Global Summit on

IMMUNOLOGY AND CELL BIOLOGY

June 25-26, 2018 | Amsterdam, Netherlands

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KEYNOTE FOURM
Treg constitute a complex network of T cell subtypes which regulate effector immune responses. Although CD4+ Treg are most known, in the recent years several CD8+ Treg subpopulations have been characterized. We identified the exact phenotype of one of these CD8+ Treg subsets (that is CD8+CD28-CD127-CD39+), allowing us to specifically recognize these cells in vivo and to study them ex vivo. Altered frequency or function of these CD8+ Treg appears to be pathogenically involved in autoimmune diseases. Moreover, these cells heavily infiltrate tumors and may circulate in the peripheral blood of cancer patients. These findings suggest their direct involvement also in the pathogenesis of cancer through the fostering of tumor immune escape. Recently, remarkable expansion of CD8+CD28-CD127loCD39+ Treg, whose frequency correlated with both clinical disease and signs of chronic immune cell activation, was observed in HIV patients.
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Rob Burgess, USA

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Craig N. Morrell, USA

Title: Disrupting the NFAT-AP-1 transcriptional complex using small molecules
Giuliana Mognol, USA

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Abdallah Elkhal, USA

Title: E-BABE-Encyclopedia of bioanalytical methods for bioavailability and bioequivalence studies of pharmaceuticals
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Title: Site attachment inhibition therapeutics: dealing with association and causation issues
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Benoit Tano, USA

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Giovani Marino Favero, Brazil

Title: From basic research to drug development: The story of copaxone (glatiramer acetate) in the treatment of multiple sclerosis and potential applications for additional pathologies
Rina Aharoni, Israel

Title: Direct evidence of viral infection and mitochondrial alterations in the brain of fetuses at high risk for schizophrenia
Segundo Mesa Castillo, Cuba

Title: Applied immuno-epidemiological research: an approach for integrating existing knowledge into the statistical analysis of multiple immune markers
Bernd Genser, Brazil
THE ROLE OF B CELLS IN DIABETIC CARDIOMYOPATHY

Diabetic cardiomyopathy (DCM) is typified by alterations in cardiac morphology and function, independent of hypertension or coronary disease. The disease is characterized by intramyocardial inflammation, cardiomyocytes apoptosis and cardiac fibrosis. The molecular mechanism that links inflammation to DCM is incompletely understood. This study investigates the role of B cells on the development of DCM. Induction of diabetes in WT mice resulted in a significant decrease in B cell infiltration into the left ventricular heart, but not in other organs, during the development of DCM. Interestingly, decreased B cell numbers correlate with the down regulation of the expression of a B cell inflammatory molecule, Allograft Inflammatory Factor-1 (AIF-1), which has been reported to enhance lymphocyte activation. However, the molecular mechanism(s) responsible for the decrease of B cell homing and AIF-1 expression in diabetic hearts as well as their relationship during the development of DCM is unknown. Focused on gaining insight into the role of AIF-1 in B cell migration, our in vitro study showed that B cell migration to cardiomyocytes is regulated by AIF-1 expression. We observed significant migration of B cells to hyperglycemic GFP-tagged AIF-1 transfected H9C2 cells compared to control cells transfected with an empty vector. Interestingly, Adenovirus AIF-1 overexpression promoted B cell homing to diabetic heart tissues, reduced inflammation and pathological remodeling. These effects of AIF-1 overexpression on the diabetes-induced cardiac dilatation and function are independent of AIF-1 effects on hyperglycemia since blood glucose levels are similar in diabetic WT mice with or without AIF-1 overexpression. This study suggests that diabetes attenuates AIF-1 expression, and this in turn, prevents B cell homing to diabetic heart tissues which in turn results in an increase of cardiac inflammation that leads to DCM.
THE POWER OF PROTEIN AND ANTIBODY ARRAYS IN STEM CELL RESEARCH

Rob Burgess
USA

Stem cells are uni-, multi- or pluripotent eukaryotic cell types which function to generate most of the basic body plan and tissues of a multicellular organism during development and even late into adulthood. The potency of stem cells is most often marked by the unique signature of proteins manufactured by these cells, which serves as a valuable tool for both cell-type identification and the discovery of new stem cell-based signaling cascades driving cell signaling, commitment and differentiation. These protein signatures may be rapidly and comprehensively characterized by the application of protein and antibody arrays.

Dr. Burgess, who has published research on stem cells in the journals Cell and Nature and has authored the textbooks Understanding Nanomedicine: An Introductory Textbook and Stem Cells: A Short Course, will review some of the most intriguing research findings to date on stem cell potency, heterogeneity and corresponding signaling cascades as revealed by the application of protein and antibody arrays.
PLATELET DERIVED β2M REGULATES MONOCYTE INFLAMMATORY DIFFERENTIATION RESPONSES TO MYOCARDIAL INFARCTION

