($p<0.001$; Log-Rank test) (Figure). Splenic germinal centers from the *E. coli*-injected ICE+/+ mouse had 88 ± 18 apoptotic bodies/hpf at 24hrs compared with 4 ± 1.5 in the ICE -/- mouse. Splenic TNFα and IL-1β mRNA production was maximal at 18hrs and was increased in the ICE+/+ mouse (TNFα 24x control; IL-1β 13x control) compared with the ICE-/- mouse (TNFα 1.4x control; IL-1β 0.6x control). Conclusion: These preliminary data suggest that ICE contributes to the septic response seen in infection with live bacteria. Support: NIH HL40871 and NIH CHRC program.

Figure: ICE genotype and sepsis survival

333.16

A pathogenic herpes-like virus from the Caribbean spiny lobster. Isolation of the virus and evidence of an innate host response

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The first virus to cause disease in a lobster species was recently described in the Caribbean spiny lobster, Panulirus argus. Pre-adult lobsters with signs of disease are lethargic, have white non-clotting hemolymph, and die within 30-90 days. Using degenerate primers for the herpesviridae DNA. polymerase gene in a nested PCR, two amplicons of approximately 195bp and 225bp were detected in hemolymph extracts from both inoculated and naturally infected lobsters. The herpes-like virus of P. argus (HLV-PA) was isolated from hemolymph using step-gradient ultracentrifugation. HLV-PA particles had an 120nm icosahedral nucleocapsid, a minimum of ten viral proteins ranging is size from 11 to 71 kD, and at least two viral proteins were present in the cytosol of hemocytes from infected lobsters. Furthermore, infection was associated with changes in the levels of some non-viral cytosolic proteins that may reveal how the crustacean innate immune system responds to a viral infection. (Supported by: NSF and NOAA/National Marine Fisheries)

333.17

Toll-like Receptor 3 (TLR3) Stimulation Initiates Anti-viral Reponses by Endometrial Epithelial Cells

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Toll-like receptors (TLRs) are pattern recognition receptors that initiate innate immune responses through recognition of pathogen associated molecular patterns. dsRNA stimulates TLR3 to produce a potent antiviral response (AVR). The role of TLRs in the endometrium is unclear, but many cytokines involved in the AVR are also involved in endometrial function. Cytokine imbalances have been linked to dysfunctions such as spontaneous abortion and endometriosis, but the triggering mechanism is unknown. We previously established that TLR3 mRNA was expressed in endometrial epithelial cells and cell lines, and we also demonstrated that dsRNA induces both IL-8 and IL-6 by TLR3-expressing cell lines. Current studies have shown predominately intracellular expression of TLR3 protein with varying levels of cell surface expression. dsRNA induced endometrial TLR3 signaling initiated an AVR, including induction of mRNA for type I interferons and IP-10. Cytometric bead array confirmed production of cytokines and chemokines in response to dsRNA by endometrial cell lines and primary endometrial epithelial cells. TLR3 specific siRNAs abrogated responsiveness to dsRNA and transfection of TLR3 negative cell lines with a TLR3 expression vector conferred dsRNA responsiveness to cells. These results indicate that endometrial cell cytokine expression profile can be modified through TLR stimulation.

NIH R21 AI55504-01

333.18

The function of myeloid differentiation factor-88 (MyD88) and Toll-like receptors in *Francisella tularensis* LVS infection in mice

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Francisella tularensis (Ft) is the etiologic agent of tularemia. Here we examine the role of MyD88 in Ft LVS (live vaccine strain) infection, a component of the signal transduction machinery of the Toll-like receptors (TLR). Moreover, we investigate the function of TLR2, TLR4 and TLR9 during Ft infection. Although wild type (WT) mice survive 10^6 LVS given intradermally (ID), MyD88 KO rapidly died following ID infection with 5×10^5 Ft LVS and even with a very low dose of Ft LVS (5×10^1), with a mean time to death of 7 ± 0.8 days. On day 5 after infection with a 10^4 dose of LVS ID, bacterial organ burdens were approximately 5 logs higher in MyD88 KO mice compared to WT controls. In vitro, bacterial growth was controlled in co-cultures containing macrophages from MyD88 KO mice and LVS immune WT lymphocytes as well as in co-cultures containing all WT cells. In contrast to MyD88 KO, TLR2 KO, TLR4 KO and TLR9 KO mice infected with 5×10^5 CFU ID were as resistant to bacterial infection as WT controls. Our results demonstrate that MyD88 is essential for host resistance to Ft LVS infection. Nevertheless, macrophages derived from MyD88 KO mice controlled bacterial replication as efficiently as WT BMMO, suggesting that MyD88 is not required at the level of the macrophage. In contrast, TLR2, TLR4 and TLR9 are not required for host resistance to Ft.

