced cells were not eliminated. Conclusions

Lentiviral vectors that express UGT1A1 reduce hyperbilirubinemia in immunocompetent Gunn rats for at least 6 months. The immune response against virally expressed UGT1A1 can be circumvented by inclusion of miR-142 target sequences, which reduce vector expression in antigen-presenting cells. This lentiviral-based gene therapy approach might be developed to treat patients with CN-I.

URL de la notice


DOI

10.1053/j.gastro.2010.05.008 [16]

Lien vers le document

http://dx.doi.org/10.1053/j.gastro.2010.05.008 [16]

Liens

[16] http://dx.doi.org/10.1053/j.gastro.2010.05.008

Publié sur Okina (http://okina.univ-angers.fr)