Craig N. Morrell
USA

Beta-2 microglobulin (β2M) is a molecular chaperone for major histocompatibility class I (MHC-I) complex, hemochromatosis factor protein (HFE), and FcRn. β2M also has immune functions independent of its chaperone roles as elevated plasma β2M has been shown to have a direct role in neurocognitive decline and is a risk factor for adverse cardiovascular events. β2M mRNA is present at high levels in platelets and β2M is part of the platelet release state. In addition to their thrombotic function, platelets are important immune regulatory cells that release many inflammatory molecules at high concentrations, contributing to leukocyte trafficking, activation, and differentiation. This includes platelet regulation of monocyte trafficking and activation, and both platelets and monocytes are activated post-myocardial infarction (MI). In mice, monocytes have coordinated responses to MI, beginning with early pro-inflammatory (Ly6Chi) monocyte responses followed by pro-reparative (Ly6Clo) responses. We have now discovered that platelet derived β2M has a direct role in inducing monocyte pro-inflammatory phenotype differentiation, and that mice lacking β2M only in platelets (Plt-β2M-/-) had a skewing towards a pro-reparative, IL-10 secretion, monocyte phenotype. Platelet β2M effects are dependent on non-canonical monocyte TGFβ receptor signaling, and a balance of platelet derived β2M and TGFβ determines monocyte inflammatory differentiation responses. Using a mouse model of myocardial infarction, Plt-β2M-/- mice had limited post-MI inflammatory monocyte responses, but instead had an early pro-reparative dominant monocyte differentiation, resulting in a rapid decline in heart function and pro-fibrotic cardiac responses. These data demonstrate a novel chaperone independent inflammatory function for platelet β2M and reveals a patho physiologically important mechanism of platelet regulated monocyte responses to myocardial injury.
Disrupting the NFAT-AP-1 Transcriptional Complex Using Small Molecules

Giuliana Mognol
USA

The physical interaction between the transcription factors NFAT and AP-1 is pivotal for both the effector immune response and for the exacerbated response that happens during autoimmune and inflammatory diseases. In the absence of AP-1, NFAT directs another program of gene expression, which resembles T cell tolerance, where the cells lose their effector function. We have screened ~200,000 small drug-like compounds using a FRET assay that allows identifying inhibitors of the NFAT-AP-1 complex on DNA. We identified 960 candidate inhibitors in the initial screen. 24 compounds were evaluated and one of them actually inhibits the in vitro assembly of the NFAT-AP-1 complex on DNA with no effect on the binding of NFAT or AP-1 individually to their consensus binding sites. This compound also inhibits the induction of cytokine genes that depend on NFAT-AP-1 interaction, such as IL2, but not of those regulated independently of NFAT-AP-1 cooperation, such as TNF. The differential effect on IL2 and TNF gene expression indicates that selective inhibition of NFAT-AP-1 complexes in preference to other NFAT transcriptional complexes may be achievable by small molecules. One caveat is that further experiments have shown that this compound binds directly to DNA and not to the interface between NFAT and AP-1 as desired. We are currently developing an ELISA assay to pinpoint inhibitors that bind at the NFAT-AP-1 interface, and plan to re-test the other 936 compounds identified in the initial high-throughput screen. A proper inhibitor targeting NFAT-AP-1 complexes might redirect T cell transcription from an effector program to a tolerance program, and might find practical applications in the treatment of autoimmune and inflammatory diseases.
NOVEL IMMUNE REGULATORY PROPERTIES OF NAD+ AND ITS BENEFITS IN DISEASE SCENARIOS

Abdallah Elkhal
USA

It is well known that MHC-TCR activation following pathogen invasion dictates CD4+ T cell differentiation. More recently, a second mechanism involving TLRs and NLRs pathways have been shown to regulate CD4+ T cell differentiation as well. Both pathways require antigen presenting cells in particular dendritic cells (DCs). Moreover, CD4+ T cell fate is tightly regulated by cytokine milieu (produced by DCs) and major transcription factors that give rise to specific T helper subset (Th1, Th2, Th17 and regulatory T cells (Tregs)). Alterations in DC-mediated CD4+ T cell regulation pathway leads to a myriad of diseases including atopic disorders, autoimmune, primary immunodeficiency, infections and cancer.

In our studies, we demonstrated that NAD+ regulates CD4+ T cell differentiation independently of cytokine milieu and well established transcription factors. It is well established that the transcription factor T-bet is critical for Th1 differentiation. Our results demonstrated that in the presence of NAD+, the frequency of T-bet-/- CD4+IFN+ T cells was twofold higher than wild-type CD4+ T cells cultured in conventional Th1 polarizing conditions. Moreover, we showed a robust and unique immunoregulatory property of NAD+ that are independent of CD4+CD25+Foxp3+ Tregs, a unique T cell lineage that is essential for maintaining immune tolerance and homeostasis. Finally, our findings indicate that following NAD+ administration MCs, exclusively, promote CD4+ T cell differentiation, both in absence of antigen and independently of major APCs. Moreover, we found that MCs mediated CD4+ T cell differentiation independently of MHC-II and TCR signaling machinery.

Collectively, our study unravels a novel cellular and molecular pathway that regulates innate and adaptive immunity via MCs, exclusively. This untapped novel and distinct pathway may serve as an alternative to bypass certain inflammatory conditions and pave the way for novel therapeutic approaches in the context of autoimmune diseases, transplantation, primary immunodeficiencies and antimicrobial resistance.
E-BABE-ENCYCLOPEDIA OF BIOANALYTICAL METHODS FOR BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES OF PHARMACEUTICALS

