Acute induction of human IL-8 production by intestinal epithelium triggers neutrophil infiltration without mucosal injury

T Kucharzik, J T Hudson III, A Lügering, J A Abbas, M Bettini, J G Lake, M E Evans, T R Ziegler, D Merlin, J L Madara, I R Williams

Aim: Neutrophil migration in the intestine depends on chemotaxis of neutrophils to CXC chemokines produced by epithelial cells. The goal of this project was to determine if acute induction of a CXC chemokine gradient originating from intestinal epithelial cells is sufficient to induce neutrophil influx into intact intestinal tissue.

Methods and results: The authors developed a double transgenic mouse model with doxycycline induced human IL-8 expression restricted to intestinal epithelial cells. Doxycycline treatment of double transgenic mice for three days resulted in a 50-fold increase in the caecal IL-8 concentration and influx of neutrophils into the lamina propria. Although neutrophils entered the paracellular space between epithelial cells, complete transepithelial migration was not observed. Doxycycline treatment also increased the water content of the caecal and colonic stool, indicating dysfunctional water transport. However, the transmural electrical resistance was not decreased. Neutrophils recruited to the intestinal epithelium did not show evidence of degranulation and the epithelium remained intact as judged by histology.

Conclusions: This conditional transgenic model of chemokine expression provides evidence that acute induction of IL-8 in the intestinal epithelium is sufficient to trigger neutrophil recruitment to the lamina propria, but additional activation signals are needed for full activation and degranulation of neutrophils, mucosal injury, and complete transepithelial migration.
expression vector designated pTRE2IL-8 was prepared by removing the same cDNA from ptetOIL-8 with BamHI and XbaI and inserting it into the pTRE2 vector (Clontech, Palo Alto, CA, USA). Transgenic mice were generated by microinjection of either the 1.2 kb Xhol/BstEII fragment from ptetOIL-8 or the 2.0 kb Xhol/AseI fragment from pTRE2IL-8 into (C57BL/6 X SJL/J)F2 or C57BL/6 eggs. Transgenic founders were identified by PCR screening. The tetOIL-8 construct was detected by PCR amplification of genomic DNA with 5′-TTGGTGTAG-3′ and 5′-GGCGTGTACGGTGGGAGG-3′ yielding a 753 bp amplimer. For the TRE2IL-8 construct, a 220 bp segment of the rabbit β-globin intron in the construct was amplified using the following primers: 5′-ATCTGGCCTTTCCTT-3′ and 5′-CCACACAGCCACACCCTTCT-3′.

Mice

Transgenic mice expressing rtTA only in the distal ileum, caecum, and proximal colon (Fabp2 rtTA transgene; abbreviated FABP-rtTA) were the kind gift of Dr Jeffrey I Gordon (Washington University, St Louis, MO, USA). The tetOluc transgene was detected by PCR using 5′-GCAATGTTCCAGGAACCAGGGCG-3′ and 5′-GGATCCCCATGACTGACACT-3′. In litters of FABP-rtTA mice mated to mice carrying a tetracycline responsive transgene, the presence of the FABP-rtTA transgene was detected by PCR with primers amplifying a 220 bp amplimer (5′-GGCTCCATTGCGATGACTTAG-3′ and 5′-CAAATGCATGAGGAGGCT-3′) (320 bp amplimer). In litters of FABP-rtTA mice mated to mice carrying a tetracycline responsive transgene, the presence of the FABP-rtTA transgene was detected by PCR with primers amplifying a 220 bp amplimer (5′-CGCCCGAAGGATGGCGCAT-3′ and 5′-GCTCCATTGCGATGACTTAG-3′). After establishment of a colony of FABP-rtTA and TRE2IL-8 double transgenic mice, double transgenic mice were backcrossed to C57BL/6 mice for four generations. Transgenic mice were induced with DOX by supplementing the drinking water with 0.5 mg/ml doxycycline HCl and 5% sucrose. All experimental protocols employing mice were approved by the Institutional Animal Care and Utilization Committee of Emory University.

