

World Journal of *Gastrointestinal Pharmacology and Therapeutics*

World J Gastrointest Pharmacol Ther 2015 May 6; 6(2): 10-27





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EDITORIAL

- 10 Inflammatory bowel disease: Traditional knowledge holds the seeds for the future
Actis GC, Pellicano R, Rosina F

MINIREVIEWS

- 17 Clinical relevance of clopidogrel-proton pump inhibitors interaction
Bouziaina SD, Tziomalos K

SYSTEMATIC REVIEWS

- 22 Clinical relevance of intestinal peptide uptake
Freeman HJ

Contents

World Journal of Gastrointestinal Pharmacology and Therapeutics

Volume 6 Number 2 May 6, 2015

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Pharmacology and Therapeutics*, Rachel Jane Gibson, PhD, Senior Lecturer, Head Gut Microbiome Group, School of Medical Sciences, University of Adelaide, North Terrace, Adelaide, SA 5005, Australia

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NAME OF JOURNAL

World Journal of Gastrointestinal Pharmacology and Therapeutics

ISSN

ISSN 2150-5349 (online)

LAUNCH DATE

May 6, 2010

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Quarterly

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Room 903, Building D, Ocean International Center,
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Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
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PUBLICATION DATE

May 6, 2015

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Inflammatory bowel disease: Traditional knowledge holds the seeds for the future

Giovanni C Actis, Rinaldo Pellicano, Floriano Rosina

Giovanni C Actis, Floriano Rosina, Hepatogastroenterology Division, Ospedale Gradenigo, 10153 Torino, Italy

Rinaldo Pellicano, Division of Gastroenterology, Ospedale Molinette, 10126 Torino, Italy

Author contributions: All authors contributed to this manuscript.
Conflict-of-interest: We hereby deny any conflict of interest with regard to the present paper.

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Correspondence to: Giovanni C Actis, MD, Hepatogastroenterology Division, Ospedale Gradenigo, Corso Regina Margherita, 8, 10153 Torino, Italy. segreteria.gel@h-gradenigo.it

Telephone: +39-011-8151211

Fax: +39-011-8151388

Received: January 16, 2015

Peer-review started: January 18, 2015

First decision: February 7, 2015

Revised: March 2, 2015

Accepted: April 1, 2015

Article in press: April 7, 2015

Published online: May 6, 2015

Abstract

Despite the level of sophistication they have reached nowadays, the available tools for treatment of inflammatory bowel disease (IBD) can at best chronicize the disease but not cure it. Chances to make leap forward from this hold-back may include designs to reach personalized treatment strategies taking advantage of modern genome associated studies, and shift resources towards unfolding inciting pathogenetic steps rather than continuing to develop drugs that address down-stream phenomena. We have arbitrarily chosen to scrutinize a few projects that may make their way in 2015 and mark

the history of IBD research. The list includes: the role of appendix as a regulating factor in pathogenesis of ulcerative colitis/proctitis; the reappraisal of (auto)immune phenomena in the era of microbiome; projects to treat IBD by stem cell infusion; recognition of the crucial pathogenetic role of gut microbiome, and attempts to modify it to treat enteric diseases, from clostridium difficile infection to IBD.

Key words: Inflammatory bowel disease; Microbiome; Stem cells; Future treatments; Curative appendectomy

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Core tip: The inflammatory diseases of the gut (inflammatory bowel disease) continue to both constitute a medical challenge, and a formidable intellectual stimulus. The latter statement is based on the accumulating evidence that the IBDS are indeed syndromes whereby a few poorly penetrating polymorphic genes can affect at once the inflammatory balance in the barrier systems of the gut, the skin, and the airways. The former statement reflects the very fact that, though described in the 19th century, IBD continues to defeat our struggle to cure it, invading yet the hitherto unaffected landscapes of the Eastern World, almost as it was a response to our efforts. We deem that the address of the initiating factors, rather than the downstream phenomena, may be a strategy to wriggle out of the hold-up. The description of interventions such as appendectomy or microbiome replacement, among other options, witnesses our own way to interpret this need in the present editorial.

Actis GC, Pellicano R, Rosina F. Inflammatory bowel disease: Traditional knowledge holds the seeds for the future. *World J Gastrointest Pharmacol Ther* 2015; 6(2): 10-16 Available from: URL: <http://www.wjgnet.com/2150-5349/full/v6/i2/10.htm> DOI: <http://dx.doi.org/10.4292/wjgpt.v6.i2.10>

INTRODUCTION

Inflammatory bowel disease (IBD) is now understood as a dysfunction of a barrier organ, whereby the antigenic gut luminal contents (from diet and autochthonous flora) come in an undue contact with the reactive sub-mucosal tissue. The players in this event include: polymorphisms of the genes governing cytokine networks; passive defense devices (defensins and epithelial sealings); inborn errors of functional structures of innate immunity (the NOD system *e.g.*); inborn knock-out of genes coding for down-regulatory circuits [e.g. interleukin (IL)10^{-/-}]; the polyfunctional microbiome. From a general prospective, this universe is ruled by a plethora of low-penetrance genes, needing to come about in a critical mass to induce disease phenotypically. Needless to say, various treatment attempts at impacting this scenario have often proven deceptive, calling for a shifted frame of mind bound to overcome the simple search for the next biological formulation following failure of the former. We have arbitrarily chosen to describe a few examples whereby the authors have essayed to see the matters from a different angle.

In one of these attempts, the authors were inspired by the observation that the gut inflammation that develops in IL-10 knock-out mice seems to have an appendiceal origin; based on this, they pursued the study of the consequences of appendectomy, finding that appendectomy tends to exert a prevalent down-regulatory modulation. Back in 2009, a large clinical study enrolled humans to receive appendectomy for their ulcerative proctitis, achieving at least clinical remission in a patient subset. It is hoped that basic and clinical research in this field will march at the same pace to identify a revolutionary strategy to tackle the problem of gut inflammation and proctitis specifically.

Cutting edge research has recently confirmed that tissues and body fluids can no longer be considered "conventionally" sterile, insofar as containing a myriad of genomic (bacterial and virologic) messages. Since these determinants are reasonably able to elicit strong immune reactions against themselves inciting inflammation, the authors argue that a few chronically inflamed patients (including Crohn's) should be immune stimulated to wipe out the indwellers, rather than immune suppress them.

Some years ago, the early claim of "cure" of a few cases of Crohn's disease after bone marrow transplant had paved the way towards the strategy of reprogramming progenitor cell lineage to terminate IBD. Programs of stem cell transplant are now very active and the clinical harvest seems promising so far.