Ponizovskiy
USA

Encyclopedia of Bioanalytical Methods for Bioavailability and Bioequivalence Studies of Pharmaceuticals (E-BABE): It is a unique encyclopedia involving bioanalytical methods for bioavailability and bioequivalence (BA/BE) studies of pharmaceuticals for suitable method selection with thousands of combinations and searches against these methods. Most scrutinized literature was collected from different sources including PubMed. This database has been curetted using published methods for all most all pharmaceuticals. Required information for regular method development/validation such as IUPAC name, structure, solubility, chromatographic conditions, instrumentation information like HPLC, LCMS detection parameters, sample preparations, recovery details, limit of detection and limit of quantification, Tmax, Cmax etc., for routine application in BA/BE studies of pharmaceuticals was incorporated including official pharmacopeias information such as European Pharmacopeia, Japan Pharmacopeia and US Pharmacopeia. Database includes drug based bioanalytical methods covering most required fields and external database links of important drug portals such as drug bank, Rxlist, MEDLINE plus, KEGG Drug ID, KEGG Compound ID, Merck manual, PubChem compound ID, PubChem substance ID and USFDA. Searching/querying the database is through drug name, chemical formula or structural search by smiles format. Keen selections of bioanalytical methods for pharmaceutical analysis or regular quality control are also possible with E-BABE. E-BABE was built understanding the needs of pharmaceutical industry and laboratories including CROs working on BA/BE studies. Presently it has nearly of 5,000 methods and it will be updated regularly.
Title
SITE ATTACHMENT INHIBITION THERAPEUTICS: DEALING WITH ASSOCIATION AND CAUSATION ISSUES

Name & Country
Simon Raymond
Australia

Abstract
New Content: CRISPR, CRISPR-Cas9 Technologies; Methodology and Solutions for Association and Causation Issues.

This talk highlights that site attachment inhibition (therapeutics involving the negation of cellular attachment, or entry/transfer, by the pathogen) is intended to consist of both: (A)Treatment of established infections; and, (B) New generation immunization programs (preventative treatment).

New generation immunization programs, based on prenatal stem cell therapy in the prenatal period and earlier spanning back to spermatogenesis and oogenesis, is intended to involve gene mutagenesis, and knockout. Validation for likely success includes inherited mutations mentioned in the references noted that provide resultant resistance (immunity) to the stated infections including HIV and Malaria. Association and causation issues need to be dealt with given that even the known CCR5 mutation has not been completely confirmed as direct/causative of the resultant resistance/immunity.

A discussion with regards to prenatal and germline stem cell therapy, in addition to CRISPR, and CRISPR-Cas9, is presented in the below link to the US NIH Library. It is not up to date with “site attachment inhibition” therapeutics, however it does provide a general discussion on the above stated topics broadly.
INTEGRATIVE IMMUNITY — QUADREPIDEMS: EFFECTS OF ENVIRONMENTAL TOXINS (PESTICIDES, INDUSTRIAL CHEMICALS, COMMON HOUSEHOLD CHEMICALS, COSMETICS AND COSMECEUTICALS) ON THE GROWING ESTROGEN-OBESEITY-ALLERGY-ANXIETY/DEPRESSION EPIDEMICS AND ENDOCRINE AND IMMUNE RESPONSES

Background: Early 1980s, the Centers for Disease Control and Prevention (CDC) through its EIS, discovered that several US states were gaining weight abnormally. In 1984, the CDC created the Behavioral Risk Factor Surveillance Survey (BRFSS) to investigate. In 1985, the CDC published the first obesity map based on BRFSS data. Obesity has become epidemic not only in North America, but in the whole world. Concurrent to the obesity epidemic, we now have the estrogen, allergy, and anxiety/depression epidemics. In 1992, The USGS published the pesticides maps and in 2001, the CDC started biomonitoring. The chemicals found in the blood and urine in individuals from different US states are reported in the CDC Fourth Report. This report is updated every two years and continues to show a growing chemical list overtime.

Objective: We sought to establish the relationship between environmental toxins, the endocrine system, and the immune system that may explain the plethora of 21st century chronic diseases.

Methods: We used an evidence-based approach called Integrative Immunity and the Healthcare Utilization Project (HCUP) database, the CDC obesity maps, the USGS pesticides maps, chemicals found in the CDC Fourth Report, and medical geography techniques, to make sense of current estrogen-obesity-allergy-anxiety/depression epidemics. Four key diagrams were conceived to relate pesticides to obesity and comorbidities, and pesticides to environmental and food allergies.

Results: We demonstrate that the areas of the heaviest pesticide spray correspond to the areas of the heaviest obesity, morbidity, mortality, allergy, and anxiety/depression and even divorce rates. Environmental toxins cause hormonal imbalance that leads to obesity and its comorbidities. Some of these toxins such as xenoestrogens have receptors on the mast cells and basophils, and cause histamine and leukotriene release that are responsible for nasal, respiratory, cutaneous, and food reactions. Acetylcholine esterase inhibitor chemicals cause depletion of neurotransmitters such as dopamine, norepinephrine and epinephrine to create mood swings. Other chemicals stimulate the immune cells to produce antibodies linked to autoimmune diseases.

Conclusion: There is a vicious cycle that goes from environmental toxins to chronic diseases. Understanding the mechanisms through which toxic chemicals affect the human body offers opportunities for adequate treatments.

