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CME Questions November #1-8

Research articles on the function of matrix metalloproteinase-3 in spinal cord injury, contributions of hepatocytes and bile ductular cells in remodeling the biliary system, and development of osteonecrosis of jaw-like lesions were selected for the November 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 traumatic spinal cord injury (SCI) and describe the blood-spinal cord barrier (BSCB).
- Describe the key roles of matrix metalloproteinases (MMPs).
- Describe the cause and effect of a ductular reaction.
- Understand the hepatocellular phenotype during injury.
- Define osteonecrosis of the jaw (ONJ).
- Understand the targets and effects of bisphosphonates (BPs) and denosumab (Dmab).

1. **Traumatic spinal cord injury (SCI) is a devastating condition that can result in permanent disability. Based on the referenced article, select the ONE statement that is NOT TRUE:** [See Am J Pathol 2014, 184:2985-3000.]

   a. SCI treatment options are limited, but significant advances have been made in understanding the pathophysiology of SCI.
   b. The blood–spinal cord barrier (BSCB) is the functional equivalent of the blood-brain barrier (BBB), providing a specialized microenvironment for the cellular constituents of the spinal cord.
   c. The barrier function of BSCB is based on the specialized system of nonfenestrated endothelial cells and their accessory structures.
   d. Autophagy of glia is the major reason for permanent neurological deficits after BSCB injury.
2. Matrix metalloproteinases (MMPs) are known to degrade extracellular matrix and other extracellular proteins and are essential for remodeling of extracellular matrix and wound healing. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:2985-3000.]

a. Blocking MMP-9 inhibits functional recovery after SCI.
b. After SCI, MMP-12 up-regulation increases BSCB permeability followed by blood cell infiltration, thereby hindering recovery of motor function.
c. After brain focal ischemia, the degradation of tight junction proteins is blocked by inhibiting MMP-2 and -9 activities.
d. Excessive proteolytic activity of MMPs can be detrimental, leading to numerous pathological conditions, including BBB/BSCB disruption after injury.

3. Chronic liver diseases are often complicated by a progressive increase in bile ductular structures, called a ductular reaction. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:3001-3012.]

a. A ductular reaction is closely associated with liver fibrosis and is an important tissue alteration to examine as a therapeutic target.
b. Ductular reactions are only observed in the periportal area and are dependent upon the presence of biliary cells.
c. Experimental studies using rodents have suggested that hepatic stem/progenitor cells or transit-amplifying cells proliferate into ductular shapes and eventually contribute to regeneration when the proliferation of hepatocytes is compromised.
d. The perportal liver stem cell niche is more complex than previously thought and includes cell types such as bile ductular cells and perportal hepatocytes.

4. The notion that the phenotype of hepatocytes is fixed once they are terminally differentiated has been challenged by recent studies. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:3001-3012.]

a. It is necessary to scrutinize the cellular origins of various types of ductular reactions by rigorous pathological examinations in appropriate hepatocyte lineage–tracing systems.
b. Mature rat hepatocytes can transdifferentiate into bile ductular cells when cultured within a type-I collagen gel matrix.
c. In a liver repopulation model using fumarylacetoacetate hydrolase–deficient mice, transplanted and repopulated hepatocytes substantially contributed to the ductular reaction induced by a 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) diet.
d. A lineage-tracing study demonstrated that hepatocytes could significantly participate in the generation of new ductules in the presence of liver injury induced by a DDC diet or bile duct ligation.

5. Whether mature hepatocytes can transdifferentiate into bile duct/ductular cells in vivo has been a matter of debate. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:3001-3012.]

a. Nagahama et al isolated centrilobular hepatocytes from Alb-Cre x ROSA26R mice and transplanted them into the liver of wild-type mice.
b. The transformation of hepatocytes into bile duct/ductular cells was not observed at the periphery of repopulated hepatocyte colonies.
c. A robust ductular reaction was closely associated with inflammation induced by retrorsine and partial hepatectomy and was further augmented by additional injurious stimuli.
d. Ductular transdifferentiation may be promoted through an increase in extracellular matrices and various inflammatory cytokines.

6. Bisphosphonates (BPs) and denosumab (Dmab) are anti-resorptive drugs that are being used to treat bone-related diseases. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:3084-3093.]

a. Users of BPs and Dmab are known to be at higher risk for developing osteonecrosis of the jaw (ONJ).
b. ONJ is clinically defined as exposed necrotic bone and unclosed overlaying oral mucosa for at least 8 weeks.
c. ONJ incidence in patients with cancer receiving intravenous BPs is reported to range from 20% to 35%.
d. ONJ induced by both drugs is a considerable clinical complication that compromises patients’ quality of life.
7. Osteoclasts play key roles in mediating ONJ. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:3084-3093.]

a. Although BPs are small molecules that may affect cells other than osteoclasts, Dmab is a fully human monoclonal antibody (Ab) that is highly specific to osteoclasts.
b. Dmab targets the receptor activator of NF-κB ligand (RANKL).
c. RANKL plays a central role in osteoclastogenesis affecting the formation, function, and survival of osteoclasts.
d. Clinically, BPs have less severe adverse effects, such as gastrointestinal tract ulceration or kidney dysfunction, when compared with Dmab.

8. Cytotoxic effects of BPs on cells other than osteoclasts further complicate roles of osteoclasts in the ONJ pathophysiological characteristics in the BP-related ONJ models. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:3084-3093.]

a. In the human RANKL knock-in mice model, Dmab treatment results in 75% reduction in serum tartrate-resistant acid phosphatase (TRAP)-5b after 10 days.
b. Dmab significantly inhibits the formation of mature osteoclasts in vivo.
c. Dmab induces ONJ in the absence of osteoclast formation without significant cytotoxic effects.
d. It is possible that ONJ development is primarily associated with unresorbed bone surfaces as a result of impaired osteoclast functions or formation by BPs or Dmab, respectively, leading to incomplete healing after dental-related traumas.