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Towards an Integrated Understanding of the Therapeutic Utility of Exclusive Enteral Nutrition in the Treatment of Crohn’s Disease

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Crohn’s disease (CD) is a chronic disease characterized by episodic and disabling inflammation of the gastrointestinal tract in genetically susceptible individuals. The incidence and prevalence of CD is rising rapidly across the world emphasizing that disease risk is also influenced by environmental and lifestyle factors, as well as the microbial community resident in the gut. Childhood-onset CD is associated with an aggressive disease course that can adversely impact patient growth and development. There is no cure for CD however new onset and recurrent cases of paediatric CD are often responsive to exclusive enteral nutrition (EEN) treatment. EEN treatment involves the exclusive consumption of an elemental or polymeric formula for several weeks and it is well established as a primary intervention. EEN treatments typically achieve remission rates of over 80% and importantly they are associated with a high rate of mucosal healing, far superior to steroids and which is prognostic of improved long-term health outcomes. Furthermore, they are safe, have few side effects, and improve nutritional status and linear growth. Surprisingly, despite the utility of EEN our understanding of the host-microbe-diet interactions that underpin clinical remission and mucosal healing are limited. Here, we review the current state of knowledge and propose that the induction of autophagy, in addition to modulation of the microbiota and coordinated effects on inflammation and epithelial cell biology, may be critical for the therapeutic effects associated with EEN. A better understanding of EEN treatment will provide new opportunities to restore gut homeostasis and prolong periods of remission, as well as provide new insights into the factors that trigger and perhaps prevent CD.

Pathobiology of Paediatric CD

The incidence of CD is characterised by a bimodal distribution with an initial peak in early adulthood (circa 14-30 years) and a second peak occurring later in life (circa 60-80 years).\textsuperscript{7} CD is characterised by discontinuous transmural lesions that can affect anywhere along the length of the gastrointestinal tract from mouth to anus, although it most commonly affects the terminal ileum and/or proximal colon.\textsuperscript{8} Up to 20% of patients are diagnosed with paediatric CD\textsuperscript{9} and early onset CD (<17 years) is associated with more extensive disease affecting multiple gastrointestinal sites and with more aggressive impact on growth and nutrition.\textsuperscript{10,12} Children with onset of CD before 6 years of age typically present with colonic disease in contrast to ileocolonic disease in older children\textsuperscript{10} and...
Nutritional Treatment of Paediatric CD

Up to 85% of paediatric CD subjects are affected by chronic malnutrition and stunting due to reductions in appetite, intake, impaired nutrient absorption and increased caloric demand driven by chronic inflammation. The treatment and management of paediatric CD is thus associated with additional challenges as this coincides with important growth and developmental events. Immunosuppressive corticosteroids are widely used to alleviate inflammation in adult CD however their use for paediatric CD is diminishing as they are complicated by further impairment of growth, bone health and development. Moreover, corticosteroids fail to address the mucosal damage which is the greatest predictor of longer term complications. Instead, nutritional restitution and mucosal healing via enteral feeding has become accepted as an effective strategy for children with CD. Enteral feeding describes the consumption of a nutritionally replete liquid diet (formula) either orally or via nasogastric tube depending on patient choice and clinical status. It is well recognised that exclusive enteral nutrition (EEN) can induce clinical remission in over 80% of newly-diagnosed CD subjects and in the absence of other therapies. EEN also restores adequate nutritional intake and status with improvements in linear growth, bone health and lean mass accumulation in children with CD. Indeed, the anti-inflammatory and growth-stimulating effects of enteral feeding precede nutritional restitution. While EEN was originally studied in the context of ileal disease it has been shown that disease location does not influence remission in CD. Importantly, EEN treatment has few side-effects, is broadly comparable to corticosteroids in inducing remission and is superior to corticosteroids in its ability to induce mucosal healing and improve future outcomes.

