Articles on regulation of keratinocyte migration by factor inhibiting hypoxia-inducible factor 1 (FIH-1), the expression and role of neurotensin in colonic inflammation, and p63 inhibition of extravillous trophoblast (EVT) migration were selected for the December 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 #4-6 are based on: Li Y, Moretto-Zita M, Leon-Garcia S, Parast MM: p63 inhibits extravillous trophoblast migration and maintains cells in a cytotrophoblast stem cell-like state. Am J Pathol 2014, 184:3332-3343; http://dx.doi.org/10.1016/j.ajpath.2014.08.006


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

- Describe the functions of factor inhibiting hypoxia-inducible factor-1 (FIH-1).
- Explain the roles of the epidermal growth factor receptor (EGFR) in skin.
- Describe the leucine-rich repeat kinase 1 (LRRK1) protein kinase.
- Describe proliferative cytotrophoblasts (CTB) and extravillous trophoblasts (EVT).
- Understand mature EVT and EVT differentiation.
- Define p63 and the alpha isoform of the N-terminally-truncated p63 (ΔNp63α).
- Define neurotensin (NT).
- Explain the characteristics of hypoxia-inducible factors HIF-1 and HIF-2.
- Describe the NT–HIF-1α–vascular endothelial growth factor (VEGF) α axis and its role in hypoxia, colonic inflammation, and intestinal angiogenesis.

1. Factor inhibiting hypoxia-inducible factor-1 (FIH-1) is a hydroxylase that negatively regulates hypoxia-inducible factor-1 alpha (HIF-1α). Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:3262-3271.]

   a. FIH-1 inhibits the activity of HIF-1α by coupling the oxidative decarboxylation of 2-oxoglutarate to the hydroxylation of HIF-1α.
   b. Proteins containing the ankyrin repeat domain (ARD), such as Notch, are additional substrates for FIH-1.
   c. FIH-1 has pleiotropic roles in maintaining epithelial homeostasis.
   d. FIH-1 negatively regulates glycogen metabolism in corneal epithelium in a HIF-1α–independent manner via the direct involvement of the Notch signaling pathway.
2. Once epidermal growth factor (EGF) binds to the EGF receptor (EGFR), numerous signaling pathways are activated that impact on cell proliferation, migration, differentiation, and survival. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:3262-3271.]

a. With respect to the skin, EGFR impacts on epidermal and hair follicle development, keratinocyte proliferation, survival, cancer, and immune homeostasis.
b. In the epidermis, EGFR signaling has been shown to inhibit keratinocyte migration and wound repair.
c. Corneal perturbations activate the EGFR and downstream Ras-Raf-Mek-Erk1/2 (Ras, Raf, mitogen-activated protein kinase kinase, extracellular signal–regulated kinase 1/2) and phosphoinositide 3 kinase–Akt (PI3K–Akt) signaling cascades.
d. Ras-Raf-Mek-Erk1/2 and PI3K–Akt pathways are required for efficient wound healing and are attenuated in patients with diabetic keratopathies.

3. Leucine-rich repeat kinase 1 (LRRK1) is a key regulator of EGFR endosomal trafficking. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:3262-3271.]

a. LRRK1 forms a complex with activated EGFR through an interaction with growth factor receptor–bound protein 2 and this complex is internalized in early endosomes.
b. LRRK1 protein kinase is one of the ROCO proteins that contain a GTPase-like domain [Ras of complex proteins (Roc)] and a C-terminal of Roc (COR) domain.
c. LRRK1 contains 12 N-terminal ankyrin repeats.
d. FIH-1 has the potential to directly interact with the ARD of LRRK1, thus impacting EGFR signaling.

4. Proper fetal development in utero requires an appropriately functioning placenta that is able to deliver oxygen and nutrients to the growing fetus. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:3332-3343.]

a. Early during human placental development, proliferative cytotrophoblast (CTB) forms cell columns, which help anchor the placenta to the uterus.
b. In the distal parts of the anchoring villi, the CTBs differentiate into a migratory phenotype, the extravillous trophoblast (EVT).
c. EVT invades the uterus, establishing blood flow to the fetoplacental unit through remodeling of maternal spiral arterioles.
d. The CTB-EVT differentiation is characterized by an integrin switch, from α1β1 in the villous CTB to α6β4 in the cell columns and α5β1 in the uterine wall.

5. Proper differentiation of placental epithelial cells, called trophoblast, is required for implantation. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:3332-3343.]

a. Mature EVTs are characterized by loss of expression of EGFR on their surface.
b. Mature EVTs gain surface expression of HLA-G and melanoma cell adhesion molecule.
c. EVT differentiation resembles cancer cell invasion, with reduction of p53 expression in the cell columns.
d. During EVT differentiation, cells acquire the ability to secrete matrix metalloproteinases.

6. p63 is highly expressed in proliferative villous CTB and required for induction of the trophoblast lineage in human pluripotent stem cells. Based on the referenced, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:3332-3343.]

a. Both in liver and breast cancer cell models, loss of p63 promotes epithelial-to-mesenchymal transition (EMT), leading to greater invasive potential.
b. The α isoform of the N-terminally-truncated p63 (ΔNp63α) maintains the stem cell state in stratified epithelia, including skin.
c. p63 regulates cell adhesion in mammary epithelium, promoting adhesion-dependent protection against cell death.
d. p63 is a member of the p53 family.

7. The term inflammatory bowel disease (IBD) is used to describe two chronic and debilitating inflammatory disorders, namely, Crohn’s disease and ulcerative colitis. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:3405-3414.]

a. The neuropeptide neurotensin (NT), via its high affinity receptor NTR1, is an important mediator of intestinal inflammation.
b. NT is a 31-amino acid neuropeptide initially isolated from murine hypothalamus.
c. In the intestine, NT is expressed in the endocrine N cells, localized in the intestinal mucosa.
d. Expression levels of NT and NTR1 are up-regulated in the inflamed colonic mucosa of animal models and IBD patients.
8. During active inflammation, such as IBD, there are severe metabolic shifts toward hypoxia. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:3405-3414.]

a. Hypoxia leads to the activation of HIF-1 and HIF-2.

b. Surgical specimens of inflamed intestine contain elevated levels of HIF-1α and HIF-2α.

c. Under normoxic conditions, HIF-2 is targeted for proteasomal degradation.

d. HIF-1 induces the expression of a broad genetic program that includes angiogenic genes, by binding on the appropriate HIF-responsive elements present on their promoter region.