PROJECT FINAL REPORT

IPODD
Intestinal Proteases: Opportunity for Drug Discovery

Grant Agreement number:	**202020**
Project acronym:	**IPODD**
Project title:	**Intestinal Proteases: Opportunity for Drug Discovery**
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Section 1: Project execution

1.1 Project objectives

IPODD (Intestinal Proteases: Opportunity for Drug Discovery) was launched in 2008 with €3 million funding from the EU seventh framework program (FP7). The project put together the expertise of 13 research teams across seven countries with the goal of pursuing new strategies for treating Inflammatory Bowel Disease (IBD).

IBD affects about 1 in every 250 people in Europe; they are chronic disorders of the gastrointestinal tract that include two main sub-types, Crohn's disease and ulcerative colitis. Both diseases involve symptoms ranging from abdominal discomfort and diarrhoea to severe abdominal pain, rectal bleeding, anaemia, and weight loss. Severe disease often results in surgery to remove damaged parts of the bowel. Removing all of the colon is an effective strategy to cure ulcerative colitis, but the effects of having a permanent stoma are stigmatising, especially in young people. Crohn's disease is incurable. IBD is therefore a major cause of disability and morbidity in western countries, interfering with personal and professional life of tens of thousands of young, active people.

IPODD took a pragmatic approach to the study of IBD: the project focused on the final steps of the inflammatory cascade in the gut, namely the control of the molecules (proteases) that destroy the tissue blocking. These final steps may lead to new therapies to prevent severe disease.

1.2 Contractors involved

IPODD teamed up 13 principal investigators in 7 Countries during its 3-years duration.

List of contractors (Principal Investigator)

- Academic Medical Centre, Amsterdam (Guy Boeckxstaens)
- Alimentary Health Limited, Cork (Jennifer Roper)
- Barts and the London School of Medicine and Dentistry, London (Thomas MacDonald, David Bulmer)
- Eberhard Karls Universität Tuebingen (Paul Enck)
- GlaxoSmithKline Research and Development Ltd, Stevenage
- Institute of Microbiology AS CR, Prague (Helena Tlaskalova)
- Technische Universität München, Munich (Michael Schemann, Dirk Haller)
- The University of Auckland, New Zealand (Lynnette Ferguson)
- University College Cork (Fergus Shanahan)
- University of Sheffield, (David Grundy)*
- University of Southampton (Sylvia Pender)
- University Tor Vergata, Rome (Giovanni Monteleone)

* Project coordinator

Note: GlaxoSmithKline withdrew from the consortium in 2010 following an internal restructuring of the company.

1.3 Background

The two main types of IBD, Crohn's disease, and ulcerative colitis, have many features in common. In both disorders, patients suffer from chronic inflammation of the intestine and often experience periods of relapse (also known as "flares") and remission, during which symptoms may be mild or absent. Some Crohn's patients may also suffer from the narrowing of the intestinal lumen (strictures) due to fibrosis, a consequence of chronic inflammation. In Crohn's disease inflammation can occur anywhere in the digestive tract but usually causes ulcers along the small and large intestine, whereas ulcerative colitis affects the colon and rectum.

The exact cause of IBD is still unknown. A widely accepted hypothesis is that microbes normally living in the intestine may trigger an aberrant immune response in genetically predisposed individuals, leading to chronic inflammation. In fact 99 different gene variants are associated with IBD suggesting that development of disease in an individual is complex and there may not be a single cause.

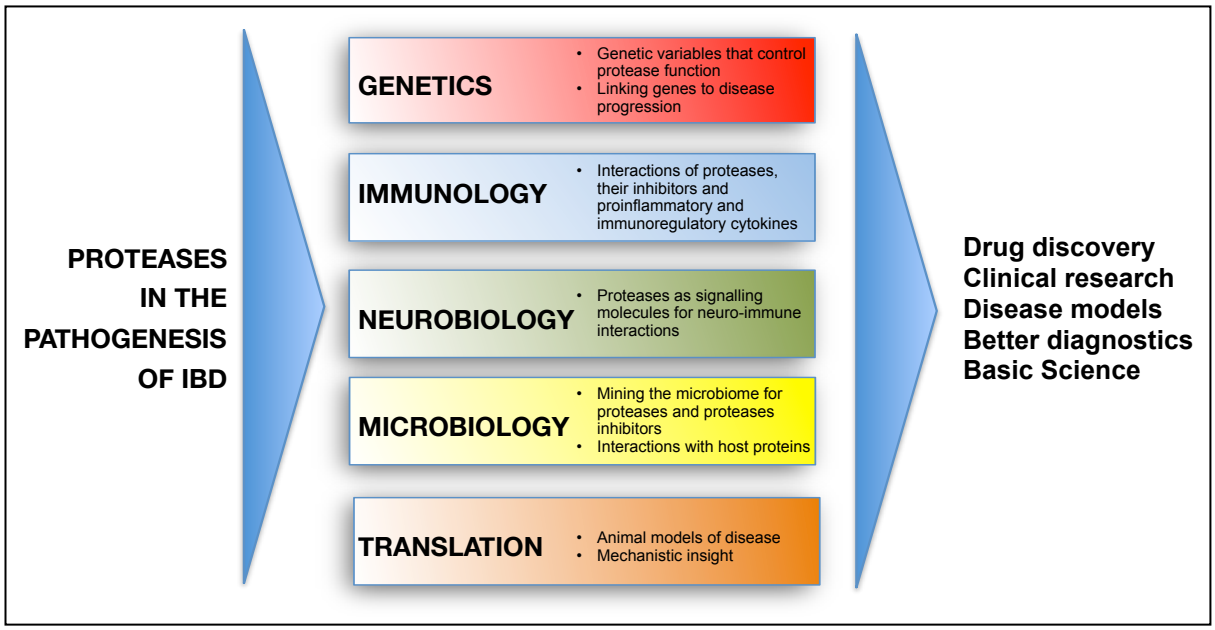


FIG 1. A summary of the factors involved in the pathogenesis of IBD

Current treatment for IBD relies on immunosuppression. Corticosteroids, the mainstay of treatment, have unacceptable side effects with long terms use. More potent immunosuppressive drugs, such as azathioprine can provide long-term benefit in Crohn's disease, but neither corticosteroids nor azathioprine alter the course of the disease, providing only symptomatic relief. More modern immune modulators, such as antibodies against TNFα, are useful in patients with severe disease. However, many patients fail to respond to any therapies, eventually requiring surgery either because their disease resists treatment or because of complications such as strictures, perforations and abscesses. Therefore, despite a significant progress in the management of IBD patients, there is clearly the need for newer therapeutic alternatives

IPODD's work focused on matrix metalloproteases (MMPs), a family of enzymes that lie at the end of the inflammation cascade. These molecules do not trigger inflammation themselves, but are involved in its final steps. About two dozens MMPs are known in humans. Because of their ability to digest proteins (proteases is a general term to indicate

"protein-breaking enzymes"), MMPs are a sort of "demolition squads" in the vanguard of inflammation. They dissolve proteins in the matrix (the space surrounding cells), clearing the way for inflammatory white blood cells. MMPs may also attack the structural proteins that hold the gut wall together, resulting in destruction of the intestinal tissue, and severe ulceration. Other proteases, like the TNFα converting enzyme (TACE) are important players in inflammation: TACE is very important in the production of TNFα, a cytokine with strong pro-inflammatory effects.

However, proteases do not function in isolation. They are tightly controlled so that all proteases in the body also have inhibitors of their function. For MMPs, the inhibitors are the tissue inhibitors of metalloproteases (TIMPs). It is thought that tissue destruction occurs when the activity of MMPs overwhelms the ability of TIMPs to protect tissues.

1.4 Work performed, approach and major achievements

IPODD was the first consortium to focus specifically on MMPs and their multifaceted role in IBD. The multidisciplinary approach taken by the consortium was reflected in the wide range of expertise of its groups, with specialists in immunology, microbiology, probiotics, neuro-gastroenterology, genetics, drug development and science communication. The project contained 9 workpackages detailed in the Project Periodic Reports and the respective Deliverable Reports submitted to the EU Commission.

At the outset of the project:

- It was unclear which proteases were most relevant to IBD or their specific role in disease;
- Little was known about the association between protease genes and IBD susceptibility;
- There was no available strategy specifically to inhibit MMP action in animals or man;
- There were little or no data about the role of MMPs and their inhibitors produced by the intestinal bacteria, and their relevance to IBD.
- The role of proteases in the perturbation of the enteric nervous system during inflammation was poorly understood

Overall, the IPODD work clarified the role of several proteases in the pathogenesis of IBD, and produced data to suggest that they may be rejuvenated as therapeutic targets.

1.4.1 Identifying the role of MMPs and their inhibitors in IBDs

A core component of IPODD's work was to find which proteases are present in the gut in IBD and to study their specific role in the disease. Researchers compared the expression of proteases in normal gut and in those affected by IBD, and looked at the role of MMP gene variants in patients. These studies provided a clearer picture of the significance of proteases in chronic gut inflammation and identified some MMPs as possible targets for drugs that may inhibit their activity. The role of TNFα converting enzyme (TACE), a major pro-inflammatory factor, was also an important field of investigation.

Key results include:

- DNA studies identify associations between variants in MMP genes and IBD in patients from New Zealand and the Netherlands.
- Characterisation of several MMPs as targets for possible inhibition by TIMPs or drugs;
- Expression profiles of MMPs in normal and inflamed gut showed MMP3 and MMP12 are particularly prominent in IBD, while TIMP3, a natural inhibitor is decreased.

- The role of MMPs and their inhibitors in gut fibrosis was examined;
- Evidence for TIMP3 control of TACE and TNF-α production in the human and mouse intestine.

1.4.2 Linking MMPs to neuro-immune mechanisms

Several studies have shown a link between nerves, the brain and the immune system in chronic gut inflammation. Nerves and immune mast cells are closely associated in the human colon. Moreover, many enteric neurons express protease-activated receptors (PAR) that can be activated by MMPs. This led IPODD to address the question of whether proteases, including MMPs, are involved in nerve-gut interactions. This field is critical to understand why IBD patients have an increased sensitivity to pain, and can explain why stress and other events affecting the brain are often associated with relapses ("flares"). IPODD researchers found evidence that proteases are involved in neuro-immune responses, including visceral sensitivity and stress-reactivated colitis. Preliminary results suggest that inhibiting proteases could reduce the sensitivity of IBD patients to gut pain and dampen the effect of stress on relapses.