Benoit Tano, M.D. is a specialist, pioneer, and the Minneapolis area’s foremost expert in the field of Integrative Immunity. Tano is the founder of Integrative Immunity Health System, PC located in Edina, Minnesota. He is Johns Hopkins-fellowship trained in allergy and clinical immunology and authored the number one bestselling book, The Layman’s Guide to Integrative Immunity (2016). He combines his vast expertise in allergy and clinical immunology and in hormone imbalance syndrome to treat the root causes of 21st-century chronic diseases.
GUT AND INTEGRATED PATHOPHYSIOLOGY OF IMMUNE RESPONSE. OBSERVATIONS FROM EXPERIMENTS IN ORAL TOLERANCE IN MICE AND THE RESPONSE ASSOCIATED WITH A MODEL OF METABOLIC SYNDROME SURGERY

Giovani Marino Favero
Brazil

The gut mucosa is the place that most contact with foreign antigenic proteins occurs and forms with the immune system an integrated, dynamic and adaptive complex that has evolved to provide effective digestion and defense. The whole intestinal area is 100-fold larger than the skin, presents the largest amount of lymphoid tissue of the body and the more number of activated lymphocytes. The Peyer’s patches and the lamina propria of the gut present a very large number of T cells. Immunoglobulin production, especially IgA, that is the only antibody secreted by mucosal, offers the first protection to neonates. For the experiment with Oral Tolerance proposed an protocol in adult Swiss mice by oral administration of a recombinant dermonecrotic toxin of brown spider Loxosceles intermedia (LiRecDT1) and its mutated form(LiRecDT1H12A) for three weeks. Our results demonstrated evidences of tolerance induction through decrease in IgG anti-der-monecrotic toxin levels, paw edema reduction and increased survey in 24h after challenge. All statistical analysis was performed using ANOVA following Bonferroni’s post hoc test. Related to bowel surgery readjustment we observed that the removal of the greater omentum decreases the secretion of cytokines, particularly IL-6, regressing other diseases associated with obesity such as bronchitis. In conclusion, the intestine can be considered the main immune organ of the body and this association between immunity and digestion begin prior to birth and mediate allergic responses and/or tolerance throughout the life of the individual.
Title
FROM BASIC RESEARCH TO DRUG DEVELOPMENT: THE STORY OF COPAXONE (GLATIRAMER ACETATE) IN THE TREATMENT OF MULTIPLE SCLEROSIS AND POTENTIAL APPLICATIONS FOR ADDITIONAL PATHOLOGIES

Name & Country
Rina Aharoni
Israel

Abstract

Multiple sclerosis (MS) is currently recognized as complex diseases in which inflammatory autoimmune reactivity in the central nervous system (CNS) results in demyelination, axonal and neuronal pathology. Treatment strategies aim to reduce the detrimental inflammation and induce neuroprotective repair processes.

The synthetic copolymer Copaxone (glatiramer acetate, GA), an approved drug for the treatment of MS, is the first and so far the only therapeutic agent to have a copolymer as its active ingredient. Using the animal model of MS - experimental autoimmune encephalomyelitis (EAE), the immunomodulatory mechanism of action of GA was elucidated. It was found that GA treatment induces immunomodulatory shift from the inflammatory towards the anti-inflammatory pathways, such as Th2-cells that cross the blood brain barrier (BBB) and secrete in situ anti-inflammatory cytokines, as well as T-regulatory cells (Tregs) that suppress the disease. Furthermore, recent studies revealed neuroprotective and repair consequences of GA treatment in the CNS. These include elevation in neurotrophic factors expressions, remyelination and neurogenesis.

Based on its immunomodulatory mode of action, additional potential applications of GA were investigated, such as prevention of immune rejection, improvement of stem cells engraftment and amelioration of inflammatory bowel diseases (IBD).
Title
DIRECT EVIDENCE OF VIRAL INFECTION AND MITOCHONDRIAL ALTERATIONS IN THE BRAIN OF FETUSES AT HIGH RISK FOR SCHIZOPHRENIA

Name & Country
Segundo Mesa Castillo
Cuba

Abstract
There is increasing evidences that favor the prenatal beginning of schizophrenia. These evidences point toward intra-uterine environmental factors that act specifically during the second pregnancy trimester producing a direct damage of the brain of the fetus. The current available technology doesn't allow observing what is happening at cellular level since the human brain is not exposed to a direct analysis in that stage of the life in subjects at high risk of developing schizophrenia.

Methods: In 1977 we began a direct electron microscopic research of the brain of fetuses at high risk from schizophrenic mothers in order to finding differences at cellular level in relation to controls.

Results: In these studies we have observed within the nuclei of neurons the presence of complete and incomplete viral particles that reacted in positive form with antibodies to herpes simplex hominis type I [HSV1] virus, and mitochondria alterations.

Conclusion: The importance of these findings can have practical applications in the prevention of the illness keeping in mind its direct relation to the aetiology and physio-pathology of schizophrenia. A study of amniotic fluid cells in women at risk of having a schizophrenic offspring is considered. Of being observed the same alterations that those observed previously in the cells of the brain of the studied foetuses, it would intend to these women in risk of having a schizophrenia descendant, previous information of the results, the voluntary medical interruption of the pregnancy or an early anti HSV1 viral treatment as preventive measure of the later development of the illness.