EEN formulae typically comprise macronutrients including amino acids or protein hydrolysates, fatty acids and simple carbohydrates along with micronutrients including vitamins and dietary elements. Proteins, fats and carbohydrates are mainly absorbed in the duodenum and jejunum implying that little of the EEN derived substrate reach the ileum and colon. The formulae are classified on the basis of their amino acid content with those containing free amino acids referred to as elemental, those containing peptides referred to as semi-elemental and those containing whole proteins referred to as polymeric. Different formulations have been widely used that vary in the composition and/or form of amino acids, carbohydrates and fatty acids for the treatment of CD and maintenance of remission. However, elemental and polymeric diets do not differ in their ability to induce or maintain remission but polymeric diet is more palatable and therefore superior for compliance. EEN is now recommended by multiple guidelines as a primary therapy in children with CD and it is also an effective treatment for adult CD although studies are confined by lower patient numbers.

Enteral nutrition therapy is typically used to induce remission but has also been used to maintain remission alone or in combination with other treatments including thiopurines, aminosalicylates and anti-TNFα agents. Furthermore, in a prospective study enteral nutrition was shown to reduce clinical and endoscopic recurrence at 1 year following surgical resection for CD and reduced the incidence of recurrence requiring biologic therapy at 5 years. EEN is a safe and effective treatment for CD although its mechanism(s) of action remain(s) to be determined. Elucidating the key factors of disease pathogenesis from other causes of immune deficiency and immune dysregulation, including monogenic disorders, is more challenging. CD is underpinned by defects in critical host functions including in innate and adaptive immunity, autophagy and gut barrier function and genome wide association studies have currently identified no fewer than 140 individual host genetic susceptibility loci. To date, no single susceptibility locus has been identified that is shared amongst all CD subjects although an increased genetic burden is associated with an earlier age of diagnosis and ileal involvement. Furthermore, nod2 susceptibility alleles are common in CD patients in European populations and are also associated with an earlier age of onset and ileal disease in Caucasians. Nod2 is required for autophagy-mediated intracellular bacterial clearance and the risk of disease increases with the possession of additional nod2 risk alleles. However, the known CD susceptibility loci only explain 13.6% of the variance in disease risk, suggesting genetic susceptibility is necessary but not sufficient for disease to develop, and it is now widely accepted that incidence and prevalence are also influenced by environmental (e.g. breastfeeding, appendectomy) factors and lifestyle (e.g. smoking, diet) choices.

Recent studies have revealed the host genotype plays a key role in modulating the microbial community resident in the gut (i.e. gut microbiota). Intriguingly, some of the genetic loci affecting bacterial colonisation overlap known CD susceptibility loci suggesting gut bacteria can drive disease in a host genotype specific manner. Indeed it is now accepted that the gut microbiota contribute to the pathogenesis of CD (Figure 1). First, germ free animal models of CD are protected from disease and the transfer of disease-associated but not healthy microbiota to Tnfα−/− mice that develop a spontaneous CD-like transmural ileitis result in the rapid onset of disease, revealing microbiota can be transferred to a susceptible host and initiate disease. Second, the microbiota varies between healthy and CD subjects and the microbiota undergo dramatic structural changes coincident with the onset of active disease. Finally, disease is responsive to antibiotics and diversion of the faecal stream and faecal microbiota transfers also offer promise for successful treatment of CD. Although these studies emphasize that the gut microbiota plays an integral role in the aetiology and treatment of CD, the host-microbe interaction(s) that influence disease risk in genetically susceptible individuals, and how they might be ameliorated, remain largely unknown.

Figure 1. CD is underpinned by host genetic susceptibilities, environmental factors, lifestyle choices and the gut microbiota.
underpinning EEN treatment will provide vital new insights into the pathogenesis of CD and support the development of improved treatment strategies.