Key results include:

- Proof that extracts from inflamed gut samples of IBD patients stimulate enteric neurons in vitro. This effect is blocked by protease inhibitors, proving their role in neuro-immune mechanisms;
- Identification of PAR1 as the main receptor involved in protease-mediated neuro-immune signalling in the human gut;
- Evidence that the expression of several MMPs is increased in stress-induced colitis and may be related to the elevated sensitivity of patients suffering from IBDs;
- Identification of TIMP-3 as a possible important biomarker for stress-induced colitis.

1.4.3 (re) Discovering the role of bacteria in IBD

One cannot overstate the importance of the trillions of microorganisms that live in the human intestine. An accepted model for IBD is that gut bacteria trigger an abnormal immune response in genetically predisposed individuals, leading to inflammation. IPODD found that bacteria are also involved in the late stages of gut inflammation: in fact, some MMPs are produced by bacteria, and not by the host. The consortium found evidence that bacterial proteases contribute to the development of inflammation. The study of enteric bacteria may lead to identify new factors involved in IBDs and to discover new inhibitors that could be used to control inflammation.

Key results include:

- Discovery of bacterial proteases involved in IBD by screening biobanks of enteric bacteria and samples from patients;
- Proof that bacterial proteases may contribute to the pathogenesis of IBD, with profiles differing between Crohn's disease and Ulcerative Colitis.

1.4.4 Developing strategies to inhibit MMP activity

A significant part of IPODD's work was aimed at testing methods that may block the effect of MMPs in the human intestine. By counteracting the action of proteases with specific

drugs, researchers from the consortium managed to reduce inflammation in animal models of IBD. They also found that a probiotic mixture used in the management of IBS and ulcerative colitis (VSL#3) has protease-inhibiting properties, which may in part explain its effectiveness. More research in this field may help design better probiotic therapies for IBDs.

Key results include:

- Significant reduction of colitis in mice treated with a selective inhibitor of MMP 3/12;
- Reduction of inflammation with a PAR-2 antagonist in murine models of colitis;
- Identification of a protease-inhibiting effect of VSL#3, a probiotic mixture used in IBD;
- Identification of an individual lacking TNFα converting enzyme (TACE). The patient does not have significant intestinal symptoms despite his impaired ability to produce an active TNFα. This shows it may be possible to inhibit TACE in the gut without major side effects.

1.4.5 Disseminating knowledge

During its three-years of activity, IPODD engaged in several initiatives to disseminate scientific knowledge and results across the project research teams involved and the lay public. Summer schools, consortium meetings and training schemes for young researchers ensured the internal transfer of know-how, while an international symposium and initiatives with patients' associations were key to publicise IPODD's work to a lay audience.

Key results include:

- Summer schools attended by 15-25 young investigators (Tuebingen 2010, Rome 2011);
- Three annual training fellowships granted to young researchers;
- Three annual meetings (Prague 2009, Tuebingen 2010 and Rome 2011) and a 2-day international public symposium (Rome 15th-16th April 2011);
- An IPODD public summary about the consortium's work, mainly targeted to patients. Translation and dissemination of the summary in 13 EU Countries across a network provided by the European Federation of Crohn's & Ulcerative Colitis Associations (EFCCA).

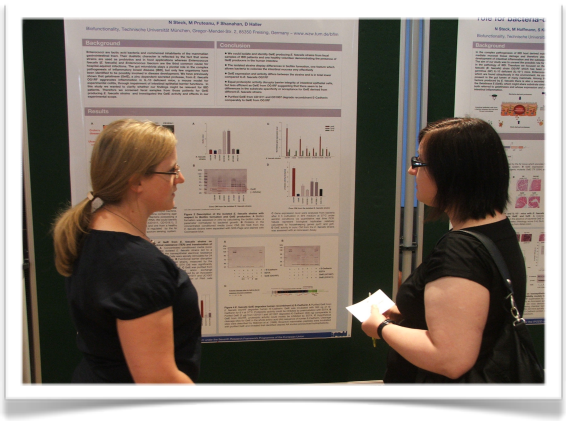
1.5 Impact and perspectives beyond IPODD

IPODD's work has greatly contributed to improve knowledge of the late stages of inflammation and the role of proteases in IBD. Results arising from the consortium, in particular, highlighted the importance of the balance between pro-inflammatory cytokines, MMPs and their inhibitors in the pathogenesis of IBD, and identified key players in the process. A next step will be to screen for compounds that inhibit proteases and test them as potential drugs for IBDs.

The work on bacterial proteases shed new light on the importance of enteric bacteria and will prompt researchers to mine these microorganisms for natural inhibitors of MMPs that may also be useful as drugs. One perspective is to engineer gut bacteria to produce protease inhibitors and use these strains as a probiotic therapy. Further research will address the role of proteases in IBD in detail, and determine whether we can harness enteric bacterial to counteract inflammation in patients.

Overall, IPODD has significantly advanced the IBD field, opening cutting-edge lines of research that in time may lead to new therapeutic approaches. Other fields, such as neuro-immunology and neuro-gastroenterology, could also benefit from the information and the

skills accumulated by the consortium. This potential will hopefully be maintained and developed with future funding opportunities.



Moments from meetings in Prague (top), Rome (left), Tuebingen (right)

Section 2a: Use and dissemination of foreground

Dissemination of IPODD's results has taken place primarily through: (a) a multi-language public summary targeted to patients and (b) peer-reviewed publications.

2.1 IPODD public summary for patients

IPODD hired a science publicist to write a public summary of its activities and results. The document was aimed at IBD patients and to the lay public in . The European Federation of Crohn's & Ulcerative Colitis Associations (EFCCA, www.efcca.org), a network that includes most IBD patient's associations in Europe, offered an excellent platform to disseminate the summary to the relevant stakeholders. So far, the text (originally in English) has been translated into German, French, Italian, Dutch, Slovenian, Slovak, Spanish, Portuguese, Finnish, Polish and Serbian/Croatian and published on the websites of 17 associations thought the EU. A copy of the summary was also included in the printed edition of EFCCA's house organ, distributed to several thousands associates. A copy of the summary is available at the following link: http://www.ipodd.eu/ipodd/news/latest/summary-of-ipodd-research-publication.

2.2 Peer-reviewed publications and collaborative effort

About 20 scientific publications, many in top journals, have arisen so far from IPODD's work. Additional papers, currently under preparation or review, may be published within the next few months. These articles, often co-authored by different IPODD groups, show both the productivity and the collaborative effort of the consortium. Where abstracts are available electronically they have been appended to this report (after Section 3).

LIST OF IPODD PUBLICATIONS (alphabetically by first author)

0. BLAYDON, D.C. et al. Neonatal-Onset Inflammatory Skin and Bowel Disease Associated with a Recessive Loss-of- Function Mutation in ADAM17. NEJM. (in press)
1. BUHNER, S.et al. (2009). Activation of human enteric neurons by supernatants of colonic biopsy specimens from patients with irritable bowel syndrome. Gastroenterology 137: 1425–1434.
2. BUHNER, S., AND M. SCHEMANN (2011). Mast cell-nerve axis with a focus on the human gut. Biochim Biophys Acta
3. DI SABATINO, A.et al. (2009). Transforming growth factor beta signalling and matrix metalloproteinases in the mucosa overlying Crohn's disease strictures. Gut 58: 777–789.
4. FRIELING, T., M. SCHEMANN, AND C. PEHL (2011). Irritable bowel syndrome--a misnomer? Z Gastroenterol 49: 577–578.
5. HOERMANNSPERGER, G.et al. (2009). Post-translational inhibition of IP-10 secretion in IEC by probiotic bacteria: impact on chronic inflammation. PLoS One 4: e4365.
6. HOFFMANN, M., S. C. KIM, R. B. SARTOR, AND D. HALLER (2009). Enterococcus faecalis strains differentially regulate Alix/AIP1 protein expression and ERK 1/2 activation in intestinal epithelial cells in the context of chronic experimental colitis. J Proteome Res 8: 1183–1192.
7. HOFFMANN, M., A. MESSLIK, S. C. KIM, R. B. SARTOR, AND D. HALLER (2011). Impact of a probiotic Enterococcus faecalis in a gnotobiotic mouse model of experimental colitis. Mol Nutr Food Res 55: 703–713.

8. KLOOKER, T. K.et al. (2010). The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome. Gut 59: 1213–1221.
9. PRUTEANU, M., N. P. HYLAND, D. J. CLARKE, B. KIELY, AND F. SHANAHAN (2011). Degradation of the extracellular matrix components by bacterial-derived metalloproteases: implications for inflammatory bowel diseases. Inflamm Bowel Dis 17: 1189–1200.
10. ROVEDATTI, L.et al. (2011). Fibroblast activation protein expression in Crohn's disease strictures. Inflamm Bowel Dis 17: 1251–1253.
11. SCHEMANN, M. (2011). Recording from human gut tissue: a major step towards more efficient drug development? Gut 60: 151–152.
12. SNOEK, S. A., M. I. VERSTEGE, G. E. BOECKXSTAENS, R. M. VAN DEN WIJNGAARD, AND W. J. DE JONGE (2010). The enteric nervous system as a regulator of intestinal epithelial barrier function in health and disease. Expert Rev Gastroenterol Hepatol 4: 637–651.
13. STECK, N.et al. (2011). Enterococcus faecalis Metalloprotease Compromises Epithelial Barrier and Contributes to Intestinal Inflammation. Gastroenterology
14. STECK, N.et al. (2009). 119 Bacterial Proteases Contribute to the Development of Chronic Intestinal Inflammation By Impairing Epithelial Barrier Function. Gastroenterology Gastroenterology Gastroenterology 136: A–21-A-22.
15. STECK, N.et al. (2011). Bacterial proteases in IBD and IBS. Gastroenterology, in press.
16. TLASKALOVA-HOGENOVA, H.et al. (2011). The role of gut microbiota (commensal bacteria) and the mucosal barrier in the pathogenesis of inflammatory and autoimmune diseases and cancer: contribution of germ-free and gnotobiotic animal models of human diseases. Cell Mol Immunol 8: 110–120.
17. VAN DEN WIJNGAARD, R. M., T. K. KLOOKER, W. J. DE JONGE, AND G. E. BOECKXSTAENS (2010). Peripheral relays in stress-induced activation of visceral afferents in the gut. Auton Neurosci 153: 99–105.
18. VAN DIEST, S. A., O. I. STANISOR, G. E. BOECKXSTAENS, W. J. DE JONGE, AND R. M. VAN DEN WIJNGAARD (2011). Relevance of mast cell-nerve interactions in intestinal nociception. Biochim Biophys Acta
19. VON, S., MARIE-ANNE et al. (2010). T2025 Probiotic-Derived Lactocepin Degrades the Pro-Inflammatory Chemokine IP-10: Impact on Chronic Intestinal Inflammation. Gastroenterology Gastroenterology Gastroenterology 138: S–615-S-616.

