Gastritis increases resistance to aspirin-induced mucosal injury via COX-2-mediated lipoxin synthesis

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Submitted 18 December 2002; accepted in final form 11 March 2003

Souza, Marcellus H. L. P., Octavio Menezes de Lima Jr., Stella R. Zamuner, Stefano Fiorucci, and John L. Wallace. Gastritis increases resistance to aspirin-induced mucosal injury via COX-2-mediated lipoxin synthesis. Am J Physiol Gastrointest Liver Physiol 285: G54–G61, 2003. First published March 13, 2003; 10.1152/ajpgi.00525.2002.—Products of cyclooxygenase (COX)-2 contribute to mucosal defense. Acetylation of COX-2 by aspirin has been shown to result in the generation of 15(R)-epi-lipoxin A4, which exerts protective effects in the stomach. In gastritis, it is possible that lipoxin A4 makes a greater contribution to mucosal defense. We tested this hypothesis in the rat, by using the iodoacetamide-induced gastritis model. Iodoacetamide was added to the drinking water for 5 days. Rats were then given the iodoacetamide-induced gastritis model. Iodoacetamide was added to the drinking water for 5 days. Rats were then given aspirin, and the extent of gastric damage was blindly assessed 3 h later. Gastric 15(R)-epi-lipoxin A4 and PGE2 levels were determined. The effects of pretreatment with a selective COX-2 inhibitor, rofecoxib, and of a lipoxin receptor antagonist were assessed. Effects of aspirin and the other test drugs on leukocyte adherence within mesenteric venules were assessed by intravital microscopy. Aspirin elicited greater lipoxin synthesis in the inflamed than in the normal stomach, and there was reduced gastric damage. Rofecoxib inhibited lipoxin synthesis and exacerbated aspirin-induced damage. The lipoxin antagonist also exacerbated aspirin-induced damage. In rats with gastritis, aspirin reduced leukocyte adherence (in contrast to an increase in normal rats), and this effect was reversed by rofecoxib or by the lipoxin antagonist. These results support the notion that aspirin-triggered lipoxin synthesis via COX-2 makes an important contribution to mucosal defense in both the normal and inflamed stomach.

cyclooxygenase; ulcer; nonsteroidal anti-inflammatory drug; lipoxigenase

IN RECENT YEARS, CONSIDERABLE evidence has emerged to suggest that cyclooxygenase (COX)-2 makes an important contribution to gastrointestinal mucosal defense. In the case of the stomach, COX-2-derived PGs have been shown to play an important role in increasing the resistance to injury associated with ischemia-reperfusion or topical application of irritants (10, 16). More recently, COX-2-derived 15(R)-epi-lipoxin A4 [15(R)-epi-LXA4] was shown to increase the resistance of the rat stomach to damage induced by aspirin (6). Formation of this lipoxin occurs after acetylation of COX-2 by aspirin (5, 15, 22). Blockade of the lipoxin A4 (LXA4) receptor or inhibition of aspirin-triggered lipoxin synthesis with a selective COX-2 inhibitor resulted in a significant exacerbation of gastric damage (6).

LXA4 and 15(R)-epi-LXA4 have been shown to act on the same receptor (24) and to exert potent anti-inflammatory effects, including inhibition of neutrophil adhesion and secretion (5, 13, 22) and aspirin-induced neutrophil adherence to the vascular endothelium (6). Also, lipoxins have been shown to suppress interleukin-8 release from cultured intestinal epithelial cells in response to stimulation with tumor necrosis factor-α (9). Thus lipoxins, including those synthesized subsequent to acetylation of COX-2 by aspirin, may exert important anti-inflammatory effects in addition to the mucosal protective actions recently described (6).

In the inflamed gastric mucosa, as in other inflamed tissues, there is elevated expression of COX-2 (1, 2, 8, 32). It is possible that in such circumstances COX-2 makes a more important contribution to mucosal defense than in the normal stomach. Moreover, aspirin-triggered lipoxin synthesis may contribute more to mucosal defense in a setting of gastritis than is seen in a normal stomach. *Helicobacter pylori*-associated gastritis has been shown to be associated with elevated COX-2 expression (2, 8, 32), elevated PG synthesis (12), and an increased resistance to injury induced by NSAIDs (11, 14), although this last is quite controversial (3). Whether or not lipoxin synthesis is upregulated in a setting of gastritis, it is associated with *H. pylori* infection or otherwise, has not been determined.

