Neonatal Maternal Deprivation Promotes *Nippostrongylus Brasiliensis* Infection in Adult Rats

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Digestive Disease Week®
and the
106th Annual Meeting of the American
Gastroenterological Association
May 14-19, 2005, Chicago, IL

- Program of the Annual Meeting of the American Gastroenterological Association, the American Association for the Study of Liver Diseases, the Gastroenterology Research Group, the Society for Surgery of the Alimentary Tract, and the American Society for Gastrointestinal Endoscopy
- Abstracts of Papers Accepted by the American Gastroenterological Association
- Abstracts of Papers Accepted by the American Association for the Study of Liver Diseases
- Abstracts of Papers Accepted by the Society for Surgery of the Alimentary Tract

provide valuable insight for design of selective mucosal modulators of IFN- γ expression in the gut.

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Negative Regulation of TNFR2 Cascades by TNFR1 Contributes to the Suppression of Colitis

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BACKGROUND&AIMS: TNF α and consequently TNF α receptor type1 (TNFR1) and type2 (TNFR2) play a critical role in the pathogenesis of IBD. The mechanism by which TNF α operates colitis is known to be very complex and multi-factorial due to the presence of two receptors. However, the functional role of interaction between TNFR1 and TNFR2 in colitis has not been fully elucidated yet. **METHODS:** To study the roles of TNFRs in a Th2-mediated colitis, TNFR1 x TCR α double knockout (DKO) (n = 18), TNFR2 x TCR α DKO (n = 29), and TNFR1 x TNFR2 x TCR α triple knockout (TKO) (n = 20) mice were generated. The presence of colitis was evaluated at 6 months of age by gross and histological examinations. The changes of phenotypes and apoptosis-associated signaling cascades in the colonic lamina propria (LP) cells were examined by real-time PCR and FACS analyses. **RESULTS:** As previously demonstrated (Gastroenterology 2002,122:134), mild form of colitis with low frequency developed in TNFR2 x TCR α DKO mice compared to TCR α KO mice. In contrast, TNFR1 x TCR α DKO mice compared to TCR α KO mice developed much more severe colitis that is associated with a significant increase in colonic LP CD4+ T cells. Interestingly, TNFR2 expressions were further upregulated on the colonic LP CD4+ T cells of TNFR1 x TCR α DKO mice compared to TCR α KO mice. In addition, the absence of TNFR1 led to the downregulation of apoptosis-associated molecules including BH3 interacting domain death agonist (Bid), Bcl-associated death promoter (Bad), and apoptosis-associated speck-like protein containing a CARD (ASC) in the colonic LP CD4+ T cells. To test whether the exacerbated colitis observed in TNFR1 x TCR α DKO mice results from the enhanced activation of TNFR2 cascades, TCR α triple knockout mice deficient in both TNFR1 and TNFR2 were generated. Of note, like TNFR2 x TCR α DKO mice, significantly less severe colitis with low frequency was observed in the TNFR1 x TNFR2 x TCR α KO mice compared to TCR α KO and TNFR1 x TCR α DKO mice.

CONCLUSION: These studies provide an evidence to address TNFR1-associated signaling cascades as a negative regulator of TNFR2 pathway in colonic LP CD4+ T cells. TNFR1 contributes to the suppression of a Th2-mediated colitis developing in TCR α KO mice.

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The Anti-Tumour-Necrosis Factor-Alpha Agents Infliximab and Onerecept Induce P38 Mitogen Activated Protein Kinase-Dependent Apoptosis in Monocytes Via Reverse TNF Signaling and Autocrine Transforming Growth Factor-Beta 1

