BIOGRAPHICAL SKETCH

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NAME: W. Allan Walker

eRA COMMONS USER NAME (credential, e.g., agency login): WAWALKER

POSITION TITLE: Conrad Taff Professor of Nutrition and Pediatrics; Chairman, Division of Nutrition, Harvard Medical School; Investigator, Mucosal Immunology & Biology Research Center, MGHfC

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
DePauw University. Greencastle, Indiana	B.S. (magna cum laude)	1959	Premedical Science English Literature
Washington University School of Medicine, St. Louis, Missouri	M.D. (cum laude)	1963	Medicine

A. Personal Statement

My laboratory has studied the development of mucosal host defense in human newborns. More recently we have studied the "crosstalk" between colonizing bacteria and the immature enterocyte. We have established human models of intestinal epithelial development to determine intestinal host defense in the newborn period. A major difference between the initial colonization in the preterm human intestine is that colonizing bacteria which in mature intestine are commensals can cause inflammation suggesting that "crosstalk" in the preterm differs from mature intestine in part due to the immaturity of the fetal enterocyte response to bacteria and their secreted products. Paradoxically, certain colonizing commensals, e.g. probiotics, can prevent the expression of a unique intestinal inflammation associated with preterm birth, namely necrotizing enterocolitis. Accordingly, we have begun to study the effect of ingested preterm breast milk on intestinal bacterial colonization and the mechanism of anti-inflammation of known probiotics on preterm infants stimulated by this dietary process. Using core facilities including a microbiota analysis core as part of a Genomics Core in an NIH funded Nutrition Center (P30 DK040561), we have analyzed specific species of bacteria in the intestine of expressed breast milk vs. formula fed premature infants. These species as well as known anti-NEC probiotics will be studied at the cellular level to determine the unique mechanisms of response by enterocytes from preterm infants using established ex-vivo fetal intestinal models and newly established enterocyte organoids.

1. Jain N, **Walker WA**. Diet and host-microbial crosstalk in postnatal intestinal immune homeostasis. Nature Rev Gastro Hepatology 2015; 12:14-25. PMID:25201040
2. Houghteling P, **Walker WA**. Why is initial bacterial colonization of the intestine important to the infant's and child's health. J Pediatr Gastro Nutr 2015; 60:294-307. PMCID: PMC4340742
3. Donnet-Hughes A, Schriffin E, **Walker WA**. Protective properties of human milk and bacterial colonization of the neonatal gut, Chapter 30, pp.250-265. In: Nutrition In Pediatrics - Basic Science and Clinical Aspects (5th Edition). Chinese Publications Inc., New Haven, CT. Eds. Duggan C, Koletzko B, Watkins J, Walker WA. 2016
4. Groer MW, Gregory KE, Louis-Jacques A, Thibeau S, **Walker WA**. The very low birth weight infant microbiome and childhood health. Birth Defects Res (Part C) Embryo Today. 2015;105:252-264. PMID: 26663857
5. Weng M, **Walker WA**. The role of gut microbiota in programming the immune phenotype. J Developmental Origin of Health and Disease 2013; 4:203-214. PMCID: PMC3864895

B. Positions and Honors

Positions and Employment

1963-67 Intern, Resident and Chief Resident in Pediatrics, University of Minnesota Hospitals, Minneapolis, MN

1964-66	Wyeth Pediatric Fellowship
1967-69	Research Fellow in Immunologic Diseases (Drs. Robert Good/Richard Hong), Department of Pediatrics, University of Minnesota, Minneapolis, MN
1969-72	Research Fellow in Medicine, (Gastroenterology, Dr. Kurt Isselbacher), Massachusetts General Hospital, Harvard Medical School, Boston, MA
1972-2013	Chief, Mucosal Immunology Laboratory, Massachusetts General Hospital *for* Children, Boston, MA
1970-71	Instructor in Medicine, Harvard Medical School, Boston, MA
1972-75	Assistant Professor of Pediatrics, Harvard Medical School, Boston, MA
1972-82	Chief of Pediatric Gastrointestinal and Nutrition Unit, Massachusetts General Hospital, Boston, MA
1975-1980	Associate Pediatrician and Pediatrician, Massachusetts General Hospital, Boston, MA
1975-	Associate Professor and Professor of Pediatrics, Harvard Medical School, Boston, MA
1982-01	Chief, Combined Program in Pediatric Gastroenterology and Nutrition, Children's Hospital and Massachusetts General Hospital, Boston, MA
1991-	Conrad Taff Professor of Nutrition, Harvard Medical School, Boston, MA
1993-	Professor, Department of Nutrition, Harvard School of Public Health, Boston, MA
1994-2016	Principal Investigator, Harvard Clinical Nutrition Research Center (P30 DK40561)
2014-	Investigator, Mucosal Immunology and Biology Research Center, MGH*f*C

