Pacific Center for Emerging Infectious Diseases Research

University of Hawai'i Mānoa

Department of Tropical Medicine, Medical Microbiology & Pharmacology

JOHN A BURNS SCHOOL OF MEDICINE, UNIVERSITY OF HAWAI'I AT MANOA

Immunity or Tissue Damage to Viruses – What Determines the Outcome?

The emphasis of the talk will be on the role that metabolism plays during viral pathogenesis. We shall explain how metabolic effects can impact on inflammatory lesions to viruses as well as how metabolism can influence viral encephalitis. Viruses rarely enter the brain but when they do, the effects can be devastating. An example is herpes simplex encephalitis (HSE) a rare disease in adults usually caused by HSV-1 occurring most commonly in persons already latently infected with the virus. Although some cases of HSE occur in persons with genetic problems of the immune system or are heavily immunosuppressed, most affected persons have no apparent problem with their immune systems. An explanation why HSE occurs in such persons is still needed. We hypothesize that HSE occurs during a coalescence of events, which includes viral reactivation from latency at a time when the immune system is being compromised, perhaps temporarily, by metabolic changes. These ideas cannot be tested in humans but we have established a mouse model in which events leading up to HSE can be evaluated. Thus, we have shown in a mouse model that inhibition of glucose metabolism with the molecule 2-deoxyglucosue (2DG) from the time of local infection with HSV-1 resulted in the majority of animals developing HSE. We anticipate that the 2DG therapy could impair two stages of immunity, which normally protect against infection of the central nervous system. The first is proposed to be a blunting of the function of an innate immune component at the infection site or within the local nerve ganglion. This prevents innate cells from functioning sufficiently to limit the extent of local viral replication and to minimize productive infection of neurons in the local ganglion. The second component is proposed to be an effect on the expansion or effector function of CD8 T cells which in normal circumstances protect neurons and prevent virus from spreading to the brain. The proposal is designed to test our guiding hypotheses. We anticipate that our findings could result in changes in diagnostic procedures and therapeutic management of HSE. Thus, in addition to the currently used antiviral drug treatment any detected metabolic abnormalities could be corrected as well, with the combination therapy minimizing the consequences of the HSE syndrome.

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Friday, May 4, 2018 at 12:00 noon
John A. Burns School of Medicine, Kaka'ako Campus
Medical Education Building, Room 202 (Access Grid)
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This seminar is supported by grant P30GM114737 (COBRE) from the National Institutes of Health.