CO.14
PARADOXICAL ROLE OF IFN IN RABV INFECTION

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A series of experiments clearly indicate that RABV infection is sensitive to type 1 IFN signaling and that P and N protein-mediated IFN evasion is efficient to promote virus replication. Nevertheless, in the course of infection, the IFN induction in the whole RABV-infected nervous system, NS, is far from being abrogated. Indeed, after injection of RABV (Challenge Virus Standard, CVS strain) into the hindlimbs of mice, a progressive infection within the spinal cord and the brain is accompanied by a robust innate immune response characterized by a type 1 IFN response. It may not be surprising that IFN can be produced in the NS during infection because the mechanisms evolved by RABV to escape the IFN response are restricted to infected neurons, the only cell type expressing the P and N proteins. These mechanisms cannot operate in glial cells because they do not express any viral proteins, glial cells being rarely infected *in vivo*. Nevertheless, glial cells are innate-immuno-competent cells and they do not need to be infected to mount an innate immune response suggesting that non infected glial cells may be the source of heterocellular IFN in the RABV -nfected NS. One can wonder what the function of the heterocellular IFN in RABV infection is. Beside intrinsic antiviral properties, IFN also controls the expression of a large number of IFN stimulated genes (ISG). The ligand of the Programmed death protein-1, (PDL-1) (also named B7-H1), is an ISG which expression is upregulated in RABV-infected NS and which has been demonstrated to be a critical factor for RABV neuroinvasiveness. Thus, it can be proposed that RABV evades the antiviral effect of IFN in the infected neurons, whereas RABV benefits from the heterocellular IFN to facilitate its progression in the NS .

CO.15
ANALYSIS OF RNA EXPRESSION BY BLOOD MONONUCLEAR CELLS STIMULATED BY HUMAN RABIES CSF

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In the absence of effective antivirals, survival from rabies has been correlated with the appearance of neutralizing antibody within 7 days of hospitalization. This adaptive humoral response follows the earlier innate immune response to rabies, which can be subverted by the rabies virus phosphoprotein. Understanding the cerebrospinal fluid (CSF) environment affecting innate and adaptive immunity to rabies virus is key to improving rabies survival. To sensitively detect the presence of cytokines, chemokines and other important immune modulators (small nucleotides and lipids) in CSF, we employed a novel bioassay whereby a well-controlled peripheral blood mononuclear cell (PBMC) population of a healthy blood donor is used asa sensitive biosensor that transcriptionally responds to these dilute disease-associated factors. The readout is a comprehensive genome-scale array. We examined 7 control CSF and 13 CSF samples from 6 patients with laboratory-confirmed rabies, dating from hospital days 4 to 26. Dog and bat rabies were equally represented. CSF was incubated with reporter (PBMC) for 9 hours, total RNA from PBMC was then extracted, labeled and analyzed using Affymetrix Human Genome U133Plus2.0 array. Unsupervised analysis separated rabies CSF from controls but did not clearly group rabies samples by patient, suggesting that rabies disease itself and associated medical treatments are greater determinants of the innate immune response to rabies measured in CSF than are intrinsic host variables. In general, interferon-induced genes were up-regulated while cytokine genes were downregulated in human PBMC responding to human rabies.

CO.16
MICROARRAY ANALYSIS OF CENTRAL NERVOUS SYSTEM ASSOCIATED WITH THE INFILTRATION OF MICROGLIA IN MICE SHOWING SIGNS OF PARALYSIS AFTER THE INTRAMUSCULAR INOCULATION OF RV (CVS-11 STRAIN)

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Rabies occurs in worldwide and more than 70 000 people die of rabies every year. As the disease progresses of patients, more specific neurological symptoms were presented including such as insomnia, anxiety, confusion, slight or partial paralysis, excitation, hallucinations, agitation, difficulty swallowing, and hydrophobia (fear of water). Patients show severe paralysis gradually and eventually dead after a coma. Mice inoculated intramuscularly (i.m.) with CVS-11 (fix strain) showed the severe hind limb paralysis on 7 days and then dead eventually, however mice inoculated with CVS-11 intracerebrally (i.c.) were dead without limb paralysis (Kojima et al. 2009 and Sugiura et al. 2011). For understanding of hind limb paralysis, mice inoculated with CVS-11, i.m. and i.c. was comparatively analysed by microarray and hisotopathology. Brains and spinal cords of mice were separatively collected after 7 days of the postinoculation of i.m. and i.c.. Viral antigens was similarly observed in both of brains and spinal cords in mice inoculated i.m. and i.c.. Pathologically, microglia was infiltrated in spinal cords in mice inoculated i.m. not but i.c.. In microarray, expression level of genes was normalized with each mock. After comparative analysis of gene expression in mice inoculated i.m. and i.c., significantly (fold change >2, /p/<0.05) changed genes were examined by Ingenuity Pathway Analysis (IPA). As the results, calcium ion related gene and immune response genes including inflammations, chemotaxis, inflammation and apoptosis were obviously up-regulated in i.m. in both of brains and spinal cords. Additionally, the /p/ values of these in spinal cords were obviously lower than those of brains. Moreover, there is significant changes of Stat4, Ifng, Irf7 and Il12 which is the central regulation factors of those responses. The evoked strong immune responses associated with the infiltration of microglia in CNS of mice infected i.m. suggest a reason of damage developed severe paralysis in mice inoculated with CVS-11, i.m.. This work was supported by a grant-in-aid for the Health and Labour Science Research Grant from the Ministry of Health, Labour and Welfare of Japan.

CO.17
PROTEOMICS ANALYSIS OF HUMAN RABIES CSF

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The pathogenesis of human rabies is incompletely understood. Wildtype rabies infection is minimally cytolytic or inflammatory, and does not include major disruption to the blood brain barrier. Cerebrospinal fluid (CSF) from human rabies patients is therefore ideally suited for direct analysis by proteomics approaches that may substantively elucidate the immune responses, alterations in metabolism and fundamental cellular mechanism that contribute to rabies pathogenesis and recovery. We examined 20 control CSF and 13 CSF samples from 6 patients with laboratoryconfirmed rabies, dating from hospital days 4 to 59. Dog and bat rabies were equally represented. Trypsin digests of CSF proteins were analyzed by liquid reversed-phase chromatography followed by mass spectrometry using a Thermo LTQ-Orbitrap. Peptide identifications