73.009

Fc/R IIA polymorphism -131H/R and malaria severity in Ghanaian children

D. Amoako-Sakyi

University of Cape Coast, Cape Coast, C/R, Ghana

Background: *Plasmodium falciparum* malaria still remains a major public health problem in most parts of the world especially in Sub Saharan Africa. Pathogenesis of severe malaria is still not fully understood and several factors have been suggested to play a role. Fc receptors constitutes a crucial link between humoral and cellular immune responses and are thought be important in the pathogenesis of severe malaria. *FcγRIIA* which belongs to the family of Fc receptors are predominantly expressed on neutrophils which have been shown to kill merozoites. Thus variants of *FcγRIIA* may influence the binding affinity of IgG and subsequently affect phagocytosis and parasite clearance. On the other hand, increased binding affinity and enhanced phagocytosis can also stimulate the release of some immune factors in quantities that are detrimental leading to severe malaria. The objective of this study was to investigate the role of the *FcγRIIA-131H/R* variant in the pathogenesis of severe malaria in Ghanaian children.

Methods: This study was a hospital based unmatched case-control study involving 290 malaria cases and controls. The study was conducted at the Korle-Bu Teaching Hospital in Accra, Ghana. PCR-RFLP was used to characterize the *FcγRIIA-131H/R* polymorphism in 210 Ghanaian children with uncomplicated malaria, severe malaria anaemia, and cerebral malaria.

Results: The study revealed that the *131HH* genotype is associated with susceptibility to cerebral malaria (OR = 4.0, 95% CI = 1.28—12.52; $p = 0.014$). The results also revealed that carriers of the R allele had a significantly lower parasitaemia ($p < 0.050$) than non-carriers.

Conclusion: The presence of *FcγRIIA-131HH* which is regarded as a low affinity variant may lead to decreased phagocytosis and poor control of parasitaemia in Ghanaian Children. This however does not exclude the possibility that IgG binding to the *FcγRIIA-131HH* variant can stimulate the release of factors that may contribute to the development cerebral malaria.

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An animal model to study antimicrobial effects on community-acquired methicillin-resistant *Staphylococcus aureus* infection

M. Ip*, E.T.Y. Leung, C. Wong, K. To

Chinese University of Hong Kong„ Shatin, Hong Kong, China

Background: Outbreaks of Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections have been reported worldwide, and a main concern is the severity of infection with fatal necrotizing pneumonia and toxic shock. Studies showed that the expression of virulence proteins by *Staphylococcus aureus* depends on the strain types and could be modulated by different agents including antibiotics. The objective of the study was to establish a murine infection model to study the in-vivo effects of commonly used antimicrobials on the severity of CA-MRSA pneumonia.

Methods: 6-to-8-week-old BALB/c mice were divided into groups of six in individually ventilated cages and injected with intranasal injection of a representative strain of CA-MRSA. The bacterial inoculum was titrated with varying concentration ranging $1 \times 107—5 \times 108$ cfu, with controls receiving same volume of broth medium. Mice were sacrificed on Day 2, 3 and 4 of infection and the lungs were dissected, placed in formalin, embedded in paraffin blocks and sectioned for histological examination. The severity of pneumonia was scored according to size of leukocyte infiltration and level of alveolar integrity and epidermis damage. Subinhibitory concentrations of antimicrobial agents (half of MIC per body weight) of vancomycin, ciprofloxacin, gentamicin were administered at different timepoints after bacterial inoculation.

Results: The severity of pneumonia varies with the bacterial inocula titrated. All infected mice developed pneumonia after 24 hours of infection after inoculation of at least 1×108 cfu bacteria. The endpoint for outcome of pneumonia was interpreted at 24 hours. Incubation of 48 and 72 hours led to increasing mortality of mice and masked the histological effects of pneumonia. The most significant effects was in the ciprofloxacin group, with 33% (2/6) mice in ciprofloxacin-treated group died and the the remainder (4/6) developed severe pneumonia of Grade 5 histologically (in terms of size and extent of necrotizing lesions) than the infected control group. The non-infected-control group remained healthy.

Conclusion: A murine model for CA-MRSA pneumonia to study effects of different drugs was established. The choice of antimicrobials that minimizes release of toxins and reduces the severity of pneumonia is an invaluable approach in improving treatment outcome in CAMRSA infections.

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73.011

Increased killing of liver NK cells by Fas/FasL and NKG2D/NKG2DL contributes to hepatocyte necrosis in virus-induced liver failure

T. Chen[1], Y. Zou[1], M. Han[1], H. Wang[1], W. Yan[1], G. Song[1], Z. Wu[1], X. Wang[1], C. Zhu[1], X. Luo[2], Q. Ning[1,*]

[1] *Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, Hubei, China*
[2] *Tonji Hospital, Wuhan, China*

Background: The role of liver NK cells in virus-induced severe viral hepatitis and subsequently hepatic failure is not well defined.

Methods: In this study, we investigated the role of liver NK cells in the development of hepatocyte necrosis in fulminant hepatic failure (FHF) and acute-on-chronic liver failure (ACLF) due to viral infection. A mouse model of FHF induced by murine hepatitis virus strain 3 (MHV-3) was used to study the role of liver NK cells. Samples from patients with hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) were examined.

