Lessons From the CCR5 Knockout Mouse Model?

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Evidence for a Role of CCR5 Deficiency in Liver Disease

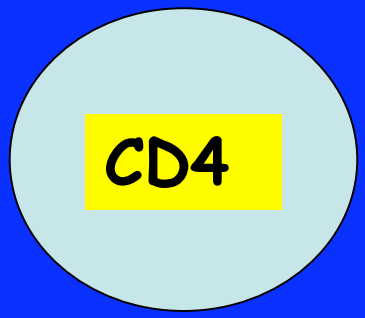
- Probably no increase in CCR5-Δ32 mutation in the frequency of HCV infection.
- Possible association of CCR5-Δ32 mutation with decreased portal inflammation and increased fibrosis in HCV.
- Increased prevalence of CCR5-Δ32 mutation in PSC and correlates with more severe disease.

The Concanavalin A Model of Hepatitis

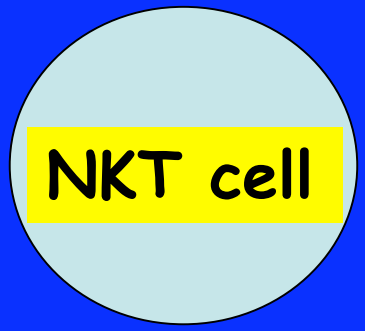
Con A Model of Hepatitis

- Single iv injection of lectin Con A in mice.
- Sudden onset of severe acute hepatitis (4h-8h) resolving within 48 hrs
- Systemic activation of immune system (T cell activation)
- Elevated hepatic levels of IFNγ, TNF-α, IL-4, MIP-1α, MIP-1β (early) & RANTES (later)
- Fas/FasL driven hepatocyte death/apoptosis

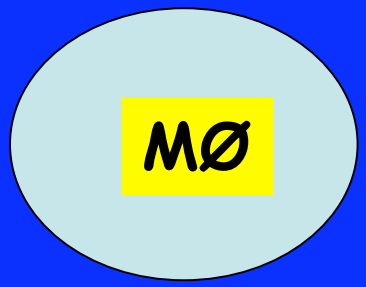
Con A Hepatitis: Important Cell Types In Pathogenesis



Directly activated by Con A; recruited to liver and secrete mainly IFNγ



Directly activated by Con A; resident to liver and secrete mainly IL-4



Kupffer cell; interact with CD4(+) T cells and secrete TNFα

Other Cell Types Involved?

A) CD 8 +ve T cells

→ limited involvement in Con A hepatitis.

B) Neutrophils

→ play role in Con A hepatitis by driving the later recruitment of CD4(+) T cells to the liver.

