A Mini-Review on high-temperature requirement serine protease A1 (HTRA1) in musculoskeletal disease and a research article and related Commentary on the pathophysiological effects of tobacco smoke extract (TSE) were selected for the May 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 #1-6 are based on: Tiaden AN and Richards PJ: The emerging roles of HTRA1 in musculoskeletal disease. Am J Pathol 2013, 182:1482-1488; dx.doi.org/10.1016/j.ajpath.2013.02.003


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

- Describe the role that HTRA1 plays in musculoskeletal disease.
- Describe the characteristics of osteoarthritis (OA).
- Understand the role of lumbar intervertebral disks (IVDs) in chronic back pain.
- Describe osteoporosis and the role of bone marrow stromal cells (BMSCs).
- Understand Duchenne muscular dystrophy (DMD).
- Discuss the characteristics of tobacco smoke-induced macrophage microvesicles (MVs).

1. The high-temperature requirement serine protease (HTRA) family constitutes a well-conserved group of proteolytic enzymes. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182: 1482-1488.]

   a. The HTRA family consists of HTRA1, -2, -3, and -4, a well-conserved group of proteolytic enzymes.
   b. The HTRA family enzymes have key roles in protein quality control as well as in the regulation of various signaling pathways through the degradation of specific substrates.
   c. HTRA3 exists solely as an intracellular protein.
   d. HTRA1 and -2 are considered to play important roles in human cancer and neurodegeneration.

2. Musculoskeletal is defined as relating to muscles and skeleton, and encompasses a wide variety of tissues, including muscles, bones, cartilage, joints, tendons, and ligaments. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182: 1482-1488.]

   a. Musculoskeletal diseases (MSDs) are generally considered to be an inevitable part of growing old.
   b. MSDs are highly prevalent.
   c. MSDs are likely to decrease over the coming years.
   d. Researchers are now focusing their attention on HTRA1 as a possible causal agent in the pathology of several closely related MSDs.
3. Osteoarthritis (OA) is the most prevalent form of arthritis. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182: 1482-1488.]

   a. OA was originally considered to be a noninflammatory disorder.
   b. OA is characterized by a breakdown in articular cartilage as well as degeneration of other joint tissues, including synovium and subchondral bone.
   c. OA is associated with a low-level inflammatory response.
   d. In OA patients, HTRA1 production is significantly decreased.

4. Acquired degenerative stenosis, by far the most common cause of chronic back pain, arises mainly from a breakdown in the structural integrity of lumbar intervertebral disks (IVDs). Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182: 1482-1488.]

   a. HTRA1 production was significantly up-regulated in degenerated IVD tissue explants and was directly correlated with the appearance of C-terminal, but not N-terminal, fibronectin fragments.
   b. IVDs are designed to counteract compressive forces on the spine and to maintain vertebral separation, thus allowing for unrestricted movement.
   c. IVD degeneration results in loss of disk height as well as increases in disk bulging and subsequent impingement of nerve roots.
   d. IVD degeneration is considered to be predominately an age-related phenomenon.

5. Osteoporosis is defined as a systemic disease characterized by reduced bone mass and low bone mineral density, with a subsequent increase in bone fragility and vulnerability to fractures. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182: 1482-1488.]

   a. Osteogenic differentiation leads to bone formation.
   b. Bone formation relies on the presence of bone marrow stromal cells (BMSCs).
   c. BMSCs are functionally active mature osteoblasts derived from progenitor cells within the bone marrow.
   d. BMSCs isolated from aged osteoporotic patients have a high propensity toward osteogenesis.

6. Duchenne muscular dystrophy (DMD) is a degenerative muscle disease. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182: 1482-1488.]

   a. DMD affects 1 in 3,500 females.
   b. DMD is due to a mutation in the dystrophin gene.
   c. DMD leads to a high susceptibility to skeletal muscle injury in patients.
   d. HTRA1 gene expression is reported to be increased by 4.4- to 5.5-fold in DMD muscle as compared to normal control tissue.

7. Cigarette smoking damages the extracellular matrix in a variety of locations, but the underlying mechanisms remain poorly understood. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182:1552-1562 and 182: 1489-1493.]

   a. Tobacco use causes cancers, emphysema, atherosclerosis, and a number of other debilitating and deadly diseases.
   b. The intracellular signaling pathway that initiates damage to the extracellular matrix after tobacco smoke extract (TSE) exposure involves ERK5.
   c. Exposure to tobacco smoke increases microvesicle (MV) generation from cultured human cells in vitro.
   d. Exposure to tobacco smoke increases MV generation in the circulation of humans in vivo.

8. MVs are small membranous structures. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 182:1552-1562 and 182: 1489-1493.]

   a. MVs are also known as microparticles.
   b. MVs are released from cells during activation or apoptosis.
   c. Exposure of human macrophages to TSE induces the release of potently proteolytic MVs.
   d. Smoke-induced macrophage MVs carry substantial gelatinolytic and collagenolytic activities that can be predominantly attributed to matrix metalloproteinase-2 (MMP-2).