Other Experience and Professional Memberships

1975-80	Academic Research Career Development Award, NIAMDD, NIH, Bethesda, MD
1980-87;1996-00	Member and Chairman, Gastrointestinal & Clinical Nutrition Study Section (GMA-2), NIH
1988-92	Member and Chairman for NIDDK Training Fellowship Committee
1989-2004	Editorial Boards: Gastroenterology, Nutrition Reviews, Pediatrics in Review, Nutritional Biochemistry, Pediatric Research; Editor- J of Pediatric Gastroenterology and Nutrition
1993-1996	Chairman Research Committee, American Gastroenterological Association
2001-2005	Member, Advisory Council, NIDDK, NIH

Honors

1984	Nutrition Award (Borden Award), American Academy of Pediatrics
1992	Fogarty International Fellowship (Sabbatical in Molecular Biology Department, Pasteur Institut with Professor Daniel E. Louvard)
1995	Shwachman Award for outstanding achievement in Pediatric Gastroenterology, North American Society for Pediatric Gastroenterology and Nutrition
1997-2007	MERIT AWARD- NICHD - R37 HD12437
1997	Hugh R. Butt Award for outstanding clinical research in nutrition, AGA
1998	Murray Davidson Award for excellence in gastroenterology, Am. Academy of Pediatrics
2008	Macy-Gyorgy Award for outstanding research in breast milk biology – International Society for Research in Human Milk and Lactation
2012	AGA Institute Council, Growth, Development and Child Health Mentor Award

C. Contributions to Science

1. **The immature fetal enterocyte immune response.** Using human fetal intestinal models, we have shown that the fetal enterocyte response to colonizing bacteria is developmentally regulated and favors an inflammation over immune homeostasis. We have reported that innate inflammatory immune response genes (TLR-4, NFκB, IL-8) are overexpressed and negative regulators of the immune response (A-20, TOLLIP, IRAK-M) are underexpressed. In addition, we have shown that toll receptors (TLR-4 and TLR-2) are overexpressed on the surface of fetal enterocytes and their expression is developmentally regulated. More recently, we have reported that the AP1 transcription system is developmentally regulated in its response to IL-1β stimulation. These observations help to explain the excessive inflammatory response to colonizing intestinal bacteria resulting in NEC.

1. Nanthakumar N, Fusunyan RD, Sanderson IR, **Walker WA**. Inflammation in the developing human intestine: A possible pathophysiologic basis for necrotizing enterocolitis. PNAS 2000; 97:6043-6048.
2. Nanthakumar N, Meng D, Goldstein AM, Zhu W, Lu K, Uauy R, Llano A, Claud EC, **Walker WA.**

The mechanism of excessive intestinal inflammation in necrotizing enterocolitis: An immature innate immune response. Plos One 2011; 6:(3):e17776. PMCID:PMC3061868