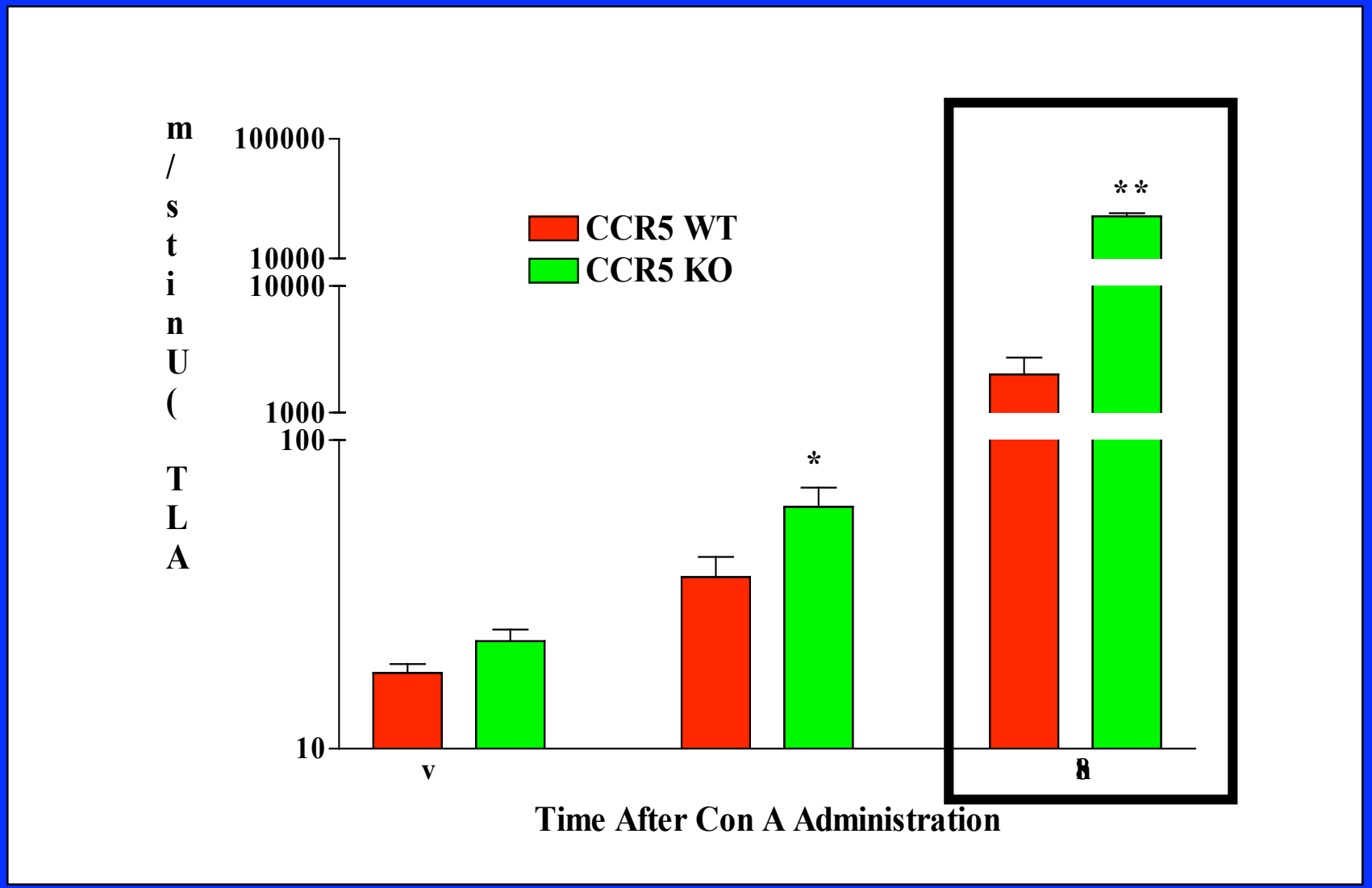
C) NK Cells

→ limited involvement.

