GULF WAR ILLNESS

Progression of intervention-focused research for Gulf War illness.

Chester JE[1,2], Rowneki M[3], Van Doren W[3], Helmer DA[3,4].

Mil Med Res. **2019 Oct 18**;6(1):31. doi: 10.1186/s40779-019-0221-x. PMID: 31627737.

The Persian Gulf War of 1990 to 1991 involved the deployment of nearly 700,000 American troops to the Middle East. Deployment-related exposures to toxic substances such as pesticides, nerve agents, pyridostigmine bromide (PB), smoke from burning oil wells, and petrochemicals may have contributed to medical illness in as many as 250,000 of those American troops. The cluster of chronic symptoms, now referred to as Gulf War Illness (GWI), has been studied by many researchers over the past two decades. Although over $500 million has been spent on GWI research, to date, no cures or condition-specific treatments have been discovered, and the exact pathophysiology remains elusive. Using the 2007 National Institute of Health (NIH) Roadmap for Medical Research model as a reference framework, we reviewed studies of interventions involving GWI patients to assess the progress of treatment-related GWI research. All GWI clinical trial studies reviewed involved investigations of existing interventions that have shown efficacy in other diseases with analogous symptoms. After reviewing the published and ongoing registered clinical trials for cognitive-behavioral therapy, exercise therapy, acupuncture, coenzyme Q10, mifepristone, and carnosine in GWI patients, we identified only four treatments (cognitive-behavioral therapy, exercise therapy, CoQ10, and mifepristone) that have progressed beyond a phase II trial. We conclude that progress in the scientific study of therapies for GWI has not followed the NIH Roadmap for Medical Research model. Establishment of a standard case definition, prioritized GWI research funding for the characterization of the pathophysiology of the condition, and rapid replication and adaptation of early phase, single site clinical trials could substantially advance research progress and treatment discovery for this condition.

CHRONIC FATIGUE SYNDROME

Open Trial of Vitamin B12 Nasal Drops in Adults With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Comparison of Responders and Non-Responders.

van Campen CLM[1], Riepma K[2], Visser FC[1].

Front Pharmacol. **2019 Sep 20**;10:1102. doi: 10.3389/fphar.2019.01102. PMCID: PMC6764214. PMID: 31616305.

Introduction: A recent study reported a favorable effect of vitamin B12 injections/oral folic acid support in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) patients. Recently, vitamin B12 nasal drops were developed as an alternative to the vitamin B12 injections. As no data are available on efficacy of this formulation, we studied vitamin B12 serum levels, the physical activity scale of the RAND-36, the number of steps on an activity meter, and the fatigue and concentration scales of the CIS20r questionnaires, before and after 3 months of treatment in ME/CFS patients.

Methods and Results: Fifty-one patients completed all measurements. Forty-four were female. Mean age was 42 years, and mean disease duration was 16 years. Median vitamin B12 levels before treatment were 328 (244-429) pmol/l, and 973 (476-1,476) pmol/l after treatment. Thirty-four patients reported a favorable response to treatment. In the non-responders, only a small but significant increase in vitamin B12 levels was observed. In contrast, in responders, the number of steps, the physical activity scale of the RAND-36, and the vitamin B12 serum levels increased significantly. The CIS20r fatigue scale decreased significantly, and the CIS20r concentration scale was unchanged.

Conclusions: Nasal drop vitamin B12 administration resulted in a significant increase in vitamin B12 serum levels and therefore may be effective. This pilot study suggest that the nasal drops may be used as an alternative to injections because two thirds of ME/CFS patients reported a positive effect, accompanied by an increased number of steps, improvement of the RAND-36 physical functioning scale and the CIS20r fatigue scale, and a significant increase in serum vitamin B12 levels.

CHRONIC FATIGUE SYNDROME (Continued)

Is a diagnostic blood test for chronic fatigue syndrome on the horizon?

Maes M[1,2,3], Rodriguez LA[4], Morris G[3].