The rapidly growing understanding of the microbiome could not avoid to bear significant impact on our clinical address on IBD. There is now consistent evidence that microbiome composition is profoundly altered in IBD, lending rationale to the use of fecal transplant as a treatment option. This is a rapidly growing matter that will not fail to produce results in the near future.

Conclusively, there are at least two added values attached to this novel mindframe. Firstly, it may take

us even closer to the now legendary promised land of personalized medicine; Secondly, we are finally driving the coach towards understanding the roots of the disease, rather than blindly aiming at its epiphenomena.

IBD: TRADITIONAL KNOWLEDGE HOLDS THE SEEDS FOR THE FUTURE

Certain anatomic/functional structures have evolved to discern between the inner "sterile" milieu and the outer "polluted" environment. The pivotal components in such "barrier organs"^[1] (the gut, skin, the airways, urinary tract) consist of a mucosal immune system (biased to tolerance) and an underneath lymphoid tissue (primed to react).

Owing to their functions, inflammation in barrier organs is constitutive; it may grow to be induced if the balance between pro- and anti-inflammatory forces is breached. Specifically, the players in this balance at the colonic level are the diet constituents, the local immune system, and the microbiome^[2,3].

In 2009, we compiled a scrutiny of the elements that factor in colon pathophysiology (unpublished data). In the lines to follow, we reappraise this rather outdated paper, with the bias to uncover current and future links to research in colonic physiology and disease.

THE MAIN COMPONENTS IN THE SYSTEM

Barrier alterations

Insofar as preventing the rise of inflammation by avoiding contact between luminal antigens and the overreactive lymphoid tissue underneath the mucosa, epithelial integrity, inter-cell sealing, and production of defensive substances are essential. Chimeric mice for a defective cadherin^[4] (a crucial factor in the sealing properties of tight junctions) exhibited unchecked intestinal inflammation; patients with active Crohn's disease showed a 50% reduction of secretion of defensins^[5], that are Paneth cell-derived cationic peptides endowed with antibacterial activity. Noteworthy, updated research is now showing that correct production and release of beta-defensins is under the control of the vitamin D receptor (see below)^[6].

Alteration of gut flora

This topic has largely been treated by others^[7] and ourselves^[8]. Such trillion-individual metagenomic world in our digestive tract has been shown to affect a range of conditions including diabetes^[9,10], obesity^[11], inflammatory disease^[12], and behavioral changes^[13]. Just two examples showing that microbiome components might influence inflammatory circuits are the following. Microbiome-derived free-fatty-acids might regulate size and function of regulatory T-cells (T-regs), activating SMAD 3 and 4^[14,15], and ameliorating experimental

colitis; Prevotella Copri can educate T-lymphocytes to secrete IL17, a key cytokine in rheumatoid arthritis^[16]. Evidence that microbiome composition can be modified by diet, has prompted intensive study programs aiming at determining the therapeutic role of fecal flora transplantation in treatment of both IBD and Clostridium difficile infection (CDI)^[17].

Alteration of innate immunity

Evolution has endowed us with a number of sensors to check the outer environment for invaders^[18]. The toll-like receptors (TLR)^[19] are membrane confined elements, the nucleotide oligomerization domains are cytoplasmic. The NODs^[20] comprise a leucine-rich repeat, a central NOD structure facilitating oligomerization, and a terminal caspase-recruitment domain. Essentially, the final common action of both TLRs and NODs leads to activation of cytoplasmic NF κ B^[21], which, upon nuclear translocation, will induce the genes of pro-inflammatory cytokines, as part of a defensive program. As a key-stone discovery by two independent teams in 2001, a loss-of-function NOD mutation was described in a significant proportion of Western Crohn's patients, but not in those of an oriental descent^[22].

Alteration of adaptive immunity

These may encompass both B-cells and T-cells misfunctions. The B-cell products ASCA and ANCA antibodies are well-studied markers of Crohn's^[23] and UC^[24] respectively. On the other hand, anomalous T-cell clones may arise in IBD as a consequence of a changed dendritic cell antigen presentation, or presentation by non-professional cells^[25]. Among such T-cell phenotype variants, the Th17 cells have received most of the attention recently.

The Th-17 lymphocytes^[26]. We wish to devote a deal of attention to these cells as they are destined to be further discussed below. Derived from TCD4⁺ lymphocytes, and CD4⁺CD25⁺Foxp3 lymphocytes, can mainly release IL17, as driven by IL-23 dependent STAT-3 activation^[27].

Physiologic roles

Rise of Th17 cells was initially demonstrated in fungi and bacteria infected milieus, suggesting a protective mission for these cells; klebsiella pneumonitis, Candida infection, and mycoplasma invasions were all demonstrated to constitute an arena for Th17 cells^[28].

Pathophysiologic roles

In the unstable milieu of the sub-clinical intestinal inflammation, Th17 cells can easily be traced to the lamina propria; in full-blown pathologic conditions, they can easily be shown to migrate to inflamed areas^[29]. The chemokine-ligand interaction CCR6-CCL20 has been found to be crucial for the homing of Th17 cells to the distal colon^[29] (see below). Arthritis has long been recognized as a co-morbidity of IBD and Th17

cells have recently been reckoned to be effectors in this pathologic events^[30]. Interaction of the chemokine CCR6 with its homologous synovial chemokine CCL20 have been shown to allow Th17 homing to arthritic sites, thus initiating bone resorption.

FUTURE RESEARCH SEEDS

The chain of evolution and function of Th17 cells as summarized above allows us to open the list of future endeavors with this topic. This list will therefore comprise: (1) The appendicitis/appendectomy model; (2) Metagenome and autoimmunity; (3) Bone marrow transplants; and (4) Microbiome modulation.

The T-cell receptor- α mutant mice (TCR- $\alpha^{-/-}$), obtained by gene targeting of the TCR-alpha gene in embryonic stem cells, is a popular mouse model that spontaneously develop ulcerative colitis-like inflammation of the colon^[31]. In 1996, the team of Bhan published the results of experiments aiming to define the reciprocal roles of appendix associated lymphoid follicles (ALF) vs that of Peyer's patches (PP) in such diseased mice. They found that: (1) the proliferative index in ALF was twice that of PP; and (2) The frequency of IgG secreting B cells in ALF of mutant mice largely exceeded that of non-mutant animals. Early appendectomy in mutant strains had two orders of consequences: (1) the number of mesenteric lymph nodes got significantly reduced; and (2) appendix ablation at 1 mo of age suppressed the development of IBD^[31]. The tenet that appendicectomy humans might be protected from ulcerative colitis in fact relies on these basic data of the 1990's. Specifically, a clinical paper issued in 2009^[32], followed in 2011 by a short communication in a letter format^[33], have shown that appendectomy might ameliorate symptoms in a limited group of patients with ulcerative proctitis. The team of Cheluvappa *et al.*^[34] in Sydney has recently reappraised the basic information on Th17 cells we collected above, to design an animal model. BALB/c mice were subjected to experimental appendicitis and appendectomy (AA), then distal colon samples were harvested. Results were validated using reverse-transcription-polymerase chain reaction. The authors mainly found that prior AA ameliorated experimental colitis. CCL20 expression was suppressed in the most distal colon 3 and 28 d after the AA was done at the proximal colon^[34]. Another piece of study from the same group^[35] has suggested that suppression of a few endothelin genes may be a mechanism in these findings. The authors conclude by wishing that this expanded knowledge on the Th17 system and CCR6/CCL20 interaction can be transferred to clinical grounds before long.

