PLENARY SESSION

Plenary Session Moderators

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Nov.16 10:40-11:30 PS-1-1

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Nov.16 11:30-12:20 PS-2-1

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Nov.17 10:40-11:30 PS-3-1

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Nov.17 11:30-12:20 PS-4-1

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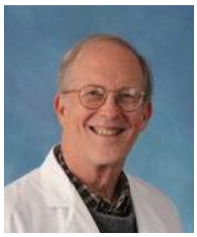
Nov.18 10:40-11:30 PS-5

PS1. The Microbiome in Health and Disease



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PS-1-1
Nov.16 10:40-11:30 Room Plenary Hall

The Microbiome in Health and Disease

The recent explosion in microbiome, gnotobiotic, genetic and immunologic techniques has resulted in a dramatic evolution of our understanding of the pathogenesis of IBD and laid the foundation for a paradigm shift toward individualized approaches to treatment and ultimate prevention and cures of Crohn's disease and ulcerative colitis. These insights have resulted in an etiologic shift from an emphasis on autoimmune processes and microbial pathogens to our current belief that IBD is the result of a dysregulated, chronic immune response to a subset of commensal bacterial species in a genetically susceptible host in which environmental triggers initiate disease onset and/or flares. Conversely, these enteric bacteria and their metabolic products such as butyrate induce protective immune responses and mucosal homeostasis in normal hosts. Our knowledge of enteric bacteria has advanced from identification of 200-300 cultivable species to 2000-3000 species detected by molecular sequencing of 16s ribosomal DNA. This bacterial load outnumbers our human cells 10:1. Functional analyses of the complex microbiota, which includes not only bacteria but fungi and viruses, has been dramatically augmented by metagenomic, proteomic and metabolomic technologies, so that we can begin to dissect the structure and function of the microbial genes that outnumber our human genes by at least 100 fold. These analyses have led to the concept that a dysbiosis (abnormal balance of beneficial/detrimental bacterial species) and functionally altered commensals contribute to disease pathogenesis, while a normal balance fosters mucosal health. Widespread use of gnotobiotic rodents have provided functional evidence that commensal bacteria provide the constant antigenic drive for dysregulated chronic T cell-mediated immune responses in susceptible hosts, that defined subsets of normal bacteria have both aggressive and protective functions, and microbial triggers may interact with genetic susceptibility. These observations lay the foundation for selective therapeutic manipulation of the microbiome. Recent evidence demonstrates that discrete microbial agents and their components/secreted products can activate specific immunologic pathways, including TH17, T reg and TR1 cells and that diet and host genetics can influence intestinal microbial ecology and function. Conversely, genetically determined defective innate immune function in some Crohn's disease patients leads to abnormal Paneth cell function and lack of clearance of invading intestinal bacteria.

These dramatic basic science advances lay the foundation for individualized prognosis and treatment that includes manipulating the intestinal microbiome and immune responses to microbial components. Ultimate prevention and cures will be the result of eliminating environmental triggers and manipulating environmental contributing factors, such as diet, correcting dysbiosis by selective elimination of detrimental and augmentation of protective microbial species and their metabolic activities as well as correcting underlying genetic abnormalities.

PS2. Intestinal Function After Transplantation

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PS-2-1
Nov.16 11:30-12:20 Room Plenary Hall

Intestinal Function After Transplantation

Intestinal failure (IF) is defined as the inability of the intestine to provide adequate nutrients and fluids for health maintenance in adults, and for growth in children. Parenteral nutrition (PN) is necessary for as long as IF persists. The grade of IF is related to the amount of PN required for maintenance and growth. PN, especially home-PN, remains the mainstay of therapy, regardless of the cause or degree of the intestinal insufficiency. However, irreversible IF together with complications of long-term PN, can result in the need for intestinal transplantation (ITx) which has become a recognized treatment of irreversible, permanent, and subtotal IF. Short-term results have improved due to a better control of acute rejection and infections, and due to careful patient selection. The one-year patient and graft survival rates, as reported in the International Registry and from the largest centers, for isolated small bowel transplantation (SBTx) and combined liver and small bowel transplantation (L-SBTx) is over 80%. The goal of ITx is to restore enough intestinal function to allow weaning from PN. By using stool balance analysis, we reported the short- and long-term intestinal functional capacity after ITx.