Expert Rev Mol Diagn. **2019 Oct 18**:1-3. doi: 10.1080/14737159.2020.1681976. PMID: 31617771. [Epub ahead of print]

Expert opinion: Most if not all biomarkers of ME/CFS are pathway biomarkers although a few etiologic or predisposing biomarkers were delineated. These biomarkers indicate the multiple immune, oxidative, and metabolic pathways that underpin the pathophysiology of ME/CFS. However, until now, no diagnostic, treatment or staging biomarkers could be developed and, therefore, future research should develop those types of biomarkers employing data mining models with biomarkers of the pathways described herein as input variables. Moreover, pathway-phenotype algorithms should be modeled which may be used to diagnose biomarker-validated symptom dimensions including disabling fatigue, cognitive impairments, post-exertional malaise, fibromyalgia-like symptoms, and irritable bowel syndrome.

All in all, a new ME/CFS diagnostic blood test useful to make the diagnosis of ME/CFS is not yet on the horizon. The way forward is to develop adequate diagnostic criteria based on machine learning and to combine biomarkers and clinical phenotypes into pathway-phenotypes using machine learning techniques [3,14].

[View full text and references of this editorial article in Expert Review of Molecular Diagnostics.]

Editorial: Advances in ME/CFS Research and Clinical Care.

Friedman KJ[1], Bateman L[2], Bested A[3], Nahle Z[4].

Front Pediatr. **2019 Sep 18**;7:370. doi: 10.3389/fped.2019.00370. PMCID: PMC6759795. PMID: 31620406. eCollection 2019.

Advances in ME/CFS Research and Clinical Care spotlights Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): a maligned, stigmatized, under-researched disease, which lacks a definitive, objective clinical test for its diagnosis, and definitive palliative and curative treatments. A few brave physicians attempt to alleviate the suffering of the afflicted. They rely upon the patients' symptoms to guide them. Physicians can provide symptomatic relief and improve upon patients' abnormal physiological and metabolic parameters by intervening to cause the latter to approach normal limits. Documented to be more severely disabling than HIV-AIDS, ME/CFS receives disturbingly little funding in the United States and around the world. ME/CFS patients constitute an identifiable, underserved population that is in need of the recognition which would raise them from their current, underserved or non-served patient status into the mainstream of healthcare worldwide. ME/CFS is a common disease worldwide, affecting approximately 1 percent of the world's population.

Despite these obstacles, and as evidenced by the articles contained herein, ME/CFS research **is** being conducted, and patient care issues **are** being addressed. Today, researchers and clinicians communicate rapidly via the internet to overcome conventional impediments to knowledge and patient care.

At the end of the twentieth and the beginning of the twenty-first century, it seemed that the United States government had finally taken the lead in promoting research and patient care for a disease which had been described in exquisite detail by its own Public Health Service in the 1930's and subsequently largely ignored, or worse, defamed. More modern efforts to inform the U.S. Department of Health and Human Services (DHHS) began with the Chronic Fatigue Syndrome Coordinating Committee from 1996 to 2001, followed by reorganization as the Chronic Fatigue Syndrome Advisory Committee (CFSAC). That committee advised the U.S. Secretary of Health and Human Services on matters related to ME/CFS, but the recommendations of the CFSAC were largely ignored until 2015. That is when the Institute of Medicine (IOM) completed an evidence-based review and published a report, commissioned in response to a recommendation from the CFSAC, and sponsored by funds from the Office of Women's Health within DHHS, the National Institutes of Health (NIH), the Centers for Disease Control (CDC), the Food and Drug Administration (FDA), the Agency for Healthcare Research and Quality (AHRQ), and the Social Security Administration (SSA). The charge to the IOM committee was to develop clinical diagnostic criteria for ME/CFS, based on the evidence, and with the input of ME/CFS stakeholders. That report described a serious health crisis, an illness characterized by significant impairment and disability, inadequate diagnostic tools, barriers to healthcare access and trained physicians, high economic costs, and lack of treatment guidelines. The report contained a dissemination plan for education of U.S. medical institutions. In the 2 years that followed, the CFSAC systematically made such recommendations to the U.S. government agencies, in terms of both research support and patient care, which may have contributed to the demise of the CFSAC. In September of 2018, the Department of Health and Human Services decided not to renew the charter of the CFSAC.

[View full text continuation and references for this editorial article in Frontiers in Pediatrics.]

HEADACHE and MIGRAINE

The Role of Onabotulinum Toxin Type A in the Management of Chronic Non-migraine Headaches.

