A Mini-Review on heritable mineralization disorders, a research article on the role of bisphenol A in molar incisor hypomineralization, and a research article on estrogen-related receptor α (ERRα) and osteopontin expression in colorectal cancer were selected for the July 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.


Questions #8-10 are based on: Boudjadi S, Bernatchez G, Beaulieu J, Carrier JC: Control of the human osteopontin promoter by ERRα in colorectal cancer. Am J Pathol 2013, 183:266-276; http://dx.doi.org/10.1016/j.ajpath.2013.03.021

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

- Discuss ectopic mineralization.
- Describe the Mendelian genetic disorders associated with metastatic and dystrophic calcification.
- Discuss mechanisms of soft tissue mineralization.
- Understand the role that endocrine-disrupting chemicals (EDCs) have on the environment.
- Describe the effects of bisphenol A (BPA).
- Discuss osteopontin (OPN) and its role in tumor progression.
- Describe the role of estrogen-related receptor α (ERRα) in endocrine-related cancer development and progression.

1. Ectopic mineralization is the deposition of calcium/phosphate complexes in connective tissues in aberrant locations. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:10-18.]

   a. Ectopic mineralization has been linked to several clinical conditions that are major causes of morbidity and mortality, such as aging, cancer, diabetes, and autoimmune diseases.
   b. Metastatic calcification refers to calcium deposition associated with elevated serum levels of phosphate and/or calcium, as in chronic renal failure.
   c. Metastatic calcinosis in the skin can be characterized clinically by irreversible nodular deposits of calcium and phosphate.
   d. Dystrophic calcification is usually secondary to some form of insult to the tissues, as seen in autoimmune diseases and cancer.

2. Mutant mouse models can serve as genetically controlled model systems to study various facets of pathological mineralization. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:10-18.]

   a. Abcc6<sup>−/−</sup> and Nt5e<sup>−/−</sup> mice serve as models for pseudoxanthoma elasticum (PXE).
   b. Enpp<sup>1<sup>−/−</sup>, tw/ttw, and asj mice are model systems for generalized arterial calcification of infancy.
   c. Ggcx<sup>−/−</sup> mice serve as an animal model for multiple vitamin K-dependent coagulation factor deficiency.
   d. Fam20a<sup>−/−</sup> mice serve as a model for amelogenesis imperfecta (AI).
3. Several genes are associated with human diseases with ectopic mineralization phenotypes. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:10-18.]

   a. ATP-binding cassette C subfamily, member 6 (ABCC6) is associated with PXE.
   b. MGP, which encodes matrix gla protein, is associated with familial idiopathic basal ganglia calcification.
   c. The sterile α motif domain containing 9 gene (SAMD9) is associated with normophosphatemic familial tumoral calcinosis (NFTC).
   d. The vitamin K-dependent γ-carboxylase gene (GGCX) is associated with multiple vitamin K-dependent coagulation factor deficiency.

4. Several Mendelian genetic disorders share phenotypic similarities with the acquired forms of metastatic and dystrophic calcification. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:10-18.]

   a. Hyperphosphatemic familial tumoral calcinosis (HFTC) is the hereditary counterpart of acquired metastatic calcinosis.
   b. HFTC is an autosomal recessive condition characterized by progressive deposition of calcium phosphate crystals in periarticular spaces and soft connective tissues.
   c. Loss-of-function mutations in the fibroblast growth factor 23 gene (FGF23) cause HFTC by increasing phosphate excretion.
   d. NFTC is a type of familial tumoral calcinosis that is associated with preceding inflammatory manifestations mostly evident in mucosal tissues.

5. PXE can serve as a prototype of multisystem ectopic mineralization disorders. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:10-18.]

   a. PXE is characterized by protean manifestations in the skin, the arterial blood vessels, and the eyes.
   b. PXE is inherited in an autosomal recessive manner.
   c. PXE is a rare disease, with an estimated prevalence of ~1:250,000.
   d. Approximately 600 distinct loss-of-function mutations in the ABCC6 gene have been encountered.

6. Endocrine-disrupting chemicals (EDCs) are environmental ubiquitous pollutants that are associated with a growing health concern. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:108-118.]

   a. An increasing prevalence of numerous adverse health effects, such as diabetes, obesity, infertility, cancers, and autism, has been linked to EDCs.
   b. Bisphenol A (BPA) is a typical EDC widely used in the production of polycarbonate plastics and epoxy resin.
   c. The widespread use of BPA in food packaging is controversial and hotly debated.
   d. It is estimated that as much as 70% of the population is contaminated by BPA.

7. BPA affects different organs and physiologic key functions. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:108-118.]

   a. Physiologic key functions affected by BPA include reproduction and sex determinism, brain development, and behavior.
   b. BPA may increase breast cancer risk and lead to obesity.
   c. Epidemiologic surveys have identified specific BPA-target genes associated with specific disease states in differentiated cell types.
   d. Sensitivity to BPA in humans is highest during adolescence.

8. Osteopontin (OPN) is a secreted matricellular glycophosphoprotein. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:266-276.]

   a. OPN is produced by osteoblasts and osteoclasts and plays an important role in bone mineral deposition.
   b. OPN is expressed in various cell types and contributes to numerous physiological processes and to the pathogenesis of a variety of disease states, including chronic inflammation and cancer.
   c. OPN is involved in almost all steps of tumor progression by regulating cell-matrix interactions and cell signaling through binding with CD77 receptors.
   d. OPN has been reported to promote metastasis by increasing tumor growth, cell migration, degradation of the extracellular matrix, cell survival in blood stream, and angiogenesis.
9. OPN is thought to be a transcriptional target of factors implicated in epithelial carcinogenesis. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:266-276.]

   a. Activated ras represses OPN expression in mice.
   b. Mutant p53 can induce OPN expression in mice.
   d. OPN regulation depends on a number of transcription factors relevant to bone biology.

10. Estrogen-related receptor α (ERRα) contributes to bone formation. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:266-276.]

   a. ERRα activity is controlled by the interaction with master regulators of energy metabolism.
   b. Like other members of the nuclear receptor superfamily, ERRα is activated by estrogen-like molecules.
   c. ERRα is overexpressed and correlates with unfavorable biomarkers and poor clinical outcome in various cancer cell types, including breast, prostate, ovarian, endometrium, and colorectal.
   d. Selective ERRα antagonists have been useful to delineate ERRα functions in vitro.