Results: Following MHV-3 infection, the number of NK cells in livers of Balb/cJ mice increased markedly, peaked at 48 h post-infection, and remained at a high level until sacrifice. In peripheral blood, spleen, and bone marrow, this number decreased significantly. Expression of CD69, cytotoxic activity, and intracellular IFN-/ and TNF-& production by liver NK cells at 48 h post-infection were all significantly upregulated. Highly activated liver NK cells were cytotoxic to MHV-3-infected hepatocytes and this effect was markedly inhibited by anti-FasL plus anti-NKG2D monoclonal antibodies. Furthermore, the accumulation of hepatic NK cells and increase in the expression of natural cytotoxicity receptors (NKP30 and NKP46) on the peripheral NK cells from patients with HBV-ACLF were correlated with disease progression.

Conclusion: These results indicate the pivotal involvement of NK cells in the pathogenesis of FHF and HBV-ACLF, and the synergetic effect of Fas-FasL and NKG2D-NKG2DL pathway in liver NK cell mediation of hepatocyte toxicity.

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73.012

CMV infection causing Adult Onset Still's Disease: A clinical case

D. Bento[1,*], R. Leite[1], R. Tavares[2], A. MIranda[2], F. Ventura[1], C. Araújo[2], K. Mansinho[1]

[1] *West Lisbon Hospital Centre, Lisbon, Portugal*
[2] *Lisbon, Portugal*

Background: CMV normally causes a mononucleosis syndrome in immunocompetent persons. Immunologic aberrations recognized with this infection include hypogammaglobulinemia, rheumatoid factor (RF), antinuclear antibodies and anticomplementary activity. CMV has been associated with inflammatory bowel diseases, rheumatoid arthritis, psoriasis and Wegener's granulomatosis. Adult Onset Still's Disease (AOSD) is an RF-negative inflammatory disorder of unknown aetiology, responsible for many cases of fever of unknown origin. It is marked by cytokine abnormalities and a predominant Th1-cell response.

Methods: A 34-year-old man presented himself to the ED on June 2007 with two weeks of fever, arthralgia and sore throat. After an empirically course with Amoxicillin Clavulanate he also experienced a self-limited morbilliform rash. On admission he exhibited 39° temperature, cervical adenopathies and mild splenomegaly. Analysis showed leucocytosis, atypical lymphocytosis, C-RP 3.53 mg/dl and ESR 21 mm/h. There was an elevation of hepatic enzymes and positive CMV IgM and IgG. The search for Hbs, p24 antigen and antibodies against HIV, HCV, EBV, *Toxoplasma gondii* and Streptolysin-O was negative.

Results: In October 2007 he remained symptomatic. His liver was biopsed. Histological sections in H&E identified epithelioid granulomas, portal inflammation, nuclear and cytoplasmic inclusions in hepatocytes and Kupfer cells. Immunohistochemistry was compatible with CMV. He was started on Valganciclovir. Fever remained intermittently. In February 2008 he maintained positive titers of CMV IgM and elevated liver enzymes. The search for other infections with cultures of peripheral blood and bone marrow was negative. Antibodies to other agents such as *Brucella* spp, *Borrelia* spp and *Coxiella burnetii* were negative. Echocardiogram, body CT scan and upper and lower GI endoscopy were normal. Markers for autoimmune/inflammatory diseases such as ANA, ANCA and RF and tumor markers were also negative. Cytometry showed an inversed TCD4+/TCD8+ ratio and low CD19+ B lymphocytes. IgA, IgG and IgM levels were low. Tetanus vaccination resulted in antibody response, excluding Common Variable Immunodeficiency.

Conclusion: In June 2008 he maintened fever and arthralgia. Analysis registered leukocytosis, ESR 77 mm/h and ferritin 6400 ng/ml. CMV IgM was negative and liver enzymes were normal. AOSD was suspected and the patient started prednisone 1 mg/kg/day. The patient had a marked improvement after institution of this therapy.

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73.013

Telbivudine preserves Th1 cytokine response and down regulates PD-L1 in MHV-3—induced viral hepatitis model

Z. Wu[1], W. Yan[1], W. Guo[1], Y. Zou[1], H. Wang[1], X. Wang[1], X. Yang[1], Y. Lu[1], X. Luo[2], Q. Ning[1,*]

[1] *Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, Hubei, China*
[2] *Tonji Hospital, Wuhan, China*

Background: Telbivudine is an orally bioavailable L-nucleoside with potent and specific anti—hepatitis B virus (HBV) activity. Recent studies have suggested a potential immunomodulatory effect of telbivudine. To address this, we sought to determine the effect of telbivudine on the immune system, particularly cytokine production and T-cell response, in the mouse hepatitis virus strain 3 (MHV-3)-induced hepatitis model.

Methods: The effect of telbivudine on virus replication and cytokines production in MHV-3 infected macrophages were investigated. In vivo the T cell response to Telbivudine treatment were also studied in MHV-3 induced viral hepatitis model.

Results: In vitro there was no significant difference in MHV-3 replication in macrophages with or without telbivudine treatment. The production of tumor necrosis factor—& and interleukin-12 was increased significantly in MHV-3—induced macrophages with telbivudine treatment. *In vivo* survival was enhanced in telbivudine-treated mice with marked normalization in clinical conditions and histologic lesions. Serum levels of interferon-/ were elevated significantly after telbivudine treatment in MHV-3—infected C3H mice. In contrast, serum interleukin-4 levels were decreased significantly. Furthermore, telbivudine treatment had a beneficial effect on T cells, restoring their ability to undergo proliferation and secrete cytokines but not to enhance cytotoxicity on infected hepatocytes. Notably, we found that telbivudine treatment suppressed programmed death ligand 1 expression on T cells.

Conclusion: These data identify an immunomodulatory mechanism of telbivudine treatment in the MHV-3—induced viral hepatitis model and provide insights into a potential additional mode of action for the management of viral hepatitis infection.

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