Plenary Lecture Abstract

Senescent cells as drivers of inflammaging

Judith Campisi
Buck Institute for Research on Aging and Lawrence Berkeley National Laboratory

Cellular senescence, like inflammation itself, is an integrated response to both deleterious stressors as well as certain beneficial physiological signals. In either case, senescent cells adopt a tripartite phenotype, which includes an essentially irreversible arrest of cell proliferation, relative resistance to apoptotic cell death, and a complex senescence-associated secretory phenotype (SASP). Senescent cells are known to increase with age in many tissues, and the SASP includes a large number of molecules that are potent initiators or mediators of inflammation. Thus, senescent cells are thought to be an important source of 'inflammaging' – the low-level chronic inflammation that is a hallmark of most aging tissues. The recent development transgenic mouse models -- and a relatively new class of drugs termed senolytics -- have allowed the selectively elimination of senescent cells, and thus have now made it possible to show a causal role for senescent cells in a growing number of age-related pathologies – at least in mice and isolated human tissues. A major challenge for the refinement of these approaches is to obtain a better understanding of the complexity, specificity and heterogeneity among senescent cells in order to more selectively suppress their deleterious effects, particularly their stimulation of inflammaging, while preserving their beneficial physiological functions.

Plenary Lecture Abstract

Evolutionary Metagenomics: How Globalization and climate change affect microbiomes

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The last 10 years have witnessed a revolution in microbiology. The advent of metagenomics studies has elucidated how microorganism determine organismal functions at a genomics scale. This new conceptual framework bears importantly on our knowledge of how complex biological systems evolve, leading to the holobiont theory of evolution, seen as the network of interactions between the host and the microbial communities that inhabit him. This lecture will focus on the evolutionary perspective emerging from studies on symbioses and their crucial role in the evolution of organismal functions. We will discuss the robustness and evolvability of the important symbiotic interactions of humans and insects with yeasts, fungi and bacteria, addressing the role of diet and geography as drivers of change of these interactions. Finally we will show evidence of how the plasticity of the microbiome is the main driver of the host adaptation to different diets and to rapidly changing environmental landscapes.

Plenary Lecture Abstract

New Paradigm for Chronic Inflammation Mediated by Glycosphingolipids

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Ganglioside GM3, a sialic acid containing glycosphingolipid, has been known to participate in insulin signaling by regulating the association of the insulin receptor in caveolae microdomains (lipid rafts), which is essential for the execution of the complete insulin metabolic signaling in adipocytes. Macrophage-secreted factors including proinflammatory cytokines, TNF-α and IL1-β, in adipose tissues have been known to limit the local adipogenesis and induce insulin resistance, however, the interplay between adipocytes and macrophages upon regulation of GM3 expression is not clear. GM3 was virtually absent in primary adipocytes differentiated from macrophage-depleted mesenteric stromal vesicular cells, which accompanies enhancement of insulin signaling and adipogenesis. We found that the expression of GM3 is governed by soluble factors including steady-state levels of proinflammatory cytokines secreted from resident macrophages. The direct involvement of GM3 in insulin signaling is demonstrated by the fact that embryonic fibroblasts obtained from GM3 synthase (GM3S) deficient mice have increased insulin signaling, when compared to wild type embryonic fibroblasts, which in turn leads to enhanced adipogeneis. In addition, GM3 expression in primary adipocytes is increased under proinflammatory conditions as well as in adipose tissue of diet-induced obese mice. Moreover, GM3S deficient mice fed high fat diets become obese but are resistant to the development of insulin resistance and chronic low-grade inflammatory states. Thus, GM3 functions as a physiological regulatory factor of the balance between homeostatic and pathological states in adipocytes by modulating insulin signaling in lipid rafts. Furthermore, we have identified the significant increases of GM3 molecular species possessing pro- inflammatory actions through TLR4. Collectively, we propose a novel inflammation amplification loop triggered by GM3 molecular species.

Plenary Lecture Abstract

Host-microbe interactions in the gut-liver axis

Hiroshi Kiyono

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The digestive tract is continuously exposed to infinite beneficial and harmful antigens including commensal and pathogenic microbe via the large surface of mucosal epithelium. The intestinal mucosa is thus equipped with multi-complexed but harmonized biological components including epithelial-mesenchymal cells, mucosal immunocompetent cells and commensal microbiota, which form “Gut Multi-ecological system (GME)” for the establishment of beneficial symbiotic condition as well as cooperative defense force. As an example, our study identified that commensal bacteria, Alcaligenes species can create “intra-tissue co-habitation niche” in the inside of Peyer’s patches (PPs), an example of commanding tissue for the induction and regulation of a balanced mucosal immunity. These intra-tissue commensal bacteria (ICB) enter PPs via M cells located in the follicle associated epithelium and newly identified Aifi-1 plays a critical role for the M cell transcytosis of commensal bacteria. Innate lymphoid cells (ILCs) type3 have been shown to play critical role by the cooperative interaction with epithelial cells for the creation of intra-tissue co-habitation niche. Further, ILC3s have been shown to regulate epithelial cell glycosylation for the creation of healthy gut microbiota and providing protective barrier against gut pathogens. These results suggested that the GME system is a key element of creation and regulation of healthy environment of the intestinal tract for the balancing act between elimination and symbiosis.

