9th World Congress on
Immunology and Cancer
December 09-10, 2019 | Barcelona, Spain

Keynote Forum

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IMMUNOLOGY AND CANCER

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Lara Oller

Hospital La Luz, Spain

Oxsealife: Embarking on a new methodology to treat haemorrhagic shock that focuses on cell recovery

Haemorrhagic shock is the result of inadequate blood flow to meet the metabolic demands of organs resulting in a flow dependent impairment of oxygen consumption by cells. Severe hemorrhage and ischaemia triggers a cascade of intracellular events that induce mitochondrial dysfunction and multiorgan failure. Therefore, patient survival after severe haemorrhagic shock depends on restoration of microvascular perfusion, tissue oxygen delivery, endothelial function and cell integrity. We investigated a novel crystalloid fluid designed for tissue oxygen delivery, Oxsealife®, with components to generate microvascular nitric oxide and scavenge reactive oxygen species generated during ischaemia-reperfusion injury. The amount of dissolved oxygen in blood progressively increased during step-wise *in-vitro* haemodilution with this fluid, demonstrating that the oxygen solubility coefficient of blood is dynamic, not static. We performed a pilot study to compare resuscitation with this novel crystalloid vs whole blood transfusion in a swine haemorrhagic shock model with animals bled to an arterial lactate oxygen debt target. Despite contributing no haemoglobin, viscosity nor oncotic potential, resuscitation with Oxsealife® after severe haemorrhagic shock restored central haemodynamic parameters comparable to stored allogeneic blood transfusion. Tissue perfusion, oxygenation and metabolic outcomes were equivalent between treatment groups. Increased consumption of bicarbonate in animals given Oxsealife® suggested greater capillary recruitment and enhanced clearance of lactate accumulated in tissues. Serum markers of organ function, animal activity during recovery, and histological analysis of tissue morphology and endothelial glycocalyx integrity confirmed functional recovery from haemorrhagic shock. We conclude that recovery of tissue oxygen delivery and organ function after haemorrhagic shock is not dependent on treatments that increase haemoglobin levels. Oxsealife® shows promise for treatment of severe haemorrhagic shock, and may reduce requirement for allogeneic blood products.

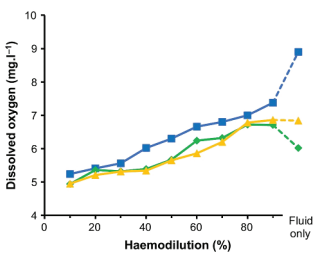

Figure 1 The oxygen solubility coefficient of blood is dynamic and increased during progressive haemodilution with Oxsealife (squares), PlasmaLyte (diamonds) and Voluven (triangles).

Biography

Lara Oller discovered the field of bloodless medicine and surgery when she was 12 years old and at that early age, she decided to commit her professional life to searching for the blood substitute. She studied medicine and was trained as anesthesiologist for this very reason. During her second year of training specialization she started and developed the project named "Oxsealife" which is an enhanced approach to haemorrhagic shock treatment and cell recovery after injury. The project also involves the renewal of the physiological fundamentals of oxygen transport. Professor Aryeh Shander, her dear mentor and associate, has been a highly valuable asset from the very beginning and now a recent collaboration with Wayne B Dyer has been achieved to expand animal studies before we get to human trials. She owns the Oxsealife patent and Dr Shander appears as a co-inventor. She is completely committed to this project and she is pleased to see it grow.

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Ricardo Moutinho Guilherme Alves Soares

Hospital Quirónsalud Madrid, Spain

Correlation between apparent diffusion coefficient values in breast magnetic resonance imaging and prognostic factors of breast invasive ductal carcinoma

Background: We wanted to examine whether the apparent diffusion coefficient values obtained by diffusion-weighted imaging techniques could indicate an early prognostic assessment for patients with invasive ductal carcinoma and, therefore, influence the treatment decision making.