The Healthy and CD Ileocolonic Gut Microbiota

The human gut microbiota provides a range of ecological and nutritional functions that supports the maintenance of host health and well-being. The vast majority of microbes are resistant to laboratory based cultivation and much of our knowledge of the structural diversity and functional capacity of the microbiota has been provided by culture independent phylogenetic profiling based on the 16S rRNA gene\textsuperscript{63, 64} and metagenomic approaches.\textsuperscript{60} The infant gut is colonised by a diverse microbiota following birth and it assumes an adult-like conformation post weaning\textsuperscript{65}. The gut microbiota is characterised by significant inter-subject variability\textsuperscript{62} nonetheless, the healthy gut possesses a core microbiota of numerically abundant bacteria that are widely shared.\textsuperscript{59, 60} The core microbiota has been proposed to help maintain gut homeostasis and several beneficial core bacteria modulate the host inflammatory response and regulate the development and effector functions of different immune cell populations.\textsuperscript{63-65} Indeed, bacteria from the core gut microbiota have been proposed as “next-generation” probiotics\textsuperscript{66} with the core gut bacterium \textit{Faecalibacterium prausnitzii} specifically proposed as a probiotic for the treatment of CD.\textsuperscript{65, 66}

At diagnosis, the treatment-naïve paediatric CD gut is already characterised by a state of dysbiosis with distinct structure-function changes to the microbiota that can be further exaggerated by antibiotic treatment.\textsuperscript{67-69} The CD associated dysbiosis is characterised by alterations in species richness driven by reductions in the abundance of key bacterial lineages affiliated with the Bacteroidetes (\textit{Bacteroides} spp.), Actinobacteria (\textit{Bifidobacteria} spp.) and Firmicutes (in particular the \textit{Clostridium leptum} and \textit{Clostridium cocoides} subgroups) that include taxa affiliated with the core microbiota; and the expansion of lineages affiliated with the Proteobacteria and Fusobacteria. Qin et al.\textsuperscript{60} also reported perturbations to these taxa and noted the core gut microbiota differed between healthy and CD subjects in adults. These observations have been broadly replicated internationally\textsuperscript{3} indicating CD is characterized by a specific dysbiosis that may be central to the development and persistence of disease. Relatively few longitudinal studies of the structure-function changes to the CD microbiota have been reported even though such studies offer the opportunity to better dissect cause-effect relationships and in particular how the gut microbiota may contribute to remission or recurrent disease. In the most comprehensive such study to date de Cruz et al.\textsuperscript{23} reported the reduced representation of bacteria from the core microbiota including saccharolytic bacteria affiliated with the Bacteroidetes and butyrate producing Firmicutes from the mucus of recurrent CD patients both at the time of corrective surgery for CD and 6 months post-operatively. These observations were broadly replicated in a North American study which reported a reduction in diversity and the relative abundance of Firmicutes affiliated bacteria in subjects with recurrent CD.\textsuperscript{24} These studies have revealed important differences between the healthy and CD gut that are coincident with the onset of active disease.

CD is characterised by defects in host pathways essential for maintaining host-microbe homeostasis implying that the inflammatory response is driven by a general response to the gut microbiota. Unexpectedly, one of the most notable observations arising from recent animal models of CD is that the ability to drive inflammation is restricted to select bacteria such as \textit{Bacteroides vulgatus} and \textit{Bacteroides thetaiotaomicron}.\textsuperscript{70-72} Similarly, CD and UC subjects are characterised by a T-cell dependent immune response that results in the production of high affinity neutralising secretory IgA directed against select inflammmogenic bacteria in the microbiota.\textsuperscript{72} Thus, reported alterations to the CD gut microbiota may largely reflect the contraction or expansion of particular lineages in response to changes in the gut environment. Critically, these studies suggest interventional strategies targeting specific members of the gut microbiota could be developed for CD.

Impact of EEN Treatment on the CD Microbiota

The ability of microbes to persist in the gut is supported by their capacity to rapidly respond and adjust their growth rate to changing environmental conditions. The human and murine gut microbiota responds rapidly to changes in diet, and diet induced changes dominate the influence of host genetics in mice.\textsuperscript{73-74} This suggests nutrient based interventions may represent a plausible strategy to prevent and/or treat chronic gut diseases. However, despite the efficacy of EEN treatments for CD our understanding of their effects on the structure and functional activity of the gut microbiota is limited.