In the present study, we used the iodoacetamide-induced gastritis model (24) in which we have previ-
ously observed an upregulation of COX-2 expression (1) to address the following questions. Is the inflamed gastric mucosa more resistant to the ulcerogenic effects of aspirin compared with a normal gastric mucosa? Is there any difference in susceptibility to gastric mucosal injury in the inflamed stomach? Is aspirin-triggered lipoxin synthesis elevated in the inflamed stomach, and does it account for differences in susceptibility to mucosal injury?

MATERIALS AND METHODS

Animals. Male Wistar rats weighing 175–200 g were obtained from Charles River Breeding Farms (Montreal, QC, Canada) and were housed in the Animal Care Facility at the University of Calgary. The rats were fed standard laboratory chow and tap water. All experimental protocols were approved by the Animal Care Committee at the University of Calgary, and the experiments were performed in accordance with the guidelines of the Canadian Council on Animal Care. Animals were intragastrically dosed with reagents and were killed by cervical dislocation. At sacrifice, the rats were killed by cervical dislocation. At sacrifice, the rats were kept on ice until use. The samples were then stored at −80°C until use.

Induction of gastritis. Gastric inflammation was induced by the addition of iodoacetamide (0.1%) and sucrose (1%) to drinking water, as described previously (1, 24). The control group was given drinking water supplemented only with sucrose (1%). All experiments were performed on the 5th day after the rats were given the modified drinking water. We previously demonstrated (1) that the administration of iodoacetamide in this way results in a significant increase in granulocyte infiltration into the rat gastric mucosa.

Effects of aspirin. Rats were deprived of food for 18–20 h, with free access to drinking water (supplemented as described above), and were then treated orally with aspirin (50 or 100 mg/kg) or vehicle (1% carboxymethylcellulose). Three hours later, the rats were euthanized for blind assessment of gastric damage (30). The lengths (in mm) of all hemorrhagic lesions were measured with digital calipers, and the gastric damage score was calculated for each stomach by summing these values. After scoring the damage, a sample of the corpus region of each stomach was fixed in neutral buffered formalin for subsequent histological assessment. Another tissue sample was excised for measurement of MPO activity (18) by using a commercially available spectrophotometric kit. MPO is an enzyme found primarily in the azurophilic granules of the neutrophils and therefore has been used extensively as a biochemical marker of the granulocyte infiltration into various tissues, including the gastrointestinal tract. Another tissue sample from each stomach was immediately frozen in liquid nitrogen and then stored at −80°C for subsequent measurement of tissue levels of PGE2 (28) and 15(R)-epi-LXA4 (6).

Effects of COX-2 inhibition. Additional experiments were performed in which rats with gastritis and healthy controls were given rofecoxib (6 mg/kg) or vehicle (saline) orally 30 min before the administration of aspirin (50 mg/kg) or vehicle (1% carboxymethylcellulose). The dose of rofecoxib was selected because it previously has been shown by us (6) to markedly suppress COX-2 activity in the rat but not to affect COX-1 activity. Three hours later, the rats were euthanized, gastric tissue was blindly scored, and tissue samples were taken for histology and for measurement of MPO, PGE2, and 15(R)-epi-LXA4.

Measurement of PGE2 and 15(R)-epi-LXA4. The frozen tissue samples (~130 mg) of the gastric corpus were homogenized in a mixture of 3.0 ml of extraction solvent (isopropyl/ethyl acetate/0.1 N HCl, 3:3:1) and 3.0 ml of distilled water centrifuged at 1,500 g for 10 min at 4°C. The organic phase was aspirated and divided into two tubes. The first was evaporated to dryness under a stream of nitrogen, then reconstituted in 1 ml of 0.1 M phosphate buffer (pH 7.4) containing 0.8% sodium azide and 0.1% gelatin. The concentration of PGE2 in these samples was then measured by ELISA by using a commercially available kit. The other half of each sample was diluted 1.5 with water and acidified to pH 3.5 with 1 N HCl. Samples were applied to a preconditioned C18 Sep-Pak column (Waters, Mississauga, ON, Canada), and after washing with 1 ml water followed by 1 ml petroleum ether, the LXA4 was eluted with 2 ml of methyl formate. The sample was then dried under a stream nitrogen and reconstituted in assay buffer.

