A research article on the role of renal tumor necrosis factor receptor-associated protein 1 (Trap1) and DNaseI in lupus nephritis, a research article describing the role of cytokines in hypertensive leg ulcer (HLU), and a research article on the neuroprotective role of the type 2 cannabinoid receptor (CB2R) in ischemic injury were selected for the March 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:
- Describe lupus nephritis.
- Discuss the role that DNaseI and Trap1 play in lupus nephritis.
- Describe the characteristics of hypertensive leg ulcer (HLU).
- Understand the role of proinflammatory cytokines in inducing an inflammatory phenotype.
- Describe the role of inflammatory cytokines and growth factors in vascular smooth muscle cell (VSMC) proliferation.
- Understand the involvement of cannabinoids and their receptors in ischemic brain injury.

1. Lupus nephritis is a serious manifestation of systemic lupus erythematosus. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182:688-700.]
   a. Lupus nephritis is a main predictor of poor outcome of systemic lupus erythematosus.
   b. Chromatin-associated autoantigens are predominantly involved in lupus nephritis.
   c. The deficiency in chromatin processing is a central factor of lupus nephritis pathogenesis.
   d. Chromatin fragments impose several inflammatory processes by interaction of Toll like receptors (TLR) 1 -4 and the Clec4e receptor.

2. DNaseI represents the main nuclease in renal tissue, but the mechanisms regulating DNaseI expression and secretion are not clear. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182:688-700.]
   a. A long nucleotide sequence in the 5’-untranslated region of DNaseI transcripts overlaps with the 5’-untranslated region of the tumor necrosis factor receptor-associated protein 1 (Trap1) gene.
   b. Transformation of mild lupus nephritis into end-stage disease coincides with renal DNaseI shutdown in (NZBxNZW)F1 mice.
   c. Down-regulation of DNaseI results in reduced chromatin fragmentation and deposition of extracellular chromatin complexes in glomerular basement membranes where they appear in complex with IgG antibodies.
   d. Loss of DNaseI activity is identified as a central factor that contributes to transformation of mild mesangial into severe diffuse-proliferative lupus nephritis in murine and human forms of the disease.
3. Trap1 is a highly conserved chaperone molecule. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182:688-700.]

   a. Trap1 belongs to the heat shock protein 90 family.
   b. Trap1 plays important roles in signal transduction, protein folding, and protein degradation.
   c. Trap1 is important for folding newly synthesized proteins or for stabilizing and refolding denatured proteins after stress.
   d. Trap1 is down-regulated during stress and functions as a death-associated protein.

4. Hypertensive leg ulcer (HLU) is an inflammatory disease. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182:806-818.]

   a. HLU is characterized by intense pain, alteration of vascularization, and skin necrosis.
   b. HLU arises predominantly in subjects older than 50 years with long-lasting high blood pressure, in the absence of significant alteration of arterial or venous macrovascularization.
   c. HLU is frequently associated with diabetes.
   d. HLU always presents unilaterally and never to the contralateral leg.

5. Proinflammatory cytokines are key factors in inducing an inflammatory phenotype in tissues such as vessels and skin. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182:806-818.]

   a. IL-17 and IL-22 are proinflammatory Th17 cytokines.
   b. IL-17 and IL-22, in association with IL-1, tumor necrosis factor-α (TNF-α), and oncostatin M (OSM), directly target keratinocytes for the induction of acanthosis, the synthesis of CXCL8, and the secretion of antibacterial peptides (S100A7, human β-defensin 2).
   c. IL-17, IL-22, and IL-1 promote epidermis differentiation.
   d. The STAT3 signaling cytokines, OSM and IL-22, induced epidermis hyperplasia.

6. Inflammatory cytokines and growth factors induce a switch from the contractile to invasive phenotype in vascular smooth muscle cells (VSMC). Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182:806-818.]

   a. IL-1β is a potent inducer of VSMC proliferation, but platelet-derived growth factor (PDGF) has an antagonistic effect.
   b. Under inflammatory stress, VSMC express IL-1α, contributing to the autocrine inflammatory loop.
   c. OSM is the only member of the IL-6 cytokine family able to induce VSMC proliferation, and matrix metalloproteinases and cytokine secretion in vitro.
   d. OSM is expressed in atherosclerotic lesions and is suspected to contribute to atherosclerosis by promoting VSMC proliferation in humans and mice.

7. Ischemic brain injury emerges as a consequence of complex pathological cascades. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182:928-939.]

   a. Excitotoxicity, mitochondrial depolarization, oxidative stress, and inflammation are complex pathological cascades that result in ischemic brain injury.
   b. During ischemic injury, endocannabinoids decrease and cannabinoid receptors are up-regulated.
   c. Treatment with cannabinoid agonists (either endocannabinoids or phytocannabinoids/synthetic cannabinoids) protects neurons against damage resulting from ischemic stroke.
   d. The effects of cannabinoids are mainly mediated by action at G-protein-coupled type 1 cannabinoid receptors (CB1Rs) and type 2 cannabinoid receptors (CB2Rs).

8. CB2R agonists produce neuroprotective effects. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182:928-939.]

   a. Mice lacking CB2Rs are more sensitive to cerebral ischemic injury.
   b. CB2R expression is up-regulated in microglia/macrophages associated with ischemic brain lesions.
   c. CB2Rs were initially thought to be expressed primarily in activated microglia and peripheral immune cells, regulating antigen presentation, cytokine/chemokine production, and cell migration.
   d. Functional CB2Rs do not exist within immune cells present in the central nervous system (CNS).