IN REVISION / SUBMITTED

SCHEMANN et al. Neurobiology of the Human Enteric Nervous System – Implications for Translational Neurogastroenterology. Neurogastroenterology and Motility. (In revision)

MUELLER et al. Demonstration of functional protease-activated receptors (PARs) in the human submucous plexus. Gastroenterology. (In revision)

MORGAN et al. Genetic variations in matrix metalloproteinases are associated with increased risk of Ulcerative Colitis. Human Immunology. (Submitted)

	Title	Main author	Title of periodical or series	Number, date or frequency	Publisher	Place of publication	Year of publication	Relevant pages	Identifier (if available)	Open access?
0.	Neonatal-Onset Inflammatory Skin and Bowel Disease Associated with a Recessive Loss-of-Function Mutation in ADAM17	S.C.Blaydon	New England Journal of Medicine	tba	Elsevier	USA	2011	In press		
1.	Mast cell – Nerve axis with a focus on the human gut	S. Buhner	Biochemica et Biophysica Acta-Molecular Basis of Disease	17.06.2011	Elsevier	Europe	2011	epub	http://www.ncbi.nlm.nih.gov/pubmed/21704703	No
2.	Activation of human enteric neurons by supernatants of colonic biopsy specimens from patients with irritable bowel syndrome.	S. Buhner	Gastroenterology	137	Elsevier	USA	2009	1425-1434	http://www.ncbi.nlm.nih.gov/pubmed/19596012	No
3.	Transforming growth factorβ signalling and matrix metalloproteinases in the mucosa overlying Crohn's disease strictures	Di Sabatino	Gut	58	BMJ	UK	2009	777-789	http://www.ncbi.nlm.nih.gov/pubmed/19201776	No
4.	Irritable Bowel Syndrome - a Misnomer?	Frieling	Z. Gastroenterol	49	Thieme	Germany	2011	577-578	http://www.ncbi.nlm.nih.gov/pubmed/21557166	No
5.	Post-translational inhibition of IP-10 secretion in IEC by probiotic bacteria: impact on chronic inflammation.,.	Hoermannsperger, G.,	PLoS One	4(2)	PLoS	USA	2009	E4365	http://www.ncbi.nlm.nih.gov/pubmed/19197385	Yes
6.	Enterococcus faecalis strains differentially regulate Alix/AIP1 protein expression and ERK 1/2 activation in intestinal epithelial cells in the context of chronic experimental colitis.	Hoffmann M,	J Proteome Res	8(3)	Wiley-VCH	USA	2009	1183-1192	http://www.ncbi.nlm.nih.gov/pubmed/19166300	No
7.	Impact of a probiotic Enterococcus faecalis in a gnotobiotic mouse model of experimental colitis	Hoffmann M,	Molecular Nutrition and Food Research	55(5)	Wiley-VCH	Germany	2011	703-13	http://www.ncbi.nlm.nih.gov/pubmed/21254393	No
8.	The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome.	Klooker	Gut	59	BMJ Journals	UK	2010	1213-1221	http://www.ncbi.nlm.nih.gov/pubmed/20650926	No
9.	Degradation of the extracellular matrix components by bacterial-derived metalloproteases: Implications for inflammatory bowel diseases	Pruteneau	Inflammatory Bowel Diseases	Volume 17, Issue 5	Wiley Online Publishing	Eire	May 2011	1189-1200	http://www.ncbi.nlm.nih.gov/pubmed/20853433	No
10.	Fibroblast Activation Protein Expression in Crohn's Disease Strictures	Rovedatti	Inflammatory Bowel Diseases	Volume 17, Number 5,	Wiley Online Publishing	USA	2011	1251-1253	http://www.ncbi.nlm.nih.gov/pubmed/20806341	No
11.	Recording from human gut tissue: a major step towards more efficient drug development?	Schemann	Gut	60	BMJ Journals	UK	2011	151-152	http://www.ncbi.nlm.nih.gov/pubmed/21205877	No
12.	The enteric nervous system as regulator of intestinal epithelial barrier function in health and disease	Snoek SA	Expert Rev Gastroenterol Hepatol.	4(5)	Future Science Group	UK	2010	637-651	http://www.ncbi.nlm.nih.gov/pubmed/20932148	no
13.	Enterococcus faecalis Metalloprotease Compromises Epithelial Barrier and Contributes to Intestinal Inflammation	Steck	Gastroenterology	26.05.2011	Elsevier	USA	2011	epub	http://www.ncbi.nlm.nih.gov/pubmed/21699778	No
14.	119 Bacterial Proteases Contribute to the Development of Chronic Intestinal Inflammation By Impairing Epithelial Barrier Function.	Steck	Gastroenterology	136	Elsevier	USA	2009	A-21 A-22	http://dx.doi.org/10.1016/S0016-5085(09)60102-5	No
15.	Bacterial proteases in IBD and IBS	Steck N	Gastroenterology	n/a	Elsevier	USA	2011	In press		No

	Title	Main author	Title of periodical or series	Number, date or frequency	Publisher	Place of publication	Year of publication	Relevant pages	Identifier (if available)	Open access?
16.	The Role of gut microbiota (commensal bacteria) and the mucosal barrier in the pathogenesis of inflammatory and autoimmune diseases and cancer: contribution of germ-free and gnotobiotic animal models of human diseases.	Tlaskalova-Hogenova H	Cellular & Molecular Immunology.	8	Chinese Society of Immunology	China	2011	110-120	http://www.ncbi.nlm.nih.gov/pubmed/21278760	No
17.	Peripheral relays in stress-induced activation of visceral afferents in the gut.	Van den Wijngaard RM	Auton Neurosci	153	Elsevier	Netherlands	2010	99-105	http://www.ncbi.nlm.nih.gov/pubmed/19716349	No
18.	Relevance of mast cell-nerve interactions in intestinal nociception.	Van Diest	Biochim Biophys Acta	n/a	Elsevier	Netherlands	2011	In press	http://www.ncbi.nlm.nih.gov/pubmed/21496484	No
19.	T2025 Probiotic-Derived Protease Degrades the Pro- Inflammatory Chemokine IP-10: Impact on Chronic Intestinal Inflammation.	Schillde, M.-A.v.,	Gastroenterology	138(5)	Elsevier	USA	2010	p. S-615-S-616.	10.1016/S0016-5085(10)62838-7	No

PARTICIPATION IN DISSEMINATION ACTIVITIES external to the consortium

Beneficiary	Type of activity	Organiser of activity	Title	Date	Place	Audience type	Audience size	Countries addressed
AMC	Oral presentation	International Society of NGM	Long-term effects of maternal separation and neonatal injury on ENS and gut function', Boston (MA)	August 26 – August 29, 2010	Boston	Basic scientists/gastroenterologist	300	US, EU, Australia
AMC	Poster	DDW	Excitation of enteric neurons by supernatants of colonic biopsies from Irritable Bowel Syndrome patients (IBS) is linked to visceral sensitivity	May 7-10 2011	Chicago	Basic scientists/gastroenterologist	15000	EU, US, Australia, Asia
IMIC	Poster	Society for Mucosal Immunology	Gut Microbiota Drive the Immune System Abnormalities Present in Nod2-Deficient Mice	8 July 2011	Université Paris Descartes, Paris, France	Attendees of 15th International Congress of Mucosal Immunology	500	International
IMIC	Poster	Society for Mucosal Immunology	IL-1 Receptor-associated Kinase-M-deficient Mice Show Hyperactivated Phenotype with Increased Production of Pro-inflammatory and Anti-inflammatory Cytokines	8 July 2011	Université Paris Descartes, Paris, France	Attendees of 15th International Congress of Mucosal Immunology	500	International
IMIC	Poster	The Japanese Society for Immunology (JSI)	Gut microbiota and lipopolysaccharide content of the diet influence maturation of the immune system: studies in germ-free mice	22-27 August 2010	Convention Center, Kobe, Japan	Attendees of 14th International Congress of Immunology	6000	International
IMIC	Talk	Society for Mucosal Immunology	Protective Effect of Oral Treatment with Antigens from Parabacteroides Distasonis in Experimental Colitis is Associated with Oral Tolerance Induction	8 July 2011	Université Paris Descartes, Paris, France	Attendees of 15th International Congress of Mucosal Immunology	500	International
QMUL	Poster	American Gastro-enterological Association	Protective Effects of Timp-3 on Gut Inflammation	May 2011	Chicago	Gastroenterologists	15,000	Worldwide

