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SOLER MARTIN SA

Acute anti-inflammatory effects of intravenous high-density lipoprotein (HDL) and intravenous immunoglobulin (IVIg)

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Objectives

To determine if acute HDL infusion (HDLi) or intravenous immunoglobulin (IVIg) infusion (IVIgi) could reduce the acute inflammatory response to endotoxin (LPS) in healthy volunteers.

Methods

Subjects were randomized to receive either HDLi or IVIgi or placebo (P) before LPS infusion. The primary endpoint was the change in plasma IL-6 levels at 24 hours post-LPS infusion.

Results

Both HDLi and IVIgi significantly reduced the acute inflammatory response to LPS, as measured by plasma IL-6 levels at 24 hours post-LPS infusion. The reduction in IL-6 levels was similar in both groups compared to placebo.

Conclusions

Both HDLi and IVIgi have anti-inflammatory effects in healthy volunteers, suggesting that these treatments may be useful in the treatment of acute inflammation.

References

1. Clark DA, et al. (2008) High-density lipoprotein infusion reduces the acute inflammatory response to endotoxin in healthy volunteers. *Thrombosis and Haemostasis* 88: 1055-1062.

2. Clark DA, et al. (2009) Intravenous immunoglobulin infusion reduces the acute inflammatory response to endotoxin in healthy volunteers. *Thrombosis and Haemostasis* 89: 1055-1062.









Introduction

Neutrophil apoptosis is critical for host defense. It is regulated by multiple cell signals and a wide range of physiological and pathological processes. In particular, the interaction between GM-CSF and CD44 is critical for neutrophil survival.

3. CD44 ligation induces phagocytosis of apoptotic cells and CD44-dependent cell death upon GM-CSF priming

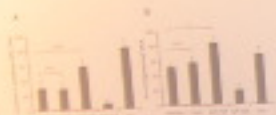
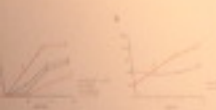


Figure 3. A. The priming effect of GM-CSF on neutrophil apoptosis. B. The effect of CD44 ligation on neutrophil apoptosis.

Results

CD44 ligation activates mainly caspase-independent death pathways in neutrophils upon GM-CSF priming



4. CD44 ligation activates mainly caspase-independent death pathways in neutrophils upon GM-CSF priming



Figure 5. A. The effect of GM-CSF priming on neutrophil apoptosis. B. The effect of CD44 ligation on neutrophil apoptosis.

5. CD44 ligation activates mainly caspase-independent death pathways in neutrophils upon GM-CSF priming

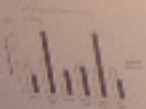


Figure 6. The effect of GM-CSF priming on neutrophil apoptosis. The graph shows the percentage of apoptotic cells over time (0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 hours) for GM-CSF (0, 10, 100 ng/ml) and CD44 ligation (anti-CD44 antibody).

6. CD44 ligation upon GM-CSF priming induces autophagic cell death

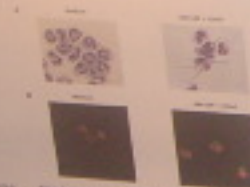


Figure 7. A. The effect of GM-CSF priming on neutrophil apoptosis. B. The effect of CD44 ligation on neutrophil apoptosis.

8. CD44 ligation activates Akt-dependent cell death pathways upon GM-CSF priming

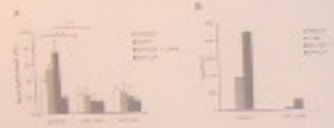


Figure 8. A. The effect of GM-CSF priming on neutrophil apoptosis. B. The effect of CD44 ligation on neutrophil apoptosis.

7. Neutrophils from sepsis and rheumatoid arthritis (RA) patients are more susceptible to CD44-mediated cell death

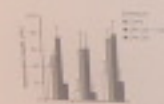


Figure 9. A. The effect of GM-CSF priming on neutrophil apoptosis. B. The effect of CD44 ligation on neutrophil apoptosis.

Conclusions

In neutrophils CD44 ligation upon GM-CSF priming

- enhances neutrophil cell death
- induces phosphatidylinositol 3-kinase and Akt-dependent cell death
- activates caspase-independent pathways
- activates ROS-dependent pathways
- induces autophagic cell death

CD44 may be an important target in inflammatory diseases like sepsis and rheumatoid arthritis

Rheumatoid Arthritis
Sepsis





