Jia C[1], Lucchese S[1], Zhang F[1], Govindarajan R[1].

Front Neurol. **2019 Sep 19**;10:1009. doi: 10.3389/fneur.2019.01009. PMCID: PMC6763695. PMID: 31616362. eCollection 2019.

Objectives: FDA has approved Onabotulinum toxin type A (BoNTA) for prophylactic treatment of chronic migraines. Recent studies have explored its potential new indications, like treating post-traumatic headaches.

Patients and Methods: This is a retrospective chart review of 717 patients, who had failed at least two prophylactic treatments and received BoNTA injections at University of Missouri Hospital from July 2014 to June 2017. Patient demographics, headache type, associated symptoms, prophylaxes tried were reported. Patient's pain severity (numeric pain scale) and frequency (number of headache days/month) pretreatment, at 6 months, and at 12 months were collected.

Results: For a single headache type, post-traumatic headaches showed reduction in headache pain severity at 6 months (2.9 ± 0.7) compared to pre-treatment (7 ± 0.7). Headache frequency for post-traumatic headaches was also reduced at 6 months (10.6 ± 2.3) and 12 months (5.1 ± 1.2) compared to pre-treatment (25 ± 1.8). For pseudotumor cerebri headaches, pain severity at pretreatment was 6.4 ± 0.6 compared to 2 ± 0.8 at 6 months, and headache days reduced at 6 months (9.8 ± 2.5) and 12 months (6 ± 4) compared to pretreatment (26 ± 2.9). Opioid use reduced by 67 ± 55.4 at 6 months and 133.3 ± 106.6 at 12 months in morphine equivalent units.

Conclusions: Onabotulinum toxin type A is effective in treating multiple types of chronic non-migraine headaches.

Post-Lumbar Puncture Headache--Does Hydration before Puncture Prevent Headache and Affect Cerebral Blood Flow?

Nowaczewska M[1], Kukulska-Pawluczuk B[2], Kaźmierczak H[3], Pawlak-Osińska K[4].

J Clin Med. **2019 Oct 17**;8(10). pii: E1710. doi: 10.3390/jcm8101710. PMID: 31627321.

Headache is a common complication after diagnostic lumbar puncture (DLP). We aimed to check whether hydration before puncture influences the incidence of post-lumbar puncture headache (PLPH) and affects cerebral blood flow. Ninety-nine patients enrolled for puncture were assigned to a group with (n = 40) or without hydration (n = 59). In the hydration group, 1000 mL 0.9% NaCl was infused and a minimum of 1500 mL oral fluids was recommended within the 24 h before puncture. A Transcranial Doppler (TCD) was performed before and after DLP. Mean velocity (Vm) and pulsatility index (PI) were measured in the middle cerebral arteries (MCAs). PLPH occurred in 28 patients (28.2%): six (15.4%) from the hydrated and 22 (37.3%) from the non-hydrated group (p < 0.023). Patients with PLPH were younger (p < 0.014) and with headaches in their histories (p < 0.036) compared with the non-headache group. Vm values in both MCAs after puncture were significantly lower than before puncture in all patients. In the PLPH group, Vm in MCAs before puncture were significantly higher and the PI was lower than in the non-headache group. Our findings suggest that hydration of patients within 24 h before puncture prevented PLPH. Twenty-four hours after puncture, significant decreases in Vm were observed in the MCAs of all patients. Low baseline values of PI and high Vm predisposed patients to PLPH.

CHRONIC PAIN

Adapting Mindfulness Training for Military Service Members With Chronic Pain.

Brintz CE[1], Miller S[2], Olmsted KR[2], Bartoszek M[3], Cartwright J[2], Kizakevich PN[2], Butler M[3], Asefnia N[4], Buben A[2], Gaylord SA[1].

Mil Med. **2019 Oct 17**. pii: usz312. doi: 10.1093/milmed/usz312. PMID: 31621856. [Epub ahead of print]

INTRODUCTION: Rates of chronic pain in military personnel are disproportionately high. Chronic pain is often associated with mental health and substance use disorders as comorbid conditions, making treatment of chronic pain complex. Mindfulness-based interventions (MBIs) are a promising behavioral approach to managing chronic pain and psychosocial sequelae. The unique nature of the military context may require adaptations to original MBIs for successful delivery in active-duty military populations. This study adapted the mindfulness-based stress reduction (MBSR) program to create a mindfulness training program that was relevant to active-duty Army personnel experiencing chronic pain. This article delineates the adaptation process employed to modify the MBSR program to the military context and discusses the resulting training program.