Concentrations of 15(R)-epi-LXA4 in the samples were measured by using a highly specific, commercially available ELISA (4). The antibody used in this ELISA is specific for 15(R)-epi-LXA4, with cross-reactivity with 15(S)-HETE and 15(R)-HETE being 0.13 and 1.25%, respectively. By using reverse-phase high-performance liquid chromatography, we confirmed that the rat stomach produced 15(R)-epi-LXA4 after aspirin administration in a COX-2-dependent manner (6).

Effects of a lipoxin receptor antagonist. To further determine any role of lipoxins in altered mucosal resistance to injury in rats with gastritis vs. normal rats, a lipoxin receptor antagonist, N-tert-butoxycarbonyl-methionine-leucine-phenylalanine (BOC) (20), was used. The two groups of rats were given BOC (10 μg/kg ip) 30 min before oral administration of aspirin (50 mg/kg) or vehicle. Three hours later, the extent of gastric damage was blindly scored, as described above.

COX-2 expression. Gastric COX-2 expression was examined by Western blotting. Samples of gastric tissue were homogenized in lysis buffer (0.1% Triton X-100, 50 mM phosphate buffer, 0.2 mM leupeptin, 1 μM aprotinin, 10 mg/ml phenylmethylsulfonyl fluoride, 50 mM Tris, and 10 mM EDTA). Samples were then centrifuged, and the protein concentration of the supernatant was determined by colorimetric assay (Bio-Rad, Hercules, CA). Protein (50 μg) was separated on a 10% polyacrylamide gel and then transferred to a nitrocellulose membrane (1). The membrane was incubated for 1 h with blocking buffer (20 mM Tris, 100 mM NaCl, 0.5% Tween 20, and 5% nonfat dried milk) and then probed overnight with a polyclonal rabbit antibody against COX-2 (1:500; Cayman Chemical, Ann Arbor, MI). The membrane was then incubated with a donkey anti-rabbit IgG secondary antibody conjugated to horseradish peroxidase (Amersham, Little Chalfont, UK) for 1 h at room temperature. A chemiluminescence reagent (Amersham) was added to visualize the labeling according to the manufacturer’s instructions. Densitometry was done by using a calibrated imaging densitometer (model GS-710; Bio-Rad) and analyzed with Quantity One software (Bio-Rad).

Intravital microscopy. Intravital microscopy was performed on postcapillary mesenteric venules in rats deprived of food for 18–20 h, as described previously (29). The rats were anesthetized with pentobarbital sodium (65 mg/kg ip). After a 15-min equilibration period, the rats, treated as described previously with iodoacetamide-supplemented water (gastritis group) or with the control solution (normal group), were randomly assigned to four groups of at least five rats each: aspirin (10 mg/kg) + vehicle (1% carboxymethylcellulose), vehicle + rofecoxib (6 mg/kg), or vehicle + vehicle. All drugs were administered intragastrically. Images of the mesenteric microcirculation were recorded every 15 min for 60 min for blind quantification of leukocyte adherence. A leukocyte was
considered adherent if it remained stationary for at least 30 s. Additional experiments were performed in which mesenteric venules of rats with gastritis were superfused with the lipoxin receptor antagonist BOC (10⁻⁹ M) for 10 min before the intragastric administration of aspirin or with LXA₄ (3⁻¹⁰ M). Effects on leukocyte adherence were then monitored for 60 min.

**Statistical analysis.** All data are expressed as means ± SE. Groups of data were compared by using Student’s t-test for unpaired data or an analysis of variance followed by a Student-Newman-Keuls test. A P value of <5% was considered significant.

**Materials.** Iodoacetamine and aspirin were obtained from Sigma (St. Louis, MO). Rofecoxib was obtained from NicOx (Sophia Antipolis, France). The ELISA kit for PGE₂ was obtained from Cayman (Ann Arbor, MI), whereas that for 15(R)-epi-LXA₄ was obtained from Neogen (Lexington, KY). Kits for measurement of MPO activity were obtained from CytoStore (Calgary, AB, Canada). All other materials were obtained from Fisher Scientific (Edmonton, AB, Canada).

