1990–94, after the diagnosis of OI, one-year survival probability is only 59.8% (95% CI 52.0–67.7%). The most common OI’s are tuberculosis (40–50%), cryptococcosis (25–40%), Pneumocystis carinii pneumonia PCP (10–20%), toxoplasmosis (5–10%) and salmonellosis (5–10%). In the northern part of Thailand, where Penicillium marneffei is endemic, this infection is as common as tuberculosis, indicating the importance of local endemic infection to be recognized as AIDS-defining illnesses. Cryptococcosis carries the worst prognosis with 1-year survival probability of 31.9% (16.8–48.1%). Since HAART became available and financially supported by Thai Government in 2001, the morbidity and mortality of HIV-infected persons have decreased remarkably. OI’s has decreased and people living with AIDS/HIV survive much longer. The emergence of drug-resistant HIV has posed problems since the second line drugs are much more expensive and not many to choose from. In addition, this group can transmit drug-resistant HIV causing primary drug-resistant HIV infection which will make it more difficult to choose the proper regimen without genotyping the virus. Thus, strong prevention and control program should remain at top priority, to stop new infection and transmission.

I-24 HIV-specific T-cell responses in a cohort of slow progressors in China
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Background: There is an urgent need for an effective vaccine to prevent HIV-1 infection, and current efforts are directed towards generating vaccine candidates that will elicit a T-cell immune response to the virus. No studies to date have described mechanisms of HIV resistance or delayed disease progression in Chinese cohorts. For both the design and the evaluation of CTL-inducing vaccines it is important to define immunodominant CTL epitopes for both the prevailing HLA types and the most common viral strains affecting that population. Moreover, it is also important to identify composite features of T-cell responses associated with good outcome and T-cell epitopes that will generate such beneficial features.

Study cohort: Current studies are limited by the facts that most of the study cohort subjects have been infected for different lengths of time; infected with different viral strains and have a diverse genetic background. In this study, we have access to a unique village cohort of patients (N = 407) who were involved in a plasma donation scheme that became contaminated with clade B HIV-1 in the period 1994–1995. 137 premature adult deaths were recorded in the village with symptoms compatible with HIV-1 disease before 2003. Of the surviving patients, none were treated before 2003: therefore the proportion of slow or non-progressors is unusually high in this cohort (>50% had CD4 counts >200 in 2004).

Results: We found that HLA-A30 and B51 were strongly associated with low viral load in this cohort. We investigated the hypothesis that immunodominant T-cell responses to conserved HIV-1 proteins restricted by these alleles could be partially responsible for good control of virus. We used ELISPOT assays to test for responses to overlapping Clade B peptides spanning the whole viral proteome and to the 202 best characterised optimal epitopes from the Los Alamos data base. We found broad T cell responses, especially directed towards the gag protein, in patients with low viral loads. The immunodominance hierarchy of epitopes restricted by common HLA molecules in the cohort showed very different patterns from a published acute cohort (Altfeld, 2006). We have sequenced the gag and nef genes from 97 patients and will present data to show that the loss of certain responses in the chronic phase of infection might be due to early selection of escape mutants.

Conclusion: We have identified a panel of immunodominant T-cell responses restricted by common HLA alleles in a Chinese slow progressor cohort. Identification of the most beneficial responses will be particular important for future vaccine design targeted to the Chinese population.

I-25 Outcomes and challenges of the China National Free Antiretroviral Treatment Program
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To combat the HIV/AIDS epidemic in China, the National Center for AIDS/STD Control and Prevention established the Division of Treatment and Care in late 2001. The pilot for the National Free ART Program began in Henan Province in 2002, and the program fully launched in 2003. Initially, treatment efforts focused on patients infected through illicit blood and plasma donations in the mid-1990s, and subsequently expanded to include HIV-infected injection drug users, commercial sex workers, pregnant women, and children. The National Free ART Database was established in late 2004, and includes data on current patients and those who were treated before 2004. Over 50,000 adult and pediatric patients have been treated thus far. Challenges for the program include integration of drug treatment services with ART, an under-resourced health care system, co-infections, stigma, discrimination, drug resistance, and procurement of second-line ART. The merging of national treatment and care, epidemiologic, and drug resistance databases will be critical for a better understanding of the epidemic, earlier identification of patients requiring ART, and improved patient follow-up. The Free ART Program has made considerable progress in providing the necessary care and treatment for HIV-infected people in China and has strong government support for continued improvement and expansion.

