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CME Questions November # 1-8

Reviews on phenotypic transitions of macrophages that orchestrate tissue repair and on the pathology of podocyte loss and a research article with related Commentary on selective activation of cannabinoid receptor 2 as a means to prevent monocyte-endothelium engagement were selected for the November 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 the role of macrophages in the healing process.
• Describe how dysregulated macrophage function can contribute to failure to heal or fibrosis in pathological situations.
• Discuss therapeutic opportunities based on macrophage manipulation.
• Understand the role that podocyte loss plays in proteinuric glomerulopathies.
• Describe the role of mitotic catastrophe in podocyte loss.
• Understand how viral infection can trigger podocyte proliferation.
• Understand the two subtypes of receptors that mediate cannabinoid actions.
• Describe how activation of cannabinoid receptor 2 in leukocytes can protect the blood-brain barrier.

1. Macrophages are essential for the efficient healing of numerous tissues. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:1352-1363.]

   a. At different stages of the healing process, macrophages can promote debridement of the injury site, cell proliferation, angiogenesis, collagen deposition, and matrix remodeling.
   b. Improper regulation of any of the macrophage functions can impair healing.
   c. Macrophages exhibit consistent phenotype and function as tissue repair progresses.
   d. Dysregulated macrophage function can contribute to failure to heal or fibrosis in several pathological situations.

2. Numerous studies have demonstrated the importance of circulating monocyte recruitment for macrophage accumulation after injury. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:1352-1363.]

   a. In mouse skin wounds, contribution of blood monocytes to the wound infiltrate is suggested by the sharp decrease in circulating CCRL<sup>x</sup>/Ly6<sup>cm</sup> monocytes that occurs within one hour after injury.
   b. Long-term treatment of mice with anti–colony-stimulating factor 1 receptor antibody depletes resident macrophages of the skin and other tissues but does not alter monocyte/macrophage recruitment to the nasal epithelium after wounding.
   c. Tissue infiltration by latex bead-labeled blood monocytes is observed after muscle injury in mice.
   d. Depletion of circulating monocytes by i.v. or i.p. delivery of clodronate-containing liposomes greatly reduces muscle macrophage accumulation.
3. Several animal studies have provided proof of concept for macrophage-based interventions, and some progress has even been made in treatment of human wounds. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:1352-1363.]

   a. In diabetic mice, blockade of IL-1β, TNFα, or IL-17 ameliorates proinflammatory macrophage activation, upregulates healing-associated genes, and accelerates skin wound healing.
   b. In a mouse model of muscle atrophy, intramuscular injection of macrophage colony-stimulating factor enhances macrophage accumulation and accelerates recovery of muscle force production.
   c. In the mdx mouse model of muscular dystrophy, genetic deletion of IFNγ ameliorates the disease while increasing whole-muscle expression of numerous M2a-related genes.

4. Podocytes represent an essential component of the kidney's glomerular filtration barrier. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:1364-1374.]

   a. Podocytes stay attached to the glomerular basement membrane via actin cytoskeleton.
   b. Mature podocytes are unable to replicate and maintain their actin cytoskeleton simultaneously.
   c. Terminal differentiation of podocytes is coupled with permanent exit from the cell cycle and arrest in a postmitotic state.
   d. Postmitotic podocytes do not have an infinite life span and physiologic loss in the urine is documented.

5. Podocyte injury is a key manifestation of proteinuric glomerulopathies, for example, minimal change disease, focal segmental glomerulosclerosis, and diabetic nephropathy. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:1364-1374.]

   a. Normal podocytes are postmitotic cells composed of a voluminous cell body with a single well-formed nucleus and primary and secondary foot processes attached to adjacent capillary loops in an interdigitating manner.
   b. Injured podocytes respond with foot process effacement, an irreversible process, thought to help injured podocytes stay attached to the glomerular basement membrane (GBM).
   c. Sustained podocyte injury is likely to cause podocyte cell detachment and/or death, which, if extensive, leads to progressive glomerulosclerosis and end-stage kidney disease.
   d. Podocyte assessment in human disease is often limited to the ultrastructural appearance of the secondary foot processes, which normally appear as teethlike, interdigitating, and slit-membrane—forming processes.


   a. Progenitor cells exhibit a mixed phenotype between parietal epithelial cells and podocytes.
   b. Progenitor cells can proliferate and differentiate generating neopodocytes during development and in postnatal and adolescent mice.
   c. Progenitor cells have the potential to become podocytes without yet displaying the complex cytoskeletal structure that prohibits an efficient mitotic division.
   d. During development, PAX2 is up-regulated as progenitors differentiate into podocytes.

7. Viral infection may trigger podocyte proliferation and cause implosion (collapse) of capillary loops. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:1364-1374.]

   a. HIV can infect podocytes (and parietal epithelial cells), leading to podocyte mitosis and HIV nephropathy.
   b. Switch to a proliferative podocyte phenotype is associated with upregulation of mature podocyte markers.
   c. Podocyte multinucleation is a predominant feature of HIV-associated nephropathy.
   d. Virus-induced podocyte mitosis is catastrophic, driving podocytes to cell death via mitotic catastrophe.

8. The development and maintenance of chronic inflammation appear to be underlying causes of numerous human diseases such as atherosclerosis, obesity, diabetes, arthritis, chronic hepatitis, bone disorders, and neurodegeneration. Based on the referenced article and the related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:1548-1558 and related Commentary, Am J Pathol 2013, 183:1375-1377.]

   a. Cannabinoids modulate immune functions and therefore have therapeutic potential for the treatment of inflammatory diseases.
   b. Two subtypes of cannabinoid receptors (CB), CB1 and CB2, mediate most cannabinoid actions.
   c. CB1 receptor is located in the central nervous system and in peripheral tissues; whereas CB2 receptor is found in the periphery and mainly in immune cells expressing high levels of CB2.
   d. CB1 agonists limit inflammatory cell migration at the site of acute and chronic injury in rodent models.