CCR5, NKT Cells and Con A Hepatitis

Ajuebor et al., J. Immunol. 2005

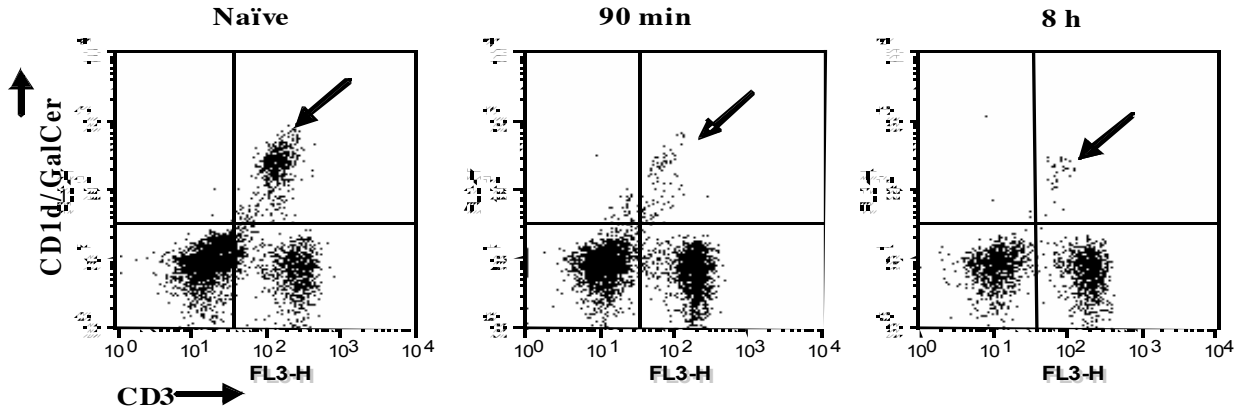
CCR5 Deficiency and Con A Hepatitis



How does CCR5 deficiency worsen Con A hepatitis?

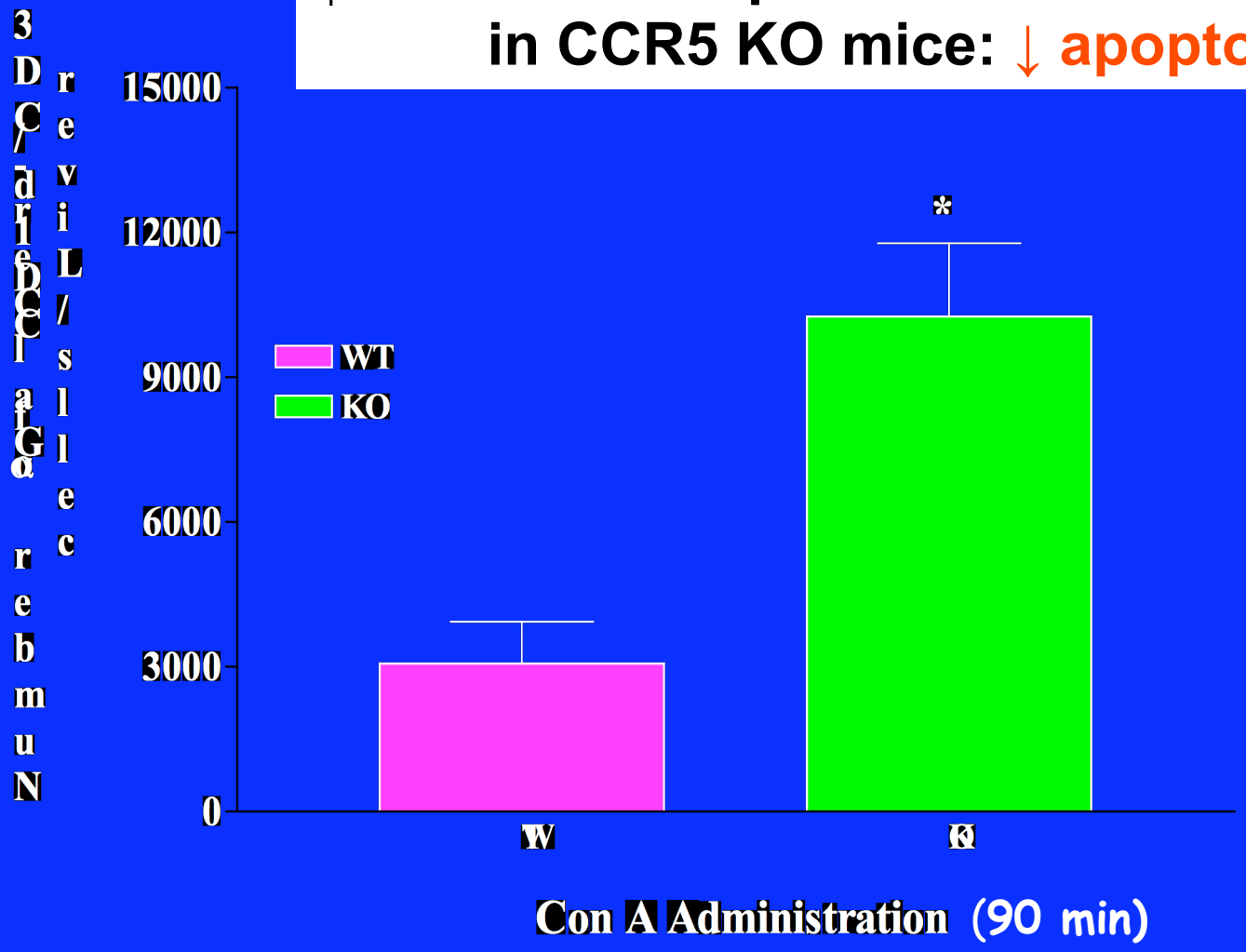
Hepatic NKT Cell Disappearance in Con A Hepatitis