The team of Amy Proall has conducted extensive basic research on the human microbiome, pushing her findings to somewhat extreme consequences^[36]. The author starts out by stressing that modern techniques are now demonstrating that not only the usual sites such as the colon are dwelled by abundant

microbiome species, but virtually all tissues or fluids within our bodies harbor trillions of yet unknown bacterial and viral phyla. The authors list a few of the implications of these revolutionary findings: (1) The inner milieu can no longer be considered sterile; (2) The concept itself of autoimmunity might be reduced to a concept of a reaction against antigenic determinants of this overwhelming microbiome, or against modified self-antigens; (3) Given these premises, the correct approach to treatment of inflammatory disease would be immunostimulation to get rid of the indwellers, rather than immune suppression. The latter will obviously lend symptom relief but will promote persistence of the inciting causes, whether bacterial, viral or else^[37]; and (4) Worth of note, this overriding antigenemia might also be fueled by the action of active transport systems. A recent paper^[38] dealing with peptide transport from the intestine, has described a carrier, pepT1, which, belonging to the superfamily of proton-coupled oligopeptide transporters, can transport oligopeptides through the cells to the bloodstream thanks to coupling with hydrogen ion. Interestingly, the authors pin-point that the activity of pep T1, can turn out to be heightened during intestinal disease such as IBD, wherein in this case bacterial flora (metagenomic) by-products may become the transported antigenic material. As a consequence of this shift, mounting of inflammatory and auto-inflammatory responses can easily be predicted. Thus, the findings of such independent work seems to lend fuel to Proall's speculation.

The authors conduct an interesting focus on the vit D receptor (VDR). Of the two recognized classes of VDR, the first, segregating to the cell nucleus, belongs to the family of the class 2 steroidal hormones receptors, and is closely linked with the retinoic acid and thyroid hormone receptors. As a protein of 427 aminoacids, the human VDR couples DNA, links the ligand, and self-activates through its three respective domains. Functionally, VDR heterodimerizes with retinoid X receptor (RXR), activating gene transcription (vit Response Elements) and protein synthesis. The other VDR is a membrane element, and as a non-genomic action, catalyzes release of cellular messengers. Noteworthy, the VDR complex conditions release of a huge number of protective molecules. When thwarted by a load of bacterial ligands it may cease producing crucial protective compounds from cathelicidine to defensins^[39], thus fully impacting on IBD pathophysiology; in addition also Vit D handling might be damaged, and a receptor leaking 1,25 vit D has been described in inflammatory conditions including Crohn's. Vit D itself, on the other hand, bears the structure of a secosteroid. Because exerting in fact a down-regulatory effect on various immunologic steps, it should be considered an immune suppressor. Based on this, the authors express doubts as to the indication for vit D in a few inflammatory conditions, including IBD.

Coherently with these premises, the authors declare to have studied the possibility of alternative

non-suppressive regimes for immune-inflammatory conditions, including satanic derivatives.

C STEM CELL THERAPY FOR IBD

The issue has recently been addressed in an exhaustive review^[40]. Stem cells characteristically undergo a process of asymmetrical cell division, giving birth to a cell with the same properties as the original cell, and another cell of multilineage differentiation potency, depending on environmental conditions. The comprehensive term "stem cells"^[41] includes: (1) embryonic stem cells, *e.g.*, pluripotent cells obtained from embryos; (2) multipotent adult stem cells including hematopoietic stem cells (HSC) and mesenchymal stem cells (MSC) found in all body tissues; and (3) induced pluripotent stem cells, defined as artificial pluripotent stem cells generated from somatic cells by the introduction of reprogramming factors.

HSC and MSC are currently used and evaluated to treat therapy - resistant Crohn's disease. The only protocol that is officially accepted requires infusion of autologous HSC^[42] following a program of cell mobilization and myeloablation^[43]. Briefly, the patient first receives cyclophosphamide and granulocyte colony stimulating factor to stimulate production and release of stem cells from blood marrow; these cells are then collected from peripheral blood and then cryopreserved until re-infusion. The therapeutic objective of autologous HSCT^[44] is the resetting of the patient's immune system thanks to the myeloablation program, which effects T-lymphocyte and memory T-cells elimination.

The first case reporting the efficacy of HSCT in the control of CD was published in 1993^[45]. It is difficult to firmly evaluate the effectiveness of this technique in CD, given the relatively low number of published cases. In the series published by Burt *et al*^[46] in 2010, the most updated series, all of the 24 patients entered remission after transplantation.

Most clinical studies have shown that MSCs can be obtained from bone marrow, adipose tissue, and umbilical cord. Being not significantly immunogenic, MSCs can be administered without a conditioning phase^[47-49].

Systemic administration of MSCs for treatment of IBD. The results of phase 1 studies have recently been published. In 2012, Liang *et al*^[50] reported the results obtained in 7 patients with IBD (4 CD and 3 UC). Remission was achieved in 5 subjects and maintained for over 24 mo in 2 of them; endoscopic improvement was demonstrated in 3 subjects. Side effects were mild.

Local MSCs therapy in fistulizing CD. The initial study dates back to 2008^[51] and reported remission in 7 of 9 CD patients with complex peri-anal fistula. At present, a phase 3 study is under way, involving the use of expanded MSCs from adipose tissue to treat complicated fistula.

D MICROBIOME MODULATION

The bacterial cells pertaining to the human microbiome

are estimated to attain the notable number of 10^{14} , dwarfing the few thousands of indwelling somatic cells. The protean characteristics and functions of the microbiome have been addressed in a number of reviews from others and ourselves^[7,8]. Results from various studies are now accumulating to point to the astonishing variety of targets that are touched by the microbiome, including effects on immunity, determination of diabetic and overweight statuses, up to influence behavior and mental health. No wonder that a deal of efforts has concentrated onto the endeavor to modulate microbiome composition and function. The array of means and strategies that have been assayed include pre-biotics, pro-biotics, antibiotics, and fecal transplant (FT). The latter technique has received a special deal of attention, and to challenge the feasibility of its translation to clinical practice, two questions may be particularly relevant: (1) Is it effective? (2) How long does its action last.

