Centenario de la Gripe Española de 1918. La peor pandemia en la historia contemporánea mundial: lecciones para el futuro

Centenary of the 1918 Spanish Influenza, the Worst Pandemic in the Recent History of the World: Lessons for the future

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ABSTRACT

The RNA synthesis machine of influenza viruses and innate immune sensing

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The Influenza A virus is an infectious agent that usually causes a mild respiratory disease and induces innate immune responses through the activation of RNA sensor RIGI. However, infections with highly pathogenic influenza viruses such as the H5N1 subtypes or the 1918 H1N1 virus, can lead to an innate immune dysregulation and severe disease. The genome of the virus is replicated and transcribed by the viral RNA-dependent RNA polymerase in the context of viral RNA-nucleoprotein (vRNP) complexes. The RNA polymerase is a complex enzyme that consists of a central core composed of the viral proteins PB1, PB2 and PA, and at least three auxiliary domains involved in viral Transcription. Various mutations in the RNA polymerase have been linked to host adaptation and viral virulence, but it is presently unclear what molecular mechanism underlies the link between RNA polymerase differences and viral pathology. Analysis of RNA isolated from transfected cells expressing viral ribonucleoproteins, cells infected with pandemic and avian influenza viruses, and lung tissues of ferrets and mice infected with the 1918 pandemic virus or H5N1 strains shows that short subgenomic viral RNAs of <125 nt in length potently activate RIG-I and induce innate immune signalling. We call these new viral RNAs mini viral RNAs (mvRNAs). The polymerases of the 1918 H1N1 pandemic virus and H5N1 subtypes are particularly efficient at generating mvRNAs in vitro and in vivo. We find that the formation of mvRNAs is directly dependent on erroneous polymerase activity and introduction of a high-fidelity mutation into the viral RNA polymerase reduces mvRNA formation and cytokine expression. In vitro, formation of mvRNAs can be stimulated by the introduction of avian adaptive mutations in the PB2 subunit of the viral polymerase, suggesting that mvRNA formation derives from a dysregulated replication of avian-adapted influenza virus strains in mammalian cells. Overall, these results provide an important advance in our understanding of the molecular basis of influenza virus virulence and suggest that mvRNAs are biomarkers for highly pathogenic influenza virus infections in mammals.

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