



CDB SEMINAR

Neil Andrew Mabbott

Institute for Animal Health, Edinburgh

Friday, March 3

12:00~13:00

Dr. Nishikawa's Lab (IBRI, 3F)

Prions and the immune system

Natural infections with transmissible spongiform encephalopathy (TSE) agents (or 'prions') are usually acquired by peripheral exposure, eg: ingestion. Following exposure, infectivity usually accumulates in lymphoid tissues before spreading to the brain. Using mouse models we have shown that follicular dendritic cells (FDCs), expressing the host prion protein (PrP^C), are critical for TSE agent replication in lymphoid tissues. TSE agent neuroinvasion is also dependent on FDCs as in their absence disease susceptibility is significantly reduced. We have shown that the temporary depletion of FDCs before peripheral inoculation with TSE agents (oral, intraperitoneal, skin lesion) blocked the early accumulation within the spleen and reduced susceptibility. The mechanisms by which TSE agents initially localize to FDCs are not known. Antigens are retained on FDCs via complement and cellular complement receptors. We have shown that in the absence of specific opsonizing complement components (C1q or C3) the spread of disease to the brain is significantly delayed. In contrast, in the absence of components of the terminal complement activation pathway (C5) pathogenesis is unaffected. Thus, in the early stages of infection, complement may contribute to the localization of TSE infectivity to FDCs in lymphoid tissues.

TSE transport mechanisms from the site of exposure (eg: gut lumen or skin) to the germinal centres in which FDCs reside are unknown. Migratory bone marrow-derived dendritic cells (DCs) sample antigens in peripheral tissues and carry them to draining lymph nodes. These observations suggest that migrating DCs might provide a cellular bridge between the site of exposure and the lymphoid tissues in which prions replicate. We have developed experimental models to investigate whether DCs transport prions to lymphoid tissues. For example, Langerhans cells (LCs) are specialized subset of DCs that continually sample their microenvironment within the epidermis and transport captured antigens to draining lymph nodes. We considered LCs likely candidates to acquire and transport TSE agents after inoculation via the skin. Data from in vitro studies suggested that LCs might acquire and degrade TSE agents after inoculation via the skin. However, when LC migration from the epidermis is blocked, TSE infectivity still reaches the draining lymph node following inoculation via the skin suggesting that LCs are not major TSE agent transporters.

Our data suggest that treatments that interfere with the critical early events of TSE pathogenesis in lymphoid tissues, offer a potential approach for early intervention in TSE diseases. However, our data also suggest that following accidental TSE infection, the time window in which such treatments may be effective is likely to vary widely according to the route of exposure.

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