Ribonuclease protection assay

To directly measure rtTA mRNA expression in tissues from FABP-rtTA mice, we performed ribonuclease protection assay on RNA was isolated from tissue using Trizol (Invitrogen). A custom cRNA probe for detecting mRNA

<table>
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<tr>
<th>Transgenic line</th>
<th>Adenovirus</th>
<th>DOX</th>
<th>IL-8 (ng/ml)</th>
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*Primary cell cultures (mostly myofibroblasts) were established from the lungs of four independent transgenic lines (two each with either tetOIL-8 or TRE2IL-8 construct). Confluent monolayers of cells were transduced with supernatant containing adenoviruses expressing rtTA. Doxycycline was added to the indicated wells at a final concentration of 2 μg/ml. The concentration of IL-8 in the supernatant three days after addition of the rtTA-expressing adenovirus was determined by ELISA.

†Ratio of IL-8 concentration in cells transduced with adenovirus and treated with doxycycline compared to cells only transduced with adenovirus.

![Diagram](https://example.com/diagram.png)
transcripts containing rtTA sequences was prepared by subcloning a 308 bp Asel-HindIII band from rtTA into pBluescript II KS- cut with SmaI and HindIII. In vitro transcription was performed with Xhol linearized plasmid DNA as template, T7 RNA polymerase, and α-32P-UTP (Amersham) using the RibopQuant kit (BDPharMingen, San Diego, CA, USA). The 385 bp labeled probe was hybridized overnight at 56°C to 20 μg of total RNA. The products were digested with RNase A and RNase T1 for one hour at 37°C. The digested RNA was subjected to electrophoresis through urea/acylamide gels to allow identification of rtTA mRNA as a 311 bp protected fragment.

Use of recombinant adenovirus encoding rtTA to test DOX inducibility of IL-8 transgenes

To test individual transgene integrations in TRE2IL-8 mice and tetOIL-8 mice, we developed a recombinant adenovirus expressing a modified form of rtTA (KrtTAFFF) with a Kozak consensus translational start site and a modified transactivator containing three minimal activation domains. KrtTAFFF cDNA was cloned into the Bgl II site in pQBI-AdBM5-GFP vector (Obiogene, Carlsbad, CA, USA). Homologous recombination was done in 293 cells that were co-transfected with vector linearised at the FseI site and long arm DNA from adenovirus 5 lacking the E1 and E3 genes. GFP positive plaques were selected after 10 days and plaque purified. Supernatants containing recombinant adenovirus were prepared by freeze-thaw lysis of 293 cells three days after adenoviral infection. The inducibility of the individual TRE2IL-8 and tetOIL-8 transgenes was analysed by transducing cultures of myofibroblasts established from neonatal lung from each independent transgenic line with recombinant adenovirus encoding rtTA. The IL-8 content of supernatants from cultures supplemented with DOX (2.0 μg/ml) or receiving no DOX was compared by ELISA. The TRE2IL-8 transgenic line with the highest induction ratio of IL-8 after administration of DOX was mated to FABP-rtTA mice to establish a colony of double transgenic mice. IL-8 expression in double transgenic FABP-rtTA × TRE2IL-8 mice was induced by adding DOX (0.5 mg/ml) to the drinking water.

ELISA for IL-8

IL-8 was measured by ELISA as previously described.

Luciferase determinations

Tissues from mice were homogenised in a buffer containing 50 mM K3PO4 (pH 7.8), 1 mM EDTA, 1 mM DTT, and 10% glycerol. Aliquots were diluted 1:5 in Reporter Lysis Buffer (Luciferase Assay System, Promega, Madison, WI, USA) and subjected to a single freeze/thaw cycle. After centrifugation (14,000 x g for 5 minutes), 100 μl of supernatant was added to 100 μl of Luciferase Assay Reagent (Promega) and light production measured using a luminometer (Turner BioSystems, Sunnyvale, CA, USA). The results were normalised to protein content of the samples and are reported as relative light units per mg of protein.