3. Meng D, Zhu W, Shi HN, Lu L, Wijendran V, Xu W, **Walker WA**. The toll-like receptor -4 in human and mouse colonic epithelium is developmentally regulated: a possible role in necrotizing enterocolits. Pediatr Res 2015; 77(3):416-24. PMCID: PMC4479150
4. Cahill CM, Rogers JT, **Walker WA**. The role of phosphoinositide 3-kinase signaling in intestinal inflammation. J Signal Transduction, 2012;12:358476. PMCID: PMC3337621
5. Claud EC, Lu L, Anton PM, Savidge T, **Walker WA**, Cherayil BJ. Developmentally-regulated IκB expression in intestinal epithelium and susceptibility to flagellin-induced inflammation. PNAS 2004; 101:7404-7408
6. Cahill C, Zhu W, Oziolor E, Yang Y-J, Tam B, Rajanaia S, Rogers JT, **Walker WA**. Differential expression of the activator protein 1 transcription factor regulates interleukin-1 beta induction of interleukin 6 in the developing enterocyte. Plos One 2016; 11(1):e0145184. PMCID:PMC4723075

2. **The role of breastmilk in preterm intestinal host defense**. We have studied the protective effect of breastmilk on neonatal intestinal host defense. We have reported that cytokines and trophic factors in colostrum stimulate anti-inflammation and other protective effects in the newborn gut. We know from clinical studies that feeding preterm infants expressed breast milk is protective against NEC. We have begun to determine the role of breast milk premature intestinal colonization and the anti-inflammatory effects of breast milk-stimulated intestinal microbiota on the fetal enterocyte. These studies will be extended as part of this grant.

    1. **Walker WA**, Iyengar RS. Breast milk, microbiota and intestinal immune homeostasis. Pediatr Res 2015; 77:220-228. PMID:25310762
    2. Gregory KE*, Samuel BS*, Houghteling P, Shan G, Ausubel FM, Sadreyev RI, **Walker WA**. Influence of maternal breast milk ingestion on acquisition of the intestinal microbiome in preterm infants. Microbiome 2016;4:68 PMID 28034306 (*shared authorship).
    3. Rautava S, **Walker WA***, Lu L*. Hydrocortisone-induced anti-inflammatory effects depend on the timing of exposure in immature human enterocytes. Am J Physiol Gastrointest Liver Physiol 2016; 310:G920-G929. (*shared senior authorship). PMCID: PMC4935478.
    4. Wijendran V, Brenna JT, Wang DH, Zhu W, Meng D, Ganguli K, Kothapalli KSD, Requena P, Innis S, **Walker WA**. Long chain poly-unsaturated fatty acids attenuate the IL-1β-induced pro-inflammatory response in human fetal intestinal epithelial cells. Pediatr Res 2015; 78:626-633. PMID: 26270575
    5. Rautava S, Lu L, Nanthakumar NN, Dubert-Ferrandon A, **Walker WA**. TGF-β2 induces maturation of immature human intestinal epithelial cells and inhibits inflammatory cytokine response induced via NF-κB pathway. J Pediatr Gastroenterol Nutr 2012; 54(5):630-638. PMCID:PMC3319014

3. **Colonizing intestinal microbiota ("pioneer" bacteria) and development of host defense.** It is apparent from work done elsewhere and in this laboratory that intestinal immune homeostasis in the human infant is dependent on an appropriate initial colonization process. The process is much more complex in colonization of the preterm gut. Preterms have dysbioses which is made worse by the degree of intestinal immaturity. Under normal circumstances, colonization results in the delayed normal development of intestinal defenses. However, certain preterm dysbioses ultimately lead to NEC. We have evidence that dysbiosis leads to intestinal inflammation, but specific "pioneer" bacteria stimulated by exclusive breast feeding can prevent the extensive inflammation of NEC. Recent studies suggest the possible mechanisms of probiotic anti-inflammation in NEC. These mechanisms will be studied in this grant.

    1. Zhou Y, Shan G, Sodergren E, Weinstock G, **Walker WA**, Gregory KE. Longitudinal analysis of preterm intestinal microbiome prior to necrotizing enterocolitis: A case-control study. Plos One 2015; 10(3): e0118632. PMCID: PMC4351051
    2. Weng M, Ganguli K, Zhu W, Shi HN, **Walker WA**. Conditioned media from *Bifidobacteria infantis* protects against *Cronobacter sakzakii*-induced intestinal inflammation in newborn mice. Am J Phys- Gastrointestinal and Liver Physiol 2014; 306:G779-G787. PMCID: PMC4010653
    3. Ganguli K, Meng D, Rautava S, Lu L, **Walker WA***, Nanthakumar N*. Probiotics prevent

necrotizing enterocolitis by modulating enterocyte genes that regulate innate immune-mediated inflammation. Am J Phys: Gastrointestinal and Liver Physiology 2013; 304:G132-G141. (* shared senior authorship) PMID: 23139215; PMCID: PMC3543644