Objectives: The main objective was to evaluate the correlation between the apparent diffusion coefficient values obtained by diffusion-weighted imaging and the key prognostic factors in breast invasive ductal carcinoma. Secondary objectives were to analyze the eventual correlations between magnetic resonance imaging findings and prognostic factors in breast cancer; and to perform a comparison between results in 1.5 and 3.0 T scanners.

Methods: Breast magnetic resonance imaging with diffusion-weighted imaging sequence was performed on 100 patients, who were proven histopathologically to have breast invasive ductal carcinoma. We compared the apparent diffusion coefficient values, obtained previous to biopsy, with the main prognostic factors in breast cancer: tumor size, histologic grade, hormonal receptors, Ki67 index, human epidermal growth factor receptor type 2, and axillary lymph node status. The Mann-Whitney U test and the Kruskal-Wallis analysis were used to establish these correlations.

Results: The mean apparent diffusion coefficient value was inferior in the estrogen receptor-positive group than in the estrogen receptor-negative group (1.04 vs 1.17 x10–3mm2/s, p=0.004). Higher histologic grade related to larger tumor size (p=0.002). We found association between spiculated margins and positive axillary lymph node status [OR=4.35 (1.49-12.71)]. There were no differences in apparent diffusion coefficient measurements between 1.5 and 3.0T magnetic resonance imaging scanners (p=0.513).

Conclusions: Low apparent diffusion coefficient values are related with positive expression of estrogen receptor. Larger tumors and spiculated margins are associated to worse prognosis. Rim enhancement is more frequently observed in estrogen receptor-negative tumors. There are no differences in apparent diffusion coefficient measurements between different magnetic resonance imaging scanners.

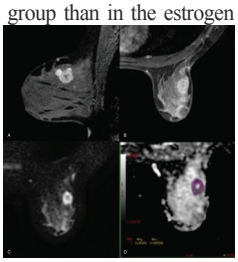

Figure 1. A 38-year-old woman with invasive ductal carcinoma in the upper external quadrant of the left breast

Biography

Ricardo is a Portuguese resident Medical Doctor at Hospital do Barlavento Algarvio in Portimão, Portugal. Studied Pharmaceutical Sciences in the Faculty of Pharmacy (Porto University) in Portugal. Graduated in Medicine by the Universidad Europea de Madrid in Spain. During his internship, he joined the Clinical Radiology Department in the Hospital Universitario Quirónsalud Madrid, in Spain, where he developed great interest in breast pathology, namely diagnosis and treatment for breast cancer. Clinical Internship in the Hospital da Beneficiência Portuguesa de São Paulo in 2015, during a period of 12 months, granted by the Universidade Anhembi Morumbi, São Paulo, Brazil. He published his work about the "Correlation Between Apparent Diffusion Coefficient Values in Breast Magnetic Resonance Imaging and Prognostic Factors of Breast Invasive Ductal Carcinoma" under the supervision of Dr. Vicente Vega Martínez, Head of the Clinical Radiology Department. Article published on July 2018 in the "Porto Biomedical Journal". Received the CIMQ17 1st prize award on best investigational work in 2017, by the Faculty of Medicine of Compostela University in Santiago de Compostela, Spain. He has a major research interest, taking part on several projects on Molecular Research and Cancer Diagnosis and Treatment. Reviewer for several peer-reviewed journals, both national and internationally.

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Dietrich Büsselberg

Weill Cornell Medicine, Qatar

Intracellular calcium regulation in neuroblastoma chemotherapy

Calcium signaling controls various process within the cell. Calcium (Ca2+), it is an important second messenger whose concentration is tightly controlled. A dysregulated calcium concentration is implicated in many pathological conditions including cancer. Here it modulates proliferation, evasion of apoptosis, invasion, migration, angiogenesis.

The presentation gives an overview of channels and pumps involved in the regulation of intra cellular calcium $[Ca2+]_i$. We present the effects of two anticancer drugs cisplatin (CDDP) and arsenic trioxide (AS_2O_3) in calcium dynamics of Neuro Blastoma (NB) chemotherapy. We show that anticancer drugs increase $[Ca2+]_i$ by different mechanisms in a time and concentration dependent manner. Assay for apoptosis demonstrated proportional increase in apoptotic cell with the increase in $[Ca2+]_i$ in NB cells exposed to CDDP. Quantification of protein expression (confocal microscopy) of IP3R1, IP3R3, RYR1, RYR3 or S100A6 following exposure to either 1 µM 72h CDDP showed upregulated protein expression. Development of resistance to chemotherapy is another problem developed in the course of cancer treatment. Our data show that calcium regulating protein expression varies between the wild type and resistant NB cell lines. Such as S100A6 protein had an altered cell distribution in resistant cell compared to the wild type. Microarray mRNA analysis reveals the calcium-dependent activation of signaling pathways involved in p53 signaling, cell cycle control and RNA transport. Also, the difference in mRNA micro array profile was evident between the wild type and the resistant cell line. In conclusion, pharmacological modulation of the $[Ca2+]_i$ response to cytotoxic drugs induced apoptosis in NB cells. Manipulating the $[Ca2+]_i$ signaling in anticancer chemotherapy opens the chances for more studies in combinatory therapy using $[Ca2+]_i$ regulating drugs (blockers/ promoters).

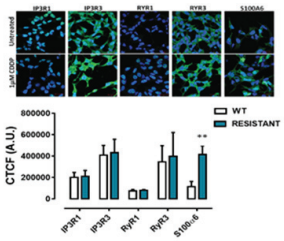

Figure 1: Calcium regulating protein expression in wildtype and neuroblastoma exposed to cisplatin

Biography

Dietrich Büsselberg is Professor of Physiology and Biophysics at Weill Cornell Medicine in Qatar and Assistant Dean for Premedical Student Affairs. Prior to coming to WCM-Q, he served as Professor of Physiology and Neuroscience at Texas Tech University, Health Science Center, Paul L. Foster School of Medicine. Dr. Büsselberg holds a State Exam for Teaching from the University of Hannover, Germany (1981) a B.S and M.S. from University of Hohenheim, Stuttgart, Germany (1987) and a Ph.D. from the University of Hohenheim (Germany), Institute of Zoology in collaboration with the University of Albany (U.S.), School of Public Health (1989).

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Hussein Fayyad-Kazan

Lebanese University, Lebanon

Human $CD8^+$ $CD25^+$ $CD127^{low}$ regulatory T cells: MicroRNA signature and impact on TGF-β and IL-10 expression

Regulatory T cells (Tregs) are central for maintaining immune balance and their dysfunction drives the expansion of critical immunologic disorders. During the past decade, microRNAs (miRNAs) have emerged as potent regulators of gene expression among which immune related genes and their immunomodulatory properties have been associated with different immune-based diseases. The miRNA signature of human peripheral blood (PB) $CD8^+$ $CD2^5$+ $CD127^{low}$ Tregs has not been described yet. We thus identified, using TaqMan Low-Density Array (TLDA) technique followed by individual quantitative real-time PCR (qRT-PCR) confirmation, fourteen miRNAs, among which twelve were downregulated whilst two were upregulated in $CD8^+$ $CD2^5$+ $CD127^{low}$ Tregs in comparison to $CD8^+CD25^-$ T cells. In a next step, microRNA Data Integration Portal (mirDIP) was used to identify potential miRNA target sites in the 3'UTR of key Treg cell-immunomodulatory genes with special focus on IL-10 and TGF-β. Having identified potential miR target sites in the 3'UTR of IL-10 (miR-27b-3p, miR-340-5p) and TGF-β (miR-330-3p), we showed following transfection, and transduction assays that overexpression of two under-expressed miRNAs, miR-27b-3p and miR-340-5p, downregulates IL-10 expression upon targeting its 3'UTR. Similarly, overexpression of miR-330-3p negatively regulates TGF-β expression. These results highlight an important impact of the $CD8^+$ Treg mirnome on the expression of genes with significant implication in immunosuppression. These observations could help in better understanding the mechanism orchestrating Treg immunosuppressive function towards unravelling new targets for treating auto- immune pathologies and cancer.