Immunofluorescence staining and confocal microscopy

Neutrophils were detected in acetone fixed frozen sections using biotinylated anti-Gr-1 (BDPharMingen) followed by phycocerythrin conjugated streptavidin (Immunotech, Portland, ME, USA). Human IL-8 was detected in 1% paraformaldehyde fixed frozen sections using biotinylated goat antihuman IL-8 (R&D Systems, Minneapolis, MN, USA) followed by streptavidin-peroxidase and FITC conjugated tyramide (Perkin Elmer Life Sciences). YoPro-3 (Molecular Probes, Eugene, OR, USA) was used as a nuclear counterstain in some experiments. Fluorescence images were acquired using a Zeiss LSM510 confocal microscope.

Transmission electron microscopy

Tissue sections were cut with diamond knives on an ultramicrotome and mounted on uncoated mesh grids. Sections were contrasted with uranyl acetate and lead citrate and examined under a Philips CM10 electron microscope.

Stool water content measurement

Stool water content was calculated by a previously described method. In brief, caecal stool samples and faecal pellets were collected in tubes. The water content of samples was...
RESULTS
Development of transgenic mice with tetracycline regulated expression of human IL-8

In order to generate a model of inducible CXC chemokine expression in the intestinal epithelium of transgenic mice, transgenic mice were first made using a transgene consisting of the human IL-8 cDNA linked to a promoter containing a modified liver fatty acid binding protein (FABP) promoter (Fig 1A). Human IL-8 binds to CXCR2 on mouse neutrophils, eliciting chemotaxis and calcium flux with a potency similar to endogenous mouse chemokines that also bind to mouse CXCR2. Use of the cDNA for human IL-8 rather than an endogenous mouse CXCR2 binding chemokine for our construct allowed development of a system in which transgene derived chemokine expression could be clearly distinguished from endogenous mouse CXC chemokine expression using immunoassays specific for human IL-8. Primary cell lines were established from neonatal lung tissue of mice representing four independent transgenic lines that had integrated either the tetOIL-8 or TRE2IL-8 transgenes. The cell lines were transduced with adenoviruses encoding a reverse tetracycline transactivator (rtTA) in the presence and absence of DOX to assay for DOX-induced IL-8 expression (Table 1). Cells from one of the TRE2IL-8 transgenic lines tested (#2) had a much higher level of IL-8 expression than any of the other lines following DOX induction, with a 200-fold increase in IL-8 in the presence of DOX. This TRE2IL-8 transgenic line was selected for further analysis.

Selection of transgenic mice with intestine specific expression of the reverse tetracycline transactivator

Two types of transgenic mice in which rtTA expression was selectively targeted to intestinal epithelial cells were evaluated for use in combination with the TRE2IL-8 mouse to generate an intestine specific inducible IL-8 mouse model. In the FABP-rtTA mice, the rtTA transgene is under the control of a modified liver fatty acid binding protein promoter (Fabpl 4X at -132 promoter) in which four extra copies of a 35 bp element important for colonic expression were inserted just upstream of the endogenous location of this element to boost the activity of the promoter in the colon. We also attempted to develop transgenic mice with rtTA expression throughout the colon using the human downregulated in adenoma (DRA) promoter. The intestinal expression of mRNA for rtTA was compared in FABP-rtTA mice and one line of DRA-rtTA mice by RNase protection assay (Fig 1B). Intestinal tissue from the FABP-rtTA mice had a much higher level of rtTA mRNA than tissue from the DRA-rtTA transgenic mice. The highest levels of expression of the FABP-rtTA transgene were detected in distal ileum and the caecum in agreement with previous analysis of the functional activity of this rtTA transgene in different tissues. We also attempted to develop transgenic mice with rtTA expression in the proximal colon (Fig 1C).