In the absence of graft rejection, ITx results in intestinal autonomy (PN weaning) despite a suboptimal intestinal function. The absorption of energy, especially fat, is not optimal, presumably largely due to alterations of the lymphatic circulation. This fat malabsorption results in a need for a high enteral energy intake, both by feeding tube and later by oral intake. Finally an optimal feeding strategy, in terms of tolerance and efficiency, should include the use of a protein hydrolysate formula as well as a formula rich in MCT. In order to achieve appropriate body weight gain, the energy intakes may exceed two times the resting energy expenditure. Careful follow-up by experienced centers remain critical to achieve long term optimal growth and overall outcome after ITx.

PS3. Diet, Microbiota and Programming of Mucosal Immunity

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PS-3-1
Nov.17 10:40-11:30 Room Plenary Hall

Diet, Microbiota and Programming of Mucosal Immunity

IThe paradigm of disease burden in the developed world has changed drastically in the last few decades from predominately infections to immune-mediated diseases (autoimmunity and allergy) because of alterations in the Western lifestyle (improved sanitation, immunizations, antibiotic usage and altered dietary intake). While these lifestyle changes have been effective in reducing the infectious disease burden, they have created an altered mucosal immunity leading to aberrant immune responses and a shift in disease burden. The principal basis for the disease burden shift is thought to be a modification in the colonization of gastrointestinal tract, particularly in the newborn period. In this lecture, I will also review the importance of nutrition during initial colonization in establishing homeostasis of intestinal immunity and preventing later expression of disease. The importance of a diverse balanced microbiota is necessary for development of an appropriate innate and adaptive immune response. There is strong evidence that disruption of the normal colonization process can lead to alterations in the important symbiotic relationship that is necessary for immune homeostasis. Infants born by Cesarean section or receiving excessive perinatal antibiotics have inadequate initial colonization and aberrant mucosal immune function. As a result later in childhood they express an increased incidence in asthma and an autoimmune disease (celiac disease). An important component of initial colonization is the infant's diet. Breast milk containing a variety of non-digestible oligosaccharides which function as prebiotics preferentially stimulate proliferation of Bifidobacteria and Lactobacilli, important health promoting bacteria, because of fermentation of the oligosaccharides into short chain fatty acids. These health promoting bacteria stimulate increased secretory IgA and decreased inflammatory cytokines, important components of immune homeostasis. Recent studies have shown that human milk oligosaccharides, but not artificial oligosaccharides, preferentially stimulate those Bifidobacteria genes that promote immune tolerance and anti-inflammation. This seminal observation underscores the importance of breast feeding in the establishment of microbiota that contribute to normal mucosal immune function. We have shown that Bifidobacterial infantis secretes factors that preferentially stimulate maturation of innate immune response genes and reduce the excessive inflammation seen in prematurity. We believe that these observations support the notion that the preferred feeding of premature infants should be mother's expressed breast milk supplemented with probiotics such as Bifidobacteria. This observation of the role of breast feeding in development of mucosal immune function have promoted additional studies on the role of diet per se in bacterial colonization and its prevention of immune-mediated disease.

PS4. Global Climate Change: Risks for Human and Planetary Health

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PS-4-1
Nov.17 11:30-12:20 Room Plenary Hall

Global Climate Change: Risks for Human and Planetary Health

Risks from climate change for human and planetary health raise increasing attention from both scientists and policy makers. Health risks result from physical hazards, temperature extremes, effects on air quality, change in patterns of transmission of infectious diseases, and potential catastrophic effects on food production leading to famine.