As to the former question, FT has been convincingly shown to treat CDI^[52]. A recent meta-analysis^[53] has examined the role of FT as a therapy for IBD. Elaboration of the data from 18 studies including 122 patients led this study to conclude that FT may be safe and effective, but controlled trials, donor selection and standardization of microbiome analysis are strongly needed.

As to the length of effect, studies on CDI have reported encouraging results. The diseased microbiome of IBD, by contrast, has shown a deal of resiliency against the actions of FT. Most of the authors have concluded that prolonged and repeated treatments are probably needed to achieve some consistent results in these premises^[54]. Last but not least, cutting-edge data from current research work^[55] are showing that a number of host genes, some with known involvement with microbial handling, exhibited consistent effects on the taxonomic structure of the microbiome across multiple cohorts. Specifically, NOD mapping work showed links between NOD polymorphisms and gut colonization with Enterobacteriaceae, allowing for the first time to envisage the chance of genetic transmission of IBD strains along with innate immunity sensors such as the NODs.

CONCLUDING REMARKS

The succinct lines above, stress the need to progressively move towards a mindset that sees IBD as a contextualized polyfactorial syndrome of outer environment misrecognition, whereby innumerable comorbidities recognize shared roots and immunological circuits, the microbiome being the crucial but not the only player. Against this background, traditional immune suppression, including the novel biologics, has revealed its inadequacy to eradicate the disease. Having set this, we arbitrarily chose to gain more insight into the projects put forward by a few world leading teams in basic and clinical IBD research. Based on previously encouraging clinical hints, Cheluvappa's

team has studied the immune-regulatory consequences of appendectomy in IBD patients and is actively pursuing a pathway to render the idea amenable to clinical application. Programs of stem cell infusion are probably bound to be the most rewarding ones in the future, yet intrinsic risks continue to require balance against the clinical gains. Facing this sometime chaotic wealth of evidence, Proall and her team see immune-inflamed patients including the IBD subjects as immune-depressed individuals which deserve immune reconstitution far more than immune suppression. Already successfully applied to the treatment of hepatitis B^[56], this proposition is less fanciful than it appears. Despite this, the gap between conceptual refinements of these approaches, and their clinical transition is still significantly wide. FT has already shown exciting promise in the treatment of CDI. Its transition to clinical treatment of IBD will depend on the availability of pharmacological strategies to overcome the resilience of microbiome in the inflammatory intestinal states.

In terms of world-wide epidemiology, one can identify at least two opposite driving forces. Rapid "occidentalization" is providing IBD with unprecedentedly wide areas of expansion in huge landscapes like China^[57]. On the other hand, one knows that life and evolution may sometimes reveal their complexity presenting as "erase-and-rewind" processes. On this line, poor or regressing life standards in certain world areas tend to make violent infection agents prevail over "sophisticated" immune inflammatory condition, threatening to absorb mental and financial energies in the future^[58], perhaps distracting commitment from the programs illustrated above.

ACKNOWLEDGMENTS

This is dedicated to O Della Casa-Alberighi, MD, who profoundly influenced my career with continuous friendship, advice, and support.

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P- Reviewer: Akiho H, Blonski W, Naser SA **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Lu YJ



Clinical relevance of clopidogrel-proton pump inhibitors interaction

Stella D Bouziana, Konstantinos Tziomalos

Stella D Bouziana, Konstantinos Tziomalos, First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, 54636 Thessaloniki, Greece

Author contributions: Bouziana SD drafted the paper; Tziomalos K revised the draft critically for important intellectual content.

Conflict-of-interest: We have no conflict of interest to declare.

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Correspondence to: Konstantinos Tziomalos, MD, PhD, Assistant Professor of Internal Medicine, First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, Kiriakidi 1, 54636 Thessaloniki, Greece. ktziomalos@yahoo.com

Telephone: +30-2310-994621

Fax: +30-2310-994773

Received: January 13, 2015

Peer-review started: January 15, 2015

First decision: March 6, 2015

Revised: March 24, 2015

Accepted: April 16, 2015

Article in press: April 20, 2015

Published online: May 6, 2015

when treated with clopidogrel. Accordingly, proton pump inhibitors are frequently administered in combination with clopidogrel to reduce the risk for GI bleeding. Nevertheless, pharmacodynamic studies suggest that omeprazole might attenuate the antiplatelet effect of clopidogrel. However, in observational studies, this interaction does not appear to translate into increased cardiovascular risk in patients treated with this combination. Moreover, in the only randomized, double-blind study that assessed the cardiovascular implications of combining clopidogrel and omeprazole, patients treated with clopidogrel/omeprazole combination had reduced risk for GI events and similar risk for cardiovascular events than patients treated with clopidogrel and placebo. However, the premature interruption of the study and the lack of power analysis in terms of the cardiovascular endpoint do not allow definite conclusions regarding the cardiovascular safety of clopidogrel/omeprazole combination. Other proton pump inhibitors do not appear to interact with clopidogrel. Nevertheless, given the limitations of existing observational and interventional studies, the decision to administer proton pump inhibitors to patients treated with clopidogrel should be individualized based on the patient's bleeding and cardiovascular risk.

Key words: Clopidogrel; Esomeprazole; Lansoprazole; Pantoprazole; Rabeprazole; Omeprazole; Cardiovascular risk; Proton pump inhibitors

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Abstract

Clopidogrel is a widely used antiplatelet agent for the secondary prevention of cardiovascular events in patients with stable coronary heart disease, acute coronary syndromes and ischemic stroke. Even though clopidogrel is safer than aspirin in terms of risk for gastrointestinal (GI) bleeding, the elderly, and patients with a history of prior GI bleeding, with *Helicobacter pylori* infection or those who are also treated with aspirin, anticoagulants, corticosteroids or nonsteroidal anti-inflammatory drugs are at high risk for GI complications

Core tip: Even though pharmacodynamic studies suggest that omeprazole can attenuate the antiplatelet effect of clopidogrel, this interaction does not appear to translate into increased cardiovascular risk in patients treated with this combination in observational studies. In the only randomized, double-blind, placebo-controlled study that assessed the cardiovascular implications of combining clopidogrel and omeprazole, patients treated with clopidogrel/omeprazole combination had reduced risk for

gastrointestinal events and similar risk for cardiovascular events. Other proton pump inhibitors also do not appear to interact with clopidogrel. However, given the limitations of existing studies, the decision to administer proton pump inhibitors to patients treated with clopidogrel should be individualized based on the patient's bleeding and cardiovascular risk.