Statistical analysis

Differences between the mean values for groups were analysed by Student’s t test. A p value of <0.05 was considered as significant.
Inducible intestinal IL-8 expression in double transgenic mice

We next bred mice that were double transgenic for the FABP-rtTA and TRE2IL-8 transgenes. These mice were induced with DOX for three days and the levels of IL-8 expression analysed in serum and tissue homogenates by ELISA. DOX induction resulted in over 60-fold induction of IL-8 expression at the protein level in the caecum and strong induction in the ileum and proximal colon (table 2).

Analysis of the kinetics of appearance of IL-8 in the intestine following DOX induction showed that the increase in IL-8 was already apparent at 24 hours and the IL-8 concentration continued to increase between 24 and 72 hours (fig 2). We also assessed the effect of DOX induction on the plasma concentration of IL-8 (table 3). Mice with just the TRE2IL-8 transgene had a low basal plasma level of IL-8 that was not affected by the administration of DOX (data not shown). DOX induction for five days in double transgenic mice resulted in a 6.9-fold induction in plasma IL-8 (table 3).

IL-8 induction in the caecum and proximal colon leads to neutrophil infiltration

We next examined the phenotypic consequences of IL-8 induction by DOX in the double transgenic mice by histology. DOX induction was associated with appearance of a dense infiltrate of Gr-1 positive neutrophils in the caecum and large intestine by 48 hours after DOX induction (fig 3A, B). However, no other histological abnormalities were detected. Some of the neutrophils in the DOX induced mice were concentrated around blood vessels within the intestinal submucosa, suggesting the IL-8 elicited exit of neutrophils from the bloodstream might be initiated at postcapillary venules found in the intestinal wall. Few if any Gr-1 positive cells were identified in control mice.

Three features of the observed neutrophil infiltrates were of particular interest. Firstly, examination of many sections of caecum from induced double transgenic mice revealed that even when the recruited neutrophils broached the basement membrane of a crypt, the neutrophils remained confined to the paracellular space below the tight junctions and were never observed to reach the crypt lumen to yield a lesion comparable to a crypt abscess (fig 3A, B). The induced IL-8 gradient was never sufficient to effect complete transepithelial migration of the neutrophils, even if DOX induction was continued for several weeks (data not shown). Secondly, even the densest neutrophil infiltrates observed did not result in histologically recognisable epithelial injury or ulceration. One contributing factor to the absence of epithelial damage by the infiltrating neutrophils may be limited degranulation of the recruited neutrophils. Transmission electron micrographs of neutrophils located within crypts revealed that the majority of the granules identified within the neutrophil cytoplasm were intact without evidence of degranulation (fig 3D and data not shown). A third feature of the neutrophil infiltrate best revealed by the immunofluorescence studies was its patchy distribution within the lamina propria (fig 4A, B). One potential explanation of this pattern of infiltration was that IL-8 was only expressed by epithelial cells derived from stem cells in a subset of intestinal crypts. Immunostaining of consecutive sections with antibodies to IL-8 and Gr-1 revealed that neutrophil infiltration was localised to the same areas where IL-8 expression was detected (fig 4C, D).

Neutrophil infiltration induced by DOX in FABP-rtTA x TRE2IL-8 mice is associated with an increase in stool water content

We used several experimental approaches to investigate whether IL-8 induced neutrophil recruitment to the intestinal mucosa could elicit any functional abnormalities in the epithelium. One parameter that was examined was the water content of the stool. We hypothesised that the influx of neutrophils might result in the release of mediators that would provoke epithelial cell ion secretion leading to net water movement into the luminal space. A statistically significant increase in the water content of both the caecal

Figure 4  Neutrophil infiltration in caecum of DOX-induced FABP-rtTA x TRE2IL-8 mice is localised to discrete patches. (A) Biotin-conjugated antibody to Gr-1 followed by streptavidin-phycocerythrin was used to localise neutrophils (red) in frozen sections of FABP-rtTA x TRE2IL-8 mice induced with DOX for five days (50 × magnification) and counterstained with YoPro-3 (pseudocoloured blue). Areas of intense neutrophil infiltration are separated by groups of crypts in which no neutrophils are detected. A similar patchy pattern of neutrophil infiltration was observed in sections from four other double transgenic mice stained with the same antibodies. (B) High power (600 ×) image of a crypt demonstrates Gr-1+ neutrophils that have migrated into the paracellular space between epithelial cells. (C) (D) Consecutive sections of caecum from five day induced double transgenic mice were stained for Gr-1 (C) and IL-8 (D) showing that Gr-1+ cells are present in the same patches where IL-8 is expressed.

