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CME Questions June #1-8

A Review on inflammation pathways in dengue disease, a research article on the role of dendritic cells in Barrett's carcinogenesis, and a research article on tumor necrosis factor receptor ablation in a mouse model of Alzheimer disease were selected for the June 2013 AJP CME Program in Pathogenesis. The authors of the referenced articles and the planning committee members and staff have no relevant financial relationships with commercial interests to disclose.


Upon completion of this month’s journal-based CME activity you will be able to:

- Discuss dengue disease.
- Describe the features of mouse models of dengue virus infection used for preclinical studies.
- Describe the characteristics of Barrett’s esophagus (BE).
- Understand the role of dendritic cells in BE.
- Describe the disease pathogenesis in Alzheimer disease (AD).

1. Dengue disease is a mosquito-borne viral disease. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182: 1950-1961.]

   a. Dengue is a spectrum of diseases caused by one of the four serotypes of dengue viruses (DENV).
   b. The four DENV serotypes (DENV-1 to -4) belong to the Flaviviridae family.
   c. The four DENV serotypes circulate concomitantly in different regions of the world, covering 100 countries in tropical and subtropical areas of the globe.
   d. Most DENV infections cause significant clinical disease with >100,000 hospitalizations of patients each year and a case fatality rate exceeding 25% in elderly populations.

2. The World Health Organization (WHO) classifies two major entities related to dengue infection: dengue fever (DF) and dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182: 1950-1961.]

   a. DF is a self-limited though debilitating febrile illness, accompanied by a combination of nonspecific symptoms, including headache, retro-orbital pain, myalgia, and occasionally hemorrhagic manifestations.
   b. DHF/DSS case definitions list the presence of four criteria: fever, hemorrhagic manifestations, thrombocytopenia, and evidence of plasma leakage.
   c. DHF is divided into four grades (I to IV), where grades III and IV are defined as DSS with hypotensive shock or narrow pulse pressure plus clinical signs of shock.
   d. A revised WHO classification of dengue disease is more specific for a particular pathogenic entity but has proven to have less sensitivity and specificity to identify cases in need of heightened care.
3. A common major technical barrier in understanding DENV infection pathogenesis is the absence of a suitable animal model that mimics dengue disease. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 2013, 182: 1950-1961.]

a. NOD/SCID mice, RAG2−/− mice, and NSG mice can be used to study DF pathogenesis, human cell virus tropism, virulence screening of dengue virus, and vaccine studies evaluating virus attenuation in vivo.

b. A particular advantage of mouse-human chimeras is that they develop marked viremia and manifest severe disease, providing a good animal model for DHF/DSS.

c. Immunocompromised AG129 mice, which lack both IFN-α/β and IFN-γ receptors, can be used to investigate tissue and cellular tropism of dengue virus and antiviral drug screening.

d. Immunocompetent BALB/c and C57BL/6j mouse strains can be used to study severe dengue disease pathogenesis, cell virus tropism, and host inflammatory and immune responses to infection.

4. Barrett’s esophagus (BE) is defined by the replacement of the normal esophageal squamous epithelium by a metaplastic columnar epithelium containing true goblet cells on histological examination. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 2013, 182: 2168-2179.]

a. BE is considered as an adaptive response after chronic gastroesophageal reflux.

b. BE prevalence is estimated to be approximately 10% in the general population.

c. BE can be classified histologically into four groups, depending on the presence or absence of dysplastic cells in the epithelium.

d. Although gastroesophageal reflux-induced esophagitis is characterized by a type 1 helper T-cell immune response, the development of BE and esophageal adenocarcinoma (EAC) is associated with a relative increase of type 2 helper T cells and the presence of an immunosuppressive cytokine pattern.

5. The tissue remodeling in BE constitutes a premalignant lesion. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 2013, 182: 2168-2179.]

a. The premalignant lesion leads to a 20-fold increase in the risk of developing an EAC.

b. EAC almost always arises after a metaplasia-dysplasia-carcinoma (MDC) sequence.

c. Survival outcomes for patients with EAC remain poor, with community 5-year survival rates of <20%.

d. BE incidence has dramatically increased in the Western world in recent years, compared with other types of cancers, with an increment of >600%.

6. Dendritic cells (DCs) are specialized antigen-presenting cells that provide a critical link between innate and adaptive immune responses. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 2013, 182: 2168-2179.]

a. Human DCs are divided into two major intrinsically different subsets: myeloid DCs (mDCs) and plasmacytoid DCs (pDCs).

b. mDCs and pDCs differ in their transcriptional program, phenotypic markers, and immunological functions.

c. mDCs circulate in the peripheral bloodstream as precursors that home to tissues where they reside as mature cells with low endocytic activity and high T-cell activation potential.

d. mDCs play a crucial role in the regulation of adaptive immunity by their unique ability to induce a primary immune response in resting naive T cells.

7. Neuroinflammation is a highly enigmatic process contributing to disease pathogenesis in Alzheimer disease (AD). Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 2013, 182: 2285-2297.]

a. AD pathophysiology is described by chronic and progressive neurodegeneration involving the genesis of extracellular amyloid β (Aβ) plaques, neurofibrillary tangles, synapse loss, inflammation, and neuronal cell death.

b. In AD-afflicted brains, microglia serve as major sources of proinflammatory mediators, including cytokines and chemokines.

(c. The pleiotropic proinflammatory cytokine tumor necrosis factor α (TNF-α) is produced in excess concurrently with increased Aβ plaque deposition, suggesting that TNF-α levels reflect the pathologic progression of AD.

d. The three known TNF-α promoter polymorphisms that have been associated with late-onset AD are linked to increased TNF-α production.

8. TNF-α signals through two differentially expressed and regulated cognate transmembrane receptors. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 2013, 182: 2285-2297.]

a. TNF-α receptor type I (TNF-R1) is induced and its expression is restricted to specific cell populations, whereas TNF-R1I is expressed constitutively on most cell types.

b. TNF-R engagement to its ligand mediates distinct cellular responses through the activation of several downstream signal transduction cascades involving the NFκB and JNK pathways.

c. TNF-R1I protein levels are reduced in patients with AD relative to nondemented control brain.

d. Both detrimental and neuroprotective roles for TNF-α have been reported in the literature.