Bouziana SD, Tziomalos K. Clinical relevance of clopidogrel-proton pump inhibitors interaction. *World J Gastrointest Pharmacol Ther* 2015; 6(2): 17-21 Available from: URL: <http://www.wjgnet.com/2150-5349/full/v6/i2/17.htm> DOI: <http://dx.doi.org/10.4292/wjgpt.v6.i2.17>

INTRODUCTION

Clopidogrel is a first-line antiplatelet agent for the secondary prevention of cardiovascular events in patients with stable coronary heart disease or with a history of non-cardioembolic ischemic stroke^[1,2]. In addition, clopidogrel is recommended in combination with aspirin for up to 12 mo in patients with acute coronary syndrome (ACS) treated either medically or invasively^[3,4]. Even though clopidogrel is safer than aspirin in terms of risk for gastrointestinal (GI) bleeding, the risk of GI bleeding is not negligible in patients treated with this agent^[5,6]. Moreover, the risk of GI bleeding further increases in patients who receive clopidogrel in combination with aspirin as well as in the elderly, in patients with a history of prior GI bleeding or with *Helicobacter pylori* infection, and in those who are also treated with anticoagulants, corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs)^[7,8]. In these patients, administration of proton pump inhibitors (PPIs) significantly reduces the risk of GI bleeding associated with clopidogrel treatment^[9,10]. Accordingly, PPIs are commonly prescribed in patients treated with clopidogrel to reduce the risk of GI bleeding^[11,12].

Even though the administration of PPIs in patients treated with clopidogrel reduces the risk for GI bleeding, some pharmacodynamic studies suggested that the antiplatelet effect of clopidogrel is also attenuated by PPIs^[13-15]. This interaction is due to the inhibition by PPIs of the cytochrome (CYP) P450 isoenzyme 2C19, which converts clopidogrel to its active metabolite^[16]. Notably, PPIs differ in their ability to inhibit CYP2C19, omeprazole being a more potent inhibitor than the other members of the class^[17,18]. Accordingly, some studies showed that omeprazole attenuates the antiplatelet effect of clopidogrel^[13-15] but others did not confirm these findings^[19,20]. In contrast, esomeprazole, lansoprazole, pantoprazole and rabeprazole did not affect platelet function in patients treated with clopidogrel^[13,15,19-22].

However, it is unclear whether these *ex vivo* findings have clinical importance, *i.e.*, if the co-administration of clopidogrel with omeprazole or other PPIs will result

in reduced protection against cardiovascular events. Notably, earlier studies suggested that atorvastatin attenuates the antiplatelet effects of clopidogrel *ex vivo* but this interaction did not translate into higher cardiovascular morbidity in patients receiving this combination^[23-25]. Indeed, observational studies that evaluated the effect of administering PPIs in combination with clopidogrel on cardiovascular events in patients who suffered an ACS or underwent percutaneous coronary intervention (PCI) reported conflicting results. In two early retrospective studies, patients treated with clopidogrel and either omeprazole or pantoprazole had higher risk of recurrent cardiovascular events than those who were given clopidogrel alone^[11,26] (Table 1). In contrast, several other retrospective studies reported that neither omeprazole nor pantoprazole increase cardiovascular morbidity when combined with clopidogrel^[10,12,27-30] (Table 1). A post-hoc analysis of the randomized controlled Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38 also reported similar findings^[31] (Table 1). In the same post-hoc analysis and in more recent observational studies, treatment with esomeprazole or lansoprazole was also not associated with increased cardiovascular risk when combined with clopidogrel^[29-31] (Table 1).

Given the well-known limitations of observational studies, these results should be interpreted with caution. Patients who are given PPIs are frequently older and have more comorbidities and despite the adjustment for these differences there is always potential for residual confounding^[10-12,26-31]. Indeed, some studies reported that PPI use is associated with increased risk for cardiovascular events regardless of the use of clopidogrel and in patients treated with ticagrelor, which does require activation by CYP2C19, suggesting that PPI use is a marker of increased cardiovascular risk and frailty^[12,30,32,33]. Moreover, none of the above-mentioned studies could adjust for over-the-counter use of PPIs and adherence to treatment^[10-12,26-31]. Many patients used PPIs intermittently, a parameter which was not considered in most studies^[10-12,26-31]. Finally, most studies evaluated very-high risk patients, *i.e.*, with a recent ACS or PCI, and it is unclear whether these results are applicable to lower-risk patients, *e.g.*, those with stable angina or history of ischemic stroke^[10-12,26-31]. Finally, the antiplatelet activity of clopidogrel is affected by several polymorphisms (Table 2)^[34] and none of these studies evaluated this parameter^[10-12,26-31]. However, both pharmacodynamic and clinical studies suggest that there is no association between CYP2C19 genotype and the impact of PPIs on the antiplatelet effect of clopidogrel^[35-37].

The only randomized, double-blind, placebo-controlled study that assessed the cardiovascular implications of combining clopidogrel and omeprazole is the Clopidogrel and the Optimization of Gastrointestinal Events Trial^[9]. In this trial, 3761 patients with an indication for dual antiplatelet treatment with aspirin and clopidogrel were randomly assigned to a fixed-dose combination of

Table 1 Major observational studies that evaluated the effects of coadministration of clopidogrel and proton pump inhibitors on cardiovascular events

Ref.	Population	n	Hazard ratio in patients who received clopidogrel and proton pump inhibitors vs patients treated with clopidogrel alone
[10]	Patients hospitalized for ACS or coronary revascularization	20596	0.99 (95%CI: 0.82-1.19, <i>P</i> = NS)
[11]	Patients hospitalized for ACS	8205	1.25 (95%CI: 1.11-1.41, <i>P</i> = NR)
[12]	Patients hospitalized for ACS	56406	0.98 (95%CI: 0.88-1.10, <i>P</i> = NS)
[26]	Patients hospitalized for ACS or coronary stent placement	2066	1.64 (95%CI: 1.16-2.32, <i>P</i> = 0.005)
[27]	Patients hospitalized for ACS or coronary stent placement	18565	1.22 (95%CI: 0.99-1.51 <i>P</i> = NS)
[28]	Patients hospitalized for ACS	13636	1.27 (95%CI: 1.03-1.57, <i>P</i> = NR)
[29]	Patients hospitalized for ACS	24471	0.75 (95%CI: 0.55-1.01, <i>P</i> = NS)
[30]	Patients who underwent coronary stent placement	13001	1.20 (95%CI: 0.91-1.58, <i>P</i> = NS)
[31]	Patients with ACS undergoing coronary stent placement	6795	0.94 (95%CI: 0.80-1.11, <i>P</i> = NS)

ACS: Acute coronary syndrome; NS: Non-significant; NR: Not reported.

