Pre-treatment with the TLR3 agonist poly(I:C) protects neutropenic mice from intracerebral Escherichia coli infection

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BACKGROUND and GOALS
Polynosic–polyctydilic acid [poly(I:C)] is a synthetic analogue of viral double-stranded RNA that stimulates Toll-like receptor (TLR3) [1]. TLR3 induces immune responses via the TLR/IL-1 receptor (TIR)-domain containing adaptor protein inducing IFN-β (TRIF) [2].

The protective effect of poly(I:C) administration has been mainly reported against viral infections but few data is available regarding their prophylactic use against bacterial infections. In vitro, poly(I:C) increased microglial phagocytosis and intracerebral killing of Escherichia coli K1 by primary cultures of microglial cells [3].

CNS infections caused by E.coli, common in newborns, old and immunocompromised persons, are associated with high rates of mortality and long-term sequelae despite adequate antimicrobial therapy [4].

Here, we assessed the protective properties of poly(I:C) pre-treatment against E. coli K1 meningoencephalitis in immunocompromised animals which were depleted of granulocytes.

METHODS
C57Bl6 wild-type (wt) mice were rendered neutropenic by daily intraperitoneal (ip) administration of the anti-Ly-6G mAb (clone 1A8) starting 4 days before infection. Three days prior to intracerebral infection with E. coli K1 (1x106 CFU/mouse), wt and TRIF-/- (trif-/-) mice received an ip injection of either 200 μg poly(I:C) or vehicle.

Kaplan-Meier survival curves were analysed by the log-rank test. In bacteriological studies, mice were sacrificed 30 h after infection. Then, bacterial titers of blood, cerebellum and spleen homogenates were determined. Also, FACs analysis of the right brain hemisphere containing the site of inoculation was performed. Differences between groups were analysed by Mann-Whitney U-test.

RESULTS
Poly(I:C) decreases the bacterial concentrations in (A) cerebellar and (B) spleen homogenates and (C) blood at the early phase of infection. Neutropenic wt mice pre-conditioned with 200 μg poly(I:C) (n=21) or treated with buffer solution (n=20) were sacrificed 30 h after infection. Each symbol represents an individual mouse. Horizontal bars indicate median values.

The protective effect of poly(I:C) correlated with an increase of both the number of NK cells (CD45+NK1.1+CD3+) and the percentage of NK cells among CD45+ leukocytes at early infection. Each symbol represents an individual mouse. Horizontal bars indicate median values. Neutropenic wt mice pre-conditioned with 200 μg poly(I:C) (n=5) or treated with buffer solution (n=6) were sacrificed 30 h after infection. Distinct cell types isolated from the inoculated brain hemisphere from PBS-intracerebrally perfused animals were analysed by using flow cytometry.

The percentage of T cells (CD45+CD3+) and regulatory T cells (CD45+CD4+CD25+FoxP3+) among CD45+ leukocytes remained unaffected.

CONCLUSIONS: Prophylactic intraperitoneal administration of 200 μg of poly(I:C) strengthened the resistance of neutropenic mice against E. coli K1 meningoencephalitis. The lack of protection in TRIF-deficient mice strongly suggests that poly(I:C) mediated protection by the TRIF signaling pathway. Poly(I:C) administration significantly reduced bacterial burdens in blood and cerebellum and spleen homogenates, and increased the amount and percentage of NK cells in the brain compared to buffer-treated animals.

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REFERENCES: