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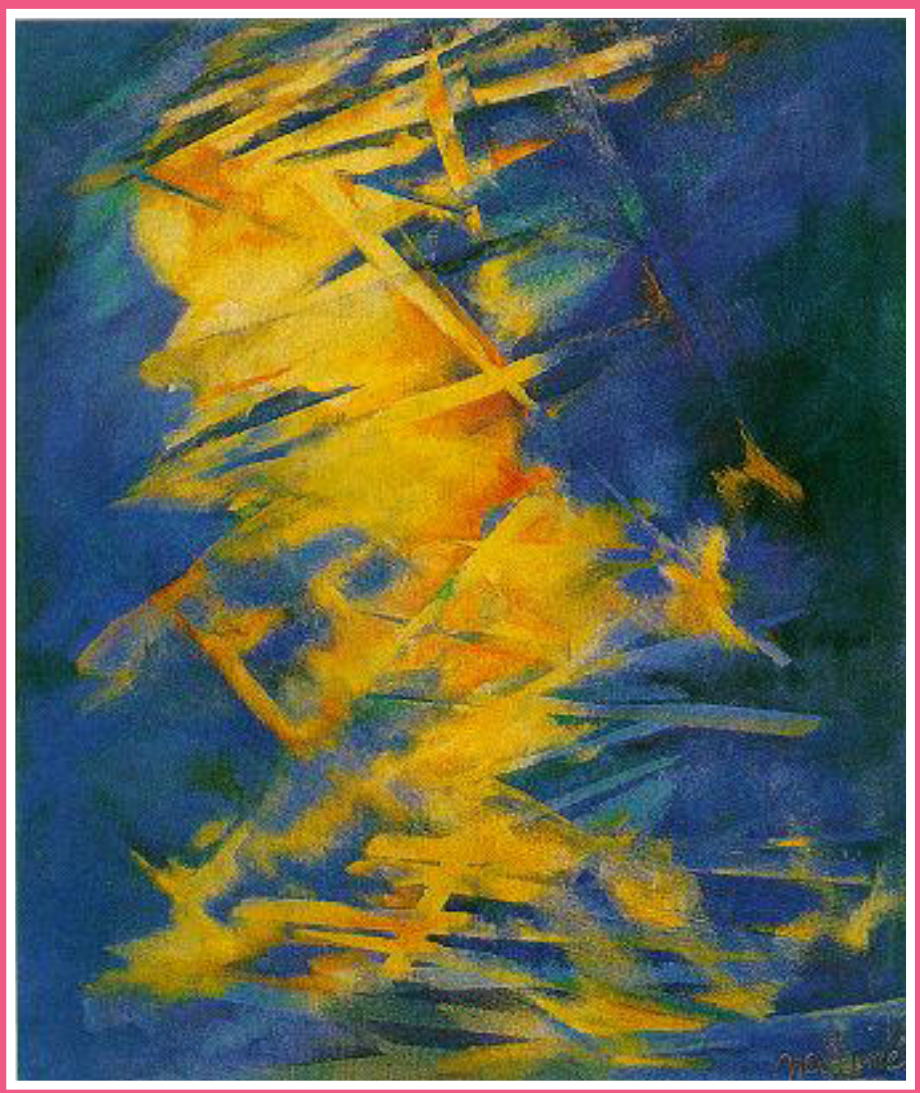

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rived macrophages (MØ) and dendritic cells (mo-DC) as screening tools to detect IIRMIs. Using purified PRR Agonists (PRRAgs) as model IIRMI and human IL-6 and IL-8 mRNA and protein as biomarkers for cell activation, we show that both primary cultures are more sensitive than PBMC in detecting IIRMI ($p \leq 0.05$). Interestingly, MØ and mo-DC showed different limits of detection (LLOD) for individual PRRAgs. In addition, PRRAgs induced increased expression of a set of pro-inflammatory genes and the profile of genes induced varied with the TLR agonist and concentration. Finally, we tested the capability of human PBMC, MØ and mo-DC for detecting impurities in a commercially available product for the treatment of autoimmune inflammatory diseases. While PBMC samples were not activated by impurities present in the product, MØ and mo-DC showed a robust activation ($p \leq 0.05$), even when low amount of product where added to the cell culture. In conclusion MØ and mo-DC constitute a suitable cell platform for testing impurities in therapeutic products, especially when these entities are present at such low levels not even detected by PBMC.

Keywords: Biotherapeutics, immunogenicity, impurities, cell-based assays.

(35) ***Brucella abortus*-STIMULATED PLATELETS ACTIVATE BRAIN MICROVASCULAR ENDOTHELIAL CELLS**

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(1) IMEX. (2) INIGEM/CICVYA-INTA. (3) INIGEM.