Concurrent Session 4 – Immunology and Virology

I-26 Immunology of HBV infection
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HBV is an enveloped, hepatotrophic, oncogenic hepatitis virus that infects hepatocytes and leukocytes of humans and chimpanzees. The clinicopathological outcomes of HBV infection are determined by both viral and host factors. HBV infects hepatocytes without triggering apoptosis, altering hepatocyte gene expression or inducing innate immune production of IFNα or IFNγ. Host determinants of outcomes are the quality, quantity, kinetics and immunoregulation of the integrated innate and adaptive immune responses. HBV subverts the innate immune response by down-regulating (1) expression of MICA, the primary ligand for the NKG2D receptors of NK cells and (2) TLR1, 2, 4 and 6 transcripts in PBMC. In addition, HBV persistence and disease progression is favored by the low production of mannose binding lectin (MBL) and reduction in the interferon-inducible APOBEC3 family of cytidine deaminases that inhibit HBV replication and hypermutate the HBV genome. Generation of polyclonal, multi-antigen-specific CD4 T-cell and CD8 cytotoxic T lymphocytes (CTL) is required for resolution of acute HBV infection through the combined effects of HBV-specific cytolyis of infected
hepatocytes and secretion of proinflammatory cytokines IFNγ and TNFα to inhibit HBV replication noncytolytically. Since these inhibitory cytokines are produced not only by CTL, but also by enriched, activated populations of hepatic NK and NKT-cells, it is now clear that NK and NKT-cells contribute to resolution of acute hepatitis B. HBV-specific T-cell immune responses are also modulated by CD4 T regulatory cells. The role of HBV-specific antibodies in resolution is less clear; however, once acute infection is resolved the combination of HBV-specific cellular and humoral immunity prevents reactivation of HBV replication from residual nuclear cccDNA templates. The risk of reactivation remains if immunological control is disrupted by immunosuppressive drugs or cytotoxic ablative chemotherapy. Persistent HBV infection, which occurs in the majority of neonates and infants but only a minority of adults, is favored by several viral and host factors. The viral factors include the subversion of innate immunity, a high rate of replication favoring mutational escape, absence of hepatocyte gene induction, tolerogenic properties of secreted HBeAg and HBsAg, HBx inhibition of proteasome processing of antigens and HBx induction of aberrant class II MHC and ICAM-1 to favor clonal T-cell energy due to absence of costimulatory signaling. Host factors associated with persistence include decreased numbers and defective function of plasmacytoid-dendritic cells, decreased expression of TLR and class I MHC, decreased production of MDL and APOBEC3 cytidine deaminases, CTLA-4 polymorphisms, CD4 T regulatory cell activity and CTL suppression mediated by paracrine activation of PD-1. Overall, chronic hepatitis B is associated with a paucity of HBV-specific CTL, activated HBV-specific CD4 helper 1 cells and hepatic inflammatory infiltrates enriched for NK, NKT and other antigen-non-specific cells. Perpetuation of antigen-non-specific inflammation favors progressive fibrosis. Better understanding of the immunopathogenesis of HBV infection has also provided insights into the mechanisms responsible for flares during chronic infection, reactivation following immunosuppression or chemotherapy, vasculitis and recurrent HBV infection after liver transplantation. Ultimately, complete understanding of the immunology of HBV infection will likely lead to new therapeutic strategies.