MATERIALS AND METHODS: The adaptation process consisted of three iterative stages: 1) Drafting the preliminary intervention protocol with recommendations from stakeholders, including military healthcare providers; 2) Refining the preliminary protocol after pretesting the sessions with research team members and a military Veteran advisory committee; and 3) Delivering the preliminary protocol to one cohort of active-duty Soldiers with chronic pain, collecting feedback, and further refining the intervention protocol.

RESULTS: Military-related adaptations to MBSR addressed three areas: military culture, language and terminology, and practical and logistical factors relevant to implementation in the military setting. This adaptation process resulted in a live, online program with six, weekly, sessions. Feedback from a military Veteran advisory committee resulted in modifications, including increasing military-relevant examples; preliminary testing with the target population resulted in additional modifications, including shortening the sessions to 75 min and structuring discussions more efficiently.

CONCLUSIONS: The adaptation process was successful in generating an engaging mindfulness training program that was highly relevant to the military context. Obtaining input from stakeholders, such as military healthcare providers and active-duty soldiers, and iterative feedback and modification, were key to the process. Moreover, the program was designed to maintain the integrity and core elements of MBIs while adapting to military culture. A future randomized controlled trial design will be used to evaluate the effectiveness of the intervention in improving chronic pain in military personnel. This program is responsive to the military's call for nonpharmacologic treatments for chronic pain that are easily accessible. If effective, the mindfulness program has the potential for widespread dissemination to complement standard care for Service Members experiencing chronic pain.

Repeated Intravenous Lidocaine Infusions for Patients with Fibromyalgia: Higher Doses of Lidocaine Have a Stronger and Longer-Lasting Effect on Pain Reduction.

Wilderman I[1], Pugacheva O[1], Perelman VS[1], Wansbrough MCT[1], Voznyak Y[1], Zolnierczyk L[1].

Pain Med. **2019 Oct 16**. pii: pnz251. doi: 10.1093/pm/pnz251. PMID: 31621870. [Epub ahead of print]

OBJECTIVES: To determine the effect of escalating doses of lidocaine infusion with or without added magnesium on pain levels and the duration of pain relief in patients with fibromyalgia (FM).

METHODS: A retrospective chart review of 74 patients diagnosed with FM who underwent at least three escalating doses of intravenous (IV) lidocaine infusions (5 mg/kg of body weight, 7.5 mg/kg, and 7.5 mg/kg of lidocaine + 2.5 g of magnesium sulfate) was conducted. Each patient's subjective impression of change in pain intensity and duration of pain relief after each treatment was recorded, along with an 11-point numeric rating scale (NRS) for pain intensity, immediately before and after each infusion.

RESULTS: Short-term lidocaine analgesia was evaluated by the reduction in NRS pain score according to the patients reported pre- (immediately before treatment) and post-treatment (immediately after treatment) values. There was a statistical difference in the NRS score reduction between doses 5 mg/kg and 7.5 mg/kg of lidocaine ($P = 0.009$). Long-term analgesia was evaluated at follow-up visits by the patient's subjective impression of change in pain intensity and duration of pain relief. There was a statistical difference in the percentage of pain relief and the mean duration of pain relief between the treatments with 5 mg/kg and 7.5 mg/kg of lidocaine ($P = 0.007$ and $P = 0.003$). Although there was a trend of greater response to magnesium sulfate as a beneficial adjunct to the lidocaine infusion, we were unable to find a statistically significant difference for any of the variables studied.

CONCLUSIONS: This study demonstrated that escalating doses of IV lidocaine to 7.5 mg/kg safely and effectively reduced the pain with prolonged effect in a significant number of patients diagnosed with fibromyalgia. Larger, prospective clinical studies are required to confirm this finding.

IRRITABLE BOWEL SYNDROME

Peroxiredoxin 1 as an inflammatory marker in diarrhea-predominant and postinfectious irritable bowel syndrome.