REGULATORY ACTIVITIES OF CYTOKINES IN DISEASE MODELS (334.1-334.13)

334.1

TNFα and skeletal muscle repair mechanisms

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We have demonstrated that TNFα is activated in injured skeletal muscle and attenuation of its signaling leads to delay in muscle functional recovery post-injury. In vitro TNFα induces proliferation and migration but suppresses differentiation of myoblasts. The responses attributed to TNFα are not a direct result of TNFα, but rather its ability to regulate the expression of TNFα responsive genes whose products directly mediate the response. TNFα delivers its signals to target cells by binding to specific cell surface membrane receptors (TNFR1 and TNFR2). DNA array or real-time PCR techniques were used to evaluate gene expression induced by TNFα in myoblast cultures. TNFα induces high expression of chemokines, (e.g. MCP-1) and adhesion molecules (VCAM-1), in proliferating or differentiating C2C12 cells and primary myoblasts. This response may be related to myoblast migration or fusion activities. Furthermore, TNFα induces moderate induction of Pax-7, a mediator of myoblast proliferation. For TNFα induced inhibition of myoblast differentiation myogenin expression was reduced. Myoblasts from TNFR1 and TNFR2 deficient mice demonstrated that TNFα induced gene expression in primary myoblasts is dependent on both receptors. These studies indicate that a complex and multifunctional role exists for inflammation, and specifically TNFα, in post-traumatic skeletal muscle regeneration and healing.

334.2

TGF-β regulates human uterine NK cell activity

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Natural killer (NK) cells, which account for a major population of lymphocytes in the human endometrium, can be a significant source of cytokines that have the potential to alter local immune responses. The aim of this study was to test whether uterine NK (uNK) cells produce cytokines and how cytokine production by uNK cells may be regulated by TGF-β. We examined cytokine production by uNK cells and uNK

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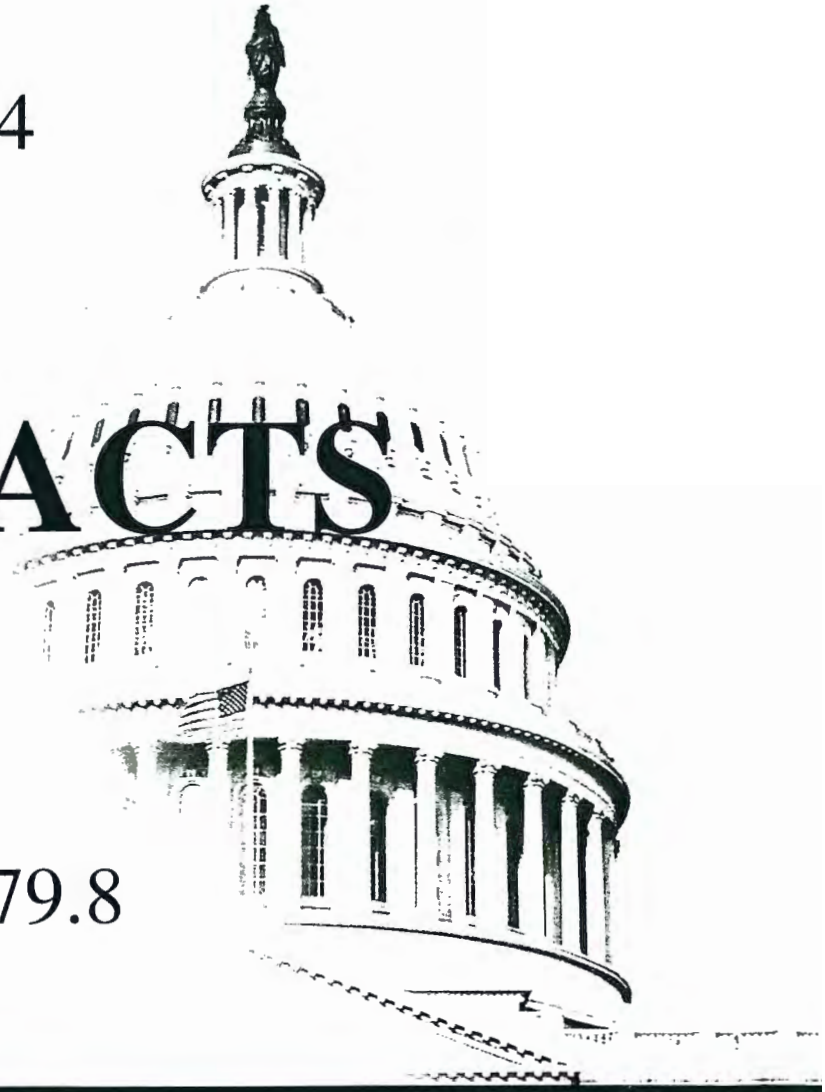

ABSTRACTS

PART I

Abstracts 15.1–479.8

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