**RESULTS**

As described previously (1, 24), rats treated with iodoacetamide exhibited a marked increase in granulocyte infiltration of the mucosa. Consistent with this observation, gastric MPO activity was approximately threefold greater in the stomach of rats treated with iodoacetamide than in controls (Fig. 1).

Oral administration of aspirin to normal rats caused hemorrhagic damage in the stomach that increased in severity in a dose-dependent manner (Fig. 1). As previously described (30), this damage was found primarily on the crests of rugal folds, and in terms of depth, it penetrated to, but not through, the muscularis mucosae. In the rats with gastritis, the extent of aspirin-induced damage was significantly less than that observed in the normal stomach (Fig. 1). Although aspirin administration significantly increased gastric MPO in normal rats, there was no significant change in MPO in rats with gastritis after aspirin administration (Fig. 1).

Previous immunohistochemical studies suggested that iodoacetamide-induced gastritis is accompanied by an increase in the expression of COX-2 in the gastric mucosa (1). However, Western blotting revealed that COX-2 expression in the stomach did not differ significantly between the normal and gastritis groups (Fig. 2). Moreover, whereas the administration of aspirin to normal rats resulted in a marked increase in gastric COX-2 expression, there was no change in COX-2 expression in the stomach of rats with gastritis in response to aspirin administration.

The experiments described above suggest that rats with prior gastritis showed increased resistance to the gastric damaging effects of aspirin. To determine whether a substance produced via COX-2 accounted for this increase in mucosal resistance to injury, we tested the effects of treatment with rofecoxib, a selective COX-2 inhibitor. The decrease in aspirin-induced gas-

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tric damage in rats with gastritis was abolished by pretreatment with rofecoxib (Fig. 3). The administration of LXA4 (2.5 μg/kg ip) to rats with gastritis that had been pretreated with aspirin and rofecoxib significantly reduced the severity of gastric damage (from 29 ± 6 to 9 ± 4 in those also receiving LXA4; \( P < 0.05; n = 5 \) per group). The administration of rofecoxib alone (i.e., no aspirin) did not cause significant gastric damage in normal rats (mean damage score of 0.3 ± 0.2; \( n = 6 \)) or in rats with gastritis (mean damage score of 0.2 ± 0.2; \( n = 6 \)).

An augmentation of aspirin-induced gastric damage by rofecoxib could be attributable to further suppression of gastric PG synthesis over that produced by aspirin itself. To test this hypothesis, gastric tissue was snap frozen and the levels of PGE2 in the tissue were determined. As shown in Fig. 4, basal PGE2 content in the stomach of normal rats vs. those with gastritis did not differ significantly. In previous studies (1), we measured the capacity of the gastric tissue to form PGE2 (rather than tissue content) and found no significant difference between rats with gastritis and healthy controls. The administration of aspirin resulted in a significant reduction in gastric PGE2 levels in both groups of rats, with the magnitude of the reduction being comparable (Fig. 4). When rofecoxib was administered along with aspirin, a further reduction of gastric PGE2 levels was observed in both groups; however, in the rats with gastritis, gastric PGE2 levels were almost completely abolished. The administration of rofecoxib alone had no effect on gastric PGE2 levels in either group.

Another mechanism through which rofecoxib might exacerbate aspirin-induced gastric damage is by suppressing the synthesis of 15(R)-epi-LXA4. Gastric 15(R)-epi-LXA4 synthesis was very low in the absence of drug treatment. After aspirin administration, 15(R)-epi-LXA4 formation was significantly greater in rats with gastritis than in healthy controls (Fig. 5). This confirms that 15(R)-epi-LXA4 formation was truly aspirin triggered. Cotreatment with rofecoxib reduced 15(R)-epi-LXA4 formation in both groups to the levels seen in rats that did not receive any drug treatment. Thus these results demonstrate that aspirin-triggered lipoxin (ATL) formation occurs via COX-2 and is enhanced in a setting in which there is increased COX-2 expression in the stomach.

