Neutrophil Extracellular Traps in Necrotizing Enterocolitis


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BACKGROUND

- Necrotizing enterocolitis (NEC) continues to be one of the major causes of morbidity and mortality in preterm infants.
- We previously showed extensive neutrophil extracellular trap formation (NETs) in intestinal tissues from infants with NEC.
- NETs is a novel cell death process in which activated neutrophils expel their nuclear content in the form of web-like structures.
- Although, NETs has been shown to exhibit antimicrobial functions by trapping and killing pathogens, NET-associated factors, specifically histones, cause “collateral damage” to the host.

OBJECTIVE

- To determine the role of NET formation in experimental NEC.
- We hypothesize that NET inhibition would decrease mortality, pro-inflammatory cytokine releases, and organ injury in NEC.

METHODS

- NEC was induced using the Dithizone/Klebsiella (DK) method.
- P14-16 CD-1 mice were injected i.p. with 33 mg/kg dithizone. Six hours after injection, mice were enterally infected with 1x10^8 CFU Klebsiella per kg.
- Cl-amidine (a PAN Peptidylarginine deiminase inhibitor), was given 15 min before oral Klebsiella and 3 hours after.
- Cl-amidine has been shown to irreversibly inhibit NET formation in multiple murine models.

RESULTS

- Effect inhibiting NET formation by Cl-amidine (80 mg/kg) on incidence and severity of NEC
  - Survival between the groups
  - H&E Intestinal histological injury scores by a blinded pathologist
  - Systemic pro-inflammatory and anti-inflammatory cytokines (IL1β, IL-10, TNF-α, IL-6, GRO-α) in plasma were measured using XMAP procartaplex® multiplex immunoassays.

CONCLUSIONS

- NET inhibition using Cl-amidine in a DK NEC model increased mortality, systemic inflammatory response, and bacteremia.
- NET formation could be one of the protective innate immune mechanisms that decreases bacterial translocation.
- Further studies are needed to determine the effect of NET inhibition in other models of NEC.
- Further studies are needed to determine the role of delayed NET/histones inhibition in NEC models.

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NEONATAL-PERINATAL MEDICINE