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Background & Aims: The pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-alpha) plays a central role in inflammatory disorders. There is growing evidence that the efficacy of anti-TNF-alpha therapies in steroid-refractory Crohn's disease (CD) may critically depend on the binding of the transmembrane precursor of TNF-alpha (mTNF-alpha), thus eliciting complex intracellular signaling events (e.g. p38 mitogen-activated protein kinase (MAPK) activation and apoptosis), a process described as 'reverse signaling'. The aim of the present study was to elucidate the differential signaling mechanisms of the two unrelated TNF-binding agents infliximab (chimeric anti-TNF-alpha antibody) and onerecept (soluble TNFR1). **Methods:** Signaling pathways induced by ligation of mTNF-alpha were investigated using phospho-specific Western blots and reporter gene assays. Apoptosis was assessed using MTT assays, caspase activity measurements, Annexin V FACS, and stable transfection of dominant-negative forms of key apoptotic molecules (dnFADD/dnFLICE). Transforming growth factor (TGF)-beta levels and their autocrine action on TGF-receptors were assessed by ELISA, blocking antibodies and siRNA approaches.

Results: Infliximab and onerecept exert immunoregulatory functions by induction of death-receptor-independent apoptosis in primary human monocytes and in the monocytic cell line THP-1 through reverse signaling via mTNF-alpha. Molecular mechanisms of mTNF-alpha-induced apoptosis involve release of cytochrome c and activation of caspase 9 and 3. Expression of dnFLICE, but not dnFADD protein could attenuate cell death. Interference with MAPK pathways indicates that p38alpha and ERK1/2 have contrasting functions in the apoptotic cascade triggered by sTNFR1 via a TGF-beta autocrine loop. While p38alpha activity is essential for sTNFR1-induced apoptosis, ERK1/2 has a protective function. Interestingly, these effects seem to depend on an autocrine loop of TGF-beta, as inhibition of TGF-beta signaling reduce both MAPK activation and apoptosis.

Conclusions: This mechanism unveils a novel aspect of the molecular function of TNF-alpha-blocking agents in CD therapy, but also suggests a physiological role of sTNFR1 in immune regulation beyond a mere neutralization of soluble TNF-alpha. Molecular dissection of TGF-beta-dependent apoptotic and non-apoptotic signaling induced by mTNF-alpha ligation may have important implications for the design of future therapeutic strategies in IBD.

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Neonatal Maternal Deprivation Promotes Nippostrongylus Brasiliensis Infection in Adult Rats.

Frédéric Barreau, Jacques Ducos de Lahitte, Laurent Ferrier, Rafael Garcia-Villar, Lionel Bueno, Jean Fioramonti

Background: Neonatal stress is known to alter immune responses (macrophages, mast cells and lymphocyte activity, and Th1 and Th2 cytokines expression) in adults, and parasite infection is modulated by the immune status of the host. The present study aimed to establish whether immune alterations induced by maternal deprivation affects the time course of Nippostrongylus brasiliensis infection and the associated intestinal alterations in adult rats.

Methods: Male Wistar rat pups were separated from their mother (3 hours/day) during postnatal days 2 to 14 (deprived rats), or left undisturbed (control). At 12 weeks of age, N. brasiliensis infection was performed by subcutaneous administration of 3000 L3 infective larvae. On days 7 and 12 after this primary infection, the number of adult worms in the jejunum, the fecal egg output, paracellular jejunal permeability (FITC-dextran flux in Ussing chamber) and jejunal myeloperoxidase (MPO) activity were measured. A secondary infection (3000 L3 larvae) was performed 21 days after the first one. On days 7 and 12 after this second infection, the number of jejunal adult worms and fecal eggs were counted. Results were expressed as the mean $\pm$ SEM.

Results: On the 7th day after a primary infection, maternal deprivation increased the number of jejunal adult worms (805 ± 75 vs 536 ± 54 ; $P < 0.05$) and the number of eggs in the feces (18060 ± 2669 vs 10560 ± 1426 ; $P < 0.05$). On the 12th day, adult worms were only observed in adult deprived rats. In absence of infection and in comparison with controls, maternal deprivation increased jejunal MPO activity (229.5 ± 43.5 vs 92.4 ± 11.1 U/g tissue) and paracellular permeability (11.6 ± 1.1 vs 7.3 ± 0.4 nmol/h/cm). In control rats, N. brasiliensis infection (day 7) increased MPO activity (162.9 ± 43.9 vs 92.4 ± 11.1 U/g, $P < 0.05$) and paracellular permeability (11.2 ± 0.6 vs 7.3 ± 0.4 nmol/h/cm, $P < 0.05$). Infection in deprived rats enhanced the increase of MPO activity (385.6 ± 44.8 vs 229.5 ± 43.5 U/g; $P < 0.05$) but not paracellular permeability (12.4 ± 0.9 vs 11.6 ± 1.1 nmol/h/cm; $P > 0.05$). After the second infection, no adult worm and fecal egg were detected in both control and deprived rats.