Beneficiary	Type of activity	Organiser of activity	Title	Date	Place	Audience type	Audience size	Countries addressed
Soton-IIR	poster	Biochemical Society	The Role of SOX-9 in the Function of Intestinal Fibroblasts	20-22 March 11	Durham UK	International	100	UK
Soton-IIR	poster	Biochemical Society	Role of a highly selective Mmp3 and Mmp12 inhibitor – UK370106 in chemical induced colitis	20-22 March 11	Durham UK	International	100	UK
Soton-IIR	poster	International Congress of Mucosal Immunology	Stress-induced colitis in TIMP-3 genetic modified mice	5-9 July 11	Paris	International	1000	France
TUM Neuro	Oral Presentation	Digestive Disease Week	Excitation of enteric neurons by supernatants of colonic biopsies from Irritable Bowel Syndrome patients (IBS) is linked to visceral sensitivity	May 7th-10th	Chicago, USA	Basic scientists, clinicians	15000	International meeting
TUM Neuro	Oral Presentation	Digestive Disease Week	Translational Gastroenterology: Use of biopsy supernatants	May 7th-10th	Chicago, USA	Basic scientists, clinicians	15000	International meeting
TUM Neuro	Oral presentation	First Nutritional Winterschool	Gut-brain axis – The little brain within us	Feb 1st-5th	Pyhätunturi, Finnland	Basic scientists, clinicians	40	International meeting
TUM Neuro	Oral presentation	German Society for Internal Medicine	Neues zur Pathogenes des Reizdarms (Novel insights into the pathophysiology of IBS)	May 1st-4th 2011	Wiesbaden, Germany	Mostly clinicians	1500	Germany
TUM Neuro	Oral Presentation	German Society for Neurogastroenterology and Motility	Submucous rather than myenteric neurons are activated by supernatants of mucosal biopsies from IBS patients	March 27th-29th 2009	Hohenkammer, Germany	Basic scientists, clinicians	70	Germany
TUM Neuro	Oral Presentation	German Society for Neurogastroenterology and Motility	Actions of mucosal biopsy supernatants on enteric neurons	March 26th-28th 2010	Freising, Germany	Basic scientists, clinicians	80	Germany
TUM Neuro	Oral Presentation	German Society for Neurogastroenterology and Motility	Actions of proteases in the human and guinea pig submucous plexus	March 26th-28th 2010	Freising, Germany	Basic scientists, clinicians	80	Germany
TUM Neuro	Oral Presentation	German Society for Neurogastroenterology and Motility	Actions of mucosal biopsy supernatants on enteric neurons	March 4th-6th 2011	Freising, Germany	Basic scientists, clinicians	80	Germany
TUM Neuro	Oral Presentation	German Society for Neurogastroenterology and Motility	Demonstration of Functional Protease Activated Receptors (PARs)in Enteric Neurons of Human Submucous Plexus	March 4th-6th 2011	Freising, Germany	Basic scientists, clinicians	80	Germany
TUM Neuro	Oral presentation	Joint Meeting Neurogastroenterology and Motility	Activation of human enteric neurons by supernatants of colonic biopsies from patients with IBS	Nov 6th-9th 2008	Lucerne, CH	Basic scientists, clinicians	800	International meeting
TUM Neuro	Oral Presentation	Joint Meeting Neurogastroenterology and Motility	Functional and structural studies on the human ENS	August 27th-30th	Chicago, USA	Basic scientists, clinicians	700	International meeting
TUM Neuro	Oral Presentation	Joint Meeting Neurogastroenterology and Motility	Submucous rather than myenteric neurons are activated by supernatants of mucosal biopsies from IBS patients	August 26th-29th 2010	Boston, USA	Basic scientists, clinicians	700	International meeting
TUM Neuro	Oral Presentation	Joint Meeting Neurogastroenterology and Motility	PAR1 and PAR2 receptor mediated actions in the human intestine	August 26th-29th 2010	Boston, USA	Basic scientists, clinicians	700	International meeting

Beneficiary	Type of activity	Organiser of activity	Title	Date	Place	Audience type	Audience size	Countries addressed
TUM Neuro	Oral Presentation	Joint Meeting Neurogastroenterology and Motility	Imaging human enteric neurons	August 26th-29th 2010	Boston, USA	Basic scientists, clinicians	700	International meeting
TUM Neuro	Oral Presentation	The European Society for Clinical Nutrition and Metabolism	ENS control of luminal transport and absorption of food	Sept 5th-8th	Nice, France	Nutrional science	2000	International meeting
TUM Neuro	Oral Presentation	United European Gastroenterology Federation	Peripheral mechanisms underlying chronic pain	Oct 23rd-27th	Barcelona, Spain	Mostly Gastroenterologists	18000	International meeting
TUM Neuro	Poster	German Society for digestive and metabolic Disorders	Excitatory actions of supernatants released from mucosal biopsies of IBS patients is mediated by proteases, serotonin and histamine	1-4 Oct 2008	Berlin, Germany	Mostly Gastroenterologists	2000	Germany, Austria, Switzerland
TUM Neuro	Poster	German Society for digestive and metabolic Disorders	Submucous rather than myenteric neurons are activated by supernatants of mucosal biopsies from IBS patients	Sept 30th – Oct 3rd 2009	Hamburg, Germany	Mostly Gastroenterologists	800	Germany, Austria, Switzerland
TUM Neuro	Poster	German Society for digestive and metabolic Disorders	Neues zur Pathogenes des Reizdarms (Novel insights into the pathophysiology of IBS)	Sept 15th-18th 2010	Stuttgart, Germany	Mostly Gastroenterologists	700	Germany, Austria, Switzerland
UAuk	4th Asia Pacific Nutrigenomics congress, Genes, diet and gut health	Angharad Morgan	GWAS in measuring human variability – are we depending too much upon them	February 2010	Auckland, New Zealand	Open	200	Wide international audience
UAuk	Nutrigenomics New Zealand workshop	Angharad Morgan	Genetic variation in the matrix metalloproteinases is associated with inflammatory bowel disease	July, 2010	Auckland, New Zealand	Nutrigenomics New Zealand (closed)	50	New Zealand
UAuk	Nutrigenomics New Zealand workshop	Angharad Morgan	Genetic variation in the matrix metalloproteinases is associated with inflammatory bowel disease	July 2009	Auckland, New Zealand	Nutrigenomics New Zealand (closed)	50	New Zealand
UAuk	Nutrigenomics New Zealand workshop	Chris Triggs	Correcting for multiple testing in genetic analyses	July 2009	Auckland, New Zealand	Nutrigenomics New Zealand (closed)	50	New Zealand
UCC	Poster Presentation	DDW 2010	Bacterial proteolytic profile in inflammatory bowel diseases	May 2010	New Orleans	GI professionals	~10000	USA
UTU	Website Liaison with EFCCA	P.Enck	Info about the project	2008-11	Web	International	n/a	All

Work with students and/or school pupils

The Education and Outreach Programme of UCC's Alimentary Probiotic Centre (APC) aims to promote an understanding and interest in APC research, and the role of science in society. Participation in the outreach programme that aims to encourage and educate young people about science included school visits giving presentations related to the secondary school Biology curriculum on the digestive system and the immune system.

QMUL hosts the Centre of the Cell (www.centreofthecell.org), a unique interactive computer-based facility with the aim of explaining the concept of the cell to school children in south-east England. In the last year, 12,000 children have visited the centre of the cell and it has garnered numerous awards.

Hrncir (IMIC) delivered 40 science and laboratory practice lessons for 3 university students as part of the Open Science II Project – the systematic integration of talented secondary-school students in scientific-research activities approved within the Operational Programme Education for Competitiveness and co-financed from the state budget of the CR and the European Social Funds, http://www.otevrena-veda.cz.

TUM NEURO hosts regular lab courses for M.Sc. students in Biology and Nutrional Science in "Neurogastroenterology". These are practical courses for 3-6 weeks once a year. It co-organizes the Spring conference of the German society of digestive and metabolic diseases 2010--inflammatory mechanisms and functional gastrointestinal diseases: implications for pathophysiology, diagnosis and therapy. This event was co-sponsored by IPODD. The report appeared in: Keller J, Schemann M. Report on the Spring Conference of the German society of digestive and metabolic diseases 2010-inflammatory mechanisms and functional gastrointestinal diseases: implications for pathophysiology, diagnosis and therapy. Z Gastroenterol. 2011 49(3):391-4.

Pender (SOTON-IIR) is the International Student Advisor in Faculty of Medicine, University of Southampton. She is responsible for pastoral support and student induction for all postgraduate international students. She received a VC award in 2010 for the activities organized for the students. She also supervises postgraduate research students.

Generation of science education material

*See www.**centreofthecell**.org* for the science education material associated with the Centre of the Cell. MacDonald (QMUL) designed an interactive game to educate children about good and bad bacteria in the gut and cytokines *http://www.centreofthecell.org/interactives/gutinfection/index.php*.

Section 2b: Use and dissemination of foreground

B1: LIST OF APPLICATIONS FOR PATENTS, TRADEMARKS, REGISTERED DESIGNS, ETC.					
Type of IP rights	Confidential YES/NO	embargo date dd/mm/yy	Application ref. e.g. EP123456	Subject / title of application	Applicant(s) as on application
None					

B2: OTHER IP								
Type of exploitable foreground	Description of exploitable foreground	Confidential YES/NO	Foreseen embargo date dd/mm/yy	Exploitable products or measures	Sectors of application	Timetable for commercial or any other use	Patents or other IPR exploitation (licenses)	Owner and other beneficiaries involved
None								

Section 3: Report on Societal Implications

A General Information *(completed automatically when **Grant Agreement number** is entered.*

Grant Agreement Number:	202020
Title of Project:	IPODD
Name and Title of Coordinator:	Professor David Grundy

B Ethics

1. Did you have ethicists or others with specific experience of ethical issues involved in the project?	○ ✔	~~**Yes**~~ **No**
2. Please indicate whether your project involved any of the following issues (tick box):		
INFORMED CONSENT		
• Did the project involve children?		
• Did the project involve patients or persons not able to give consent?		
• Did the project involve adult healthy volunteers?		
• Did the project involve Human Genetic Material?	✔	
• Did the project involve Human biological samples?	✔	
• Did the project involve Human data collection?		
RESEARCH ON HUMAN EMBRYO/FOETUS		
• Did the project involve Human Embryos?		
• Did the project involve Human Foetal Tissue / Cells?		
• Did the project involve Human Embryonic Stem Cells?		
PRIVACY		
• Did the project involve processing of genetic information or personal data (eg. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)		
• Did the project involve tracking the location or observation of people?		
RESEARCH ON ANIMALS		
• Did the project involve research on animals?	✔	
• Were those animals transgenic small laboratory animals?	✔	
• Were those animals transgenic farm animals?		
• Were those animals cloning farm animals?		
• Were those animals non-human primates?		
RESEARCH INVOLVING DEVELOPING COUNTRIES		
• Use of local resources (genetic, animal, plant etc)		
• Benefit to local community (capacity building ie access to healthcare, education etc)		
DUAL USE		
• Research having potential military / terrorist application		

C Workforce Statistics

3 Workforce statistics for the project: Please indicate in the table below the number of people who worked on the project (on a headcount basis).