Zhang Y[1,2], Wu XX[1], Li S[1], Wu JF[1], Han S[3], Lin ZJ[3], Ding SZ[3], Gong WJ[1,3].

Neurogastroenterol Motil. **2019 Oct 15**:e13741. doi: 10.1111/nmo.13741. PMID: 31613423. [Epub ahead of print]

BACKGROUND: Low-grade inflammation occurs in some patients with irritable bowel syndrome (IBS). However, the exact inflammatory markers of IBS and the relationship of these markers with IBS subtypes and symptoms are poorly defined. Peroxiredoxin 1 (PRDX1) plays an important role in inflammatory responses, including intestinal inflammation. We investigated whether PRDX1 is associated with the diagnosis, subtypes, and symptom severity of IBS.

METHODS: A total of 177 IBS patients and 174 sex- and age-matched healthy controls (HCs) were recruited. The PRDX1 levels in the sera and colonic mucosa of the participants were detected by enzyme-linked immunosorbent assays and immunohistochemistry. The severity of IBS symptoms was assessed using the IBS Severity Scoring System (SSS) questionnaire.

RESULTS: The PRDX1 levels in the sera ($F = 71.81$, $P < .001$) and colonic mucosa ($F = 5.359$, $P < .001$) of postinfectious (PI-IBS) and diarrhea-predominant IBS (IBS-D) groups were significantly higher than those of the other three IBS subtypes and HC group. The PRDX1 level in the serum and colonic mucosa of IBS-D (serum, $P < .01$, mucosa, $P < .001$) and PI-IBS (serum, $P < .05$, mucosa, $P < .001$) groups with the most severe symptoms was significantly higher than that in the groups with mild and moderate symptoms. Correlation analysis revealed that in patients with IBS-D ($P < .001$) and PI-IBS ($P < .05$), the levels of PRDX1 and TNF-α in sera had a significant positive correlation with IBS-SSS.

CONCLUSION: Elevated PRDX1 in the serum and colon mucosa may be closely related to the progression of IBS (especially IBS-D and PI-IBS) and the expression of gastrointestinal symptoms.

The long-term effect and adherence of a low fermentable oligosaccharides disaccharides monosaccharides and polyols (FODMAP) diet in patients with irritable bowel syndrome.

Weynants A[1], Goossens L[1], Genetello M[2], De Looze D[3], Van Winckel M[2].

J Hum Nutr Diet. **2019 Oct 22**. doi: 10.1111/jhn.12706. PMID: 31637777. [Epub ahead of print]

BACKGROUND: Short-term trials with a low-FODMAP (fermentable oligosaccharides disaccharides monosaccharides and polyols) diet (LFD) show promising results in the symptomatic management of irritable bowel syndrome (IBS). The present study investigated the long-term adherence to an LFD diet, factors associated with adherence, and associations between LFD and quality of life (QOL), IBS symptoms and disease course on a long-term basis.

METHODS: A retrospective cross-sectional study was conducted. Two hundred and thirty-four patients were enrolled from Ghent University hospital. Health-related QOL, long-term adherence to the LFD, disease course and IBS symptoms were assessed using a validated and self-developed questionnaire.

RESULTS: Ninety (38.5%) patients completed the questionnaires. The median time span between the first dietary consultation and completion of the questionnaires was 99.5 weeks (approaching 2 years). The predominant disease course was mild IBS with an indolent course (43.0%). Eighty percent reported still following a diet in which certain FODMAP-rich food types are avoided. Eighty patients (88.9%) were satisfied that they follow or had followed the diet. The IBS-QOL did not differ between patients following the diet strictly and patients deviating from the diet ($P = 0.669$). Patients still following the LFD experienced less severe abdominal pain than patients who stopped following the diet ($P = 0.044$).

CONCLUSIONS: The long-term adherence and satisfaction with the LFD is high in patients with IBS. Nevertheless, patients indicated that it was difficult to follow the LFD in daily life. Practical issues, social factors and the absence of symptoms were indicated as the main reasons for a drop in adherence.

IRRITABLE BOWEL SYNDROME (Continued)

Identification of Gut Microbiota and Metabolites Signature in Patients With Irritable Bowel Syndrome.

