The 2013 Rous-Whipple Award Lecture on regulation of transendothelial migration of leukocytes and review articles on how pathogens hijack the epigenome and novel mouse models for liver cancer research were selected for the April 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:

- Describe the process of transendothelial migration (TEM).
- Define lateral border recycling compartment (LBRC) and its role in transcellular migration.
- Understand that pathogens develop strategies to promote their survival by manipulating the epigenome.
- Recognize that host cell responses are rapidly activated when infiltrated by an organism.
- Understand hepatocellular carcinoma (HCC) and its risk factors.
- Describe the etiology of intrahepatic cholangiocarcinoma (ICC).
- Define the hydrodynamic transfection technique for generation of mouse models for liver cancer research.

1. Electron microscopic studies of leukocytes in the process of transendothelial migration (TEM) show that they squeeze in amoeboid fashion between tightly apposed endothelial cells. Based on the referenced Rous-Whipple Award Lecture, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:886-896.]

   a. It takes 5 to 6 minutes for a leukocyte to completely traverse the endothelial border in vitro or in vivo.
   b. Endothelial cells play a major role in the regulation of most metabolic and physiologic processes, including blood pressure, glucose metabolism, thrombosis, hemostasis, and inflammation.
   c. Blocking antibodies against the homophilic interaction domain of platelet endothelial cell adhesion molecule (PECAM), when added to either the leukocyte or the endothelial cell in vitro transmigration assays, block TEM as completely as adding them to both cells at the same time.
   d. Blocking PECAM–PECAM interactions has no effect on adhesion of leukocytes to or locomotion on the endothelium.

2. Targeted recycling of the lateral border recycling compartment (LBRC) seems to be necessary for TEM of neutrophils, monocytes, and lymphocytes under all conditions tested. Based on the referenced Rous-Whipple Award Lecture, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:886-896.]

   a. Most (>90%) leukocyte TEM takes place at endothelial cell borders.
   b. Transcellular migration refers to the migration of leukocytes through the endothelial cell cytoplasm.
   c. Under certain in vitro conditions up to 50% of neutrophils can migrate transcellularly.
   d. During transcellular migration, the LBRC migrates from the endothelial border to surround the leukocyte for the duration of its passage.
3. Due to the emergence of drug-resistant strains and newly discovered pathogens, infectious diseases remain a major concern for public health. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:897-911.]

a. Host organisms respond to infection by initiating inflammatory and immune responses in an attempt to clear organisms from their systems.
b. Pathogens have adapted to alter host cell functionality to their own advantage.
c. Pathogens use a wide variety of strategies to manipulate host cells to their benefit.
d. *Shigella flexneri*, a Gram-positive bacterium, hides inside neutrophils and induces nonapoptotic programmed cell death before being absorbed by macrophages.

4. When an organism enters a host cell, the host cell responses are rapidly activated in an attempt to eradicate the organism. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:897-911.]

a. *Plasmodium* spp. parasites, responsible for malaria, invade and replicate inside liver cells.
b. *Plasmodium* spp. induce changes in transcription of >1000 hepatocyte genes.
c. Some of the induced changes in mRNA can be detected as soon as 15 minutes after infection.
d. Transcriptional dysfunction induced by cellular infection by *Plasmodium* spp. is an ordered, sequential process, with different gene sets being altered throughout the infection process.

5. DNA methylation patterns correlate tightly with transcriptional data and can change dramatically when cells encounter a pathogen. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:897-911.]

a. DNA methylation was previously thought to be a stable modification, but is now known to be dynamic, changing even within a single cell cycle.
b. Integration of viral DNA into host DNA induces local changes in DNA methylation.
c. Urokinase-type plasminogen activator is essential for activation of hepatocyte growth factor.
d. Hepatitis B viral infection is an important etiologic factor in the development of gastric carcinoma.

6. Primary liver cancer represents a major health problem worldwide. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184:912-923.]

a. According to the World Health Organization, liver cancer represents the fifth leading cause of cancer-related death worldwide, accounting for approximately 300,000 deaths in 2008.
b. Hepatocellular carcinoma (HCC) accounts for approximately 80% of all primary liver caners.
c. Epidemiological and molecular studies have demonstrated that the development of HCC spans several decades.
d. Patients with hepatitis B or hepatitis C chronic infection are at a much higher risk for developing HCC than noninfected individuals.

7. Primary liver cancers, including HCC and intrahepatic cholangiocarcinoma (ICC), are leading causes of cancer-related deaths worldwide. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184: 912-923.]

a. In the past decades, the incidence of ICC has been increasing in the United States and the Western world.
b. ICC accounts for approximately 25% of primary liver cancer.
c. Liver fluke infection is the major risk factor in countries, such as Thailand, where ICC is prevalent.
d. Epidemiological data suggest that hepatitis B or hepatitis C infection, alcohol abuse, diabetes, and obesity are major risk factors for ICC in Western countries.

8. Genetically modified murine models demonstrate the oncogenic or tumor-suppressor potential of target genes and illustrate how these genes contribute to tumor initiation and progression, but they have several limitations. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2014, 184: 912-923.]

a. Hydrodynamic transfection uses a hydrodynamic force produced by the pressurized injection of a large volume of DNA solution into blood vessels, permeabilizing the capillary endothelium and generating pores in the plasma membrane of the surrounding parenchyma cells.
b. After the hydrodynamic transfection, the pores of the plasma membrane close, trapping the DNA inside the parenchymal cells.
c. The standard hydrodynamic transfection procedure consists of a rapid tail vein injection of physiological solution, equivalent to 30% of body weight, in which the plasmid DNA is diluted.
d. The most successful application of the hydrodynamic technique is gene delivery to hepatocytes in mice.