4. Meng D, Zhu W, Ganguli K, Shi H, Walker WA. Anti-inflammatory effects of *Bifidobacterium longum subsp infantis* secretion on fetal human enterocytes are mediated by TLR4 receptors. Am J Physiol Gastrointest Liver Physiol 2016, 311:G744-G753. PMCID: PMC5142200
5. Ganguli K, Collado MC, Rautava J, Lu L, Satokari R, von Ossowski I, Reunanen J, de Vos WM, Palva A, Isolauri E, Salminen S, **Walker WA**, Rautava S. *Lactobacillus rhamnosus GG* and its SpaC pilus adhesion attenuate inflammatory responsiveness in the fetal human gut and modulate TLR-related gene expression. Pediatri Res 2015; 77:528-5354. PMID: 25580735
6. Guo S, Gillingham T, Guo Y, Meg D, Zhu W, **WalkerWA***, Ganguli K*. Secretions of *Bifidobacteraium infantis* and *Lactobacillus acidophilus* protect intestinal epithelial barrier function. J Pediatr Gastroenterol Nutr 2017 (to be published March 2017) (*shared senior authorship).
7. Jiang F*, Meng D*, Zhu W, Weng M, Kasper DL, Walker WA. The Symbiotic Bacterial Surface Factor Polysaccharide A on *Bacteroides fragilis* Inhibits IL-1 β-Induced Inflammation in Human Fetal Enterocytes via Toll Receptors 2 and 4. Plos One 2017:12(3) (in press) (*shared authorship).

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=Allan+Walker+%5BAuthor+-+Full%5D

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

P30 DK040561 Walker (PI) 08/12-08/17
NIH
Nutrition Obesity Research Center at Harvard
Specific aims of project: The major specific aims are: 1) to provide research in basic areas of biology relevant to problems in clinical nutrition; 2) to promote the study of clinical nutrition and application of knowledge derived there from within the HMS, MIT and HSHP community; 3) to promote interactions among scientists and clinical investigators to show relevance to advancing the science of clinical nutrition; and 4) to attract "basic" investigators into the domain of clinical nutrition to promote an environment and mechanism to develop new investigator-initiated research (**Note**: The competing renewal of this grant will be reviewed in March, 2017)

Role: Program Director and PI

P01 DK033506 Walker (PI) 09/11-8/17 (no cost extension)
NIH-NIDDK
Barrier Function of the GI Tract in Health and Disease
The major objective remains the development of a multidisciplinary, mechanistic approach to characterize the role of the enterocyte in mucosal barrier function at the interface between microbial luminal stimuli and lymphoid effector responses. Using three intestinal inflammatory disease states (necrotizing enterocolitis, celiac disease and inflammatory bowel disease) as prototypic diseases to study in general the role of intestinal microbes interacting with the intestinal mucosa in health and disease, they will share their expertise to define the pathogenesis of inflammation in the intestine. The focus of the studies will be the enterocyte as it involves microbial "crosstalk," lymphoid-epithelial interactions, inappropriate developmental responses, its functions as a barrier to microbial penetration, and as a site for beneficial effects of health promoting bacteria in intestinal inflammation. The research focuses on both basic and translational aspects of the interaction between the host and the gut microbial ecosystem (microbes and/or their derived molecules) and how these interactions combine to play a role in intestinal inflammation (**Note**: The competing renewal of this grant will be reviewed in April, 2017)

Completed Research Support

R01 HD059126 Walker (PI) 02/11-09/16
NIH-NICHD/NIDDK
Maturation of Intestinal Immunity and NEC

R01-HD012437-29 Walker (PI) 2/09-10/16
NIH-NICHD/NIDDK