Zhu S[1], Liu S[1], Li H[1], Zhang Z[1], Zhang Q[1], Chen L[1], Zhao Y[1], Chen Y[2], Gu J[3], Min L[1], Zhang S[1].

Front Cell Infect Microbiol. **2019 Oct 18**;9:346. doi: 10.3389/fcimb.2019.00346. PMCID: PMC6813219. PMID: 31681624. eCollection 2019.

Background and Aims: Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder. However, the underlying mechanism of IBS is not fully understood. The aim of this study was to investigate potential mechanism and novel biomarkers of IBS through evaluation of the metabolomic and microbiologic profile.

Methods: Fecal samples were collected from 15 irritable bowel syndrome patients and 15 healthy controls. By using gas chromatography coupled to time-of-flight mass spectrometry (GC-TOFMS) and 16S rDNA amplicon sequencing, fecal metabolites and microbiota of healthy controls and the IBS patients were measured.

Results: IBS patients had a significantly differential metabolite profile as compared to healthy controls, and 4 clusters with 31 metabolites, including a group of amino acids and fatty acids, were significantly up-regulated as compared to the healthy controls. In addition, 19 microbes were significantly up-regulated, and 12 microbes were down-regulated in the IBS group, when compared with the healthy controls. Some clusters of fecal metabolites or microorganisms were significantly correlated with the severity of IBS symptoms, such as the frequency of abdominal pain/discomfort and the number of bowel movements. Correlation of the metabolite levels with abundances of microbial genera showed some statistically significant metabolite-microbe associations. Four differentially abundant amino acids clustered together were positively correlated with some microbes, including *Lachnospira, Clostridium*, and so on.

Conclusion: The finding of this study puts a global perspective on metabolomics and microbiota profiling in IBS patients and provides a theoretical basis for future research on pathophysiology of IBS.

Candidate single nucleotide polymorphisms of irritable bowel syndrome: a systemic review and meta-analysis.

Zhu S[1], Wang B[1], Jia Q[1], Duan L[2].

BMC Gastroenterol. **2019 Oct 15**;19(1):165. doi: 10.1186/s12876-019-1084-z. PMCID: PMC6792237. PMID: 31615448.

BACKGROUND: Genetic factors increase the risk of irritable bowel syndrome (IBS). Analysis of single nucleotide polymorphisms (SNPs) has been used in IBS patients, but the findings are inconsistent. The goal of this review was to synthesize all the published SNPs studies of IBS through meta-analysis to objectively evaluate the relevance of SNPs to IBS risks.

METHODS: IBS - related polymorphisms studies from 2000 to 2018 were searched. Pooled odds ratios with a 95% confidence interval for each SNP were evaluated through five genetic models. Ethnicity, ROME criteria and IBS subtypes were defined for subgroup analyze.

RESULTS: Ten relevant genes were evaluated. SNPs rs4263839 and rs6478108 of TNFSF15 associated with an increased risk of IBS; IL6 rs1800795 increased the risk for Caucasian IBS patients which diagnosed by Rome III criteria; and IL23R rs11465804 increased the risk for IBS-C patients. IL10 rs1800896 GG genotype associated with a decreased risk of IBS. No evidence supported the association of GNβ3 rs5443, TNFα rs1800629, and IL10 rs1800871 to IBS in this study.

CONCLUSIONS: This meta-analysis presents an in-depth overview for IBS SNPs analysis. It was confirmed that polymorphisms of TNFSF15 associated with increased IBS risk, while IL10 rs1800896 associated with decreased IBS risk. It might offer some insights into polymorphisms of inflammation factors which might affect IBS susceptibility. Moreover, the analysis also emphasizes the importance of diagnostic criteria and phenotype homogeneity in IBS genetic studies.

IRRITABLE BOWEL SYNDROME (Continued)

Immune Activation in Functional Gastrointestinal Disorders.

Burns G[1,2,3,4,5], Pryor J[1,2,3,4,5], Holtmann G[1,2,3,4,5], Walker MM[1,2,3,4,5], Talley NJ[1,2,3,4,5], Keely S[1,2,3,4,5].

