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Mark E. Sobel, MD, PhD, Director of Journal CME Programs

CME Questions September #1-8

An article and related Commentary on the regulation of nerve conduction velocity by the inositol-polyphosphate-4-phosphatase II gene and an article on regulation of skin would healing by FOXO1 were selected for the September 2014 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:

- Define multiple sclerosis (MS).
- Understand visual, motor, and somatosensory evoked potentials.
- Explain experimental autoimmune encephalomyelitis (EAE).
- Describe quantitative trait loci (QTL) and the challenges associated with QTLs.
- Understand skin wound healing.
- Recognize that skin healing is highly associated with the aging process.
- Define the mammalian forkhead box O (FOXO) family of transcription factors.
- Describe what is known related to the FOXO family’s role in wound healing.

1. **Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE:** [See Am J Pathol 2014, 184:2420-2429 and Am J Pathol 2014, 184:2369-2370.]
   a. MS results in large focal demyelinated lesions and diffuse neurodegeneration in the entire brain and spinal cord.
   b. The cause of MS is unknown, but current concepts favor an inflammatory process driven by autoimmunity.
   c. Central aspects of MS, such as inflammation, demyelination, and neurodegeneration, are partly reproduced by an autoimmune disease in different animal species, experimental autoimmune encephalomyelitis (EAE).
   d. EAE is induced by active sensitization with brain antigens, proving that MS is solely induced by environmental factors.

2. **Reduced nerve conduction velocity resulting from axonopathy or demyelination strongly affects the quality of life. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE:** [See Am J Pathol 2014, 184:2420-2429 and Am J Pathol 2014, 184:2369-2370.]
   a. The impairment of nerve conduction, measured by visual, motor, and somatosensory evoked potentials (SEPs), is a common feature of neurodegenerative and neuroinflammatory diseases.
   b. The measurement of visual evoked potentials (VEPs) is one of the most sensitive diagnostic tools in early MS.
   c. VEP findings at first presentation best predict clinical disability within one year.
   d. Multimodal evoked potentials correlate well with clinical disability in early MS and allow prediction of disease evolution.
3. A strong tool to investigate the pathophysiology of a complex disease is to identify the underlying genetic control. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:2420-2429 and Am J. Pathol 2014, 184:2369-2370.]

   a. Linkage analyses in animal models such as EAE may yield quantitative trait loci (QTLs).
   b. Genetic analyses in rodent EAE have led to the identification of more than 60 QTLs.
   c. The central challenge for interpreting QTLs is that the genomic regions identified are generally large, and extensive work is required to positionally clone the quantitative trait genes (QTG) involved.
   d. Three EAE QTMs controlling the latency of cortical MEPs were identified in a mouse model of EAE.

4. *Inpp4b*, a Mg\(^{2+}\)-independent phosphatase involved in the phosphoinositide 3-kinase signaling pathway, has been identified as the mouse gene controlling the latency of cortical MEP (cMEP). Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:2420-2429 and Am J. Pathol 2014, 184:2369-2370.]

   a. Two SNP variants of *Inpp4b* were identified in the coding regions of exons 13 and 14, resulting in amino acid exchanges from serine to arginine (S474R) and histidine to proline (H548P).
   b. Mouse strains carrying a longer-latency cMEP allele had the amino acid RP, whereas mouse strains carrying a shorter-latency cMEP allele had the amino acid SH, suggesting that *Inpp4b* structural polymorphism is associated with the speed of neuronal conduction.
   c. The human *INPP4B* gene is located on chromosome 4, in a region associated with MS.
   d. The authors showed a major loss of myelin in animals carrying the allele associated with reduced nerve conduction velocity, suggesting that *Inpp4b* has a direct effect on myelination.

5. The skin plays a major role in protecting us against extrinsic traumatic factors such as microbes, UV radiation, heat, and chemicals. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:2465-2479.]

   a. Damage to the skin immediately triggers tissue repair mechanisms alongside a robust inflammatory response for host defense.
   b. Skin wound healing is generally considered to consist of two phases.
   c. During an acute wound inflammatory response, many neutrophils rapidly migrate into damaged tissues to protect against microbes, followed by macrophages that contribute to formation of granulation tissue.
   d. In parallel with connective tissue repair, epithelial cells migrate over the newly forming granulation tissue to cover the wound site in a process known as re-epithelialization.

6. Tissue repair speed and quality are dependent on aging and metabolic status at a whole-body level, in addition to local immunity and cellular responses at the wound site. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:2465-2479.]

   a. The skin is one of the clearest indicators of aging, and skin healing is highly associated with the aging process.
   b. Elderly individuals are known to exhibit impaired healing.
   c. Skin repair occurs perfectly, without scarring, until very late in gestation (embryonic day 19 in the mouse and the end of the third trimester in humans).
   d. A worldwide increase in patients with delayed skin wound healing due to an abnormal healing process is linked with aging, diabetes, malnutrition, chemotherapy, and hereditary diseases.

7. The mammalian forkhead box O (FOXO) is a family of transcription factors consisting of FOXO1, FOXO3A, FOXO4, and FOXO6. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:2465-2479.]

   a. The FOXO proteins remain transcriptionally active in the nucleus in the absence of environmental and growth factors.
   b. Modification of FOXO leads to its translocation to the cytoplasm and/or its degradation.
   c. FOXO1 plays a key role in aging and caloric restriction and exhibits antineoplastic characteristics.
   d. *Foxo3A* deficiency in embryonic mice has been shown to be lethal, causing abnormal vascular development.

8. Sarcopenia is an age-associated degenerative condition resulting in the loss of skeletal muscle mass and muscle tissue repair. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:2465-2479.]

   a. In skin wounds, *Foxo3A* and *Foxo6* are overly expressed in the transcription factor binding sites of promoters from many differentially expressed genes in the epidermis.
   b. In diabetic mice, impaired skin wound healing is associated with enhanced activation of FOXO1.
   c. Re-epithelialization during scalp wound healing is impaired in keratinocyte-specific Foxo1\(^{-}\) mice.
   d. Levels of expression of FOXO1 in keratinocytes, fibroblasts, and inflammatory cells in keloid sites are markedly higher in African Americans compared with Japanese.