Remarkably, despite decreased nutrient delivery to the distal gut EEN treatment does not appear to affect the total microbial load in CD. Using quantitative real time PCR Shiga et al.\textsuperscript{75} reported the total bacterial load in faeces was not affected following a 6 week EEN intervention although a significant reduction in the \textit{Bacteroides fragilis} affiliated population was seen. A separate study also applied quantitative real time PCR and similarly reported that the total bacteria load was not altered during an 8 week EEN intervention although \textit{Bacteroides/Prevotella} affiliated bacteria were significantly reduced in subjects achieving clinical remission.\textsuperscript{76} The nutrient sources supporting the maintenance of microbial load in faeces during EEN treatment are largely unknown but are likely both host and microbiota derived. In contrast, numerous studies report enteral diets impact the diversity and richness of the CD microbiota. Lionetti et al.\textsuperscript{77} reported exclusive use of EEN for 8 weeks to be associated with significant changes to the gut microbiota as assessed by temperature gradient gel electrophoresis. The children remained in remission for up to 8 months following introduction of a free diet supplemented with polymeric formula although the gut microbiota was further altered. Separately, Leach et al.\textsuperscript{78} also reported alterations to the gut microbiota following an 8 week EEN intervention with changes to taxa affiliated with \textit{Bacteroides/Prevotella} spp. associated with a reduction in CD activity and inflammation. The alterations were largely sustained for up to 4 months following resumption of a solid diet and stability of the \textit{C. leptum} group that includes \textit{F. prausnitzii} was associated with reduced CD activity and inflammation. The abundance of \textit{F. prausnitzii} has also been reported to be reduced following an enteral diet\textsuperscript{79, 80} although variations in the ability of taxonomic groupings classified as \textit{Faecalibacterium} spp. to respond to the dietary interventions have been observed suggesting that important intraspecies variations exist that influence the ability of individual strains to colonise and persist in the CD gut.\textsuperscript{81} To date relatively few studies have assessed the impact of EEN treatment on the gut microbiota of paediatric cohorts by deep sequencing of the 16S rRNA gene and/or metagenomic DNA. Kaakoush et al.\textsuperscript{82}
reported EEN treatment induced remission in 80% of new-onset CD subjects and this was associated with a significant decrease in microbial diversity. Relapse was associated with an increase in diversity and the abundance of specific Firmicutes affiliated lineages as revealed by both 16S rRNA profiling and targeted metagenomic analyses. Quince et al.,77 reported EEN treatment achieved a remission rate of 62% in CD subjects and noted a significant reduction in microbial diversity that was largely reversed following resumption of a habitual diet. Interestingly, EEN treatment further increased the state of dysbiosis with a reduction of bacterial taxa both positively and negatively associated with faecal calprotectin. Similarly, Lewis et al., reported EEN treatment achieved a remission rate of 45% and this was associated with an initial increase in dysbiosis that was largely reversed in responders but not non-responders following the 8 week intervention.80 Together these observations imply that EEN treatments may mediate their effects at least partly by affecting the structure-function activity of the microbiota and suggest the efficacy of EEN treatments could be further improved by selectively promoting the growth of beneficial gut bacteria.

Our understanding of the impact of EEN treatment on the gut microbiota has also been informed by animal models of CD. In one of the more insightful studies Kajiura et al.,51 reported that an elemental diet significantly suppressed inflammation in an IL-10 deficient cell transfer mouse model of colitis and this was associated with a decrease in the abundance of Lactobacillus spp. and an increase in Enterococcus spp. Lactobacillus sp. and to a much lesser extent Enterococcus sp. isolates were subsequently shown to induce TNFα and IL-6 production using a RAW macrophage cell line. A similar study using T-cell receptor α-chain deficient mice that develop colitis revealed that an elemental diet prevented the onset of disease by specifically reducing the abundance of the pathobiont B. vulgatus.52 Separately, when IL-10 deficient mice inoculated with Helicobacter trogontum to induce colitis were provided EEN, the pathogen load in colonic tissue was reduced, and there was also a restoration of barrier function and normalised inflammatory response.83