Con A Administration



CCR5 Deficiency and NKT Cell Survival

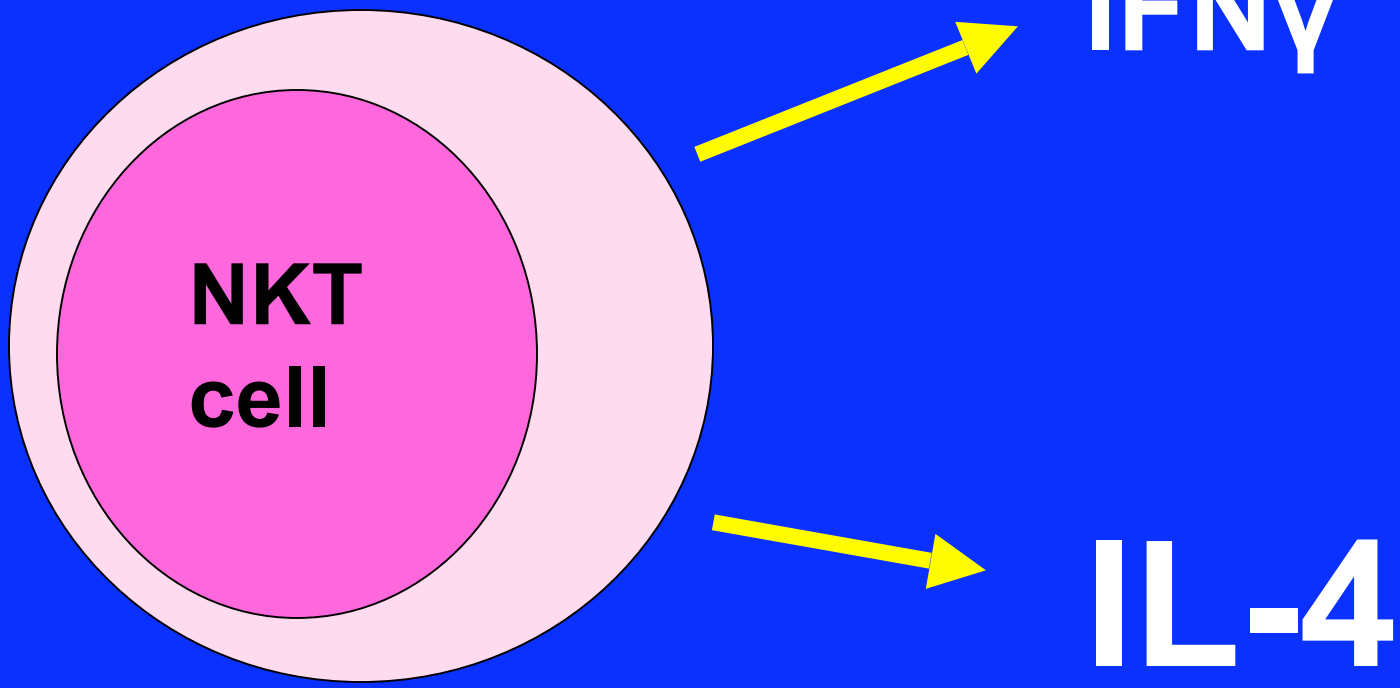
↑ survival of hepatic NKT cells after Con A in CCR5 KO mice: ↓ apoptosis



How Do Surviving NKT Cells Promote Con A Hepatitis ?

