exosomes. Proposed functions of these vesicles include roles in cell-cell signalling, removal of unwanted proteins, and the transfer of pathogens between cells. One such pathogen which exploits this pathway is the prion, the infectious particle responsible for the transmissible neurodegenerative diseases such as Creutzfeldt-Jakob disease (CJD) of humans or bovine spongiform encephalopathy (BSE) of cattle. Here we have investigated the generation of infectious prions in a cell culture system and characterised the forms of prion protein packaged into exosomes. We find that exosomes from these infectious cells are capable of transmitting infection to further uninfected cells suggesting cellular co-factors necessary for the generation of prion infectivity are contained within these vesicles. This work is mirrored by our studies on another protein involved in neurodegenerative disease, the amyloid precursor protein (APP) which is associated with Alzheimer's disease (AD). These results provide further evidence for a novel pathway in which PrP and APP fragments are released from cells and has implications for the analysis of APP processing and diagnostics for prion and Alzheimer's disease.

1SA2-04 プリオン感染における株多様性の存在と株間干渉現象の意義 Meaning of Strain diversity and Interference Seen in Prion Infection

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Each strain among infectious agents responsible for transmissible spongiform encephalopathies (TSE) has distinct biological characteristics. Because the pattern of histopathological changes including deposition of abnormal prion protein (PrP^{Sc}) in the brain is noticeably different and reproducible, it has been suggested that each strain has a unique cell tropism, however, the mechanism underlining this phenomenon are unknown. Mouse-adapted scrapie agents, 22L and Chandler isolate could infect Neuro2-a cells overexpressing mouse-PrP (N2a58) cells more efficiently rather than a neuroprogenitor cell line (1C11). Contrary, a human TSE agent, Fukuoka-1 (FK-1) could efficiently infect 1C11 and a hypothalamic neuronal cell (GT1-7 cells) but not to N2a58. In addition to the cell-tropism, virus-like "interference" between strains has also observed in pure cell culture system, and this virus-like phenomenon was independent from PrP-res. Furthermore, we found the innate immune responses to the prion-infection could be involved in latent infection of prion. These data suggest that infectious agent has quit similar properties to virus and transmission could be controlled by unknown factors other than PrP.

1SA2-05 強い神経細胞死活性を持つアルツハイマー病患者に由来する アミロイドβ凝集体

High-mass amyloid beta-protein assembly with a unique toxic surface from Alzheimer's disease brains

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Alzheimer's disease (AD) is the most common human neurodegenerative disease causing progressive dementia in the elderly. Conversion of amyloid β -protein ($A\beta$), a physiological derivative of amyloid precursor protein (APP), into neurotoxic supramolecular $A\beta$ assemblies is suggested to be a key event initiating AD. Extensive preclinical data suggested that $A\beta$ assemblies acquire a surface structure that is not present in a physiological $A\beta$ monomer and thereby induces synaptic impairment and eventual neuronal loss by interacting with neurons through their surface. Besides $A\beta$ fibrils, soluble forms of $A\beta$ assemblies with neurotoxicity have been produced in vitro or isolated from APP-expressing hamster cells and AD-model mice. These studies all support the toxicity of nonfibrillar $A\beta$ assemblies. However, although dimers that induce synaptic impairment without neuronal loss were recently isolated from AD patient brains, $A\beta$ assemblies that cause neuronal loss have not been isolated from AD patient brains. Therefore, it is essential to isolate the actual $A\beta$ assemblies present in human AD brains and to characterize their native properties in order to understand the mechanisms underlying $A\beta$ neurotoxicity and to develop more effective and safe therapies. We report here isolation and characterization of patient-derived, toxic, high-mass $A\beta$ assemblies.

1SA2-06 Implication of endogenous retrovirus in prion diseases

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Prion diseases are the unconventional fatal neurodegenerative disorders in the central nervous system (CNS). The conversion process induced by conformational change from cellular prion protein (PrP^C) to abnormal isoform (PrP^{Sc}) is the key molecular event in the pathogenesis of prion diseases, but the mechanism still remains unknown. Related to the conversion, previous evidences suggested that various molecules in host can function as cellular cofactors PrP^{Sc} formation. In here, we summarize our current studies about involvement of RNA molecule and endogenous retroviruses in prion diseases. In order to identify RNA function in prion diseases, we employed chemicals, Lithium aluminum hydride (LiAlH₄), that can cleave phosphodiester bonds of RNA and then assess the effects on the infectious agent. LiAlH₄ destroyed PrP^{Sc} and extended the scrapie incubation period in mice, and the results suggest RNA molecules can be important in maintaining the structure of PrP^{Sc}. To clarify implication of endogenous

