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

Viral proteins and viral RNAs; a coordinated mechanism to increase influenza virus pathogenicity

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Influenza A virus (IAV) genetic determinants for high virulence have been extensively studied, especially for highly virulent viruses such as the 1918 that produced the most devastating human pandemic or the recent new and mild H1N1 2009 pandemic. Despite extensive studies, no clear common pathogenicity traits have been determined, although the prominent contribution of the viral polymerase, has been described.

Viral polymerase plays a crucial role controlling the expression of the viral and the host genome as well as viral pathogenicity. Despite the functional association between viral and cellular transcription; a requisite for the viral cap-snatching transcription mechanism, the viral polymerase triggers the degradation of the RNA polymerase II when viral transcription is completed. This degradation contributes to the host-cell shut-off and to diminish the antiviral response. IAV uses additional mechanisms to control the antiviral response, such as the induction of epigenetic changes in specific histone residues that control the interferon signaling pathway, possibly through alterations in cellular sensors of viral RNAs. A pivotal role is carried out by methylation of lysine 79 of histone 3, together with a general role of decreased histone acetylation.

The use of next-generation sequencing has allowed the detection of defective viral genome RNAs (DVGs) in virus particles. The DVGs have the 3' and 5' ends of the parental RNA segments, and most have a single, large central deletion that generates viral RNAs of 180-1000 nucleotides. The presence of DVGs potentiates the host response in cultured cells and in animal models possibly through recognition of double-stranded RNA by receptors that activate antiviral signaling cascades. The underlying mechanism involved in DVGs production is not fully understood since changes in different viral proteins modulate DVGs accumulation. However, it is well characterized that specific point mutations at the viral polymerase subunits control DVGs production and decreased levels of DVGs

correlate with increased pathogenesis in mice; conversely increased levels diminish the in vivo pathogenesis. Performing genomic analysis of viruses isolated from a cohort of previously healthy IAV infected patients with highly severe/fatal outcome, we showed that these viruses accumulated fewer DVGs than viruses isolated from a cohort of mild infected patients. We suggest that low DVGs abundance constitutes a new virulence pathogenic marker in humans and reduced accumulation of DVGs constitutes a virulent factor itself, regardless the mutations responsible. Further characterization of a recombinant virus with a point mutation in the PA subunit that produces low amount of DVGs has shown that it replicates efficiently in the heart, causes cardiac disorders and induce sudden death in infected animals. The data indicate that influenza virus uses a plethora of mechanisms to increase the pathogenicity; viral proteins and viral RNAs work coordinately to accomplish an efficient infection mediated by this virus that possess low genomic information.