Figure 5  DOX induction of FABP-rtTA x TRE2IL-8 mice does not change the basal transmural resistance of the caecum. Double transgenic mice and controls (n = 4 for each group) were induced for five days by DOX supplementation of the drinking water. Caecal tissue from the mice was mounted in Ussing chambers for measurement of the basal transmural resistance, which is reported as the mean (SD). The difference between the groups was not statistically significant (p > 0.05). Similar results were obtained in a second experiment with groups of six mice.

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and colonic stool was observed in double transgenic mice after DOX induction (table 4). To determine if the increased water content was associated with other perturbations in epithelial ion transport and resistance, Ussing chamber experiments were performed. The mean transmural electrical resistance of the caecal tissue recovered from DOX induced double transgenic mice was comparable to the value for DOX treated control mice (fig 5). Basal short circuit current and the change in short circuit current elicited by forskolin stimulation were also not significantly altered (data not shown). In addition, the in vivo permeability of the intestine to orally ingested FITC dextran (molecular weight of 4000 kDa) in double transgenic and control mice 24 hours after DOX induction was not statistically different (data not shown).

**DISCUSSION**

The directed migration of leukocytes is controlled by multiple classes of chemotactic factors including chemokines, leukotrienes, complement derived anaphylatoxins, eicosanoids, and bacterially derived peptides such as fMLP. Identifying the specific contributions made by an individual species of chemotactic factor in vivo represents a substantial experimental challenge. We developed a novel mouse model featuring DOX inducible transgenic expression of a CXCR2 binding chemokine by intestinal epithelial cells in order to determine whether a CXC chemokine gradient alone is sufficient to elicit complete transepithelial migration of neutrophils. This in vivo model demonstrates that acute induction of the human CXC chemokine IL-8 restricted to the intestinal epithelial cells is sufficient to efficiently trigger extravasation of neutrophils from the vasculature, accumulation of neutrophils within the lamina propria, and penetration by the neutrophils through the epithelial basement membrane to reside in the paracellular space beneath the tight junction. However, the induced chemokine gradient does not result in full activation of the recruited neutrophils and the recruited neutrophils fail to breach the tight junctions to reach the intestinal lumen. Based on these results, we hypothesise that CXCR2 ligands such as IL-8 that are to be predominantly released from the basolateral side of polarised epithelial cells are competent to elicit neutrophil recruitment into the lamina propria, but require the concurrent presence of additional chemotactic and/or activating signals to effect complete transepithelial migration and to fully activate the recruited neutrophils.

The inducible transgenic mouse model of chemokine expression described in this report proved useful for analysis of the functional consequences of inducible IL-8 expression despite the restriction of the neutrophil infiltration to localised areas in the caecum. The increased water content of the caecal and colonic stool in the induced double transgenic mice after three days of DOX induction demonstrates that the recruited neutrophil result in a local perturbation of epithelial cell water transport leading to an increased water content. While DOX was the only tetracycline used in this study to induce IL-8 expression, 4-epidoxycyline is an alternative DOX derivative that also efficiently induces rtTA activity and has the advantage of not exerting an antibiotic effect on the intestinal bacterial flora. One characteristic feature of the inducible IL-8 expression model described in this report is the patchy distribution of the neutrophil infiltrates in the caecum and colon that corresponded to the areas of IL-8 expression. Variegated expression of transgenes is known to be a common occurrence when tandem arrays containing a transgene sequence randomly integrate into genomic DNA. The most likely explanation of the patchy neutrophil infiltrates in the present model is epigenetic silencing of either the FABP-rtTA transgene, the TRE2IL-8 transgene, or both transgenes in intestinal epithelial cells in which the FabPL knockout promoter is normally active.