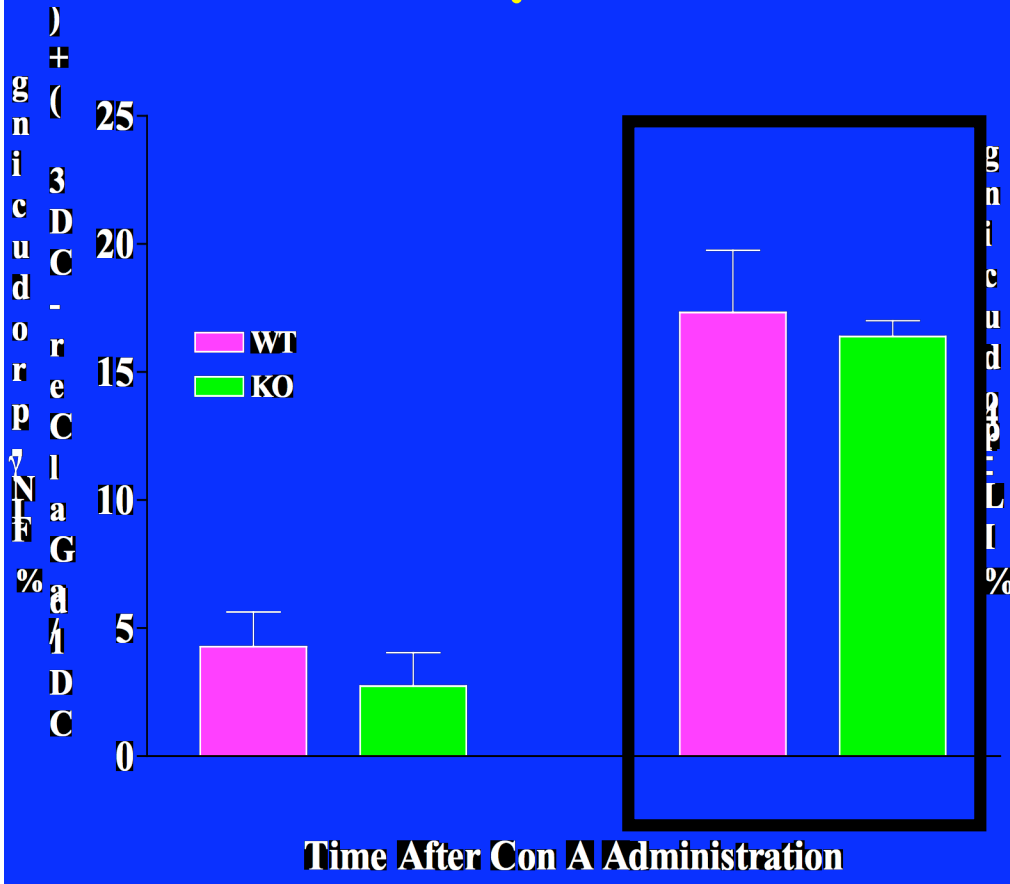
→ Differential Cytokine Production?

