AUTOIMMUNE HEPATITIS EXPERIMENTAL MODEL BASED ON ADENOVIRAL INFECTIONS

Authors: Pascal Lapierre[1], Kathie Béland[2] and Fernando Alvarez[2,3,4]

Affiliations: [1]Immunovirology Laboratory, INRS-Institut Armand-Frappier, Laval (Quebec), H7V 1B7, Canada. [2]Division of Gastroenterology, Hepatology and Nutrition, Sainte-Justine University Hospital, Montreal (Quebec), H3T 1C5, Canada; [3]Departments of Microbiology & Immunology and [4]Pediatrics, Faculty of Medicine, Université de Montréal, Montreal (Quebec), H3C 3J7, Canada.

Keywords: Autoimmunity; liver; adenovirus

FOOTNOTE

Corresponding author: Fernando Alvarez, MD; Division of Gastroenterology, Hepatology and Nutrition, Sainte-Justine University Hospital, 3175 Côte-Sainte-Catherine, Montreal (Quebec), H3T 1C5, Canada. Email: Fernando.alvarez@umontreal.ca

Abbreviations: AIH, autoimmune hepatitis; CYP2D6, cytochrome P450 2D6.

Grant support: This work was supported by the Canadian Institutes of Health Research (CIHR) grant MOP-86506 to F.A. P.L. is the recipient of a Fellowship from the Fonds de Recherche du Québec - Santé (FRQS).

To the Editor:

We read with great interest the paper by Hardtke-Wolenski *et al*. (1) that describes the development of an animal model of autoimmune hepatitis based on a self-limited adenoviral infection. Administered adenovirus encoded for formiminotransferase-cyclodeaminase, a targeted liver antigen in type 2 AIH, identified in 1999 (2). This report confirms our previously published findings that a self-limited adenoviral infection, with a virus encoding for the same protein, can lead to the development of an AIH in mice (3), a fact neither discussed nor mentioned in the report by Hardtke-Wolenski *et al.*

The authors claim that *danger signals* are necessary for the initiation of an autoimmune response against the liver based on adenoviral infections and hydrodynamic transfection experiments with an observation period of 12 weeks. These results are in contrast with previous findings in models of AIH based on DNA vaccination (4-7) or adoptive transfer (8), where a peripheral activation of T cell specific to a liver autoantigen, in absence of inflammation (*danger signals*), led to an active autoimmune response against the liver. These important points are not addressed in the Hardtke-Wolenski *et al.* report.

The authors describe the development of fibrosis in their model based on silver staining of liver sections. Silver staining of reticulin proteins mainly reflects changes in the liver structure as in figure 2c, where mild alterations are observed, that can be interpreted as the result of hepatocyte lysis secondary to the lymphocyte infiltration. Why wasn't a

trichrome staining performed? This would have allowed to visualize collagen deposition, the hallmark of liver fibrosis.

The authors discuss an interesting point on the need of a predisposing genetic background (NOD in this case) for the development of an AIH in mice, an observation we previously reported in our model of type 2 AIH (5). However, the complete absence of an AIH in C57BL/6 and FVB/N mice in their model is rather puzzling. We (3) and others (9) found that an AIH could be triggered in both these mouse strains. This could be attributed to the observation period, since it is not clear if C57BL/6 and FVB/N mice were followed for more than 12 weeks (we observed the development of an AIH approximately 8 months after adenoviral infections in our model (3)). It could also be the result of the pfu of adenovirus used, an important factor in the outcome of an adenoviral infection (10) or their adenovirus construction since our vector encoded for CYP2D6 in addition to formiminotransferase-cyclodeaminase (3) and Christen's team published adenoviral vector encoded only for CYP2D6 (9).

REFERENCES

1. Hardtke-Wolenski M, Fischer K, Noyan F, Schlue J, Falk CS, Stahlhut M, Woller N, et al. Genetic predisposition and environmental danger signals initiate chronic autoimmune hepatitis driven by CD4+ T cells. Hepatology 2013.

2. Lapierre P, Hajoui O, Homberg JC, Alvarez F. Formiminotransferase cyclodeaminase is an organ-specific autoantigen recognized by sera of patients with autoimmune hepatitis. Gastroenterology 1999;116:643-649.

3. Piche C, Beland K, Lapierre P, Massie B, Alvarez F. Different sites of xenoantigen delivery lead to a virally induced late-onset hepatitis in mice through molecular mimicry. Liver Int 2011;31:1306-1314.

4. Lapierre P, Beland K, Yang R, Alvarez F. Adoptive transfer of ex vivo expanded regulatory T cells in an autoimmune hepatitis murine model restores peripheral tolerance. Hepatology 2013;57:217-227.

5. Lapierre P, Beland K, Djilali-Saiah I, Alvarez F. Type 2 autoimmune hepatitis murine model: the influence of genetic background in disease development. J Autoimmun 2006;26:82-89.

6. Lapierre P, Djilali-Saiah I, Vitozzi S, Alvarez F. A murine model of type 2 autoimmune hepatitis: Xenoimmunization with human antigens. Hepatology 2004;39:1066-1074.

7. Djilali-Saiah I, Lapierre P, Vittozi S, Alvarez F. DNA vaccination breaks tolerance for a neo-self antigen in liver: a transgenic murine model of autoimmune hepatitis. J Immunol 2002;169:4889-4896.

8. Bowen DG, Zen M, Holz L, Davis T, McCaughan GW, Bertolino P. The site of primary T cell activation is a determinant of the balance between intrahepatic tolerance and immunity. J Clin Invest 2004;114:701-712.

9. Holdener M, Hintermann E, Bayer M, Rhode A, Rodrigo E, Hintereder G, Johnson EF, et al. Breaking tolerance to the natural human liver autoantigen cytochrome P450 2D6 by virus infection. J Exp Med 2008;205:1409-1422.

10. Krebs P, Scandella E, Odermatt B, Ludewig B. Rapid functional exhaustion and deletion of CTL following immunization with recombinant adenovirus. J Immunol 2005;174:4559-4566.