Extreme weather events may also lead to major population displacement and conflicts because of food insecurity, desertification and changing sea levels. The prospects for biofuels as a renewable energy source for transport add further technical and moral complexity to the relations between energy, food, and health. The competition between the food related uses of land and fuel production from crops or other uses of land is already affecting billions of people worldwide as energy prices rise, affecting food prices. Agricultural products are no longer considered exclusive for human food use but are now increasingly a source of biofuels. Basic food staples are presently worth their price based on equivalence of raw materials for fuel. Sugar cane, corn and other cereals are now increasingly being used to produce starches that are fermented to produce alcohol and other biofuels. Thus the price of these staple foods is now tightly linked to the price of oil, gas and fossil fuels. Greenhouse-gas emissions continue to rise; agricultural sources (crops and animal husbandry) and related use, are presently exceeding the emissions resulting from power generation and fuel used for transport. Methane and nitrous oxide, combined, have presently displaced carbon dioxide on a quantitative basis as the most significant source of emissions from this sector. Methane is a potent greenhouse gas whose full contribution to climate change is considered to be more than half that of carbon dioxide.

Lappé's "diet for a small planet" argument that feeding a population on a diet of animal protein sources requires 5-10 time more farmland than does a diet based on vegetable source protein. Presently as Chinese, other Asian, European, and US farmers begin to run short of land for crop expansion, the increasing demand for meat in developing economies is forcibly extending intensive agriculture into the tropical rainforests of the Southern Hemisphere especially Brazil and Paraguay; as well as to some African countries. Both conventional and organic systems of animal husbandry contribute similarly in terms of energy use and emissions of greenhouse gas per unit production. Organic production uses less total energy per kilogram of meat output than conventional production however it emits more greenhouse gases. Feeding animals higher-quality digestible feed-grain concentrates reduces methane emissions from enteric fermentation thus achieving more efficient of conversion of actual food energy. Thus in absolute terms, the total greenhouse-gas emissions from feed-grain based production methods—especially methane—are less than from pasture-based methods. That difference, however, also reflects the predominant reliance on extensive methods, worldwide.

Food and Health interact in multiple ways. Food provides energy and nutrients, and its acquisition requires the expenditure of energy. In post-hunter-gatherer societies, with progressively increasing inputs of extra energy resources, the scale of catching, gathering, and producing food has been greatly expanded and methods intensified. Today, relations between energy, food, and health have become complex and multifaceted, raising serious policy concerns at national and international levels. Substantial and widespread public-health problems of under-nutrition and obesity exist—often coexisting within the same population. Policy responses to the connections between food production, energy, climate, and health should include countering the world's rapidly increasing consumption of meat and animal sources of food which poses health risks by exacerbating climate change and by direct contribution to the causation of certain diseases. There is some good news: food production capacity has increased greatly; maternal and child nutrition in high-income populations and groups has improved; health and life expectancies have increased, at least partly because of nutritional gains; and refrigeration, transport, and open markets have increased year-round access to healthy foods for many populations. Meanwhile, health risks are also accruing: the expansion of food production is depleting land cover and biodiversity, with diverse consequences for human wellbeing and health; major elemental cycles are being disrupted; industrial production of refined energy rich food sources, marketing, and over-consumption leading to overweight and obesity increase the risks of most chronic non-communicable diseases. These are now the main cause of death and disability on a global basis.

Since human-induced climate change is now occurring and most likely progressing at a steadily accelerating rate additional actions are necessary to prevent future disasters.

We must first help populations at risk of adverse health effects from climate change to minimize those risks. Secondly minimize total greenhouse-gas emissions from live-stock production, which would include change in land use. If we are to avert dangerous climate change, the primary need is for radical change in energy generation technologies and energy use. A universal policy of demand reduction for all animal products in all countries, irrespective of current levels, would be politically difficult, not least because of its obvious inequity. This has in fact sidestepped in most policy documents; by contrast the use of demand management in areas such as energy policy has been favored. Reductions in the intensity of production of greenhouse gases and of animal products, and in consumer demand are urgently needed. An effective contraction and convergence policy would therefore seek to: both reduce greenhouse-gas emissions per unit of meat or milk produced coupled to a reduction consumption of meat (especially ruminant red meat) and milk from the current high levels in high-income countries, with predicted health benefits; and taper the rise in consumption of meat and milk in developing countries, also with predicted health benefits.