Biography
Segundo Mesa Castillo: As Specialist in Neurology, he worked for 10 years in the Institute of Neurology of Havana, Cuba. He has worked in Electron Microscopic Studies on Schizophrenia for 32 years. He was awarded with the International Price of the Stanley Foundation Award Program and for the Professional Committee to work as a fellowship position in the Laboratory of the Central Nervous System Studies, National Institute of Neurological Diseases and Stroke under Joseph Gibbs for a period of 6 months, National Institute of Health, Bethesda, Maryland, Washington D.C. USA, June 5, 1990. At present he is member of the Scientific Board of the Psychiatric Hospital of Havana and give lectures to residents in psychiatry.
APPLIED IMMUNO-EPIDEMIOLOGICAL RESEARCH: AN APPROACH FOR INTEGRATING EXISTING KNOWLEDGE INTO THE STATISTICAL ANALYSIS OF MULTIPLE IMMUNE MARKERS

Bernd Genser
Brazil

Background: Immunologists often measure several correlated immunological markers, such as concentrations of different cytokines produced by different immune cells and/or measured under different conditions, to draw insights from complex immunological mechanisms. Although there have been recent methodological efforts to improve the statistical analysis of immunological data, a framework is still needed for the simultaneous analysis of multiple, often correlated, immune markers. This framework would allow the immunologists’ hypotheses about the underlying biological mechanisms to be integrated.

Results: We present an analytical approach for statistical analysis of correlated immune markers, such as those commonly collected in modern immunological studies. We demonstrate i) how to deal with interdependencies among multiple measurements of the same immune marker, ii) how to analyse association patterns among different markers, iii) how to aggregate different measures and/or markers to immunological summary scores, iv) how to model the inter-relationships among these scores, and v) how to use these scores in epidemiological association analyses. We illustrate the application of our approach to multiple cytokine measurements from 818 children enrolled in a large immunological study (SCAALA Salvador), which aimed to quantify the major immunological mechanisms underlying atopic diseases or asthma. We demonstrate how to aggregate systematically the information captured in multiple cytokine measurements to immunological summary scores aimed at reflecting the presumed underlying immunological mechanisms (Th1/Th2 balance and immune regulatory network). We show how these aggregated immune scores can be used as predictors in regression models with outcomes of immunological studies (e.g. specific IgE) and compare the results to those obtained by a traditional multivariate regression approach.

Conclusion: The proposed analytical approach may be especially useful to quantify complex immune responses in immunological studies, where investigators examine the relationship among epidemiological patterns, immune response, and disease outcomes.
Title: Human C-Cbl and Cbl-b Proteins Are More Highly Expressed in the Thymus Compared to the Testis
Mazo KONE, Nigeria

Title: Functional Screening Reveals Low Fever Mediates Circulating TNF-α Level and Upregulated Expression of Proinflammatory Cytokines in P. vivax compared to P. falciparum infected Malaria
Mohammad Sohail, India

Title: Identification of triple negative breast cancer by immunohistochemistry in the region of sidi belabbes
Tarfaoui Louiza, Algeria

Title: Cellular and molecular mechanisms of intracellular survival of Staphylococcus aureus in macrophages involving pattern recognition receptor and chemokine receptors
Biswaudev Bishayi, India

Title: C-reactive protein as an early marker of opportunistic infections in HIV
Nagesh Wadgera, India

Title: Analysis of the Role of Genetic Polymorphisms of Innate Immune Signaling Factors in Inflammatory Disease
Kaarthikeyan G, India

Title: Insulin modulation of TLR4 expression in murine macrophages: possible involvement of PI3K/Akt and ERK1/2 signalling pathway
Soumojit Pal, India

Title: Syringic acid, a phenolic compound attenuated arthritis by inhibition of Cytokines in Complete Freund's Adjuvant induced arthritis in rats
Shilpee Chanda, India

Title: A study of the interaction mechanism of GTP with CodY of Bacillus anthracis
Shikha Joon, India

Title: Sero-prevalence of cryptococcal antigenemia in HIV positive individual having CD4 counts <100 cells/mm3
Sundar Khadka, India
Title

HUMAN C-CBL AND CBL-B PROTEINS ARE MORE HIGHLY EXPRESSED IN THE THYMUS COMPARED TO THE TESTIS

Name & Country

Mazo KONE
Nigeria

Abstract

Background and objectives: c-Cbl and Cbl-b are two members of the Cbl family proteins, with a crucial role of downregulation of tyrosine kinase receptors. They act as E3 ubiquitin ligases and are multivalent adaptor proteins, making them important in maintaining homeostasis in the body. This study investigated the expression level in thymus and testis in normal conditions.

Methods: The expression level was assessed by immunohistochemistry of tissue microarrays of normal thymus and testis biopsies.

Results: Cbl-b and c-Cbl proteins were found to be highly expressed in normal testis and thymus, indicated as yellowish brown granules in the cytomembrane and cytoplasm compared to controls. The c-Cbl appears to be more highly expressed than the Cbl-b in the thymus, while c-Cbl appears slightly stronger than Cbl-b in the testis. The thymus was found with a higher grade compared to the testis.

Conclusion: In this work we concluded, that in normal condition, thymus tissue expresses more Cbl family proteins (c-Cbl and Cbl-b) than the testis tissue in humans.