Table 2 Polymorphisms that potentially affect the antiplatelet effect of clopidogrel

Polymorphism	Mechanism of reduced antiplatelet effect of clopidogrel
CYP2C19*2, CYP2C19*3, CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*7, CYP2C19*8	Reduced metabolism of clopidogrel to its active metabolite
C3435T polymorphism of the <i>ABCB1</i> gene	Overexpression of the drug efflux pump P-glycoprotein leading to reduced intestinal absorption of clopidogrel
Q192R polymorphism of the <i>paraoxonase-1</i> gene	Reduced metabolism of clopidogrel to its active metabolite

clopidogrel/omeprazole (75/20 mg) or clopidogrel plus placebo^[9]. The study was designed to end once 143 GI events (primarily bleeding) had occurred but ended prematurely due to interruption of funding after only 55 GI events had occurred^[9]. Sample size calculation was not performed for the cardiovascular endpoint (nonfatal myocardial infarction, ischemic stroke, coronary revascularization or cardiovascular death)^[9]. Patients treated with clopidogrel/omeprazole combination had reduced risk for GI events (1.1% vs 2.9% in patients treated with clopidogrel plus placebo; *P* < 0.001) and similar risk for cardiovascular events (4.9% vs 5.7%, respectively; *P* = 0.98)^[9]. Unfortunately, the premature interruption of the study and the lack of power analysis in terms of the cardiovascular endpoint do not allow definite conclusions regarding the cardiovascular safety of clopidogrel/omeprazole combination^[9]. In addition, the pharmacokinetics of the combined omeprazole-clopidogrel pill might be different from free combinations, even though data suggest that spacing the two medications does not affect the inhibitory effect of omeprazole on the antiplatelet action of clopidogrel^[9,15,38].

In light of these conflicting data, the American Heart Association, American College of Cardiology and the American College of Gastroenterology issued an expert consensus document recommending that PPIs should be considered only in those patients treated with clopidogrel who are at high-risk for GI bleeding, including those with a previous history of GI bleeding, with *Helicobacter pylori* infection, who are treated with NSAIDs, corticosteroids or anticoagulants, and the elderly^[16]. On the other hand, the United States Food

and Drug Administration and the European Medicines Agency revised the labelling of clopidogrel, which now mentions that omeprazole and esomeprazole should be avoided in patients treated with clopidogrel, that other acid-lowering agents with minimal or no inhibitory effects on CYP2C19 should be considered and that lansoprazole and pantoprazole have less inhibitory effect on the antiplatelet action of clopidogrel than omeprazole and esomeprazole^[39,40].

In conclusion, even though pharmacodynamic studies suggest that omeprazole can attenuate the antiplatelet effect of clopidogrel, this interaction does not appear to translate into increased cardiovascular risk in patients treated with this combination. Other PPIs also do not appear to interact with clopidogrel. However, given the limitations of existing studies, the decision to administer PPIs to patients treated with clopidogrel should be individualized based on the patient's bleeding and cardiovascular risk.

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P- Reviewer: Chiu CT, Cosmi E, Leone A, Vassalle C **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Lu YJ



Clinical relevance of intestinal peptide uptake

Hugh James Freeman

Hugh James Freeman, Department of Medicine, University of British Columbia, Vancouver V6T 1W5, Canada

Author contributions: Freeman HJ contributed all to this paper.

Conflict-of-interest: No conflict of interest declared.

Data sharing: No data sharing.

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Correspondence to: Dr. Hugh James Freeman, MD, CM, FRCPC, FACP, Department of Medicine, University of British Columbia, 2211 Wesbrook Mall, Vancouver V6T 1W5, Canada. hugfree@shaw.ca

Telephone: +1-604-8227216

Fax: +1-604-8227236

Received: October 9, 2014

Peer-review started: October 9, 2014

First decision: November 14, 2014

Revised: November 22, 2014

Accepted: March 30, 2015

Article in press: April 2, 2015

Published online: May 6, 2015

Abstract

AIM: To determine available information on an independent peptide transporter 1 (PepT1) and its potential relevance to treatment, this evaluation was completed.

METHODS: Fully published English language literature articles sourced through PubMed related to protein digestion and absorption, specifically human peptide and amino acid transport, were accessed and reviewed. Papers from 1970 to the present, with particular emphasis on the past decade, were examined. In addition, abstracted information translated to English in PubMed was also included. Finally, studies and reviews relevant to nutrient or drug uptake, particularly in human intestine

were included for evaluation. This work represents a summary of all of these studies with particular reference to peptide transporter mediated assimilation of nutrients and pharmacologically active medications.

RESULTS: Assimilation of dietary protein in humans involves gastric and pancreatic enzyme hydrolysis to luminal oligopeptides and free amino acids. During the ensuing intestinal phase, these hydrolytic products are transported into the epithelial cell and, eventually, the portal vein. A critical component of this process is the uptake of intact di-peptides and tri-peptides by an independent PepT1. A number of "peptide-mimetic" pharmaceutical agents may also be transported through this carrier, important for uptake of different antibiotics, antiviral agents and angiotensin-converting enzyme inhibitors. In addition, specific peptide products of intestinal bacteria may also be transported by PepT1, with initiation and persistence of an immune response including increased cytokine production and associated intestinal inflammatory changes. Interestingly, these inflammatory changes may also be attenuated with orally-administered anti-inflammatory tripeptides administered as site-specific nanoparticles and taken up by this PepT1 transport protein.

CONCLUSION: Further evaluation of the role of this transporter in treatment of intestinal disorders, including inflammatory bowel disease is needed.

Key words: Dietary peptides; Peptide transport; Peptide transporter 1; Intestinal inflammation; Drug absorption; Bacterial peptides

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Core tip: Intestinal uptake of intact di-peptides and tri-peptides occurs by an independent epithelial transport process for protein assimilation. This carrier may also be used to absorb specific drugs and bacterial peptide products that may result in inflammatory disease.

Freeman HJ. Clinical relevance of intestinal peptide uptake. *World J Gastrointest Pharmacol Ther* 2015; 6(2): 22-27 Available from: URL: <http://www.wjgnet.com/2150-5349/full/v6/i2/22.htm> DOI: <http://dx.doi.org/10.4292/wjgpt.v6.i2.22>

INTRODUCTION

Protein digestion and absorption in humans depends on initial enzymatic hydrolysis in the stomach and proximal small intestine. The hydrolytic products include oligopeptides and amino acids that ultimately undergo small intestinal uptake into the portal vein. A critical step in this overall uptake process involves a transmembrane protein [peptide transporter 1 (PepT1)], located in the brush border that can transport nutrient peptides into the enterocyte^[1-3]. In addition, studies have also demonstrated that PepT1 is able to transport some pharmaceutical agents along with bacterial by-products from the intestinal lumen that may trigger an ongoing and persistent inflammatory intestinal mucosal response.