It is clear that mitigation alone will not solve the problem of climate change. Adaptation will be necessary to avoid, or at least reduce, much of the possible damage, and since we need many of the benefits of adaptation today, regardless of climate change in the future (e.g. increased drought protection of agriculture, improved flood protection, more efficient use of water, better malaria control), many of the adaptive strategies for climate change can be "win–win". We need to find a blend of mitigation and adaptation to meet the challenge of climate change. Mitigation can buy time for adaptation (for example, delaying impacts until improved technology and management can handle them), and adaptation can raise thresholds of tolerance that need to be avoided by mitigation (for example, by increasing drought tolerance of crops). Considered separately, they appear inadequate to meet such a challenge, but combined they would make a powerful response. What we do or fail to do now and in the coming years will affect the health and well being of humans and of planet earth. Unless we have a better option we must act now to prevent future catastrophes.

PS5. Liver Formation and Disease: Lessons from Fish and Mouse

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PS-5-1
Nov.18 10:40-11:30 Room Plenary Hall

Liver Formation and Disease: Lessons from Fish and Mouse

The liver has a remarkable capacity to regenerate after injury and partial hepatectomy (PH) in rodents has been useful for investigating the underlying mechanisms. Following PH, hepatocytes in the remaining liver tissue start proliferating such that normal liver mass is restored; the regenerative response is then terminated. To support this hepatocyte proliferation, the liver remnant transiently accumulates lipids that supply the energy and membrane components needed for cell division. However, it is unclear what molecular species of lipids are involved and whether PH affects other tissues. Matrix-assisted laser desorptional/ionization (MALDI) mass spectrometry is often used to analyze low molecular weight compounds such as lipids. A recent refinement called “imaging mass spectrometry” (IMS) allows visualization of the amount and distribution of individual molecular species in tissue sections. We used IMS to identify lipid species in murine liver regenerating after PH. IMS revealed that a single TLC band comprised major 19 TG species. Similarly, IMS showed a single phospholipid TLC band to be major 13 species. In adipose tissues, PH induced changes to expression of genes regulating lipid metabolism. Finally, IMS of phosphatidylcholine species demonstrated distribution gradients in lobules that resembled hepatic zonation. IMS is thus a novel and power tool for analyzing lipid species with high resolution.

Over the last ten years, there have been major advances in our understanding of the molecular and cellular mechanisms underlying liver development. These advances have been achieved through reverse genetics approaches, such as the use of knockout and transgenic mice, as well as through forward genetics approaches employing mutant fish. The examination of many such murine and piscine mutants with defects in liver formation and/or function have pinpointed numerous factors crucial for hepatic cell differentiation and growth. In addition, these studies have permitted the identification of several important liver-specific markers that allow the contributions of various cell types to hepatogenesis to be monitored. We have generated a strain of medaka fish carrying a mutation of the gene encoding “yes-associated protein” (YAP). YAP is a transcriptional co-activator that contributes to the regulation of multiple cellular processes. Recently, YAP was shown to play an important role in organ size control in both Drosophila and mammals, and to be inhibited by the Hippo signaling pathway. In mouse liver, either transgenic overexpression of YAP or knockout of Hippo pathway genes results in enlargement of this organ and the eventual development of hepatic tumors. In vitro, YAP overexpression promotes cell proliferation and induces oncogenic transformation. YAP also plays a critical role in maintaining stem cell pluripotency, as knockdown of YAP leads to loss of this property in murine embryonic stem (ES) cells, and YAP overexpression suppresses ES cell differentiation. In this symposium, I will describe the current state of our knowledge of the shared molecular mechanisms that underlie liver development in species as diverse as fish and mice. A better molecular understanding of liver formation may provide new insights into both normal liver biology and liver disease.