NKT Cell Cytokine Secretion in Con A Hepatitis

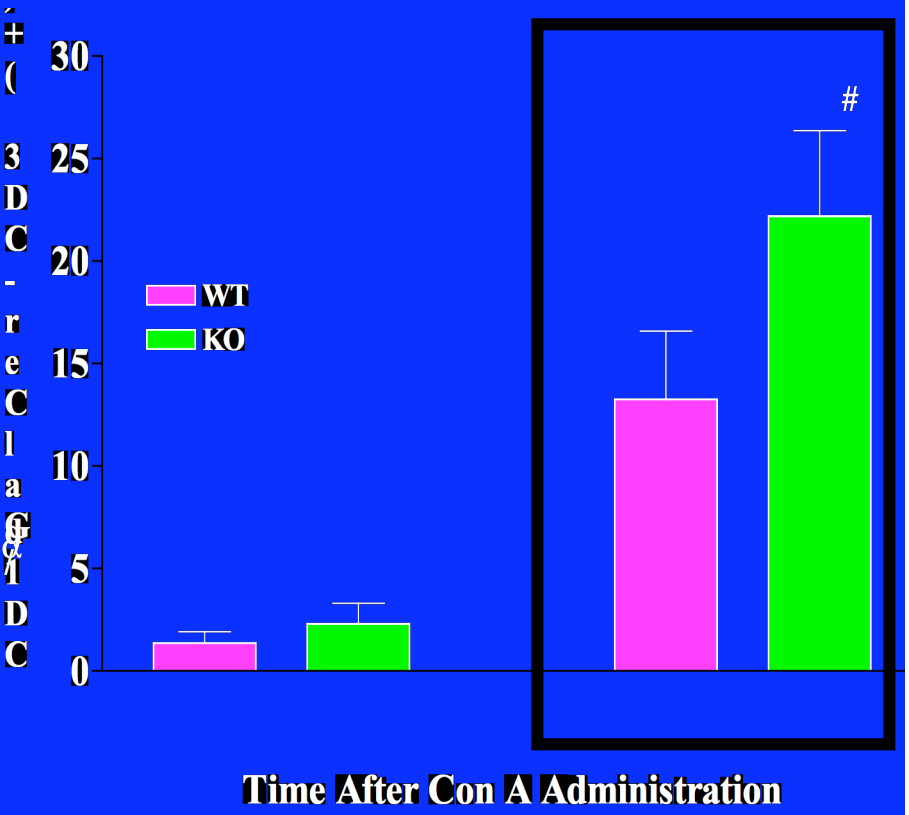


CCR5 Deficiency: NKT Cell Cytokine Production

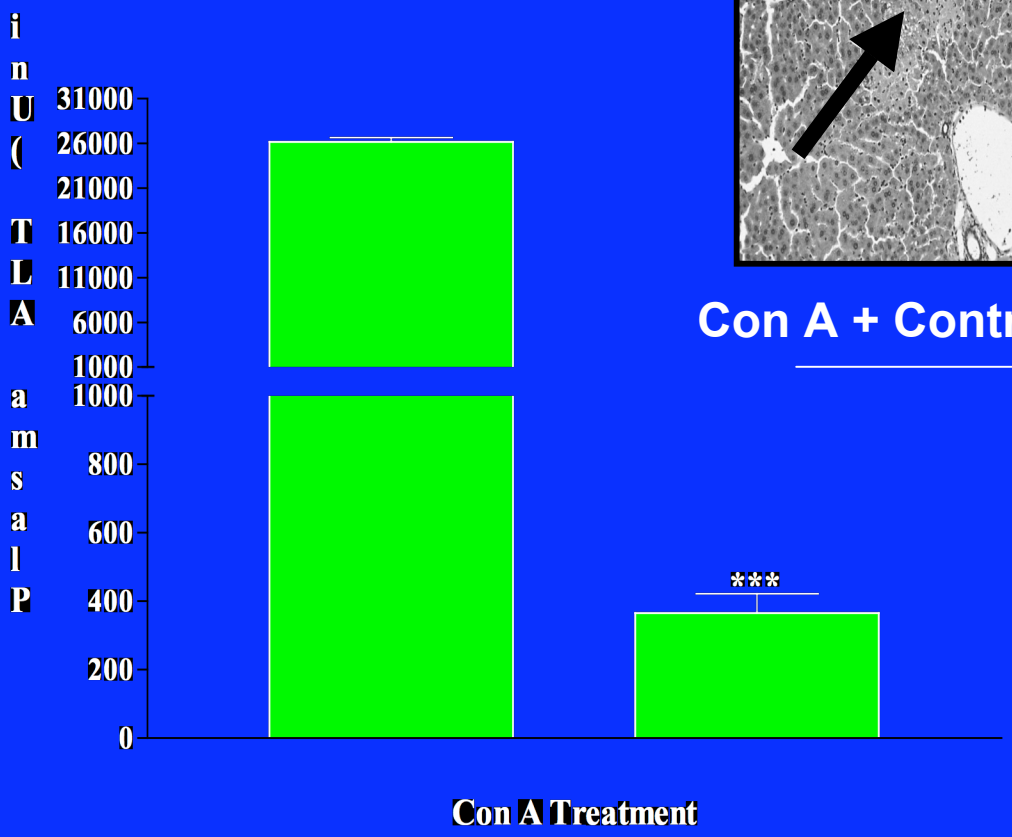
IFN-γ

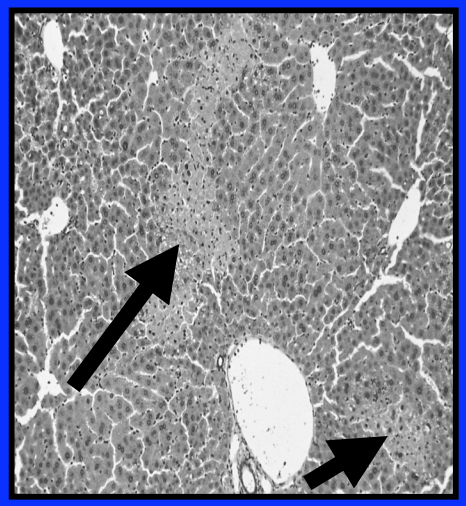


IL-4

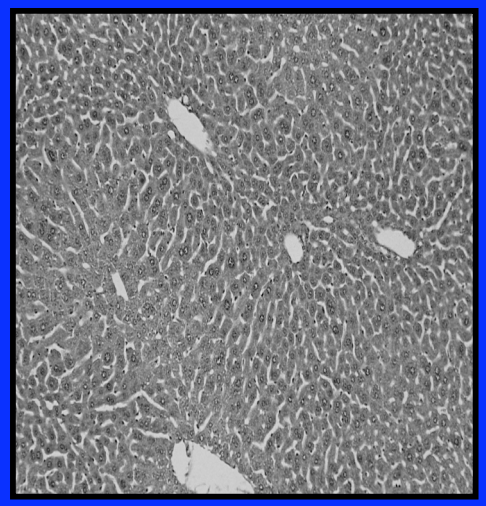


IL-4 mAb Neutralization Prevents Con A Hepatitis in CCR5 KO





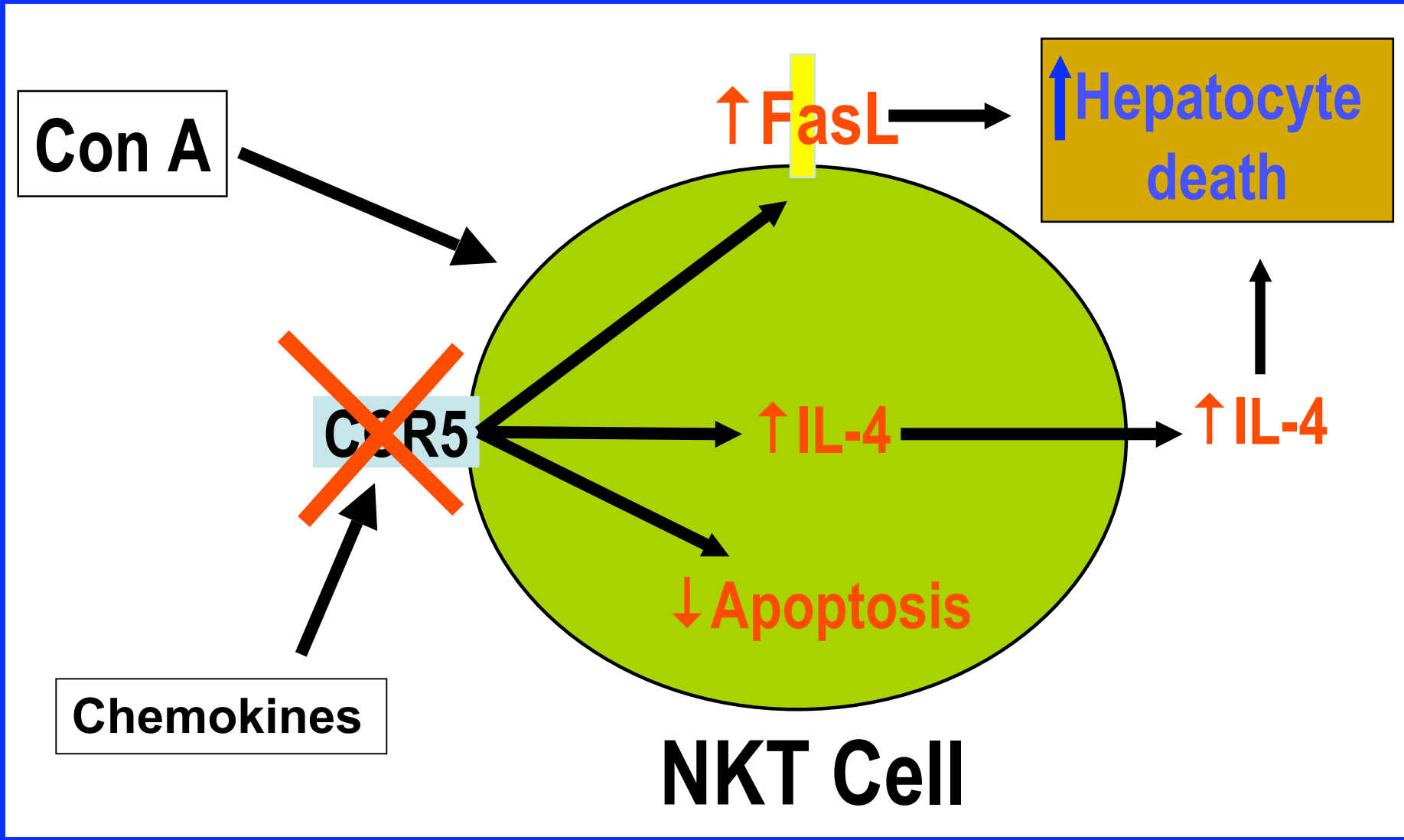
Con A + Control IgG



Con A + IL-4 mAb

CCR5 KO

NKT Cell Effector Function Modulation by CCR5



Ajuebor et al., J. Immunol. 2005

CCR5 Deficiency Leads to Increased Hepatic Levels of CCR5 Ligands and Enhanced Mononuclear Cell Infiltration of the Liver in Con A Hepatitis

Moreno et al. Hepatology 2005;42:854-862.

CCR5 Deficiency and CCL Levels

CCR5 KO compared to wt controls after Con A:

(i) ↑ serum levels of CCL3, CCL4, CCL5.

(ii) ↑hepatic mRNA expression of CCL3, CCL4, CCL5.

(iii) ↑ hepatic recruitment of CCR1 expressing mononuclear cells (CD4, CD8, mac 1 +, NK cells, NKT cells)

Effects of Chemokine Neutralization in Con A-treated CCR5 KO mice?

(i) CCL5/RANTES mAb treatment of CCR5 KO mice significantly reduced serum ALT levels.

(ii) CCL5 mAb treatment significantly ↓ hepatic mononuclear cell infiltration.

(iii) Effects not observed with CCL3 and CCL4 neutralization (except mild ↓ cell infiltration with CCL4 mAb, but no change in ALT).