Biography

Hussein Fayyad-Kazan is a full time professor at the Lebanese University-Faculty of Science. He got his Bachelor degree in Biochemistry in 2005 from the Lebanese University-Faculty of Science. Later on, he continued his studies in the Free University of Brussels (ULB) where got his Master's Degree in Molecular Biology and Biotechnology in 2007 and then a PhD in December 2010. Thereafter, He did a postdoc in the Laboratory of Experimental Hematology-Jules Bordet Institute-ULB till September 2018 where he worked on several Molecular Immunology topics. He have about sixty scientific papers being published in high impact factor journals. His research work is focused on Cancer Biology and Molecular Immunology.

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David Hassin

Ben- Gurion University of the Negev, Israel

Killing of latently HIV-infected CD4 T cells by autologous CD8 T cells is modulated by Nef

The role of HIV-specific CD8 T cell activity in the course of HIV infection and the way it affects the virus that resides in the latent reservoir resting memory cells is debated. The PBMC of HIV-infected patients contain HIV-specific CD8 T cells and their potential targets, CD4 T cells latently infected by HIV. CD4 T cells and CD8 T cells procured from PBMC of HIV-infected patients were co-incubated and analyzed: Formation of CD8 T cells and HIV-infected CD4 T cell conjugates and apoptosis of these CD4 T cells were observed by fluorescence microscopy with *in situ* PCR of HIV LTR DNA and quantified by imaging flow cytometry using anti-human activated caspase 3 antibody and TUNEL assay. The conjugation activity and apoptosis were found to be much higher in patients with acute HIV infection or AIDS compared to patients in chronic infection on antiretroviral therapy (ART) or not. Patients on ART had low grade conjugation and apoptosis of isolated CD69, CD25 and HLA-DR-negative CD4 T cells (latent reservoir cells) by CD8 T cells. We demonstrate in HIV-infected patients, that CD8 T cells conjugate with and kill HIV-infected CD4 T cells, including HIV-infected resting memory CD4 T cells, throughout the course of HIV infection. We propose that in HIV-infected patients CD4 T cell annihilation is caused in part by ongoing activity of HIV-specific CD8 T cells. HIV Nef protein interacts with ASK 1 and inhibits its pro-apoptotic death signaling by Fas/FasL, thus protecting HIV-infected cells from CD8 T cells killing. A peptide that interrupts Nef-ASK1 interaction that had been delivered into CD4 T cells procured from patients on ART resulted in the increase of their apoptosis inflicted by autologous CD8 T cells. We suggest that elimination of the HIV-infected latent reservoir CD4 T cells can be achieved by Nef inhibition.

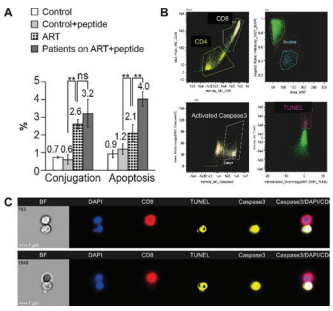

Figure 1. Inhibition of HIV Nef interaction with ASK1 in the CD4 T cells procured from patients on ART results in increased susceptibility to killing by autologous CD8 T cells

Biography

David Hassin, MD, specializations in internal medicine, infectious diseases and AIDS medicine. Research experience: 1) adenovirus in vitro DNA replication. 2) DNA amplification of SV40 DNA in cells transformed by SV40 exposed to carcinogens. 3) The study of cytotoxic T lymphocytes (CTL) in mice infected by mengovirus (picornavirus). 4) The physiological effect of CTL on myocytes *in vitro*. 5) The study of Fas/Fas ligand and perforin granzyme activity of CTL interacting with allogeneic cells in a mouse model. 6) Killing of latently HIV-infected CD4 T cells by autologous CD8 T cells.

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