Type of Position	Number of Women	Number of Men
Scientific Coordinator		1
Work package leader	1	8
Experienced researcher (i.e. PhD holders)	9	11
PhD Students	6	6
Other	11	4

4 How many additional researchers (in companies and universities) were recruited specifically for this project?	1
Of which, indicate the number of men:	
Of which, indicate the number of women:	1

D Gender Aspects

5	**Did you carry out specific Gender Equality Actions under the project ?**	○ X	Yes No

6 Which of the following actions did you carry out and how effective were they?

		Not at all effective				Very effective
❑	Design and implement an equal opportunity policy	○	○	○	○	○
❑	Set targets to achieve a gender balance in the workforce	○	○	○	○	○
❑	Organise conferences and workshops on gender	○	○	○	○	○
❑	Actions to improve work-life balance	○	○	○	○	○
○	Other:					

7 Was there a gender dimension associated with the research content – i.e. wherever people were the focus of the research as, for example, consumers, users, patients or in trials, was the issue of gender considered and addressed?

○ Yes- please specify

X No

E Synergies with Science Education

8 Did your project involve working with students and/or school pupils (e.g. open days, participation in science festivals and events, prizes/competitions or joint projects)?

✔ Yes- please specify — See p.15 above

○ No

9 Did the project generate any science education material (e.g. kits, websites, explanatory booklets, DVDs)?

✔ Yes- please specify — See p.15 above

○ No

F Interdisciplinarity

10 Which disciplines are involved in your project? *[See drop –down menus]*

1	Main discipline	3	
1.5	Associated discipline [Menu]	3.1	Associated discipline [Menu]

G Engaging with Civil society and policy makers

11a	**Did your project engage with societal actors beyond the research community?** *(if 'No', go to Question 14)*	✔ ○	Yes No

11b If yes, did you engage with citizens (citizens' panels / juries) or organised civil society (NGOs, patients' groups etc.)?

○ No

○ Yes- in determining what research should be performed

○ Yes - in implementing the research

✔ Yes, in communicating /disseminating / using the results of the project

11c In doing so, did your project involve actors whose role is mainly to organise the dialogue with citizens and organised civil society (e.g. professional mediator; communication company, science museums)?	✔ ○	Yes No

12 Did you engage with government / public bodies or policy makers (including international organisations)

- ○ No
- ○ Yes- in framing the research agenda
- ○ Yes - in implementing the research agenda
- ✔ Yes, in communicating /disseminating / using the results of the project

13a Will the project generate outputs (expertise or scientific advice) which could be used by policy makers?

- ○ Yes – as a **primary** objective (please indicate areas below- multiple answers possible)
- ○ Yes – as a **secondary** objective (please indicate areas below - multiple answer possible)
- ✔ No

13b If Yes, in which fields?

Agriculture		Energy		Human rights	
Audiovisual and Media		Enlargement		Information Society	
Budget		Enterprise		Institutional affairs	
Competition		Environment		Internal Market	
Consumers		External Relations		Justice, freedom and security	
Culture		External Trade		Public Health	
Customs		Fisheries and Maritime Affairs		Regional Policy	
Development Economic and Monetary Affairs		Food Safety		Research and Innovation	
		Foreign and Security Policy		Space	
Education, Training, Youth		Fraud		Taxation	
Employment and Social Affairs		Humanitarian aid		Transport	

13c If Yes, at which level?

- ○ Local / regional levels
- ○ National level
- ○ European level
- ○ International level

H Use and dissemination

14 How many Articles were published/accepted for publication in peer-reviewed journals?		**23**
15 How many new patent applications ('priority filings') have been made? *("Technologically unique": multiple applications for the same invention in different jurisdictions should be counted as just one application of grant).*		**-**
16 Indicate how many of the following Intellectual Property Rights were applied for (give number in each box).	Trademark	**-**
	Registered design	**-**
	Other	**-**
17 How many spin-off companies were created / are planned as a direct result of the project?		**-**
Indicate the approximate number of additional jobs in these companies:		

18 Please indicate whether your project has a potential impact on employment, in comparison with the situation before your project:

❑	Increase in employment, or	❑	In small & medium-sized enterprises
❑	Safeguard employment, or	❑	In large companies
❑	Decrease in employment,	x	None of the above / not relevant to the project
❑	Difficult to estimate / not possible to quantify	❑	

19 For your project partnership please estimate the employment effect resulting directly from your participation in Full Time Equivalent (*FTE* = *one person working fulltime for a year*) jobs:	*Indicate figure:*
Difficult to estimate / not possible to quantify	x

I Media and Communication to the general public

20 As part of the project, were any of the beneficiaries professionals in communication or media relations?

✔ Yes ○ No

21 As part of the project, have any beneficiaries received professional media / communication training / advice to improve communication with the general public?

○ Yes ✔ No

22 Which of the following have been used to communicate information about your project to the general public, or have resulted from your project?

✔	Press Release	❑	Coverage in specialist press
❑	Media briefing	❑	Coverage in general (non-specialist) press
❑	TV coverage / report	❑	Coverage in national press
❑	Radio coverage / report	❑	Coverage in international press
✔	Brochures /posters / flyers	✔	Website for the general public / internet
❑	DVD /Film /Multimedia	❑	Event targeting general public (festival, conference, exhibition, science café)

23 In which languages are the information products for the general public produced?

✔	Language of the coordinator	✔	English
✔	Other language(s)		

Question 10: Drop down menu will include the Classification of Scientific Disciplines according to the Frascati Manual 2002 (Proposed Standard Practice for Surveys on Research and Experimental Development, OECD 2002):

FIELDS OF SCIENCE AND TECHNOLOGY

1. NATURAL SCIENCES

1.1 Mathematics and computer sciences [mathematics and other allied fields: computer sciences and other allied subjects (software development only; hardware development should be classified in the engineering fields)]

1.2 Physical sciences (astronomy and space sciences, physics and other allied subjects)

1.3 Chemical sciences (chemistry, other allied subjects)

1.4 Earth and related environmental sciences (geology, geophysics, mineralogy, physical geography and other geosciences, meteorology and other atmospheric sciences including climatic research, oceanography, vulcanology, palaeoecology, other allied sciences)

1.5 Biological sciences (biology, botany, bacteriology, microbiology, zoology, entomology, genetics, biochemistry, biophysics, other allied sciences, excluding clinical and veterinary sciences)

2 ENGINEERING AND TECHNOLOGY

2.1 Civil engineering (architecture engineering, building science and engineering, construction engineering, municipal and structural engineering and other allied subjects)

2.2 Electrical engineering, electronics [electrical engineering, electronics, communication engineering and systems, computer engineering (hardware only) and other allied subjects]

2.3. Other engineering sciences (such as chemical, aeronautical and space, mechanical, metallurgical and materials engineering, and their specialised subdivisions; forest products; applied sciences such as geodesy, industrial chemistry, etc.; the science and technology of food production; specialised technologies of interdisciplinary fields, e.g. systems analysis, metallurgy, mining, textile technology and other applied subjects)

3. MEDICAL SCIENCES

3.1 Basic medicine (anatomy, cytology, physiology, genetics, pharmacy, pharmacology, toxicology, immunology and immunohaematology, clinical chemistry, clinical microbiology, pathology)

3.2 Clinical medicine (anaesthesiology, paediatrics, obstetrics and gynaecology, internal medicine, surgery, dentistry, neurology, psychiatry, radiology, therapeutics, otorhinolaryngology, ophthalmology)

3.3 Health sciences (public health services, social medicine, hygiene, nursing, epidemiology)

4. AGRICULTURAL SCIENCES

4.1 Agriculture, forestry, fisheries and allied sciences (agronomy, animal husbandry, fisheries, forestry, horticulture, other allied subjects)

4.2 Veterinary medicine

5. SOCIAL SCIENCES

5.1 Psychology

5.2 Economics

5.3 Educational sciences (education and training and other allied subjects)

5.4 Other social sciences [anthropology (social and cultural) and ethnology, demography, geography (human, economic and social), town and country planning, management, law, linguistics, political sciences, sociology, organisation and methods, miscellaneous social sciences and interdisciplinary , methodological and historical S1T activities relating to subjects in this group. Physical anthropology, physical geography and psychophysiology should normally be classified with the natural sciences].

6. HUMANITIES

6.1 History (history, prehistory and history, together with auxiliary historical disciplines such as archaeology, numismatics, palaeography, genealogy, etc.)

6.2 Languages and literature (ancient and modern)

6.3 Other humanities [philosophy (including the history of science and technology) arts, history of art, art criticism, painting, sculpture, musicology, dramatic art excluding artistic "research" of any kind, religion, theology, other fields and subjects pertaining to the humanities, methodological, historical and other S1T activities relating to the subjects in this group] .