Biography

Mazo has been initiated to the world of research during both his Bachelor and Master. Time during which, he received basics training in biology of Cancer, Physiolopathology of Metabolic diseases, Infectious diseases and many more. However he quickly developed an interest for the molecular biology of cancer, physiology of the cell and infectious diseases. He worked on the oncogenic properties of Human c-Cbl and Cbl-b as Master project work. Currently he is doing a PhD in Cell Biology and Genetics at the University of Ibadan in Nigeria. His research is on congenital infections in pregnancy both in Mali and Nigeria. In general Mazo’s research works are axed on molecular biology of cancer and infectious diseases. He is the leader of Rachetes Algeria since 2012, the promoter and the manager of The Biomedical researcher project.
**Title**

FUNCTIONAL SCREENING REVEALS LOW FEVER MEDIATES CIRCULATING TNF-α LEVEL AND UPREGULATED EXPRESSION OF PROINFLAMMATORY CYTOKINES IN P. VIVAX COMPARED TO P. FALCIPARUM INFECTED MALARIA

**Name & Country**

Mohammad Sohail  
India

**Abstract**

Clinical implications of proinflammatory cytokines and its functional analysis during malarial severity are poorly elucidated and substantially unknown. Thus, its clinical relevance and disease association prompted us to address the paradoxical role of TNF-α; triggers pyrogenic response and inflammatory cytokine mediated pathogenesis, employing ELISA, PCR-RFLP, semi-quantitative RT-PCR, qRT-PCR and immunoblotting. The genotypic distribution of TNF-α promoter position 308G/A in P. falciparum was significant (p=0.012) whereas P. vivax was not significant but strongly associated (OR=3.8). Polymorphism significantly influences serum TNF-α level in both vivax and falciparum infection. Interestingly, we significantly observed mutation specific up regulation of TNF-α mRNA expression in all the three genotypes (GG, GA and AA) of vivax as compared to falciparum patients. Further all other serum cytokines (IL-1β, IL-6, IL-8, IFN-γ and IL-2) levels are significantly (p<0.0001) elevated; whereas IL-10 was significantly (p<0.0001) depleted in patients. Most intriguingly, we observed significantly higher serum TNF-α (130.2pg/ml) in patients with lower or no fever compared to higher fever (112.7pg/ml). To elucidate the hypothesis of regulatory role of fever specific induction of TNF-α, we investigated and interestingly observed significantly upregulated expression of TNF-α mRNA and protein in vivax infection as compared to falciparum patients with low fever. Similarly, significant alterations in other inflammatory cytokines (IL-1β, IL-8 and IFN-γ) genes expression showed prominent fold induction in vivax as compared to falciparum at the level of mRNA. Association of genetic polymorphism, expression of proinflammatory cytokines and mutation specific induction of TNF-α, augments pathology and up regulates transcriptional changes. Further, novel observations demonstrate a critical role of low fever that regulates the TNF-α induction in association with other inflammatory cytokines; suggesting a multipathway mechanisms and indispensable regulatory events mediate the expression and induction of inflammatory cascade in TNF-α mediated clinical symptoms and pathology, highlighting biological significance in host defense mechanisms in human malaria.
IDENTIFICATION OF TRIPLE NEGATIVE BREAST CANCER BY IMMUNOHISTOCHEMISTRY IN THE REGION OF SIDI BELABBES

Name & Country

Tarfaoui L
Nigeria

Abstract

Introduction: Breast cancer is the most common malignancy and the leading cause of cancer death in women worldwide. Breast cancer is a complex and heterogeneous disease. Recent microarray studies divided breast cancer into several distinct subtypes associated with different phenotypes and clinical courses.

Objectives: We lack molecular data in certain molecular subtypes with a particularly aggressive phenotype such “triple negative” breast cancer (TNBC) and for which no targeted therapy exists. Thus, there is an urgent need to identify patients with triple negative breast carcinomas and specific markers that may constitute potential future therapeutic targets. This work consists on a retrospective epidemiological study of breast cancers distribution recorded between January 2010 and December 2012 at the Sidi-Bel-Abbes university hospital. Furthermore, identification of TNBC was done by estrogen, progesterone and HER2 receptors immunohistochemical assessment. Next, we determined the TNBC clinical features.

Results: Triple negative breast cancer represents an important subgroup of breast cancer (16% ) and affect a high proportion of young women (44%) . TNBC were associated with a high SBR grade, more frequently grade II and III (62,96% and 25,95% respectively), the presence of axillary lymph nodes (51.85%) as well as the ductal histological type (62.92%). TNBC were highly positive for Ki67.

Conclusion: Identification of patients with TNBC may benefit from a more aggressive approach to adjuvant therapy. We, therefore, emphasize the importance of routine staining of triple negative breast cancer. TNBC patients are not eligible for targeted agents suggesting an urgent need to identify potential therapeutic targets.
Cellular and molecular mechanisms of intracellular survival of Staphylococcus aureus in macrophages involving pattern recognition receptor and chemokine receptors

BiswaDev Bishayi
India

Staphylococcus aureus has long been considered to be an extracellular pathogen which may occasionally survive and even multiply within macrophages resulting in prolonged and recurrent infections. The mechanism of persistence of staphylococci in its hosts, despite the induction of seemingly sufficient levels of humoral and mucosal antibodies, remains unexplained. An interesting field worthy of study in susceptibility to infection is the ability developed by many virulent strains of pathogens to evade immunity through TLRs. Although Chemokine receptors (CXCR1 and CCR2) participate in the macrophage response of Gram-positive bacteria, a substantial role of chemokine receptors in host defense against S. aureus infection in murine macrophages, was still unclear.

