A Mini-Review on hyaluronan/CD44 signaling in epidermal functions, and an article characterizing an orthotopic animal model of pseudomyxoma peritonei (PMP) were selected for the July 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.

Questions #1-6 are based on: Bourguignon LYW: Matrix hyaluronan-activated CD44 signaling promotes keratinocyte activities and improves abnormal epidermal functions. Am J Pathol 2014, 184:1912-1919; http://dx.doi.org/10.1016/j.ajpath.2014.03.010


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

• Describe matrix hyaluronan (HA) and its function.
• Understand the relationship between HA and cell surface receptor CD44.
• Explain the link between phosphatidylinositol 3-kinase (PI3K) and HA signaling.
• Describe how HA leads to altered cytoskeleton-mediated cell functions.
• Elucidate the role of HA in aged skin.
• Define and characterize pseudomyxoma peritonei (PMP).

1. In the epidermis, extracellular matrix (ECM) components form an integral part of the hemidesmosomes and mediate keratinocyte attachment to the underlying basement membrane. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:1912-1919.]

   a. Matrix hyaluronan (HA) is a major glycosaminoglycan in the ECM of most mammalian tissues, including the epidermis and dermis.
   b. HA has been implicated in several skin epidermal functions.
   c. CD44 is the predominant HA receptor on the cell surface of keratinocytes.
   d. CD44 is encoded by two genes that contain 11 exons.

2. CD44 knockout mice show a significant reduction in endogenous HA on the keratinocyte cell surface and the loss of certain keratinocyte functions. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:1912-1919.]

   a. CD44 and endogenous HA are expressed in the epidermal keratinocytes of CD44 wild-type mouse skin.
   b. No CD44 and little endogenous HA can be detected in the epidermal keratinocytes of CD44 knockdown or CD44 knockout mouse skin.
   c. HA promotes the interaction between CD44 and several Rho-specific guanine nucleotide exchange factors (GEFs) that down-regulate RhoA, leading to several important cellular functions.
   d. Down-regulation of CD44 in cultured keratinocytes significantly inhibits HA-mediated keratinocyte differentiation and lipid synthesis.
3. The epidermis continuously undergoes self-renewal, proliferation, survival, and differentiation. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184: 1912-1919.]

   a. Phosphatidylinositol 3-kinase (PI3K) signaling to AKT promotes keratinocyte differentiation.
   b. HA-CD44 interaction and Gab-1-associated PI3K activation are positively linked during the stimulation of cellular transformation.
   c. HA activates the PI3K-AKT pathways that lead to cell motility and cell survival-signaling pathways.
   d. The active mutant of the p85 subunit of PI3K exerts its action on the cleavage of CD44 during cell migration.

4. HA promotes the interaction between CD44 and several Rac1-specific GEFs that up-regulate Rac1, leading to altered cytoskeleton-mediated cell functions. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184: 1912-1919.]

   a. Protein kinase N (PKN) 2 belongs to a family of serine-threonine kinases known to interact with Rac1 in a GTP-dependent manner.
   b. The N-terminal region of PKN2 contains five homologous sequences of approximately 120 amino acids, which form an antiparallel coiled-coil fold.
   c. PKN has been found to regulate intermediate filaments, such as vimentin, glial fibrillary acidic protein, and other neurofilament proteins.
   d. Rac1-PKN2 appears to be preferentially activated by HA-CD44 signaling.

5. HA within the epidermis has been found to rapidly turn over. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184: 1912-1919.]

   a. HA fragments, referred to as small HAs (HAs), promote transcriptional activation and differentiation, whereas large HA fragments (HAL) induce proliferative genes and migration.
   b. HA fragmentation may play a key role in the sequential phases of tissue injury and repair.
   c. An age-related decrease in HA production has been found in both rodent and human aged skin.
   d. Aging is associated with impaired wound healing and the delayed resolution of a variety of skin diseases.

6. HAs fragments are capable of inducing epidermal differentiation through phosphorylation of CD44 in keratinocyte culture in vivo. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184: 1912-1919.]

   a. Topical application of HA fragments can penetrate through both mouse and human skin via active transport.
   b. HA and its catabolic products are known to selectively activate CD44-mediated keratinocyte signaling that regulates keratinocyte proliferation, migration, differentiation, lamellar body formation/secretion, and wound healing.
   c. Topical application of HAs up-regulates keratinocyte differentiation and promotes permeability barrier repair in aged mouse skin.
   d. Because neither HAs nor HAL corrects epidermal defects in aged CD44 knockout mice, it is likely that CD44 mediates HA-associated epidermal functions in aged mouse skin.

7. Pseudomyxoma peritonei (PMP) is an uncommon peritoneal mucinous carcinomatosis confined to the peritoneal cavity. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184: 1920-1929.]

   a. PMP is characterized by the progressive accumulation of mucinous tumor tissue in the peritoneal cavity without extraperitoneal growth that leads to intra-abdominal compression and a fatal outcome.
   b. PMP has an intestinal origin and results from the perforation of a mucinous appendiceal neoplasm.
   c. Complete cytoreductive surgery with hyperthermic intraperitoneal chemotherapy is now a well-established treatment option for patients with PMP.
   d. Treatment failure and recurrence are rare.

8. Histopathologically, PMP is graded from disseminated peritoneal adenomucinosis to peritoneal mucinous carcinomatosis. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184: 1920-1929.]

   a. PMP presents as large patches of mucinous deposits that contain many cells organized as a high-proliferative epithelium.
   b. The evaluation of patients with PMP is based on computed tomography.
   c. No functional imaging modality has a proven efficacy in the follow-up of PMP patients.
   d. The main blood supply of the PMP tumor arises from the superior mesenteric artery.