To determine whether the elevated ATL formation in the stomach of rats with gastritis contributed to the observed decrease in the severity of aspirin-induced damage, we examined the effects of the lipoxin receptor antagonist BOC in this model. The administration of BOC to normal rats did not in itself cause gastric damage. However, when BOC was given with aspirin, it significantly increased the severity of damage (Fig. 6). In rats with gastritis, in which there was significantly less aspirin-induced damage than in healthy controls, coadministration of BOC with aspirin resulted in a significant increase in the severity of gastric damage.
damage. The damage scores in the rats with gastritis did not differ significantly from those in control rats given aspirin plus BOC.

Because adherence of leukocytes to the vascular endothelium appears to play an important role in the pathogenesis of aspirin-induced gastric damage (27), we compared these effects of aspirin in normal rats vs. rats with gastritis. Although there is a low level of basal leukocyte adherence in healthy rats, we observed a progressive increase in leukocyte adherence in the rats with gastritis during the 60-min period after oral administration of aspirin (Fig. 7). Indeed, the level of leukocyte adherence in rats with gastritis that did not receive any drug treatment was comparable, by the end of the experiment, to that seen in normal rats treated with aspirin (Fig. 7). The administration of aspirin to the rats with gastritis produced a completely different response than was observed in the normal rats. Rather than increasing leukocyte adherence, aspirin administration significantly reduced this response in the rats with gastritis (Fig. 7). Moreover, cotreatment with rofecoxib reversed this effect; that is, the reduction of leukocyte adherence caused by aspirin administration to rats with gastritis was abolished if rofecoxib was also administered. The elevated leukocyte adherence in rats with gastritis was significantly attenuated by exposure of the venules to LXA₄ (3 μM). There was an average of 13.3 ± 1.8 adherent leukocytes (per 100 μM vessel length) 15 min after exposure of the vessels to vehicle. At the same time after exposure of the vessels to LXA₄, there were only 8.3 ± 0.3 adherent leukocytes (P < 0.05; n = 4 in each group).

In normal rats, rofecoxib alone caused an increase in leukocyte adherence comparable to that seen with aspirin, and the combination of the two drugs produced leukocyte adherence of a comparable magnitude to that seen with either drug alone.

Results in the rats with gastritis suggest that a product of COX-2 reduced aspirin-induced leukocyte adherence. Given the inhibitory effects of LXA₄ on leukocyte adherence, we tested the possibility that this mediator, derived from COX-2, accounted for the reduction of leukocyte adherence in rats with gastritis treated with aspirin. Treatment with the lipoxin receptor antagonist BOC alone had no effect on leukocyte adherence (Fig. 8). However, the administration of BOC before aspirin administration resulted in a complete reversal of the decrease in leukocyte adherence caused by aspirin alone.

DISCUSSION

Results of the present study indicate that inflamed gastric tissue is more resistant to aspirin-induced damage than noninflamed gastric tissue. The administration of aspirin to rats with iodoacetamide-induced gastritis resulted in the development of hemorrhagic lesions ~70% less extensive than when the same dose of aspirin was given to healthy rats. The ability of aspirin to cause gastric damage is primarily related to inhibition of mucosal PG synthesis (26), which has been shown to greatly reduce the ability of the tissue to withstand injury induced by a wide array of potentially toxic substances (31). However, gastric PG levels were similar in rats with gastritis and healthy rats, and aspirin suppressed gastric PG levels to the same extent in both groups. Thus the increased resistance of the inflamed stomach to aspirin-induced gastric damage...
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Fig. 8. Leukocyte adherence 60 min after ASA (50 mg/kg) in normal rats and rats with gastritis, and the effects of preexposure to the lipoxin A₄ receptor antagonist BOC (10 μM). Each bar represents the mean ± SE for at least 4 rats, and the data shown are for the final time period in the experiment. Leukocyte adherence in the absence of treatment with aspirin was significantly greater in rats with gastritis than in normal rats (\(P < 0.05\)). Aspirin significantly reduced leukocyte adherence in rats with gastritis (\(P < 0.05\) vs. the other gastritis groups). This effect was abolished if the rats were also treated with BOC.

