FoxP3-Expressing T Regulatory Cells (T-regs) Increase with the Severity of Active Disease in Chronic Hepatitis C

Adam D. Toll, M.D. and John L. Farber, M.D.
Department of Pathology, Thomas Jefferson University Hospital, Philadelphia, PA, United States.

Abstract

Background: The hepatitis C virus (HCV) leads to chronic disease in 80% of those infected and is associated with a chronic inflammatory response that is mediated by both cytokine producing (CD4+) and cytotoxic T cells (CD8+). FoxP3-expressing, CD4+, CD25+ T cells (T-regs) are a subset of T lymphocytes that inhibit immune responsiveness and, thereby, control immunological reactions. Whether FoxP3+ T regulatory cell-mediated suppression is a factor in HCV persistence and/or the course of chronic liver injury has not been defined. In order to assess the association between these T regulatory cells and the severity of chronic hepatitis C, we evaluated liver biopsies for the density of FoxP3-expressing cells in relation to the degree of inflammation.

Design: Forty liver biopsies from patients with chronic hepatitis C were obtained from the archives of the Department of Surgical Pathology of Thomas Jefferson University Hospital. The biopsies were selected to be equally divided between those with mild and moderate-severe necroinflammatory activity based on a modified histological activity index (HAI) after Ishak et al. (J Hepatol 22:696, 1995). The biopsies were stained for FoxP3 (eBioscience Cat #14-4777-82). A representative area of portal inflammation was photographed at 400X, and the percentage of FoxP3+ cells relative to the total number of lymphocytes was calculated.

Result: The 20 cases of mild chronic hepatitis C had a mean necroinflammatory (HAI) score of 2.7 ± sd 1.1, whereas the moderate to severe cases had a mean HAI score of 7.6 ± sd 0.7 (p< 0.001, student t-test). The number of lymphocytes in a 400X field was greater in the moderate-severe cases than in the mild cases (412 ± sd 92 versus 182 ± sd 102; p<0.001, student t-test). The mean percentage of FoxP3+ T cells among the mild cases was 14.2 ± sd 4.2 (p<0.001, student t-test).

Conclusion: In chronic hepatitis C, FoxP3+ T regulatory cells increased with greater inflammation that reflected, in turn, more severe liver disease. Thus, the density of T-regs reflected the activity of the chronic hepatitis. Such a conclusion does not support the hypothesis that greater activity in chronic hepatitis C is related to a reduced level of regulatory control by FoxP3+ T cells (T-regs).

Background

The hepatitis C virus (HCV) leads to chronic disease in 80% of those infected and is associated with a chronic inflammatory response that is mediated by both cytokine producing (CD4+) and cytotoxic T cells (CD8+). FoxP3-expressing, CD4+, CD25+ T cells (T-regs) are a subset of T lymphocytes that inhibit immune responsiveness and, thereby, control immunological reactions. Whether FoxP3+ T regulatory cell-mediated suppression is a factor in HCV persistence and/or the course of chronic liver injury has not been defined. In order to assess the association between these T regulatory cells and the severity of chronic hepatitis C, we evaluated liver biopsies for the density of FoxP3-expressing cells in relation to the degree of inflammation.

Design

Forty liver biopsies from patients with chronic hepatitis C were obtained from the archives of the Department of Surgical Pathology of Thomas Jefferson University Hospital. The biopsies were selected to be equally divided between those with mild and moderate-severe necroinflammatory activity based on a modified histological activity index (HAI) after Ishak et al. (J Hepatol 22:696, 1995). The biopsies were stained for FoxP3 (eBioscience Cat #14-4777-82). A representative area of portal inflammation was photographed at 400X, and the percentage of FoxP3+ cells relative to the total number of lymphocytes was calculated.

Result

The 20 cases of mild chronic hepatitis C had a mean necroinflammatory (HAI) score of 2.7 ± sd 1.1, whereas the moderate to severe cases had a mean HAI score of 7.6 ± sd 0.7 (p< 0.001, student t-test). The number of lymphocytes in a 400X field was greater in the moderate-severe cases than in the mild cases (412 ± sd 92 versus 182 ± sd 102; p<0.001, student t-test). The mean percentage of FoxP3+ T cells among the mild cases was 14.2 ± sd 4.2 (p<0.001, student t-test).

Conclusions

In chronic hepatitis C, FoxP3+ T regulatory cells increased with greater inflammation that reflected, in turn, more severe liver disease. Thus, the density of T-regs reflected the activity of the chronic hepatitis. Such a conclusion does not support the hypothesis that greater activity in chronic hepatitis C is related to a reduced level of regulatory control by FoxP3+ T cells (T-regs).