Several studies have also revealed that nature of the dietary composition can also impact disease course. Intriguingly, the monotonous nature of EEN treatments may also contribute to their efficacy as mice fed a varied diet were characterised by a reduction in microbial diversity and were more susceptible to DSS induced colitis in comparison to mice fed a monotonous diet.64 It must however be noted that the monotonous diets examined as part of this study were standard rodent diets likely to directly impact the host genetic factors it is now recognised that environmental factors also play a key role in undermining effective gut barrier function. For instance healthy first degree relatives of CD subjects exhibit increased permeability and subclinical inflammation but of particular interest are the observations that the spouses of CD subjects exhibit increased gut permeability implying that shared environmental factors also play a key role.93,94 These environmental factors remain to be identified but they could include a shared diet and a sharing of the microbiota through co-habitation.95,96 While the mechanism underpinning mucosal healing by EEN remains to be fully determined Nahidi et al.,77 demonstrated that a polymeric formula was as effective as the TNFα inhibitor infliximab and superior to hydrocortisone in maintaining gut barrier function in TNFα treated Caco-2 monolayers. This was mediated in part by maintaining tight junction integrity, as measured by transepithelial electrical resistance and the distribution of tight junction proteins.

Enteral nutrition also exerts anti-inflammatory effects and Guihot et al.,98 demonstrated that the gut-associated lymphoid tissue (GALT) of rats fed enteral diets was modified irrespective of the dietary form of the nitrogen. In particular there was a marked reduction in the number of intraepithelial lymphocytes and the expression of the major histocompatibility class II complex in epithelial cells that correlated with a reduction in the number of gastric Lactobacillus spp. A separate series of studies by Faria and colleagues99,100 revealed that conventionalised mice fed an elemental diet from weaning were characterised by a poorly developed GALT similar to that observed in germ or antigen free mice. Low levels of secretory IgA (sIgA) were reported suggesting the elemental diet resulted in a reduction in antigenic load that mitigated the influx and/or proliferation of immune cells in the gut. The elemental diets also resulted in a systemic effect with a reduction in levels of circulating IgA and IgG. The introduction of a casein containing diet to adult mice fed an elemental diet restored secretory IgA production and serum immunoglobulin levels.112 While the authors suggested these differences were driven directly by the nature of the protein source a major criticism of these studies is that they did not examine the impact of the different diets on the structure-function

Impact of EEN Treatments on the Host

In addition to its effects on the gut microbiota EEN treatments are also broadly considered to have two distinct but interrelated effects on the gut – the restoration of gut barrier function and subsequent mucosal healing, and the normalisation of the CD inflammatory response. CD subjects are characterised by defects in gut barrier function that result in increased permeability and potential antigenic stimulation by luminal derived substances. In addition to host genetic factors it is now recognised that environmental factors also play a key role in undermining effective gut barrier function. For instance healthy first degree relatives of CD subjects exhibit increased permeability and subclinical inflammation but of particular interest are the observations that the spouses of CD subjects exhibit increased gut permeability implying that shared environmental factors also play a key role.93,94 These environmental factors remain to be identified but they could include a shared diet and a sharing of the microbiota through co-habitation.95,96 While the mechanism underpinning mucosal healing by EEN remains to be fully determined Nahidi et al.,77 demonstrated that a polymeric formula was as effective as the TNFα inhibitor infliximab and superior to hydrocortisone in maintaining gut barrier function in TNFα treated Caco-2 monolayers. This was mediated in part by maintaining tight junction integrity, as measured by transepithelial electrical resistance and the distribution of tight junction proteins.
activity of the microbiota. Nonetheless, these studies suggest enteral diets can exert a profound impact on the GALT with possible implications for CD.

Separately, CD subjects treated with an elemental diet for 4 weeks demonstrated a reduction in production of pro-inflammatory cytokines and normalisation in the IL-1ra/IL-1 ratio which correlated with mucosal healing. The ex vivo exposure of CD ileal and colonic biopsies to enteral diets induced an anti-inflammatory effect irrespective of whether the diets were elemental or polymeric, although this effect was not observed using biopsies from healthy or ulcerative colitis subjects. Further in vitro experiments using a colonic HT-29 cell line revealed a TNFα induced inflammatory response could be ameliorated by a polymeric formula and this effect was mediated through specific modulation of the NF-κB signalling pathway. Interestingly, the production of IL-8 from a TNFα stimulated HT-29 cell line can be suppressed in a dose dependent manner by glutamine, arginine and vitamin D. Here, glutamine and arginine enhance production of the anti-inflammatory molecule nitric oxide and suppress activation of NF-κB and p38 mitogen-activated protein kinase by blocking phosphorylation within the respective signalling pathways. For instance, both glutamine and arginine directly inhibit IκB activity and as expected this effect is further enhanced by curcumin - a known inhibitor of IκB. Based on these observations, glutamine and arginine are likely beneficial treatments.