Central nervous system invasion by bacteria of the genus *Brucella* results in an inflammatory disorder called neurobrucellosis. Blood-brain barrier activation is a common feature of human neurobrucellosis, but the underlying mechanisms are largely unknown. The aim of this work was to investigate the influence of *B. abortus* (*B.a.*)-activated platelets (PTL) on human brain microvascular endothelial cells (HBMEC). For this, supernatants (SN) from *B.a.*-stimulated human PTL were used to stimulate HBMEC. Expression of ICAM-1 (CD54) and secretion of IL-6, IL-8 and MCP-1 were evaluated to determine HBMEC´ activation. SN from *B.a.*-stimulated PLT induced a significant secretion of IL-6, IL-8, MCP-1 and the up-regulation of CD54 expression in a dose-dependent manner compared with SN from unstimulated PLT ($p<0.001$).To avoid the possible implication of *B.a.* outer membrane vesicles (OMV) we ultra-centrifuged the SN (to eliminate OMV). HBMEC were stimulated with ultra-centrifuge SN and we observed no differences on HBMEC' activation compared with non-centrifuge SN ($p>0.05$), demonstrating that a soluble factor released from PLT was implicated on HBMEC' activation. SN from heat-killed *B.a.*-stimulated PTL also activated HBMEC indicating that B.a.' viability was not necessary in activating PLT. Soluble CD40L was not implicated on HBMEC' activation, as an anti-CD40L antibody could not block cytokine secretion or ICAM-1 up-regulation. Treatment of SN with trypsin eliminate the effect ($p<0.0005$), demonstrating that the PLT effector is a protein. These results demonstrate that *B.a.*-stimulated PTL can activate brain endothelial cells, and this could be implicated on the entry to B.a. to the central nervous system.

Brucella abortus – platelets - brain microvascular endothelial cells - Neurobrucellosis

(43) **ROLE OF HUMAN LUNG FIBROBLASTS IN THE *Brucella abortus* INFECTION BY INHALATION**

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Inhalation of contaminated aerosols is one of the most common forms for human infection by *Brucella abortus*. Together with epithelial and endothelial cells, fibroblasts are an important component of the alveolar respiratory barrier. While the interaction of *Brucella* with human lung epithelial cells has been studied, its interaction with human lung fibroblasts remains unknown. In this work, we investigated the ability of *B. abortus* 2308 to infect and induce inflammatory mediators in a cell line of normal human lung fibroblasts (MRC-5). The cells were infected for 2 h and then incubated with gentamicin to kill extracellular bacteria (time 0 p.i.). At 2, 24 and 48 h p.i., cells were lysed to determine CFU of intracellular bacteria, and culture supernatants were collected at 48 h p.i. to measure cytokines. Results showed that *B. abortus* infects and replicates in lung fibroblasts and that its survival depends on a functional *virB* operon. The infection induced the secretion of interleukin-8 (IL-8) ($p<0.0001$), which secretion was mediated by p38 MAPK and NF-κB pathways, and monocyte chemotactic protein 1 (MCP-1) ($p<0.0001$), which secretion depended on p38 MAPK, NF-κB and PI3K pathways. Furthermore, the infection increased the gelatinase/collagenase activity ($p<0.0001$). The cytokine secretion did not depend on bacterial viability since heat-killed *B. abortus* and *B. abortus* lipopolysaccharide were also able to induce IL-6, IL-8 and MCP-1 secretion. In addition, the secretion of IL-6 and MCP-1 by fibroblasts increased significantly upon stimulation with conditioned medium (CM) from *B. abortus*-infected macrophages as compared to stimulation with CM from non-infected cells. These results suggest that human lung fibroblasts respond to *B. abortus* infection producing chemokines either directly or by stimulation with soluble factors secreted by infected macrophages.

Keywords: *Brucella*, human lung fibroblasts, cytokines, chemokines

(1012) **CATHEPSIN L3 FROM Fasciola hepatica induces IL-1β AND IL-18 SECRETION IN DENDRITC CELLS AND PROMOTES AN IN VIVO IFN-γ RESPONSE**

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Cathepsin L3 (CL3) is expressed in the juvenile stage of *F.hepatica* and has collagenolytic activity, however there is no information about its interaction with the immune system. The aim of this work was to study the ability of CL3 to modulate dendritic cells (DC) activation and its effect on adaptive immune response. DC were differentiated from bone marrow cells of C57BL/6 (WT) or NLRP3 KO mice with GM-CSF and cultured at different times with CL3. DC were pulsed with recombinant CL3, an inactive variant recombinant (rvCL3) or LPS/ATP. IL-1β and IL-18 secretion were quantified in supernatants by ELISA. Moreover, to study the ability of CL3 to induce a specific immune response, WT mice were intraperitoneally immunized with CL3 plus MPLA, three times at 48 h intervals. After 7 days of last immunization, lymph node cells (LNC) were recovered, re-stimulated with CL3 and IFN-γ production was studied. Statistical analyses were performed by ANOVA. To determine the uptake of CL3 by DC, we analyzed the presence of labeled CL3 into DC by confocal microscopy. Although after treatment, there was some colocalization between CL3 with lysosome, the presence of labeled CL3 in the cytoplasm of DC was evident. Besides, CL3 promotes IL-1β and IL-18 production in WT DC, at similar levels than those secreted by LPS/ATP-stimulated DC and this effect was not observed when DC were treated with rvCL3. However, when NLRP3KO DC were treated with CL3, IL-1β and IL-18 secretion were significantly diminished ($p \leq 0,05$). On the other hand, increased levels of IFN-γ in CL3 re-stimulated LNC from CL3-MPLA immunized mice were observed ($p \leq 0,01$).

Our results suggest that CL3 up-taking by DC induces IL-1β and IL-18 production-dependent on NLRP3, which in turn was dependent on CL3 enzymatic activity. This event could be related to the uptake of CL3 that promote the inflammasome activation. The up-regulation of these cytokines may be involved in IFN-γ production.

(1080) **AKAP350 REGULATES NATURAL KILLER CYTOTOXICITY BY CONDITIONING CELL POLARIZATION AT THE IMMUNE SYNAPSE**

Alejandro Pedro Pariani (1), Evangelina Almada (1), Florencia Hidalgo (1), Facundo Tonucci (1), Anabela Ferreti (1),