MATERIALS AND METHODS

Fully published English language literature articles sourced through PubMed related to protein digestion and absorption, specifically human peptide and amino acid transport, were accessed and reviewed. Papers from 1970 to the present, with particular emphasis on the past decade, were examined. In addition, abstracted information translated to English in PubMed was also included. Finally, studies and reviews relevant to nutrient or drug uptake, particularly in human intestine were included for evaluation. This work represents a summary of all of these studies with particular reference to peptide transporter mediated assimilation of nutrients and pharmacologically active medications.

RESULTS

Assimilation of dietary protein in humans involves gastric and pancreatic enzyme hydrolysis to luminal oligopeptides and free amino acids. During the ensuing intestinal phase, these hydrolytic products are transported into the epithelial cell and, eventually, the portal vein. A critical component of this process is the uptake of intact di-peptides and tri-peptides by an independent PepT1. A number of "peptide-mimetic" pharmaceutical agents may also be transported through this carrier, important for uptake of different antibiotics, antiviral agents and angiotensin-converting enzyme inhibitors. In addition, specific peptide products of intestinal bacteria may also be transported by PepT1, with initiation and persistence of an immune response including increased cytokine production and associated intestinal inflammatory changes. Interestingly, these inflammatory changes may also be

attenuated with orally-administered anti-inflammatory tripeptides administered as site-specific nanoparticles and taken up by this PepT1 transport protein.

DISCUSSION

Gastric and pancreatic phases

Critical nutrients derived from digested protein are absorbed in the intestinal tract, specifically amino acids and peptides, during health as well as during disease. Normally, gastric and pancreatic enzymes initiate hydrolysis of dietary and other luminal proteins from endogenous sources. As a result of this initial hydrolytic phase, an array of free amino acids and different oligopeptides of variable length appear in the small intestinal lumen. Information on human protein digestion and absorption has been previously reviewed and updated^[1-3].

Intestinal phase

Protein digestion studied in human volunteers using long intestinal tubes showed that infused bovine serum albumin appeared to be completely hydrolyzed before the distal ileum^[4]. A host of brush border microvillus membrane transport proteins are located in the intestinal epithelial cell resulting in the uptake of specific substrates into the enterocyte. These transporters are specialized membrane proteins that can recognize, bind and translocate a specific substrate or multiple different substrates across the brush border membrane into the epithelial cell. In addition, other transport proteins involved in this process have been detected and characterized to a limited extent on the basolateral membrane. Most free amino acids that present on the luminal or apical surface of the epithelial cell are transported by both brush border and basolateral membranes into the portal venous blood. A number of brush border membrane amino acid carriers, linked to different ions, have been defined that result in transport of basic, neutral and anionic amino acids. For oligopeptides, however, different cellular transport routes are evident.

Peptide uptake

For both di-peptides and tri-peptides, a separate membrane protein, PepT1, is present that appears to have very broad substrate capacity and, theoretically, it is believed, could transport all possible di-peptides and tri-peptides into the epithelial cell^[5]. For 20 different amino acids, a total of 400 di-peptides and 8000 tri-peptides have been enumerated. For those peptides that consist of 4 or more amino acids, brush border enzymes must first hydrolyze each of these to free amino acids, di-peptides and tri-peptides. Then, substrate uptake into the epithelial cell follows. Once inside the epithelial cell, cytoplasmic enzymes hydrolyze these di-peptides and tri-peptides further into free amino acids for transport into the portal venous blood. Most oligopeptidases are aminopeptidases, acting to

remove an amino acid residue from the amino-terminus of the peptide. Peptide chain length determines the location of hydrolysis with longer peptides hydrolyzed at the brush border and di-peptides and tri-peptides mainly in the cytoplasm^[6]. A number of other brush border and cytoplasmic peptidases are present. In particular, proline-containing oligopeptides are poorly hydrolyzed by most peptidases, yet are very important for assimilation of many normal dietary proteins with a high proline content (e.g., gliadin). Proline-specific dipeptidases are also located in the brush border membrane and cytoplasmic portion of the cell and these serve to hydrolyze most proline-containing peptides (e.g., dipeptidyl aminopeptidase IV)^[7]. Particularly important was the early observation that amino acids infused into human intestine in peptide form are more readily absorbed than if infused into the intestinal lumen as free amino acids^[8]. Some peptides, particularly in other non-human mammalian species, are incompletely hydrolyzed and may be transported out of enterocytes into the circulation, likely by a novel peptide transporter located in the baso-lateral membrane of the epithelial cell^[9,10]. Other routes of uptake into the enterocyte have been hypothesized to exist^[5]. For example, so-called "cell penetrating peptides" may carry peptides into the cell, either by direct penetration through the apical membrane or associated with endocytosis. Finally, enhanced permeability of the tight junctions between epithelial cells may result in increased paracellular uptake.

PepT1

The peptide transporters are part of a proton-coupled oligopeptide transporter superfamily, or peptide transporter family^[10,11]. PepT1 (or SLC15) has several transmembrane domains and acts as a cotransporter with hydrogen ions (H^{+ion})^[12]. After uptake of di-peptides or tri-peptides along with H^{+ion} into the enterocyte, H^{+ion} is then removed from the cell through the sodium-hydrogen (Na^{+ion}/H^{+ion}) exchanger on the brush border membrane in exchange for Na^{+ion} . The Na^{+ion} is then moved out of the cell by a Na^{+ion}/K^{+ion} ATPase pump on the basolateral membrane where 3 Na^{+ion} are transported out of the cell and 2 K^{+ion} are transported into the cell causing the epithelial intra-cellular electrochemical gradient to normalize.

Tissue and cellular distribution studies have also located this carrier protein in intestinal and renal brush border membranes along with lysosomal membranes. Interestingly, most PepT1 activity is located in the proximal small intestine (specifically, duodenum and jejunum), but some activity exists in other intestinal sites, including the ileum and colon. As little dietary protein actually normally reaches the distal portions of the intestine, some investigators have suggested that endogenous proteins might serve as proteolytic substrates for intestinal microflora, particularly in the colon. In addition, a transcription factor, CDX2,

that appears to play important roles in proliferation, differentiation and maturation of epithelial cells, has been shown to specifically regulate this enterocyte brush border membrane transporter, PepT1^[13].