One of the more striking characteristics of the neutrophil infiltrates induced by DOX in the caecum of double transgenic mice was the presence of minimal tissue injury and the absence of complete transepithelial migration of neutrophils. As acute bacterial infection at a mucosal site results in neutrophil infiltration typically results in complete transepithelial migration of neutrophils and is accompanied by tissue injury, we conclude that other chemotactic and activating factors for neutrophils are needed to bring about this “complete” neutrophil response. Along these lines, studies of chemotactic factors elicited by infection of model intestinal epithelia with Salmonella have identified basolaterally secreted chemokines as well as an apically secreted molecule originally designated PEEC for pathogen elicited epithelial chemoattractant. Purification and biochemical characterisation of PEEC has recently identified this material as the eicosanoid hepxolin A3. Based on the absence of complete transepithelial migration in our model, indicated previously, we have used these model systems to test the hypothesis that a combination of chemotactic factors is needed to elicit neutrophil infiltration in vivo.
we speculate that apically secreted chemotactic factors derived from the epithelial cells such as hepoxilin A₃ are also necessary to drive neutrophils across epithelial tight junctions to reach the luminal space. While the chemokine IL-8 has been shown previously to elicit degranulation of human neutrophils, most of the granules in the neutrophils infiltrating intestinal tissue in the double transgenic mouse model appeared to be intact as assessed by transmission electron microscopy. We speculate that more efficient degranulation of mouse neutrophils recruited by CXCR2 binding chemokines may require additional activating stimuli. Interestingly, recruitment of leukocytes without concurrent inflammatory activation has been observed in other chemokine overexpressing transgenic mice.

Another explanation of the absence of degranulation in the inducible IL-8 mice is that IL-8 elicited degranulation of human neutrophils may be primarily a function of the CXCR1 receptor found only on human neutrophils rather than the CXCR2 receptor shared between mouse and human neutrophils.

Future studies on this inducible mouse model of intestinal IL-8 expression and neutrophil infiltration will be focused in several areas. As several small molecule CXCR2 antagonists have shown inhibitory activity in other animal models of chemokine induced inflammation this model provides an ideal in vivo system to assess the activity of candidate drugs that act by interfering with CXC chemokine binding to CXCR2. Secondly, these mice represent an excellent in vivo model in which to characterise how neutrophil infiltration modifies epithelial gene expression since the inflammatory infiltrate is restricted to the intestinal epithelium. Finally, the intense neutrophil infiltrate achieved by use of a tissue specific promoter for rTfA provides proof of principle that similar models of inducible, localised neutrophil infiltration can be created by using other lines of rTfA transgenic mice in which promoters with different patterns of tissue specific expression are substituted for the Fabp2 promoter used in this study.

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EDITOR’S QUIZ: GI SNAPSHOT

Hypoalbuminaemia and gastric mass

Clinical presentation
A 45 year old woman presented with longstanding dyspepsia associated with oedema and a 4 kg weight loss over the previous six months. She gave no history of haematemesis or blood in stool, nocturnal sweating, or chronic diarrhoea. There was no familial history of gastric carcinoma. Surgical history included cure of eventration. Physical examination revealed tenderness in the epigastrium. Routine laboratory investigations revealed: haemoglobin 9.6 g/l (normal range 10–14), mean corpuscular volume 80 fl (normal range 75–95), serum albumin 25 g/l (normal range 35–50), C reactive protein 3 (normal range <10), lactate dehydrogenase 355 IU (normal range <600), and β2 microglobulin 2 (normal range 0.5–1.2). The patient underwent upper gastrointestinal endoscopy with gastric biopsy and endoscopic ultrasound of the stomach (fig 1–3).

Question
What is the diagnosis? What other entities could present with this endoscopic and histological picture?
See page 1589 for answer
This case is submitted by:

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