Gastroenterol Hepatol (N Y). **2019 Oct**;15(10):539-548. PMCID: PMC6883739. PMID: 31802978.

There is growing appreciation that functional gastrointestinal disorders (FGIDs) such as functional dyspepsia and irritable bowel syndrome are heterogeneous conditions linked by subtle inflammation within the gastrointestinal (GI) tract. The literature suggests that while the symptoms of these diseases may manifest with similar clinical presentations, there are significant differences in triggers and disease severity among patients classified into the same subtype. It is hypothesized that the subtle inflammation observed in these patients is related to an imbalance in GI homeostasis. Disruption of the delicate homeostatic balance within the GI tract can result from any number or combination of factors, including dysbiosis, loss of barrier integrity, genetic predisposition, or immune responses to dietary or luminal antigens. This article discusses the interplay between the immune system, microbiota, and luminal environment in FGIDs. In addition, the article proposes emerging immune pathways, including those involving T-helper type 17 response and innate lymphoid cells, as potential regulators of the subtle inflammation characteristic of FGIDs that warrant investigation in future studies.

OTHER RESEARCH OF INTEREST

Reduced Expression of Immune Mediators by T-Cell Subpopulations of Combat-Exposed Veterans With Post-Traumatic Stress Disorder.

Xiong Y[1], Wang Z[2,3], Young MRI[1,4].

Front Psychiatry. **2019 Sep 18**;10:693. doi: 10.3389/fpsyt.2019.00693. PMCID: PMC6759996. PMID: 31620037.

Post-traumatic stress disorder (PTSD) has been suggested to be associated with an inflammatory immune state, although few studies have examined peripheral blood lymphocytes in subjects that have PTSD and compared immune parameters to subjects that experienced similar trauma, but did not develop PTSD. An exploratory approach was undertaken to compare phenotypes of blood $CD4^+$ and $CD8^+$ subpopulations and their expression of immune mediators between Veterans of the Iraq and Afghanistan wars who experienced similar levels of combat, with some developing PTSD and other not. The results of this study did not demonstrate evidence of enhanced immune activation of peripheral blood lymphocytes. Instead, the results showed a decline in expression of the pro-inflammatory mediator IFN-γ and the cytotoxin granzyme B in $CD8^+$ subpopulations from Veterans with PTSD. While the reductions in expression of IFN-γ and granzyme B did not reach statistical significance when examining the $CD8^+$ cell population as a whole, the declines were significant when examining the $CD8^+$ cell subpopulations, with different mediators being reduced in different subpopulations. The most prominent decline in IFN-γ expression was by the unconventional $CD8^{dim}CD3^+$ T-cell subpopulation that has been associated with chronic infection and immune fatigue. The decline in granzyme B was most prominent in the NK-containing $CD8^{dim}CD3^-$ subpopulation of Tcells. Consequently, analysis of blood leukocyte subpopulations, rather than bulk lymphocyte groups, reveals a dampened level of immune reactivity in combat-exposed Veterans with PTSD compared to combat-exposed Veterans without PTSD.

OTHER RESEARCH OF INTEREST (Continued)

RNA Transcription and Splicing Errors as a Source of Cancer Frameshift Neoantigens for Vaccines.

Shen L[1], Zhang J[1], Lee H[1,2], Batista MT[1], Johnston SA[3].

Sci Rep. **2019 Oct 2**;9(1):14184. doi: 10.1038/s41598-019-50738-4. PMCID: PMC6775166. PMID: 31578439.

The success of checkpoint inhibitors in cancer therapy is largely attributed to activating the patient's immune response to their tumor's neoantigens arising from DNA mutations. This realization has motivated the interest in personal cancer vaccines based on sequencing the patient's tumor DNA to discover neoantigens. Here we propose an additional, unrecognized source of tumor neoantigens. We show that errors in transcription of microsatellites (MS) and mis-splicing of exons create highly immunogenic frameshift (FS) neoantigens in tumors. The sequence of these FS neoantigens are predictable, allowing creation of a peptide array representing all possible neoantigen FS peptides. This array can be used to detect the antibody response in a patient to the FS peptides. A survey of 5 types of cancers reveals peptides that are personally reactive for each patient. This source of neoantigens and the method to discover them may be useful in developing cancer vaccines.

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