PUBLICATION ABSTRACTS

New England Journal of Medicine. Manuscript ID: 11-00721.R1

0. Neonatal-Onset Inflammatory Skin and Bowel Disease Associated with a Recessive Loss-of- Function Mutation in ADAM17.

Complete List of Authors:	Blaydon, Diana; Barts and The London School of Medicine and Dentistry, Blizard institute Biancheri, Paolo; Barts and The London School of Medicine and Dentistry, Blizard institute Di, Wei-Li; UCL Institute of Child Health and Great Ormond Street Hospital, Department of Paediatric Dermatology Plagnol, Vincent; Cambridge Institute for Medical Research, Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory Cabral, Rita; Barts and The London School of Medicine and Dentistry, Blizard institute Brooke, Matthew; Barts and The London School of Medicine and Dentistry van Heel, David; Barts and The London School of Medicine and Dentistry, Blizard institute Rüschendorf, Franz; Mac Delbrück Center for Molecular Medicine Toynbee, Mark; Barts and The London School of Medicine and Dentistry, Blizard institute Walne, Amanda; Barts and The London School of Medicine and Dentistry, Blizard institute o'Toole, Edel; Barts and The London School of Medicine and Dentistry, Blizard institute Martin, Joanne; Barts and The London School of Medicine and Dentistry Lindley, Keith; UCL Institute of Child Health and Great Ormond Street Hospital, Department of Gastroenterology Vulliamy, Tom; Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Paediatrics Abrams, Dominic; Barts and The London NHS Trust, Cardiology Research Department MacDonald, Tom; Barts and The London, School of Medicine Harper, John; Great Ormond Street Hospital for Children, Paediatric Dermatology Kelsell, David; Barts and The London School of Medicine and Dentistry, Blizard institute
Keywords:	Dermatology General < Dermatology, Inflammatory Bowel Disease < Gastroenterology, Genetics General < Genetics, Immunology General < Immunology/Allergy, Bacterial Infections < Infectious Disease, Childhood Diseases < Pediatrics
Abstract:	We studied two siblings with autosomal recessive neonatal inflammatory skin and bowel lesions. The affected female died suddenly aged 12 of parvovirus B19 myocarditis and her brother has mild cardiomyopathy. Using a combination of genome-wide SNP homozygosity mapping and targeted sequence capture followed by next generation sequencing, we have identified the first human loss of function mutation in ADAM17 (encoding a disintegrin and metalloproteinase 17, ADAM17 (also called TACE, tumor necrosis factor-α-converting enzyme)) as the likely underlying cause of this syndrome. Peripheral blood mononuclear cells from the surviving male patient (aged 17) showed high lipopolysaccharide-induced production of interleukin (IL)-1ß and IL-6, but impaired TNF-α release. Despite repeated skin infections, the surviving patient leads a relatively normal life.

Gut. 2009 Jun;58(6):777-89. Epub 2009 Feb 6.

1. Transforming growth factor beta signalling and matrix metalloproteinases in the mucosa overlying Crohn's disease strictures.

Di Sabatino A, Jackson CL, Pickard KM, Buckley M, Rovedatti L, Leakey NA, Picariello L, Cazzola P, Monteleone G, Tonelli F, Corazza GR, MacDonald TT, Pender SL.
Source

First Department of Medicine, Fondazione IRCCS Policlinico S. Matteo, Centro per lo Studio e la Cura delle Malattie Infiammatorie Croniche Intestinali, University of Pavia, Pavia, Italy.

Abstract

BACKGROUND AND AIMS:
In addition to its crucial role in dampening tissue-damaging immune responses in the gut, **transforming growth factor beta** (TGFbeta) is a potent profibrogenic agent inducing collagen synthesis and regulating the balance between **matrix**-degrading **matrix metalloproteinases** (MMPs) and their inhibitors (TIMPs). TGFbeta signalling was investigated by analysis of Smad proteins and MMPs/TIMPs in the **mucosa overlying strictures** in patients with **Crohn's disease** (CD).

METHODS:
Specimens were collected from macroscopically normal **mucosa overlying** strictured and non-strictured gut of patients with fibrostenosing CD. Isolated myofibroblasts were cultured with anti-TGFbeta blocking antibody or TGF **beta** 1. TGFbeta transcripts were analysed by quantitative reverse transcription-PCR (RT-PCR). Smad proteins and MMPs were determined by immunoblotting. MMP-12 activity was measured by a real-time MMP-12 activity assay. An in vitro wound-healing scratch assay was used to assess myofibroblast migration.

RESULTS:
TGFbeta transcripts, phosphorylated Smad2-Smad3 (pSmad2-3) and TIMP-1 proteins were higher in **mucosa overlying strictures** than in **mucosa overlying** non-strictured areas. In contrast, **mucosa overlying** strictured gut had lower expression of Smad7, MMP-12 and MMP-3. Myofibroblasts from **mucosa overlying** strictured gut showed higher TGFbeta transcripts, a greater pSmad2-3 response to TGFbeta, increased TIMP-1, lower Smad7, increased collagen production and reduced migration ability compared with myofibroblasts from **mucosa overlying** non-strictured gut. TGFbeta blockade increased myofibroblast MMP-12 production and migration, more obviously in myofibroblasts isolated from **mucosa overlying** non-strictured compared with strictured gut.

CONCLUSIONS:
Changes in TGF-**beta** signalling and MMP production were identified in the **mucosa overlying strictures** in CD which may give a window into the process of fibrosis.

PMID: 19201776 [PubMed - indexed for MEDLINE]

Biochim Biophys Acta. 2011 Jun 17. [Epub ahead of print]

2. Mast cell-nerve axis with a focus on the human gut.

Buhner S, Schemann M.

Abstract

This paper summarizes the current knowledge on the interactions between intestinal mast cells, enteric neurons and visceral afferents which are part of the gut brain axis. The focus of this review is on the relevance of the mast cell nerve axis in the human intestine. Similarities and important differences in the organization of the mast cell nerve axis between human and rodents are discussed. Functionally important human mast cell mediators with neural actions in the human ENS are histamine (H1-4 receptors), proteases (PAR1 receptors), several cytokines and chemokines and probably also serotonin (5-HT(3) receptors). On the other hand, mediator release from human intestinal mast cells is modulated by neuropeptides released from enteric and visceral afferent nerves. This article is part of a Special Issue entitled: Mast Cells in Inflammation.

PMID: 21704703 [PubMed - as supplied by publisher]

Gastroenterology. 2009 Oct;137(4):1425-34. Epub 2009 Jul 28.

3. Activation of human enteric neurons by supernatants of colonic biopsy specimens from patients with irritable bowel syndrome.

Buhner S, Li Q, Vignali S, Barbara G, De Giorgio R, Stanghellini V, Cremon C, Zeller F, Langer R, Daniel H, Michel K, Schemann M.

Source

Human Biology, Technische Universität München, Freising, Germany.

Abstract

BACKGROUND & AIMS:

Pathological features in irritable bowel syndrome (IBS) include alterations in mucosal cell content and mediator release that might alter signaling to nearby submucosal neurons.

METHODS:

Voltage sensitive dye imaging was used to record the effects of mediators, released from mucosal biopsies of IBS patients, on cell bodies of 1207 submucosal neurons from 76 human colonic tissue specimens. Supernatants, containing these mediators, were collected following incubation with colonic mucosal biopsies from 7 patients with diarrhea-predominant IBS (D-IBS), 4 with constipation-predominant IBS (C-IBS), and 4 healthy controls. Serotonin, histamine and tryptase concentrations in supernatants and lamina propria mast cell density were determined.

RESULTS:

In contrast to controls, IBS supernatants significantly increased the rate of spike discharge in 58% of human submucosal neurons. Neurons that responded to IBS supernatant had a median spike frequency of 2.4 Hz compared to 0 Hz for control supernatants. Supernatants from C-IBS and D-IBS evoked similar spike discharge. The activation induced by IBS supernatants was inhibited by histamine receptor (H1-H3) antagonists, 5-HT3 receptor antagonist, and protease inhibition. Serotonin, histamine and tryptase levels in supernatants correlated with the spike discharge induced by the supernatants. Mast cells density as well as histamine and tryptase levels in supernatants were higher in IBS than in controls.

CONCLUSIONS:

Mediators released from mucosal biopsies of IBS patients can activate human submucosal neurons. The activation required histamine, serotonin and proteases but was not associated with IBS subtype. Altered signaling between mucosa and the enteric nervous system might be involved in IBS pathogenesis.

PMID: 19596012 [PubMed - indexed for MEDLINE]

Z Gastroenterol. 2011 May;49(5):577-8. Epub 2011 May 9.

4. Irritable bowel syndrom--a misnomer?

[Article in German]

Frieling T, Schemann M, Pehl C.

PMID: **21557166** [PubMed - in process]

PLoS One. 2009;4(2):e4365. Epub 2009 Feb 6.

5. Post-translational inhibition of IP-10 secretion in IEC by probiotic bacteria: impact on chronic inflammation.

Hoermannsperger G, Clavel T, Hoffmann M, Reiff C, Kelly D, Loh G, Blaut M, Hölzlwimmer G, Laschinger M, Haller D.

Source

Chair for Biofunctionality, ZIEL-Research Center for Nutrition and Food Science, Technische Universität München, Freising-Weihenstephan, Germany.

Erratum in

PLoS One. 2009;4(6). doi: 10.1371/annotation/583d95a8-c18c-4c66-92be-1b1505802d86. Hörmannsperger, Gabriele [corrected to Hoermannsperger, Gabriele].

Abstract

BACKGROUND:

Clinical and experimental studies suggest that the **probiotic** mixture VSL#3 has protective activities in the context of inflammatory bowel disease (IBD). The aim of the study was to reveal bacterial strain-specific molecular mechanisms underlying the anti-inflammatory potential of VSL#3 in intestinal epithelial cells (**IEC**).

METHODOLOGY/PRINCIPAL FINDINGS:

VSL#3 inhibited TNF-induced **secretion** of the T-cell chemokine interferon-inducible protein (**IP-10**) in Mode-K cells. Lactobacillus casei (L. casei) cell surface proteins were identified as active anti-inflammatory components of VSL#3. Interestingly, L. casei failed to block TNF-induced **IP-10** promoter activity or **IP-10** gene transcription at the mRNA expression level but completely inhibited **IP-10** protein **secretion** as well as **IP-10**-mediated T-cell transmigration. Kinetic studies, pulse-chase experiments and the use of a pharmacological inhibitor for the export machinery (brefeldin A) showed that L. casei did not impair initial **IP-10** production but decreased intracellular **IP-10** protein stability as a result of blocked **IP-10 secretion**. Although L. casei induced **IP-10** ubiquitination, the **inhibition** of proteasomal or lysosomal degradation did not prevent the loss of intracellular **IP-10**. Most important for the mechanistic understanding, the **inhibition** of vesicular trafficking by 3-methyladenine (3-MA) inhibited **IP-10** but not IL-6 expression, mimicking the inhibitory effects of L. casei. These findings suggest that L. casei impairs vesicular pathways important for the **secretion** of **IP-10**, followed by subsequent degradation of the proinflammatory chemokine. Feeding studies in TNF(DeltaARE) and IL-10(-/-) mice revealed a compartimentalized protection of VSL#3 on the development of cecal but not on ileal or colonic **inflammation**. Consistent with reduced tissue pathology in IL-10(-/-) mice, **IP-10** protein expression was reduced in primary epithelial cells.