The objective was to study the involvement of cell surface TLR-2 and MCP-1R/CCR-2 and CXCR1 receptor on the intracellular survival of Staphylococcus aureus along with altered production of reactive oxygen species (ROS) and cytokines. In the current setup, we found that infection of peritoneal macrophages with S. aureus resulted in TLR2/ MCP-1R/CCR-2 or CXCR1-mediated cytokine production and increased oxidative killing of internalized bacteria which were abrogated by TLR and CCXR1/CCR2 receptor blocking. This approach also may have relevance whether TLR-2/ MCP-1R/CCR-2 or CXCR1 mediated cytokine production and release of ROS has any further impact for correlating bone destruction or S. aureus infection induced septic arthritis.
Title

C-REACTIVE PROTEIN AS AN EARLY MARKER OF OPPORTUNISTIC INFECTIONS IN HIV

Name & Country

Nagesh Wadgera

India

Abstract

Opportunistic infections account for the majority of death in untreated patients with AIDS. CRP is a highly sensitive marker of infection & inflammation and its level increase with infection. The present Study was undertaken among 100 HIV+ patients, at ART center Victoria Hospital Bangalore. With the informed consent of the patient, a generalized proforma was filled up consisting of patient’s clinical presentation and diagnosis. Their CRP level and CD4 count were measured. 56 HIV+ patients were asymptomatic and acted as control giving a negative test for CRP (<6mg/l), Showing no base line rise in CRP. Patients with infectious diagnosis showed a positive test for CRP, while patients on treatment were negative. Among the infectious cases, bacterial infection showed high level of CRP (mean 32mg/l) compared to viral/fungal infection (mean 9mg/l). Combinations of opportunistic infections produced a high level of CRP (mean 45mg/l). A graph of CRP along x-axis and CD4 count along Y-axis were plotted which showed a negative correlation (r=0.2324, p<0.01 and |z|=2.40). From the graph, the CRP level at which ART can be started is >92.413mg/l [taking <200 (cells/µl) as the CD4 count at which ART is started]. Patients showing negative test for CRP need not be started with ART, as their CD4 count is found to be approximately 329 cells/µl. CRP level in HIV patients has a prognostic significance and can be used as an early marker of Opportunistic infections.
Periodontitis is a chronic inflammatory disease of multifactorial etiology. The gram negative anaerobes are the main etiological agents in causing periodontal destruction. The genetic risk factors plays a major role in determining the susceptibility to periodontal disease. The virulence factors of these anaerobes like lipopolysacharide (LPS) are screened by the pattern recognition receptors like Toll like receptors and innate immune signaling cascade is activated. This signaling cascade is regulated by many microRNAs like miR146a. This microRNA146a negatively regulates TLR4 pathway by blocking interleukin 1 receptor associated kinase (IRAK1), TNFReceptor associated factor(TRAF6). This miR146a is in turn regulated by apolipoprotein E(apoE). ApoE is a major cholesterol carrier and plays an important role in maintaining lipid homeostasis. ApoE selectively regulates TLR4- and TLR3-mediated signaling. The apoE may suppress the Th1 immune response by modulating IL-12 production. The inactive pro inflammatory cytokine IL-1beta secreted by this signaling cascade is activated by Nod like receptors called NLRP3 in cytoplasm. The genetic changes of these signaling and regulatory factors of innate immune system might determine the susceptibility to periodontal destruction. Thus the aim of this study was to determine the association of the genetic polymorphisms of miR146a, apoE and NLRP3 with periodontitis in south Indian population. The study was approved by the institutional ethics committee of Saveetha university.(017/10/2013/IEC/SU) The study included three groups- chronic periodontitis group (n=81), aggressive periodontitis group (n=80) and healthy controls (n=167) After getting informed consent, five ml of venous blood was collected by vein puncture. DNA extraction was done according to modified Millers et al technique. The gene polymorphisms of miR146a (rs2910164), NLRP3 (rs10802501, rs10754558), apoE was analyzed using specific primers in real time PCR.

Conclusion: Thus our study concludes that the allelic frequency of NLRP3(rs10802501), miR146a (rs 2910164) and apoE polymorphisms were associated with periodontitis in south Indian population. The biological plausibility of this association has to be analysed with further studies.
Title

INSULIN MODULATION OF TLR4 EXPRESSION IN MURINE MACROPHAGES: POSSIBLE INVOLVEMENT OF PI3K/AKT AND ERK1/2 SIGNALLING PATHWAY

Name & Country

Soumojit Pal
India

Abstract

Toll-like receptor (TLR) mediated diet-induced obesity or insulin resistance is involved in the pathogenesis of type 2 diabetes. In obesity, macrophage accumulation in insulin target tissues (visceral adipose tissues) and TLR4 dependent up-regulation of cytokines promotes chronic inflammation, which in its turn leads to diabetic complications including nephropathy, atherosclerosis and retinopathy. Conversely, reducing glucose levels with insulin therapy is associated with decreased inflammation, mortality and incidence of sepsis in critically ill patients. However, importance of insulin signaling in macrophage function and polarization is not well characterized and molecular mechanisms underlying insulin modulation of TLR4 induction in murine macrophages is yet to be determined. In this study participation of insulin-mediated PI3K/Akt and ERK1/2 signaling during high glucose (HG) and/or lipopolysaccharide (LPS)-induced TLR4 expression in murine macrophages has been investigated. Present results show that while expression of insulin receptor (IR) remains unchanged, insulin alone could attenuate HG and/or LPS -induced TLR4 expression in duration-dependent manner, at both m-RNA as well as protein level. Further, insulin either alone or in presence of HG and LPS could up-regulate PI3K/Akt and ERK1/2 phosphorylation (activation) in vitro. More interestingly, in PI3K as well as ERK1/2 inhibited cells (using wortmannin and U0126 respectively), insulin failed to reverse HG or LPS action on TLR4 induction completely. Collectively, participation of PI3K/Akt and ERK1/2 signaling cascades has pivotal influence in insulin modulation of TLR4 expression induced by glucose or LPS in murine macrophages. This area of research is beneficial for further understanding of the interplay between insulin signalling and host immune system in metabolic diseases.
SYRINGIC ACID, A PHENOLIC COMPOUND ATTENUATED ARTHRITIS BY INHIBITION OF CYTOKINES IN COMPLETE FREUND’S ADJUVANT INDUCED ARTHRITIS IN RATS.