Increased resistance of the inflamed gastric mucosa to aspirin-induced damage could be attributable to the increased ATL formation. We have previously shown that LXA₄ is a very potent protective agent in the stomach (6). On a molar basis, LXA₄ exhibited similar potency to PGs in terms of reducing the severity of aspirin-induced damage. The observation that the lipoxin receptor antagonist BOC markedly increased the severity of aspirin-induced gastric damage is consistent with the hypothesis that ATL production was involved in the increased resistance to damage in rats with gastritis. Like BOC, rofecoxib given alone did not cause gastric damage, but when given with aspirin, the extent of damage was markedly increased relative to that induced by aspirin alone. The combination of aspirin with a selective COX-2 inhibitor (celecoxib) has recently been reported to cause significantly more damage in healthy human volunteers than was seen with either drug alone (7). Moreover, ATL formation was observed after aspirin administration and its production was inhibited when celecoxib was coadministered with aspirin (7). It is noteworthy that in a large clinical trial of celecoxib in patients with arthritis, the combination of low-dose aspirin with celecoxib was found to produce four times as many ulcer complications as the use of celecoxib alone (23).

We (27) have previously proposed that adherence of neutrophils to the vascular endothelium after the administration of aspirin or other NSAIDs is a critical event in the pathogenesis of gastric damage induced by these agents. Consistent with this hypothesis, we observed that, in contrast to the increase in leukocyte adherence observed after aspirin administration to normal rats, there was a marked reduction of leukocyte adherence in rats with gastritis after aspirin administration. Under basal conditions, leukocyte adherence within mesenteric postcapillary venules was found to be elevated compared with that seen in normal rats. This is consistent with what we observed when similar studies were carried out in rats with adjuvant-induced arthritis, which we attributed to elevated expression of endothelial adhesion molecules as a consequence of high circulating levels of proinflammatory cytokines (17). The reasons for the elevated leukocyte adherence in the rats with gastritis are not yet clear. However, the reduced leukocyte adherence after aspirin administration to the rats with gastritis is consistent with the observed increase in ATL formation. Lipoxins have

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very well characterized inhibitory effects on several neutrophil functions (5, 13), including leukocyte adherence. We (6) previously showed that LXA₄ could markedly suppress aspirin-induced leukocyte adherence in normal rats, whereas the lipoxin receptor antagonist BOC markedly increased aspirin-induced leukocyte adherence. In the present study, LXA₄ significantly reduced leukocyte adherence in the rats with gastritis, where basal levels of leukocyte adherence were significantly elevated above that seen in healthy controls.

It should be noted that the receptor for LXA₄ and its carbon-15 epimer (ATL) belongs to a family of receptors activated by chemotactic peptides, serum amyloid protein A, and the glucocorticoid-activated, neutrophil-derived, anti-inflammatory protein annexin-1 (19). The lipoxin receptor antagonist that we used (BOC) can also antagonize the receptor for formylated chemotactic peptides (19). Whereas our data point to an important role for LXA₄ in gastric mucosal defense, it is entirely possible that other agonists of the lipoxin receptor may also modulate the resistance of the gastric mucosa to damage. Moreover, other anti-inflammatory substances, including annexin-1, may modulate gastric mucosal defense.

In the present study, we focused on gastric mucosal injury induced by aspirin. ATL formation appears to be a major contributor to the increased resistance of the inflamed gastric mucosa to damage induced by aspirin. However, this mechanism would not explain any increased gastric resistance to nonaspirin NSAIDs. The formation of ATL is due to the unique interaction of aspirin with COX-2 (5, 15, 22). Other NSAIDs competitively interfere with the ability of COX-2 (and COX-1) to convert arachidonic acid to cyclic endoperoxides (PGG₂ and PGH₂) but do not lead to the formation of 15(R)-HETE or 15(R)-epi-LXA₄.

In summary, the results of this study provide evidence that aspirin administration results in ATL formation, and this occurs to a greater extent in the inflamed than in normal mucosa. The increased formation of ATL, which occurs via COX-2, appears to explain, in large part, the increased resistance of the inflamed mucosa to aspirin-induced damage. Other factors may also contribute to the increased resistance of the inflamed gastric mucosa to tissue injury.

This work was supported by a grant from the Canadian Institutes of Health Research (CIHR). J. L. Wallace is an Alberta Heritage Foundation for Medical Research Scientist. O. Menezés de Lima, Jr. is supported by a CIHR/Solvay Pharma/Canadian Association of Gastroenterology Fellowship. S. R. Zamuner is supported by a CIHR/Janssen Pharmaceutica/Canadian Association of Gastroenterology Fellowship.

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