I-27 New cell culture and mouse models of HBV replication
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Hepatitis B virus (HBV) infection is a worldwide health problem. Understanding of the HBV life cycle especially the replication mechanism may provide potential targets for the development of anti-HBV treatment. Cell culture and animal models with HBV replication are the most important tools for studies on the mechanism of HBV replication, the pathogenesis of HBV-related liver diseases, and the selection of anti-HBV drugs. Hepatotropism is a prominent feature of hepatitis B virus (HBV) infection. Cell lines of non-hepatic origin do not independently support HBV replication hepatic origin. In our study, a new HBV nonhepataoma cell replication system has been developed where a recombinant RNA synthesized and consequently HBV replication are controlled by the ectopic expression of liver-enriched transcription factors. We show that the nuclear hormone receptors, hepatocyte nuclear factor 4 (HNF4) or retinoid X receptor α (RXRα) plus peroxisome proliferator-activated receptor α (PPARα), support HBV replication in non-hepatic cells, indicating these liver-enriched transcription factors represent a major determinant governing the hepatotropism of HBV. With this new HBV replication system, many roles of the liver-enriched transcription factors in controlling HBV transcription and replication have been identified. Until recently, most in vivo studies on HBV have been performed by using HBV transgenic mice. However, the acquisition of transgenic mice is very time-consuming and laborious, because expensive microinjection equipment and complicated technology is needed. Recently, we developed a new mouse model with HBV replication by using a hydrodynamic procedure that provides a simple, convenient and useful tool for molecular-biological studies on HBV, and for the selection of anti-HBV drugs.

I-28 Association between epidermal growth factor gene polymorphisms and the risk of hepatocellular carcinoma in patients with hepatitis B virus chronic infection
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Aims: Epidermal growth factor (EGF) is a multifunctional growth factor, and plays an important role in tumorigenesis, including hepatocellular carcinoma (HCC). A single nucleotide polymorphism (SNP) at position 61 in the 5′-untranslated region (UTR) of the EGF gene has been reported to modulate the transcription level of this gene and associated with the level of EGF protein expression in serum or plasma. In present study the relationship between EGF 61A/G polymorphism, EGF protein expression level, and risk of HCC in patients with hepatitis B virus chronic infection were assessed.

Materials and Methods: EGF gene 61A/G allele was genotyped in ten human HCC cell lines and one immortalized normal liver cell line. Furthermore, genomic DNA samples from 195 HCC patients, 149 cirrhosis patients, and 186 healthy control subjects were also examined. Polymerase chain reaction restriction fragment-length polymorphism (PCR-RFLP) was used to determine the EGF polymorphism genotype. EGF protein in different polymorphism genotype from healthy control subjects was quantified by using an enzyme-linked immnosorbent assay (ELISA). HCC cell lines with different polymorphic genotype were subjected to growth assay in the presence of gefitinib, one EGFR blocker.

Results: Six of the examined HCC cell lines were GG genotype (HBxF344, Hep3B, SKHep1, SNU182, SNU387 and SNU449), 3 were GA genotype (HepG2, PLC/PRF5 and SMMC7721), SNU475 and the immortalized LO2 was AA genotype. Allele frequencies of EGF SNP61*A and SNP61*G in control group were 28.76% and 71.24%, while they had a respectively 2.3- and 1.9-fold odds of developing HCC risk. Concordantly, a significant higher EGF protein level in GG and GA genotype compared to AA genotype was found. In addition, EGF gene polymorphisms at position 19, 61 and 193 had a respectively 2.3- and 1.9-fold odds of developing hepatocellular carcinoma compared with patients with the AA genotype, indicating that AA genotype may have lower HCC risk. Concordantly, a significant higher EGF protein level in GG and GA genotype compared to AA genotype was found. In addition, EGF gene polymorphisms at position 19, 101, 341 were also examined from 78 healthy subjects, 53 HCC patients, all were homozygote. In order to confirm whether EGFR blocker can affect the proliferation of cell with different genotypes, six cell lines were treated by gefitinib. We observed that cell proliferation of HBxF344, SKHep1 with the GG genotype was reduced by gefitinib.