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Recent advances in the field of nutritional immunology:

Nutritional Immunology: Role in Health and Disease Carefree, AZ, USA, 10–15 July 2011

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Abstract

Every 4 years, researchers in the cross-disciplinary field of nutritional immunology convene for a FASEB-sponsored meeting entitled, “Nutritional Immunology: Role in Health and Disease”, which was held this summer in Carefree, AZ, USA. The scope of the conference encompassed a diverse list of research topics, including, but not restricted to, obesity and immune dysfunction, nutrient–gene interactions, mucosal immunity and a discussion of future directions for the field. Here, we summarize some of the findings shared at the conference, specifically focusing on obesity, immunological function of dietary components (n-3 polyunsaturated fatty acids and flavanoids), gut immunity and the microbiota, and relevant emerging technologies and databases.

Keywords

diet; infectious disease; inflammation; mucosal immunity; n-3 fatty acids; obesity; phytochemicals; Toll-like receptor; vitamin A

Obesity & immune function

Kate Claycombe (USDA-ARS Grand Forks Human Nutrition Research Center, ND, USA) discussed the role of chronic inflammation in obesity-associated insulin resistance. Her research suggests a role for the n-3 polyunsaturated fatty acid (PUFA), eicosapentaenoic acid (EPA), in regulating the inflammatory response and improving insulin resistance induced by consumption of a high fat diet. In mice, supplementation of EPA to a high fat diet, despite weight gain, increased plasma adiponectin levels and prevented glucose

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intolerance (hyperglycemia and hyperinsulinemia) induced by HF feeding. Furthermore, the mechanism by which n-3 PUFA reduced insulin resistance involved downregulation of Toll-like-receptor (TLR)-2 expression and NF- κ B activation and translocation, leading to reduced inflammatory gene expression and secretion.

Claudio Procaccini (IESO-CNR, Italy) discussed the role of leptin as an immunomodulator, which in turn promotes CD4⁺ T helper (Th1)-cell differentiation, autoreactive T-cell survival and inflammatory cytokine release, reviewed in [1]. Proliferation of regulatory T cells (Tregs), important antagonists of autoimmune reactions, is constrained by leptin. Furthermore, leptin neutralization (via leptin antagonists or genetic mouse models lacking functional leptin or its receptor) reverses the anergic state of Tregs, thereby enhancing their proliferation. Since circulating leptin levels are elevated in the obese, these results suggest that leptin may play a pivotal role in the control of immune tolerance in relation to body fat mass.

Melinda Beck (University of North Carolina, NC, USA) discussed how obesity impairs both the primary and secondary responses to influenza virus. Her findings show that in obese mice, lung dendritic cells fail to efficiently present influenza antigen to T cells and memory T-cell functionality is impaired. Overall, obese mice infected with influenza have increased lung pathology and a higher rate of mortality in comparison to lean infected mice. Vishwa Dixit (Pennington Biomedical Center, LA, USA) discussed how diet-induced obesity accelerates thymic aging by inducing defects in thymic stromal cells (TEC) and hematopoietic stem cells. Via lineage-tracing, indelibly marked FoxN1 TECs transition and give rise to local tissue fibroblasts and fibroadipogenic cells via the epithelial–mesenchymal transition (EMT) process. However, caloric restriction was able to inhibit EMT and thymoadipogenesis, thereby favorably impacting thymic aging and immunosenescence.

n-3 PUFAs, lipid rafts & immune function

It has previously been shown that n-3 PUFAs can alter numerous physical properties of cell membranes and disrupt membrane domain organization through changes in lipid rafts and/or by targeting signaling networks [2]. Membrane lipid rafts are defined as transient sphingolipid/cholesterol assemblies of high molecular order that coalesce under specific circumstances in order to compartmentalize signaling proteins. Robert Chapkin (Texas A&M University, TX, USA) discussed how n-3 PUFA alter T-cell activation and signaling at the immunological synapse (IS) by inhibiting mitochondrial translocation, thereby reducing mitochondrial Ca²⁺ uptake, which in turn limits cytosolic Ca²⁺ levels and blocks the phosphatase activity of calcineurin. Ultimately, these events reduce the dephosphorylation and nuclear translocation of NFAT and suppress the transcription of genes involved in T-cell activation. Furthermore, n-3 PUFA down-modulate the migration and activation status of PKC θ and phospholipase C (PLC) γ -1 to the IS, suggesting that dietary n-3 PUFA alter the spatiotemporal regulation of critical signaling proteins at the IS by affecting the biophysical properties of lipid rafts. Demonstrating that the effects of n-3 PUFA are cell type dependent, Saame Raza Shaikh (Eastern Carolina University, NC, USA) discussed his recent data in which dietary n-3 PUFA (from mixed fish and flaxseed oil) enhanced B-cell activation in response to lipopolysaccharide (LPS) by increasing surface

CD69 expression and *ex vivo* cytokine secretion. In contrast, treatment of murine B220⁺ B cells with docosahexaenoic acid (DHA), not EPA, suppressed IL-6 secretion in response to LPS stimulation. Furthermore, n-3 PUFA were shown to disrupt the spatial distribution of outer leaflet GM1 clustering of B cells and EL4 cells (murine lymphoma cell line typically used as a surrogate antigen-presenting cell), which was associated with changes in protein distribution. Additionally, dietary n-3 PUFA promoted an increase in membrane order upon increasing raft size in splenic B cells.