Plenary Lecture Abstract

Role of the Microbiota in Health and Inflammatory Disease

Gabriel Nuñez
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The mechanisms that allow enteric pathogens to colonize the intestine in the presence of the microbiota and how host immunity and the indigenous microbiota regulate pathogen colonization remain poorly understood. Our laboratory is using *Citrobacter rodentium*, a mouse pathogen that models human infections by enteropathogenic *E. coli*, to understand the mechanisms that regulate the colonization and clearance of the pathogen in the gut. These studies have revealed how the pathogen colonizes and replicates successfully early during infection and how host immunity and the indigenous microbiota cooperate to eradicate the pathogen in the later stage of the infection. These studies have also revealed that Clostridia species protect the host from colonization by *C. rodentium* and *Salmonella enterica* in the intestine. Furthermore, these studies have shown that the intestine of mice after birth lack protective Clostridia species providing a mechanism to account for the enhanced susceptibility of mice and humans to enteric infection during the neonatal period. In addition to their protective role, bacterial symbionts can also induce inflammatory disorders such as Crohn's disease in genetically susceptible individuals. We will show new results that demonstrate that particular symbiotic bacteria can accumulate in the intestine and trigger Crohn's disease-like colitis in mice with mutations relevant to the development of inflammatory bowel disease.

Plenary Lecture Abstract

Host-microbe interactions in the gut-liver axis

Maria Rescigno
Humanitas University, Milan, Italy

The microbiota is emerging as an important environmental factor influencing several functions of our body. Many disorders have been associated to a disequilibrium of the microbiota that is called dysbiosis, these include not only gut disorders as inflammatory bowel disease and colorectal cancer, but also systemic disorders like type II diabetes and even neurodegenerative disorders. How does dysbiosis impact on our life? We have described the existence of a vascular barrier in the gut that resembles the blood brain barrier. This barrier excludes the microbiota from entering the portal circulation and reaching the liver and other systemic districts. In this context we have analyzed how microbiota dysbiosis impacts on the barrier and may induce the development of several disorders in the gut liver axis. In particular we have observed the effect of diet on the microbiota and the capacity to interfere with barrier permeability in the context of Non-alcoholic steatohepatitis (NASH) and type II diabetes. We also evaluated how drugs commonly used to treat NASH impact on the gut vascular barrier.

Plenary Lecture Abstract

What matters most the microbes or their metabolites?

Jerry Wells
The University of Wageningen, The Netherlands

The mammalian microbiota produces dozens of microbial metabolites some of which accumulate in the bloodstream. Alterations in microbiome-associated metabolite levels and activity are implicated in the pathogenesis of a growing number of illnesses. The origin and influence of specific microbiome-modulated metabolites will be discussed. The first part of the talk focuses on new insights into the anti-inflammatory effects of acetate and evidence for its epigenetic effects outside the gut. The second part of the talk focuses on non-ribosomal synthesized (NRPS) small molecules that have the potential to modulate microbe-microbe and microbe-host interactions. The identification of a mammalian commensal producing a heat-stable and protease-resistant antibiotic via a non-ribosomal peptide synthetase (NRPS) gene cluster will be described. The molecule acts as a potassium ionophore, with antiviral, anti-parasitic and antibacterial activities and was only previously known to be produced by restricted species of soil dwelling Streptomyces. The effect of colonisation of piglets with the antibiotic producing strain will be presented.

Plenary Lecture Abstract

Thinking outside the mouse: ex-vivo dissections of enteric neuro-immune-microbiome cross talks.

Nissan Yissachar
The Faculty of Life Sciences, Bar-Ilan University, Israel

Investigations of host-environment interactions in the gut would greatly benefit from a culture system that preserved cellular architecture yet allowed tight experimental control. We have devised a microfabricated organ culture system that viably preserves the multicellular architecture of the mouse intestine, with luminal flow to control environmental parameters and permit experimental perturbation with microbes, drugs or nutrients. Using this system, we analyzed the early response of intestinal tissue to a panel of commensal bacteria, that triggers the development of either Th17 or T regulatory (Treg) cells in vivo. Remarkably, Th17 and Treg inducers showed diametrically opposite regulation of a neuronal-specific geneset, notably nociceptive neuropeptides. Electrophysiology and calcium imaging showed direct activation of sensory neurons by the Treg-inducing microbes. Thus, differential involvement of the enteric nervous system may partake in bifurcating pro- or anti-inflammatory responses to the gut microbiota.