The transporter has been cloned from several mammalian species, including humans, with a size estimated to be about 708 amino acids^[14]. Of particular clinical importance, PepT1 may accept other non-nutrients for uptake, including pharmaceutical agents that have similar structural characteristics and actually mimic peptide substrates. These "peptide-mimetic" therapeutic agents include some antibiotics like cephalosporins and penicillins, some anti-viral agents (e.g., acyclovir, ganciclovir) and inhibitors of angiotensin-converting enzyme. Each may undergo uptake across the intestinal epithelial cell through the PepT1 transporter^[15-17]. Important molecular insights into proton coupled peptide transporters have resulted from evaluation of crystal structures of bacterial transporters combined with some biochemical studies of transport, including use of genetically modified animals have recently been reviewed^[18,19].

Peptide transporter regulation

A number of factors may serve to regulate PepT1, including altered dietary intake^[20,21]. For example, increased expression of PepT1 may be caused by an increased quantity of dietary protein, as well as the specific amino acid composition of the dietary protein. Behavioral changes may also affect expression of the transporter. In particular, a diurnal rhythm in PepT1 expression may occur due to feeding behavior, increasing at night in some mammalian species that tend to be nocturnal feeders^[22,23], a pattern abolished by fasting or imposed daytime feeding^[24]. Increased expression of PepT1 during food deprivation or starvation may also occur, particularly with mucosal changes and reduced intestinal surface area associated with long-term parenteral feeding. Developmental factors also play a role in alteration of transporter expression, especially at the time following birth with suckling of a high protein milk diet and then the post-weaning phase with a shift from milk to solid food^[25].

Peptide transporter in disease

PepT1 expression persists with intestinal disease, even with severe mucosal damage. Normally, PepT1 is expressed to only a limited extent in the colon compared to the small intestine^[26]. In the short bowel syndrome, PepT1 expression is increased in the colon, possibly serving to conserve amino acids^[27]. Similar changes have been reported in the colon of patients with inflammatory bowel diseases^[28]. As a result of PepT1 up-regulation associated with the inflammatory process, dipeptides and tripeptides from bacteria in the colonic lumen may be transported by PepT1 into epithelial cells. Some of these bacterial peptides include N-formylmethionyl-leucyl-phenylalanine, a

tripeptide from *Escherichia coli*, muramyl dipeptide (MDP), found in the cell walls of gram negative and gram positive bacteria, and L-Ala-(γ)-D-Glu-meso-diaminopimelic acid (Tri-DAP), a cell wall byproduct of gram negative bacteria. After uptake into the intestinal cell, the NF- κ B pathway is activated while downstream pro-inflammatory cytokine and chemokine production are enhanced. Some bacterial peptides probably also gain access by a paracellular pathway. Added studies demonstrate that Tri-DAP transport is mediated by PepT1 expressed intestinal epithelial cells, but not in cells that did not express PepT1^[29]. In the lamina propria of intestinal mucosa, these bacterial peptides may then be taken up by macrophages causing up-regulation of major histocompatibility class I molecules and increased cytokine and chemokine production, further contributing to the inflammatory process^[30]. Others have reported that colonic expression of the PepT1 was down-regulated during intestinal inflammation^[31]. Interestingly, PepT1 may play an important interactive role with receptors of the innate immune system to eliminate pathogens^[32]. For example, ligands specific for members of the nucleotide-binding oligomerization domain (NOD) family of receptors, specifically NOD 1 and NOD 2 present in cytoplasm, may be transported by PepT1. Activation of NOD leads to NF- κ B activation. A linkage with NOD mutations and risk of Crohn's disease has been reported^[33-35]. In addition, recent studies suggest that PepT1 polymorphisms may be associated with development of inflammatory bowel disease in some Scandinavian populations^[36]. Recently, cellular and molecular mechanism underlying NOD 2 risk-associated polymorphisms in Crohn's disease have been reviewed^[37]. Finally, a specific tri-peptide (Lys-Pro-Val) or KPV has anti-inflammatory activities that may be transported by PepT1 and cause inhibition of NF- κ B activation^[38]. KPV encapsulated in polysaccharide for release primarily in the colon may reduce inflammatory mucosal changes^[39]. Similarly, a PepT1-transportable soy tripeptide VPY reduced intestinal inflammation, suggesting its use as a possible treatment for inflammatory bowel disease^[40].

Recently, it has been hypothesized that different microbial genomes within the intestinal tract may play a role in the immune response in several inflammatory diseases^[41]. Further clinically-relevant studies focused on the human intestinal microbiome and the potential role of PepT1 are needed.

COMMENTS

Background

Assimilation of dietary protein in humans involves gastric and pancreatic enzyme hydrolysis to luminal oligopeptides and free amino acids. During the ensuing intestinal phase, these hydrolytic products are transported into the epithelial cell and, eventually, the portal vein.

Research frontiers

A critical component of this process is the uptake of intact di-peptides and tri-peptides by an independent peptide transporter transmembrane protein, peptide transporter 1 (PepT1). In recent years, a number of "peptide-mimetic"

pharmaceutical agents may also be transported through this carrier, important for uptake of different antibiotics, antiviral agents and angiotensin-converting enzyme inhibitors. In addition, specific peptide products of intestinal bacteria may also be transported by PepT1, with initiation and persistence of an immune response including increased cytokine production and associated intestinal inflammatory changes. Interestingly, these inflammatory changes may also be attenuated with orally-administered anti-inflammatory tri-peptides administered as site-specific nanoparticles and taken up by this PepT1 transport protein.

Innovations and breakthroughs

Further evaluation of the role of this transmembrane transport protein, PepT1, in transport of pharmaceutical agents is needed. This may provide novel approaches to treatment, particularly for intestinal disorders. In particular, use of agents that employ this peptide transporter to permit access into intestinal cells may have a special role in inflammatory bowel disease treatment.

Applications

From a practical perspective, use of agents that particularly localize to the intestinal mucosal cells might have an important role in localization of treatment regimens rather than use of current systemically-applied pharmaceutical or biological agents.

Terminology

The PepT1 transporter is a special transmembrane intestinal transport protein located in the microvillus membrane. Its role as a nutrient transporter, specifically for di-peptides and tri-peptides is well established. However, in recent years, its role in uptake of several pharmaceutical agents has become apparent, including its potential relevance for management of inflammatory intestinal disorders.

Peer-review

Conceptually, the peer reviewers have raised the important linkage of this peptide transporter and the modern "metagenomic revolution" that should further our understanding of intestinal, particularly inflammatory, disorders. Added studies are also needed that explore these intestinal uptake processes and role of this PepT1 transporter in the developing human intestinal tract, particularly in fetal and neonatal settings.

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P- Reviewer: Actis GC, Catania VA **S- Editor:** Tian YL
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