Dietary flavanoids & immune function

Dayong Wu (Tufts University, MA, USA) discussed how the active ingredient in green tea, epigallocatechin-3-gallate (EGCG), has utility in the treatment of autoimmune disorders by dose-dependently attenuating the clinical symptoms of experimental autoimmune encephalomyelitis (EAE) (i.e., leukocyte infiltration and demyelination). EGCG decreased the number of Th1 and Th17 cells, increased Tregs residing in both secondary lymphoid organs and the CNS, and reduced the production of inflammatory cytokines (IL-6, IL-17, IFN- γ and TNF- α) and transcription factors (T-bet and ROR γ t). Susan Percival (University of Florida, FL, USA) presented findings from her recent human intervention studies, in which consumption of green tea compounds (L-theanine and green tea catechins) resulted in greater $\gamma\delta$ -T cell proliferation, reduced inflammatory biomarkers and reduced cold and flu symptoms compared with placebo. Similar promising findings were reported in human intervention studies following the consumption of aged garlic extract and cranberry pulp. Rodney Johnson (University of Illinois, IL, USA) discussed how in the aged brain, microglial cells (resident macrophages) over-react, producing excessive levels of inflammatory cytokines causing behavioral pathology and defects in cognition in response to infection. A total of 4 weeks of supplementation with dietary luteolin in aged mice counteracted this process by reducing microglial cell activation, improving spatial working memory, and restoring the expression of inflammatory markers (IL-1 β) in the hippocampus to levels observed in young adult mice. Jeremy Spencer (University of Reading, UK) discussed the mechanisms through which flavanoids protect neurons against stress-induced injury and suppress neuroinflammation, reviewed in [3]. Additionally, he discussed the outcome from a recent human intervention study assessing the prebiotic potential of cocoa flavanols. High consumption of cocoa flavanols (494 mg/day) affected the growth of select gut microflora by increasing bifidobacterial and lactobacilli populations while decreasing clostridia counts, in addition to reducing plasma triacylglycerol and C-reactive protein concentrations.

Mucosal immunology & the microbiota

The interaction between dietary components and their influence on the microbiota was discussed by several presenters. Pauline K Lund (University of North Carolina, NC, USA) discussed how a high fat diet and the intestinal microflora interact to elicit intestinal inflammation, obesity and insulin resistance. Specifically, animals conventionally housed and fed a HF diet induced low-grade inflammation in the small intestine, which was not apparent in germ-free mice. Belfour Sartor (University of North Carolina, NC, USA) discussed the use of prebiotics in the treatment of inflammatory bowel disease (IBD), noting

the importance of key commensal bacteria in the pathogenesis of chronic immune-mediated intestinal inflammation. Under germ-free conditions, genetically susceptible rodents in the absence of commensal bacterial antigens and TLR ligands failed to develop inflammation; however, when exposed to nonpathogenic commensal microbiota, they rapidly develop mucosal immune activation and colitis. Lora Hooper (University of Texas Southwestern, TX, USA) described the molecular mechanism of RegIII γ bactericidal activity, whose expression is triggered when bacteria colonize intestinal surfaces. RegIII γ binds to peptidoglycan on the surface of Gram-positive bacteria forming a hexameric pore in the bacterial inner membrane. RegIII $\gamma^{-/-}$ mice exhibit defects in the ability to limit bacterial colonization of the intestinal mucosal surface and exhibit increased bacterial penetration of the intestinal tissues, demonstrating the significance of this mechanism in mucosal defense and maintaining homeostasis with the intestinal microbiota.

With respect to vitamins and mucosal immune function, Margherita Cantorna (Pennsylvania State University, PA, USA) discussed the association between low vitamin D status and increased risk of autoimmune diseases and IBD. She demonstrated that vitamin D and its receptor (VDR) are required for the development and function of two cell types, inducible natural killer T cells and CD4/CD8 $\alpha\alpha$ intraepithelial lymphocytes. Additionally, J. Rodrigo Mora (Harvard Medical School, MA, USA) discussed the intricacies of retinoic acid (RA) and gut-homing T cells and demonstrated a critical role for RA-dependent gut-tropic T cells in oral tolerance.

Emerging technologies

Robert Hancock (University of British Columbia, BC, Canada) introduced the manually curated InnateDB database that integrates other databases describing pathways involved in innate immunity and inflammation, and determines the nonlinear interactions between the proteome, genome and the metabolome [101]. Additionally, Hancock introduced the Meta-analysis of Gene Expression (MetaGEX) that can be utilized to examine new strategies to target inflammatory pathways. The use of these tools led to the development of an antimicrobial peptide used as an innate defense regulator to protect the host from microbial infections by boosting the innate immune response, while having no direct antimicrobial activity. Jasmina Saric (Imperial College London, UK) introduced her research examining metabolic and immune changes upon parasite infections in mice using multivariate analysis of nuclear magnetic resonance spectroscopy and cytokine profiling. This type of multidimensional analysis reveals novel metabolic and immune interactions upon parasitic infections.

Cassandra Jabara (University of North Carolina, NC, USA) discussed using next-generation massively parallel sequencing to determine small variants (<0.5%) in viral populations that can have an impact on antiretroviral drug therapy. This method can be extended to examine the impact of nutrition on the transcriptome. Edward Dennis (University of California San Diego, CA, USA) discussed the Lipid Metabolites and Pathways Strategy (LIPID MAPS), which integrates transcriptome, proteome and lipidome datasets.

Overall, the cross-disciplinary nutritional immunology meeting successfully provided researchers with the opportunity to collaborate and engage in informal thought-provoking discussions and is set to reconvene again in 4 years time.

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