ELSEVIER

Role of Antinuclear Antibodies in Experimental and Clinical Liver Transplantation

T. Nakano, C.-Y. Lai, S. Goto, L.-W. Hsu, Y.-C. Lin, Y.-H. Kao, S. Kawamoto, K.-C. Chiang, N. Ohmori, T. Goto, S. Sato, K. Ono, B. Jawan, Y.-F. Cheng, and C.-L. Chen

ABSTRACT

Objective. We recently reported that autoreactive antibodies (Abs) against nuclear histone H1 was transiently induced at an early phase after orthotopic liver transplantation (OLT) in a tolerogenic rat OLT model and possessed immunosuppressive activity. It was also reported that nuclear antigen, high-mobility group box 1 (HMGB1) protein was one of the initiators of the immune reaction. The present study sought to evaluate the role of antinuclear Abs in experimental and clinical liver transplantation.

Materials and Methods. We prepared 3 animal models: natural tolerance model (DA liver into PVG); acute rejection model (DA liver into LEW); and drug-induced tolerance model (acute rejection model + cyclosporine [CsA]). In addition, we examined clinical samples, including 1 drug-free patient, to measure the antihistone H1/HMGB1 titers at various times after OLT.

Results. In a natural tolerance model, antihistone H1 and HMGB1 Ab was induced during the rejection and the tolerance induction phases, respectively. Those Ab responses were also confirmed in a drug-induced tolerance model, whereas no such responses were shown in an acute rejection model. In our clinical drug-free patient, antihistone H1/HMGB1 titer was significantly higher after cessation of CsA than that in healthy volunteers.

Conclusions. Antinuclear Ab is actively expressed in accordance with overcoming rejection episodes with subsequent tolerance induction in both a natural tolerance model and a drug-induced tolerance model. We also observed a similar tendency in our clinical drug-free patient. These results suggested that antinuclear Abs may be useful markers to determine the timing to withdraw immunosuppressants.

IN OUR PREVIOUS STUDY, we demonstrated that autoreactive antibodies (Abs) against nuclear histone H1 possessed immunosuppressive activity.[1,2] On the other hand, nuclear-binding protein high-mobility group box 1 protein (HMGB1) was recently discovered to be an inflammatory cytokine.[3] However, the essential role of nuclear antigens and corresponding Abs in transplant immunology has not been clarified. In this study, we investigated the role of antinuclear Abs in experimental and clinical liver transplantation.

MATERIALS AND METHODS

Orthotopic liver transplantation (OLT) was performed using the combinations of DA ($RT1^a$) to PVG ($RT1^c$) (DA-PVG), DA to LEW ($RT1^l$) (DA-LEW), and DA-LEW + cyclosporine (CsA; 15 mg/kg/d, 0–14 days after OLT).[4] Recipient serum after OLT (post-OLT serum) was collected at various times. Clinical samples including 1 drug-free patient were obtained with informed consent from the patients or parents, as well as approval from the institutional ethics committee. The antihistone H1/HMGB1 titer in post-OLT sera was measured by an enzyme-linked immunosorbent assay (ELISA) as previously described.[1]

From the Chang Gung Memorial Hospital-Kaohsiung Medical Center, Department of Surgery, Kaohsiung, Taiwan.

Address reprint requests to Chao-Long Chen, MD, Chang Gung Memorial Hospital, Department of Surgery, 123 Ta-Pei Road, Niao-Sung, Kaohsiung 833, Taiwan. E-mail: clchen@adm.cgmh.org.tw

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RESULTS

We first checked the antinuclear Ab titer in a rat tolerogenic OLT model (DA-PVG). The antihistone H1 titer (A405 nm) transiently increased during the rejection phase (days 7–21) to a maximum of 0.834 ± 0.185 ($P < .01$) compared with naïve PVG serum (0.238 ± 0.076). Additionally, anti-HMGB1 titer (A405 nm) was significantly up-regulated during the tolerance induction phase (maximum 0.736 ± 0.057, $P < .01$) compared with naïve PVG serum (0.373 ± 0.025) in place of antihistone H1 Ab. In a drug-induced tolerance model (DA-LEW + CsA) under CsA treatment (0–14 days after OLT), antihistone H1 titer was significantly higher (0.607 ± 0.007, day 7) than that of a DA-LEW acute rejection model (0.299 ± 0.015, day 7) and naïve LEW rats (0.059 ± 0.043). Similar to the DA-PVG natural tolerance model, antihistone H1 titer was down-regulated in the later phase after OLT, and anti-HMGB1 titer gradually and significantly up-regulated (maximum 1.141 ± 0.007) after cessation of CsA in a drug-induced tolerance model. To evaluate the significance of antinuclear Abs in clinical liver transplantation, we next examined the drug-free patient (complete cessation of CsA and steroid), measuring Ab titer against nuclear histone H1 and HMGB1. Antihistone H1/HMGB1 titer in this drug-free patient was dramatically up-regulated after cessation of CsA and maintained at a high level (0.747–1.10 and 0.702–0.840) during "drug-free tolerance" compared with healthy volunteers (0.238 ± 0.065 and 0.152 ± 0.045).

DISCUSSION

Our present results indicated that antinuclear Abs are actively expressed during reversal of rejection episodes and following tolerance induction both in a natural tolerance model (DA-PVG) and a drug-induced tolerance model (DA-LEW + CsA). We also found a similar tendency in our drug-free patient. Clinical evidence suggests that antinuclear autoreactive Abs are associated with the pathogenesis of autoimmune disorders, whereas antihistone H1 and HMGB1 Abs possess strong immunosuppressive activity.[1,5] Recently, we demonstrated that antihistone H1 Abs led to the induction of immature dendritic cells (DCs) and inhibition of the activity of natural killer cells during the rejection phase in a tolerogenic rat OLT model.[6] Similarly, anti-HMGB1 Ab regulated the expression of CD80, 83, and 86 on DCs.[5] These results suggested that antinuclear Abs may suppress cross-talk between antigen-presenting cells and T cells. A spontaneous or active autoimmune response against nuclear antigens, such as histone H1 and HMGB1, may be indispensable to overcome acute rejection and to induce tolerance.

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