CONCLUSIONS/SIGNIFICANCE:

We demonstrate segment specific effects of **probiotic** intervention that correlate with reduced **IP-10** protein expression in the native epithelium. Furthermore, we revealed **post-translational** degradation of **IP-10** protein in **IEC** to be the molecular mechanism underlying the anti-inflammatory effect.

PMID: 19197385 [PubMed - indexed for MEDLINE] PMCID: PMC2634842 **Free PMC Article**

J Proteome Res. 2009 Mar;8(3): 1183-92.

6. Enterococcus faecalis strains differentially regulate Alix/AIP1 protein expression and ERK 1/2 activation in intestinal epithelial cells in the context of chronic experimental colitis.

Hoffmann M, Kim SC, Sartor RB, Haller D.

Source

Chair for Biofunctionality, ZIEL-Research Center for Nutrition and Food Science, Technische Universitat Munchen, 85350 Freising-Weihenstephan, Germany.

Abstract

Monoassociation of germfree Interleukin 10 gene deficient (IL-10-/-) 129SvEv but not wild-type mice with **Enterococcus faecalis** induces severe **chronic colitis**. Bacterial strain-specific effects on the development of **chronic intestinal** inflammation are not understood. We investigated the molecular mechanisms of E. **faecalis** OG1RF (human clinical isolate, colitogenic) and E. **faecalis** ms2 (endogenous isolate from an IL-10-/- mouse) in initiating **chronic experimental colitis** using IL-10-/- mice. Monoassociation of IL-10-/- mice for 14 weeks revealed significant differences in colonic inflammation (3.6 +/- 0.**2** and **2**.4 +/- 0.6 for OG1RF and ms2, respectively) (n = 5 mice in each group) (histological scoring (0-4)). Consistent with the tissue pathology, gene **expression** of the pro-inflammatory chemokine interferon-gamma inducible **protein**-10 (IP-10) was significantly higher in **intestinal epithelial cells** (IEC) derived from E. **faecalis** OG1RF monoassociated IL-10-/- mice. We further compared the **differentially** E. **faecalis** induced **colitis** on the **epithelial** level by 2D-SDS PAGE coupled with MALDI-TOF MS. Proteome analysis identified 13 proteins which were **differentially** regulated during disease progression in the epithelium of E. **faecalis**-monoassociated IL-10-/- mice. Regulation of **Alix**/**AIP1 protein expression** and ERK1/**2** phosphorylation was validated in primary IEC and **epithelial** cell lines, suggesting a protective role for **Alix**/**AIP1** in the process of disease progression. **Alix**/**AIP1 protein expression** was further characterized in **epithelial** cell lines using siRNA-mediated knock-down. Our study demonstrates E. **faecalis** strain-specific induction of **colitis** in IL-10-/- mice after 14 weeks of monoassociation. Our study suggests that **Alix**/**AIP1 protein expression** and ERK1/**2 activation** are decreased in severe **colitis**.

PMID: 19166300 [PubMed - indexed for MEDLINE]

Mol Nutr Food Res. 2011 May;55(5):703-13. doi: 10.1002/mnfr.201000361. Epub 2011 Jan 20.

7. Impact of a probiotic Enterococcus faecalis in a gnotobiotic mouse model of experimental colitis.

Hoffmann M, Messlik A, Kim SC, Sartor RB, Haller D.

Source

Technische Universität München, Chair for Biofunctionality, ZIEL - Research Center for Nutrition and Food Science, CDD - Center for Diet and Disease, Freising-Weihenstephan, Germany.

Abstract

SCOPE:

IL-10-deficient (IL-10(-/-)) mice are susceptible to the development of chronic intestinal inflammation in response to the colonization with commensal Enterococcus faecalis isolates. The aim of this study was to characterize the impact of a probiotic E. faecalis strain in germ-free, wild-type (WT), and disease-susceptible IL-10(-/-) mice.

METHODS AND RESULTS:

The probiotic E. faecalis and the colitogenic control strain OG1RF induced IL-6 and IFN-γ inducible protein-10 secretion in the murine intestinal epithelial cell line Mode K. Epithelial cell activation involved nuclear factor κ B, p38 and extracellular signal-regulated kinase 1/2-dependent pathways. Mouse embryonic fibroblasts from WT and toll-like receptor-2-deficient (TLR-2(-/-)) mice confirmed that both E. faecalis strains trigger pro-inflammatory responses via the pattern recognition receptor TLR-2. Monoassociation of germ-free IL-10(-/-) mice with the probiotic E. faecalis strain revealed pro-inflammatory epithelial cell activation and colonic tissue pathology. The non-pathogenic nature of E. faecalis was confirmed in monoassociated WT mice. 2-DE and MALDI-TOF MS identified the ER stress chaperone Hspa5 (glucose-regulated protein 78) and 3-mercaptopyruvate sulfurtransferase as key targets in the epithelium from IL-10(-/-) and TLR-2(-/-) mice.

CONCLUSION:

This study shows the potential of probiotic bacteria to initiate pro-inflammatory responses in the disease-susceptible but not the normal host.

PMID: 21254393 [PubMed - in process]

Gut. 2010 Sep;59(9):1213-21. Epub 2010 Jul 21.

8. The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome.

Klooker TK, Braak B, Koopman KE, Welting O, Wouters MM, van der Heide S, Schemann M, Bischoff SC, van den Wijngaard RM, Boeckxstaens GE.

Source

Department of Gastroenterology, Academic Medical Center, Amsterdam, The Netherlands.

Abstract

BACKGROUND:
Mast cell activation is thought to be involved in visceral hypersensitivity, one of the main characteristics of the irritable bowel syndrome (IBS). A study was therefore undertaken to investigate the effect of the mast cell stabiliser ketotifen on rectal sensitivity and symptoms in patients with IBS.

METHODS:
60 patients with IBS underwent a barostat study to assess rectal sensitivity before and after 8 weeks of treatment. After the initial barostat, patients were randomised to receive ketotifen or placebo. IBS symptoms and health-related quality of life were scored. In addition, mast cells were quantified and spontaneous release of tryptase and histamine was determined in rectal biopsies and compared with biopsies from 22 age- and gender-matched healthy volunteers.

RESULTS:
Ketotifen but not placebo increased the threshold for discomfort in patients with IBS with visceral hypersensitivity. This effect was not observed in normosensitive patients with IBS. Ketotifen significantly decreased abdominal pain and other IBS symptoms and improved quality of life. The number of mast cells in rectal biopsies and spontaneous release of tryptase were lower in patients with IBS than in healthy volunteers. Spontaneous release of histamine was mostly undetectable but was slightly increased in patients with IBS compared with healthy volunteers. Histamine and tryptase release were not altered by ketotifen.

CONCLUSIONS:
This study shows that ketotifen increases the threshold for discomfort in patients with IBS with visceral hypersensitivity, reduces IBS symptoms and improves health-related quality of life. Whether this effect is secondary to the mast cell stabilising properties of ketotifen or H(1) receptor antagonism remains to be further investigated. Trial Registration Number NTR39, ISRCTN22504486.

Comment in

Gut. 2011 Mar;60(3):423; author rpely 423.
Gastroenterology. 2011 Jun;140(7):2132-6; discussion 2136.

PMID: 20650926 [PubMed - indexed for MEDLINE]

Inflamm Bowel Dis. 2011 May;17(5):1189-200. doi: 10.1002/ibd.21475. Epub 2010 Sep 17.

9. Degradation of the extracellular matrix components by bacterial-derived metalloproteases: implications for inflammatory bowel diseases.

Pruteanu M, Hyland NP, Clarke DJ, Kiely B, Shanahan F.

Source

Alimentary Health Ltd, Cork, Ireland. mpruteanu@ahealth.ie

Abstract

BACKGROUND:
Proteolytic degradation of the extracellular matrix, a feature of mucosal homeostasis and tissue renewal, also contributes to the complications of intestinal inflammation. Whether this proteolytic activity is entirely host-derived, or, in part, produced by the gut microbiota, is unknown.

METHODS:
We screened the bacterial colonies for gelatinolytic activity from fecal samples of 20 healthy controls, 23 patients with ulcerative colitis, and 18 with Crohn's disease (CD). In addition, the genes encoding metalloproteases were detected by conventional or real-time polymerase chain reaction (PCR).

RESULTS:
Gelatinolytic activity was found in approximately one-quarter of samples regardless of the presence of inflammation and without any attempt to enhance the sensitivity of the culture-based screen. This was associated with a diversity of bacteria, particularly in CD, but was predominantly linked with Clostridium perfringens. Culture supernatants from C. perfringens degraded gelatin, azocoll, type I collagen, and basement membrane type IV collagen, but different isolates varied in the degree of proteolytic activity. Results were confirmed by detection of the C. perfringens colA gene (encoding collagenase) in fecal DNA, again regardless of the presence or absence of inflammation. However, the biologic significance and potential implications of microbial-derived proteolytic activity were confirmed by reduced transepithelial resistance (TER) after exposure of rat distal colon to culture supernatants of C. perfringens in Ussing chambers.

CONCLUSIONS:
The study shows that microbial-derived proteolytic activity has the capacity to contribute to mucosal homeostasis and may participate in the pathogenesis of inflammatory bowel disease.

PMID: 20853433 [PubMed - in process]

Inflamm Bowel Dis. 2011 May;17(5):1251-3. doi: 10.1002/ibd.21446. Epub 2010 Aug 30.

10. Fibroblast activation protein expression in Crohn's disease strictures.

Rovedatti L, Di Sabatino A, Knowles CH, Sengupta N, Biancheri P, Corazza GR, MacDonald TT.

PMID: 20806341 [PubMed - in process]

Gut. 2011 Feb;60(2):151-2.

