ABSTRACT
The 1918 influenza A H1N1 virus caused the worst pandemic of influenza ever recorded. To better understand the pathogenesis and immunity to the 1918 pandemic virus, we generated recombinant influenza viruses possessing two to five genes of the 1918 influenza virus. Recombinant influenza viruses possessing the hemagglutinin (HA), neuraminidase (NA), matrix (M), nonstructural (NS), and nucleoprotein (NP) genes or any recombinant virus possessing both the HA and NA genes of the 1918 influenza virus were highly lethal for mice. Antigenic analysis by hemagglutination inhibition (HI) tests with ferret and chicken H1N1 antisera demonstrated that the 1918 recombinant viruses antigenically most resembled A/Swine/Iowa/30 (Sw/Iowa/30) virus but differed from H1N1 viruses isolated since 1930. HI and virus neutralizing (VN) antibodies to 1918 recombinant and Sw/Iowa/30 viruses in human sera were present among individuals born before or shortly after the 1918 pandemic. Mice that received an intramuscular immunization of the homologous or Sw/Iowa/30-inactivated vaccine developed HI and VN antibodies to the 1918 recombinant virus and were completely protected against lethal challenge. Mice that received A/PR/8/34, A/Texas/36/91, or A/New Caledonia/20/99 H1N1 vaccines displayed partial protection from lethal challenge. In contrast, control-vaccinated mice were not protected against lethal challenge and displayed high virus titers in respiratory tissues. Partial vaccine protection mediated by baculovirus-expressed recombinant HA vaccines suggest common cross-reactive epitopes on the H1 HA. These data suggest a strategy of vaccination that would be effective against a reemergent 1918 or 1918-like virus.

Hepatitis C Virus and HIV Envelope Proteins Collaboratively Mediate Interleukin-8 Secretion through Activation of p38 MAP Kinase and SHP2 in Hepatocytes

Anuradha Balasubramanian, Ramesh K. Ganju and Jerome E. Groopman
Division of Experimental Medicine, Beth Israel Deaconess Medical Center, Harvard Institutes of Medicine, Boston, Massachusetts, USA

ABSTRACT
Hepatitis C virus (HCV) infects approximately 40% of human immunodeficiency virus (HIV) patients, and the resulting hepatic dysfunction that occurs is the primary cause of death in patients with co-infection. We hypothesized that hepatocytes exposed to HCV and HIV proteins might be susceptible to injury via an “innocent bystander” mechanism. To assess this, we studied the effects of envelope proteins, E2 of HCV and gp120 of HIV, in model HepG2 cells. Upon co-stimulation with HCV-E2 and HIV-gp120, we observed a potent proinflammatory response with the induction of IL-8. Furthermore, our studies revealed that HCV-E2 and HIV-gp120 act collaboratively to trigger a specific set of downstream signaling pathways that include activation of p38 mitogen-activated protein (MAP) kinase and the tyrosine phosphatase, SHP2. Both specific inhibitors of p38 MAP kinase and sodium vanadate, a potent protein-tyrosine phosphatase inhibitor, blocked IL-8 production in a dose-dependent manner. The role of p38 MAP kinase and SHP2 was further defined by transiently overexpressing dominant negative mutants of these proteins into HepG2 cells. These studies revealed that overexpression of an inactive p38 MAP kinase or SHP2 mutant partially abrogated HCV-E2- and HIV-gp120-induced IL-8 production. Further studies revealed that IL-8 induction was not mediated through activation of the NF-kappa B pathway. However, HCV-E2 plus HIV-gp120 was shown to increase the DNA binding activity of AP-1. These results emphasize that expression of the proinflammatory chemokine IL-8, induced by HCV-E2 and HIV-gp120, may be mediated through p38 MAP kinase and SHP2 in an NF-kappa B-independent manner, albeit through AP-1-driven processes.