Towards an Integrated Mechanism of Action for EEN treatment

Surprisingly, and despite its efficacy, we know relatively little about the precise mechanisms of action of EEN treatment. EEN treatment is unlikely to act by directly affecting host tissues in the ileum and colon and instead we propose that it exerts its therapeutic effects by independently modulating several key factors underpinning inflammation in CD. First, it is notable that EEN treatment does not significantly impact the microbial load in faeces although the structure of the microbiota is significantly altered. Second, we anticipate the functional activity of the microbiota is changed in response to the reduction in nutrient load and the production of short chained fatty acids at least is known to be affected by EEN treatment. This may restrict the growth and activity of inflammogenic bacteria and together with the limited dietary content this likely reduces the extent of antigenic stimulation. Third, EEN nutrients are unlikely to directly affect ileal or colonic tissues due to the highly absorbable nature of the formulae. The amino acid requirements of enterocytes are primarily provided for by first pass catabolism of lumen supplied dietary amino acids and with the exception of glutamine it has been suggested that enterocytes are limited in their ability to utilise arterial supplied amino acids. This suggests that predominantly basolaterally supplied amino acids may not fully support the nutritional requirements of the mucosa raising the intriguing proposition that ileal enterocytes may experience nutrient stress during EEN treatment. Amino acid limitation and other nutrient stress inhibit the serine/threonine kinase mTOR resulting in the activation of autophagy. We hypothesise that EEN treatment induces autophagy and alleviates intracellular stress and inflammation by augmenting clearance of intracellular bacteria and other damaged or non-essential cellular components. In support of this hypothesis the induction of autophagy by nutrient starvation or mTOR inhibition reduces the intracellular survival of adherent invasive E. coli and IL-8 production in neutrophils and a small molecule enhancer of autophagy improves bacterial clearance in HeLa cells and suppress IL-1β secretion in macrophages bearing the CD associated ATG16L1 T300A risk allele. Inhibition of mTOR by celastrol or everolimus also ameliorates colitis in IL-10 deficient mice with the former and presumably the latter exerting their effect by up-regulating autophagy. Furthermore, the mTOR inhibitor rapamycin is an effective rescue therapy for the management of refractory paediatric CD although the mechanism of action has not yet been determined. Finally, starvation induced autophagy in Caco-2 cells reduces paracellular permeability by enhancing the tight junction barrier. Thus, in addition to reversing the effects of malnutrition affected with gut function the period of “bowel rest” afforded by enteral feeding may further support mucosal healing by limiting the growth and functional activity of potentially antagonistic microbes while simultaneously inducing autophagy to repair damaged host cells (Figure 2).

Concluding Remarks and Perspectives

EEN treatments are safe and their efficacy in inducing clinical remission and mucosal healing and supporting ongoing clinical and mucosal remission during the treatment of CD is well-established. The mechanism of action has not yet been conclusively determined although this might inform the development of more effective...
therapeutic strategies. This could translate the effectiveness of EEN treatment to adults and the 20% of paediatric CD subjects that do not respond to current dietary interventions. It remains to be discovered whether the effects of EEN are mediated via its action on the gut microbiota and/or on the host. However, based on the available evidence we contend that EEN exerts its principal therapeutic effect by restricting the growth and metabolic activity of the microbiota and enhancing autophagy resulting in a reduced inflammatory response and improved barrier function.

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Towards an Integrated Understanding of the Therapeutic Utility of Exclusive Enteral Nutrition in the Treatment of Crohn’s Disease

Abstract

Introduction

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References

Novelty: The therapeutic effects associated with EEN may be mediated by co-ordinate effects on the host gut mucosa and microbiota.