Suppressive Role of CD72 in Experimental Autoimmune Encephalomyelitis

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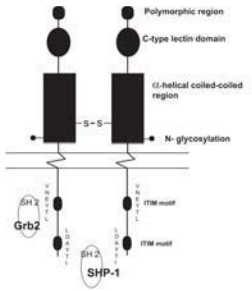
Introduction

CD72, a type II transmembrane protein expressed predominantly on B cells, acts as a negative regulator of B cell signaling and activation, and promotes B cell apoptosis through the B-cell receptor. However, whether CD72 plays a role in autoimmunity *in vivo* is unknown. We found that aged CD72-deficient mice naturally developed lupus-like autoimmune disease. To examine whether CD72 might play a role in multiple sclerosis [MS], we induced experimental autoimmune encephalomyelitis (EAE), a useful animal model for MS, in both wild-type (WT) and CD72-deficient (CD72KO) mice. We found that immunization with MOG (35-55) peptide induced an earlier onset and more severe clinical disease in CD72KO mice than in WT mice. MOG-specific CD4$^+$ T cells proliferate more in response to antigen presentation by CD72KO B cells as compared to WT B cells. However, CD72KO mice have comparable anti-MOG (35-55) IgM and IgG responses following EAE induction as compared to WT mice. The present results indicate that CD72 may play an important role in the modulation of human autoimmune diseases such as lupus and MS.

CD72



- 45-kDa type II transmembrane glycoprotein
- Member of C-type lectin family
- Expressed on large pre-B cells through mature B cells but not on plasma cells
- Expression regulated by BSAP and PU.1
- Polymorphism on extracellular domain
- Negatively regulates BCR-mediated signaling
- Promotes cell cycle arrest and apoptosis

Results

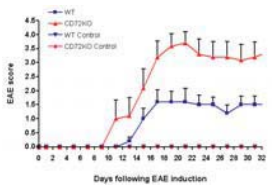


Figure 1. CD72KO mice display earlier onset and increased severity of MOG (35-55)-induced EAE. C57BL/6 WT and CD72KO mice were immunized with MOG (35-55) peptide (Cat# 60130-1) plus pertussis toxin at days 0 and 2. EAE score was monitored daily. WT and CD72KO, n = 10; WT control and CD72KO control, n = 5.

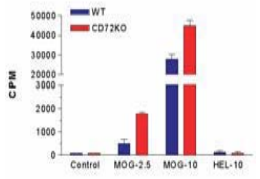


Figure 2. CD72KO splenocytes enhance MOG-specific CD4$^+$ T cell proliferation as compared to WT splenocytes. WT and CD72KO splenocytes were co-cultured with MOG-specific CD4$^+$ T cells for 5 days. [3H]-thymidine was added for the last 18 hrs. MOG (35-55) peptide: 2.5 µg or 10 µg/ml; negative control HEL antigen: 10 µg/ml.

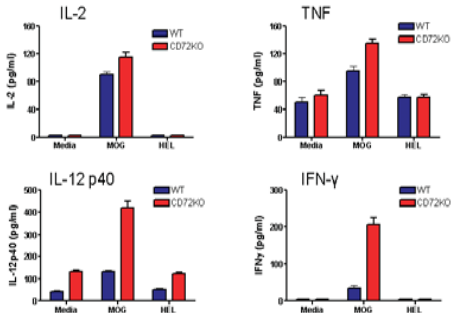


Figure 3. MOG-specific CD4$^+$ T cells co-cultured with CD72KO splenocytes enhance IL-2, TNF, IFN–γ, and IL-12p40 cytokine production. MOG-specific CD4$^+$ T cells co-cultured with wild-type (WT) or CD72KO splenocytes for 48h and 72h, and stimulated with MOG (2.5 µg/ml) or HEL (10 µg/ml).

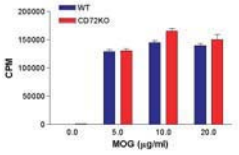


Figure 4. MOG-specific CD4$^+$ T cells proliferate equally in response to antigen presentation by CD72KO and WT dendritic cells. WT and CD72KO dendritic cells were co-cultured with MOG-specific CD4$^+$ T cells for 5 days. [3H]-thymidine was added for the last 18 hrs.

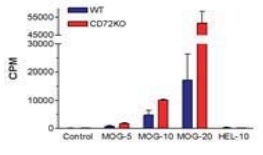


Figure 5. MOG-specific CD4$^+$ T cells proliferate more in response to antigen presentation by CD72KO B cells as compared to WT B cells. WT and CD72KO B cells were co-cultured with MOG-specific CD4$^+$ T cells for 5 days. [3H]-thymidine was added for the last 18 hrs. MOG (35-55) peptide: 2.5 µg or 10 µg or 20 µg/ml; negative control HEL antigen: 10 µg/ml.

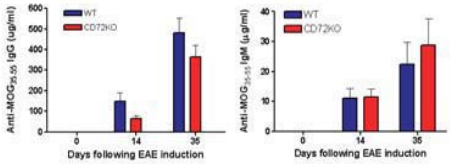


Figure 6. CD72KO mice have comparable anti-MOG35-55 IgM and IgG responses following EAE induction as compared to WT mice. WT and CD72KO mice were immunized with MOG (35-55) peptide plus pertussis toxin at days 0 and 2. Sera were collected on days 0, 14, and 35. Day 0, WT and CD72KO n = 10; Day 14, WT n =10, CD72KO n = 8; Day 35, WT n = 10, CD72KO n = 4.

Conclusions

- CD72KO mice show more severe EAE when induced by MOG (35-55) [Cat# 60130-1].
- CD72KO mice have more brain inflammatory lesions following EAE induction.
- CD72KO splenocytes induce enhanced MOG-specific CD4$^+$ T cell proliferation.
- MOG-specific CD4$^+$ T cells co-cultured with CD72KO splenocytes have enhanced IL-2, TNF, IFNγ and IL-12p40 cytokine responses.
- MOG-specific CD4$^+$ T cells proliferate more in response to antigen presentation by CD72 KO B cells.
- CD72KO mice have comparable anti-MOG (35-55) IgM and IgG responses after EAE induction as compared to WT mice.