Conclusions: Neonatal maternal deprivation favors a primary infection by N. brasiliensis in adult rats and enhances the jejunal inflammation induced by the parasite. However, maternal deprivation does not induce severe breakdown of immunity to N. brasiliensis, since the parasite does not develop after a secondary infection.

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Hibernation Confers Resistance To Organ Damage Following Intestinal Ischemia-Reperfusion

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Mammalian hibernation is accompanied by a suite of physiologic events that are life-threatening for non-hibernating species such as humans. These include extended fasting (up to 6 months) and major changes in intestinal blood flow as animals repeatedly cycle into and out of the torpid state. We hypothesized that endogenous defense mechanisms that minimize injury to intestinal tissues during the hibernation season may also increase resistance to imposed intestinal ischemia-reperfusion (I/R) injury. We used a model of superior mesenteric artery (SMA) occlusion (20 min) followed by reperfusion (60 min) in rats, summer ground squirrels, and hibernating squirrels that had fully aroused between bouts of torpor (i.e., all animals had body temperatures of 37-38 °C). Sham animals from each group were anesthetized and the SMA was isolated, but not occluded. Intestinal I/R induced severe damage to the ileum with massive epithelial shedding and mucosal damage in rats and summer squirrels, but not hibernators. Histological damage scores were 3.7-fold higher in I/R vs sham rats and 3.4-fold higher in I/R vs sham summer squirrels ($p < 0.01$ for both). In contrast, there was no difference in damage scores for I/R vs. sham hibernators ($p = 0.16$). We assessed neutrophil invasion into remote organs by mucosal myeloperoxidase activity (MPO). Compared with sham animals, MPO activity after I/R increased significantly in liver (6-fold) and lung (3-fold) in rats but not in the hibernators. The results support the hypothesis that the hibernation phenotype provides enhanced protection against intestinal I/R injury. Identification of mechanisms that underlie this effect may provide new targets for therapeutic treatment or pretreatment to minimize intestinal I/R injury in humans. Supported by US Army grant DAAD190110455.

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Intraluminal Oxygen Prevents Mucosal Ischemic Damage in a New Model of Complete Local Small Bowel Ischemia in Pigs

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Introduction

Microvascular ischemia of the gastrointestinal tract is an important, and difficult to treat disorder. It is an important mechanism underlying e.g. radiation proctitis, Crohn's disease and anastomotic leakage after esophageal and colorectal resections. In the latter, it is the main contributor to anastomotic leakage, morbidity and mortality. We explored a new approach by applying intraluminal oxygen in an animal model with complete local GI-ischemia.

Methods

In large pigs, a 70 cm small bowel loop was isolated, vessels were ligated and 2 tubes placed intraluminally at both ends; over these tubes tight ligatures were placed, thereby interrupting the collateral intramural vessels, creating complete small bowel ischemia. Complete hemodynamic monitoring, as well as blood gas sampling, was performed. Oxygen (5 ml/min) was administered intraluminally in the middle part of the ischemic loop, via a multi channel catheter connected to a prototype applicator. Mucosal blood flow and oxygen saturation were measured. Complete ischemia was maintained for 2 hr. Afterwards, transmural tissue samples were taken for histopathology from the ischemic loop (in the middle part, 10, 20 and 30 cm proximal and distal). Mucosal damage was graded according to the Chiu classification (grade 0 to 4).

Results

Six pigs received no oxygen (sham) and 6 pigs received oxygen (treatment). Hemodynamic parameters remained stable and did not differ between both groups; no evidence of systemic inflammatory response was found. In both groups no mucosal blood flow was detectable. The sham-group showed severe ischemia, the treated group showed macroscopically almost