Title

Name & Country

Shilpee Chanda
India

Abstract

Aim and objective: To evaluate the anti-arthritis potential of Syringic acid in Freund’s complete adjuvant induced arthritis in rats and to study the underlying mechanism. Methods: Rheumatoid arthritis was induced in male Wistar rats by sub-plantar injection of 0.1ml of Complete Freund’s adjuvant into right hind paw on day 0. The treatment of Syringic acid (25, 50 and 100mg/kg) and standard drug, Indomethacin (1mg/kg) was started from day 0 and continued up to day 21. The body weight, paw volume, paw thickness and arthritic index were determined on day 0, 3, 7, 10, 14, 18 and 21. On day 22, rats were sacrificed and hematological, biochemical, anti-oxidant parameters, the thymus and spleen indices and cytokine level were estimated. Histopathological examination of the injected paw of the rat was performed. Results: Syringic acid showed significant (p<0.05) reduction in paw volumes at doses 50mg/kg and 100mg/kg. Syringic acid showed significant reduction in Tumor Necrosis Factor-α (TNF-α) and Interleukin-6 (IL-6) levels in the serum, while increase in the anti-oxidant and biochemical parameter. The histopathology showed reduced cellular infiltration, synovial line thickening and joint erosion of cartilage. Conclusion: The restoration of the levels of TNF-α and IL-6 to normal may be contributing to the anti-arthritis potential of Syringic acid and could be a promising therapeutic alternative in the treatment of Rheumatoid arthritis.
A study of the interaction mechanism of GTP with CodY of Bacillus anthracis

Shikha Joon

India

Bacillus anthracis, a prioritized bioterrorism agent, is a gram-positive, sporulating, non-motile, aerobic bacterium which causes the fatal zoonotic disease, anthrax, with humans as contingent victims. CodY, a global transcriptional regulator, controls diverse cellular activities such as metabolism, amino acid biosynthesis and transport systems, nitrogen uptake, motility, sporulation, pellicle, and biofilm formation, and most importantly virulence in almost all low G+C gram-positive bacteria. In B. anthracis, about 500 genes are perceived to be the targets of CodY, including the master regulator AtxA, which is pivotal to the manifestation of toxic constituents; namely a lethal factor, edema factor and protective antigen. GTP and Branched Chain Amino Acids are the metabolic effectors of CodY, which affects its DNA-binding ability. In order to gain an insight into the interaction mechanism of CodY and GTP, of which scarce is known presently, we carried out an in vitro GTP binding assay. We have demonstrated that CodY of B. anthracis binds to GTP. Homology modeling and sequence/structure analysis of CodY of B. anthracis revealed conserved GTP binding residues. Interestingly, we found that the CodY of B. anthracis could undergo autophosphorylation with GTP as a phosphoryl group donor. Furthermore, the phosphorylation site mutant (Ser215 to Ala215) of CodY failed to retain this autophosphorylation activity and hence is the critical residue involved in autophosphorylation. Since the Ser215 lies in the Helix-turn-Helix DNA binding motif of CodY and is conserved amongst its homologs, autophosphorylation may be speculated as a self-regulatory mechanism of CodY activity in the cell. Inquisitively, we proceeded to test the GTPase activity of CodY by thin-layer chromatography and found that the recombinant protein could withal hydrolyze GTP, albeit weakly, as quantified spectrophotometrically. Predicated on these findings, we conclude that in contrast to its homologs in other organisms, CodY of B. anthracis exhibits unique biochemical attributes such as GTP hydrolysis and autophosphorylation, which might be further exploited as a novel drug target.
Title
SERO-PREVALENCE OF CRYPTOCOCCAL ANTIGENEMIA IN HIV POSITIVE INDIVIDUAL HAVING CD4 COUNTS < 100 CELLS/MM3

Name & Country
Sundar Khadka
India

Abstract

Background: Cryptococcus neoformans is one of the most common opportunistic pathogen in individuals with Acquired Immuno Deficiency Syndrome (AIDS). It causes an estimated 1 million cases of cryptococcal meningitis (CM) per year among HIV/AIDS and resulting in 600,000 deaths per year. Cryptococcal antigen (CrAg), a biologic marker of cryptococcal infection, is detectable in sera in median of 3 weeks before symptoms of meningitis appear and is most commonly found in patients with CD4 < 100 cells/mm3.

Methods: This was a cross sectional, study conducted in HIV Reference unit, National public health laboratory from July to December 2015. Whole blood sample was used to determine CD4 counts by flow cytometry using the BD fluorescent-activated cell sorter system. Cryptococcal antigen testing was performed on plasma using the Cryptococcal Latex Agglutination test an antibody-agglutination reaction.

Results: The overall prevalence of positive serum cryptococcal antigen was 18.2% (18 of 99) by using Cryptococcal antigen lateral flow assay. The mean age of the patients were 38 years ranging from 13 to 69 years. The study comprised 72 (72.8%) males and 27 females (27.2%).

Conclusions: Lateral flow easy is simple test which can be done at any ART site without need of any specialized instrument providing results in short time.