11. Recording from human gut tissue: a major step towards more efficient drug development?

Schemann M.

Source

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Comment on

Gut. 2011 Feb;60(2):204-8.

Gut. 2011 Feb;60(2):281-2.

PMID: 21205877 [PubMed - indexed for MEDLINE]

Expert Rev Gastroenterol Hepatol. 2010 Oct;4(5):637-51.

12. The enteric nervous system as a regulator of intestinal epithelial barrier function in health and disease.

Snoek SA, Verstege MI, Boeckxstaens GE, van den Wijngaard RM, de Jonge WJ.

Source

Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam, The Netherlands.

Abstract

The intestinal epithelia proliferate and differentiate along the crypt villus axis to constitute a barrier cell layer separating some 10^{13} potentially harmful bacteria from a sterile mucosal compartment. Strict regulatory mechanisms are required to maintain a balance between the appropriate uptake of luminal food components and proteins, while constraining the exposure of the mucosal compartment to luminal antigens and microbes. The enteric nervous system is increasingly recognized as such a regulatory housekeeper of the epithelial barrier integrity, in addition to its ascribed immunomodulatory potential. Inflammation affects both epithelial integrity and barrier function and, in turn, loss of barrier function perpetuates inflammatory conditions. The observation that inflammatory conditions affect enteric neurons may add to the dysregulated barrier function in chronic disease. Here, we review the current understanding of the regulatory role of the nervous system in the maintenance of barrier function in healthy state, or during pathological conditions of, for instance, stress-induced colitis, surgical trauma or inflammation. We will discuss the clinical potential for advances in understanding the role of the enteric nervous system in this important phenomenon.

PMID: 20932148 [PubMed - indexed for MEDLINE]

Gastroenterology. 2011 May 26. [Epub ahead of print]

13. Enterococcus faecalis Metalloprotease Compromises Epithelial Barrier and Contributes to Intestinal Inflammation.

Steck N, Hoffmann M, Sava IG, Kim SC, Hahne H, Tonkonogy SL, Mair K, Krueger D, Pruteanu M, Shanahan F, Vogelmann R, Schemann M, Kuster B, Sartor RB, Haller D.
Source

Chair for Biofunctionality, ZIEL-Research Center for Nutrition and Food Science, Technische Universität München, Freising-Weihenstephan, Germany.

Abstract

BACKGROUND & AIMS:
Matrix metalloproteases (MMPs) mediate pathogenesis of chronic **intestinal inflammation**. We characterized the role of the gelatinase (GelE), a **metalloprotease** from **Enterococcus faecalis**, in the development of colitis in mice.

METHODS:
Germ-free, interleukin-10-deficient (IL-10(-/-)) mice were monoassociated with the colitogenic E **faecalis** strain OG1RF and isogenic, GelE-mutant strains. **Barrier** function was determined by measuring E-cadherin expression, transepithelial electrical resistance (TER), and translocation of permeability markers in colonic **epithelial** cells and colon segments from IL-10(-/-) and TNF(ΔARE/Wt) mice. GelE specificity was shown with the MMP inhibitor marimastat.

RESULTS:
Histologic analysis (score 0-4) of E **faecalis** monoassociated IL-10(-/-) mice revealed a significant reduction in colonic tissue **inflammation** in the absence of bacteria-derived GelE. We identified cleavage sites for GelE in the sequence of recombinant mouse E-cadherin, indicating that it might be degraded by GelE. Experiments with Ussing chambers and purified GelE revealed the loss of **barrier** function and extracellular E-cadherin in mice susceptible to **intestinal inflammation** (IL-10(-/-) and TNF(ΔARE/Wt) mice) before **inflammation** developed. Colonic **epithelial** cells had reduced TER and increased translocation of permeability markers after stimulation with GelE from OG1RF or strains of E **faecalis** isolated from patients with Crohn's disease and ulcerative colitis.

CONCLUSIONS:
The **metalloprotease** GelE, produced by commensal strains of E **faecalis**, **contributes** to development of chronic **intestinal inflammation** in mice that are susceptible to **intestinal inflammation** (IL-10(-/-) and TNF(ΔARE/Wt) mice) by impairing **epithelial barrier** integrity.

PMID: 21699778 [PubMed - as supplied by publisher]

Gastroenterology
Volume 136, Issue 5, Supplement 1 , Pages A-21-A-22, May 2009

14. 119 Bacterial Proteases Contribute to the Development of Chronic Intestinal Inflammation By Impairing Epithelial Barrier Function

Natalie Steck, Micha Hoffmann, Carrie M. Hew Ferstl, Sandra C. Kim, Bo Liu, Rudi F. Vogel, R. Balfour Sartor, Dirk Haller

PDF

No abstract is available. To read the body of this article, please view the PDF online.

15. Bacterial proteases in IBD and IBS

STECK, N.et al. (2011). Bacterial proteases in IBD and IBS. Gastroenterology, in press.

Cell Mol Immunol. 2011 Mar;8(2):110-20. Epub 2011 Jan 31.

16. The role of gut microbiota (commensal bacteria) and the mucosal barrier in the pathogenesis of inflammatory and autoimmune diseases and cancer: contribution of germ-free and gnotobiotic animal models of human diseases.

Tlaskalová-Hogenová H, Stěpánková R, Kozáková H, Hudcovic T, Vannucci L, Tučková L, Rossmann P, Hrnčíř T, Kverka M, Zákostelská Z, Klimešová K, Přibylová J, Bártová J, Sanchez D, Fundová P, Borovská D, Srůtková D, Zídek Z, Schwarzer M, Drastich P, Funda DP.

Source

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Abstract

Metagenomic approaches are currently being used to decipher the genome of the **microbiota** (microbiome), and, in parallel, functional studies are being performed to analyze the effects of the **microbiota** on the host. Gnotobiological methods are an indispensable tool for studying the consequences of bacterial colonization. Animals used as **models** of **human diseases** can be maintained in sterile conditions (isolators used for **germ-free** rearing) and specifically colonized with defined microbes (including non-cultivable **commensal bacteria**). The effects of the **germ-free** state or the effects of colonization on disease initiation and maintenance can be observed in these **models**. Using this approach we demonstrated direct involvement of components of the **microbiota** in chronic intestinal inflammation and development of colonic neoplasia (i.e., using **models** of **human inflammatory** bowel disease and colorectal carcinoma). In contrast, a protective effect of **microbiota** colonization was demonstrated for the development of **autoimmune** diabetes in non-obese diabetic (NOD) mice. Interestingly, the development of atherosclerosis in **germ-free** apolipoprotein E (ApoE)-deficient mice fed by a standard low-cholesterol diet is accelerated compared with conventionally reared animals. **Mucosal** induction of tolerance to allergen Bet v1 was not influenced by the presence or absence of **microbiota**. Identification of components of the **microbiota** and elucidation of the molecular mechanisms of their action in inducing pathological changes or exerting beneficial, disease-protective activities could aid in our ability to influence the composition of the **microbiota** and to find bacterial strains and components (e.g., probiotics and prebiotics) whose administration may aid in disease prevention and treatment.

PMID: 21278760 [PubMed - in process]

Auton Neurosci. 2010 Feb 16;153(1-2):99-105. Epub 2009 Aug 27.

17. Peripheral relays in stress-induced activation of visceral afferents in the gut.

van den Wijngaard RM, Klooker TK, de Jonge WJ, Boeckxstaens GE.

Source

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Abstract

Multiple organs are targeted by the stress response, but the focus of this article is on **stress-induced activation** of **visceral afferents** in the **gut**. During recent years it became apparent that mast cells are pivotal in this response. **Peripheral** corticotrophin releasing factor (CRF) induces their degranulation whereupon mast cell mediators activate **visceral afferents**. In addition, these mediators are responsible for **gut** barrier dysfunction and subsequent influx of luminal antigens and bacteria. Some research groups have begun to investigate the possible importance of barrier dysfunction for enhanced **visceral** sensitivity. After reviewing the current knowledge on CRF-induced mast cell degranulation we will discuss these groundbreaking papers in a more elaborate way. They form the basis for a hypothesis in which not only CRF-induced but also antigen-mediated mast cell degranulation is relevant to stress-related afferent **activation**. Part of this hypothesis is certainly speculative and needs further investigation. At the end of this article we sum up some of the unanswered questions raised by others and during this review.

PMID: 19716349 [PubMed - indexed for MEDLINE]

Biochim Biophys Acta. 2011 Apr 7. [Epub ahead of print]

18. Relevance of mast cell-nerve interactions in intestinal nociception.

van Diest SA, Stanisor OI, Boeckxstaens GE, de Jonge WJ, van den Wijngaard RM.
Source

Tytgat Institute for Liver and **Intestinal** Research, Academic Medical Center, Amsterdam, The Netherlands.

Abstract

Cross-talk between the immune- and nervous-system is considered an important biological process in health and disease. Because **mast** cells are often strategically placed between nerves and surrounding (immune)-cells they may function as important intermediate cells. This review summarizes the current knowledge on bidirectional interaction between **mast** cells and nerves and its possible **relevance** in (inflammation-induced) increased **nociception**. Our main focus is on **mast** cell mediators involved in sensitization of TRP channels, thereby contributing to **nociception**, as well as neuron-released neuropeptides and their effects on **mast** cell activation. Furthermore we discuss mechanisms involved in physical **mast cell-nerve interactions**. This article is part of a Special Issue entitled: **Mast** cells in inflammation.

PMID: 21496484 [PubMed - as supplied by publisher]

19. T2025 Probiotic-Derived Lactocepin Degrades the Pro-Inflammatory Chemokine IP-10: Impact on Chronic Intestinal Inflammation

Gastroenterology (May 2010), 138 (5), Supplement 1, pg. S-616
Marie-Anne von Schillde; Gabriele Hörmannsperger; Carl-Alfred Alpert; Hannes Hahne; Christine Bäuerl; Michael Blaut; Dirk Haller

Abstract

No abstract

10.1016/S0016-5085(10)62838-7

Permalink: http://resolver.scholarsportal.info/resolve/00165085/v138i0005_s1/s_tpldtpiiocii