retrovirus in prion diseases, we utilized mouse model expressing high titer of murine leukemia viruses (MuLVs) that is endogenous retroviruses in mouse. We analyzed the expression of MuLVs after scrapie infection and examined incubation period and the levels of PrP^{Sc} in scrapie infected mice. Results of the study showed that scrapie infection influenced the expression of MuLVs and the progression of scrapie pathogenesis was accelerated by MuLV. Subsequently, we established in vitro models with high concentration of MuLV for the intensive study between endogenous retrovirus and prion diseases. In addition, to verify the study, we are investigating the prevalence of human endogenous retroviruses (HERVs) in patients with human prion diseases.

1SA2-07 鳥、ブタ、そしてパンデミックインフルエンザ

Avian, swine, and pandemic influenza

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Since 2003, the H5N1 highly pathogenic avian influenza virus (HPAIV) has seriously affected poultry in Asia. Well over 500 million birds have died from infection or been killed for the control purposes. A HPAIV is generated when a nonpathogenic virus brought in by migratory birds from nesting lakes in the north is transmitted to chickens via domestic ducks, geese, quails, turkeys, etc. and acquires pathogenicity for chickens with repeated multiple infections in the chicken population. This pathogenicity does not mean for other species of birds and mammals, nor does it for humans. It was confirmed that more than 420 people have been infected with the H5N1 virus, 60% of whom died in Asia, the Middle East and Africa since 2004. Against this backdrop, it is assumed that the H5N1 virus will acquire the ability to transmit among humans and wreak havoc as a new virus. The WHO has warned for the past decade that this avian influenza virus is in the final stages of acquiring the ability to infect humans. In response, some of the nations have formulated emergency plans, including measures such as stocking an inactivated H5N1 vaccine for humans.

Now, swine-origin H1N1 influenza viruses transmit to humans more than 50,000 in over 100 countries, and WHO declared that the situation is now phase 6, stage of pandemic influenza. This must become a member that cause seasonal influenza. No one is interested in avian influenza any more although the situation of HPAI in the world.

I would like to stress the importance of surveillance of avian and swine influenza, and that preparedness for pandemic influenza should be based on the measures how to control the seasonal influenza.

1SA2-08 Avian influenza virus: from migratory bird infection to peptide inhibitor discovery

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Highly pathogenic avian influenza virus (HPAIV) H5N1 has spread around the world and causes worldwide concern about a possible human pandemic, either by HPAIV or a new virus variant with some segments from the HPAIV. In 2005, the reservoir hosts of the influenza virus became the victim of the HPAIV H5N1 in population, occurred in northwestern China, Qinghai Lake. In the following years until 2008, the unique group of viruses was isolated in the Qinghai Lake wild birds, Clade 2.2. In 2009, a new clade of viruses was isolated in the same area. Both of these clades are not the major viruses causing human infections in China or elsewhere. The phylogenetics and the impact to the environment of these outbreaks are discussed. In light of the increase of current drug-resistant strains of the influenza virus, we hypothesized that HIV T-20 like peptides derived from HA2 of influenza virus might be used as fusion inhibitors. One peptide was demonstrated to be a potent inhibitor for influenza virus.

1SA2-09 ウイルスペクターと非ウイルススペクターの遺伝子発現効率の定量的比較解析：細胞取込から転写・発現まで

Quantitative analysis of transfection efficiency between viral and non-viral vector: From cellular uptake to transcription/translation

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To improve transfection efficiency of non-viral vectors, quantitative and mechanism-based analysis of transfection efficiency between viral and non-viral vectors is essential for improving the effectiveness of non-viral vectors. We performed a systematic and quantitative comparison of the cellular uptake and subsequent intracellular distribution of exogenous DNA transfected by viral and non-viral vectors in living cells. As a model, adenovirus (Ad) and LipofectAMINE PLUS (LFN) were used for comparison since they are highly potent and widely used viral and non-viral vectors, respectively. Once taken up by a cell, Ad exhibited comparable endosomal escape and slightly more higher nuclear transfer efficiency compared with LFN. In contrast, LFN requires three orders of magnitude more intra-nuclear gene copies to exhibit a trans-gene expression comparable to the Ad, suggesting that difference of transfection efficiency principally arises from differences in nuclear transcription efficiency, and not from a difference in intracellular trafficking between Ad and LFN. We have further examined the contribution of transcription and translation processes to the overall differences in the trans-gene expression efficiency of nucleus-