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Severe outcome in influenza virus infected patients is associated with reduced accumulation of defective viral genomes

Influenza A virus (IAV) infection can be severe or even lethal in toddlers, the elderly and patients with certain medical conditions. Infection of apparently healthy individuals nonetheless accounts for many severe disease cases and deaths, suggesting that viruses with increased pathogenicity co-circulate with pandemic or epidemic viruses. Looking for potential virulence factors, we have identified a viral genetic determinant that contributes to infection outcome. A polymerase mutation identified in a fatal IAV case, when introduced into two different recombinant virus backbones, led to reduced defective viral genomes (DGs) production and increased pathogenesis in mice. These data provide genetic support for the association of pathogenicity and low DGs accumulation induced by mutations present in pathogenic viruses circulating in humans. Testing this association, we performed a genomic analysis of viruses isolated from a cohort of previously healthy individuals who suffered highly severe IAV infection requiring admission to intensive care unit, and patients with fatal outcome who additionally showed underlying medical conditions. These viruses were compared with those isolated from a cohort of mild IAV patients. Viruses from highly severe/fatal outcome patients showed significantly fewer DGs accumulation than control viruses, suggesting that low DGs abundance constitutes a new virulence viral pathogenic marker in humans, regardless of the mutations responsible.

Figure 1: Different amounts of defective viral genomes are detected in viruses from either severe/fatal or mild case. NGS sequencing of RNA from purified virions. (A) Scheme of influenza virus defective genomes (DGs). Black squares denote the jumping reads (B) Scatter plot representation of DGs proportions, calculated as jumping reads per million (RPM) of reads that align the viral genome, found in viruses isolated from influenza A virus infected patients. Red and blue boxes indicate the interquartiles with values representing the intermediate 50% of the population. Red Severe-Fatal cases; Blue, Mild cases. Horizontal bars inside each box indicate the median value. Significance was determined by a two-tailed Mann-Whitney test; p = 0.0117 (* p <0.05).

Biography

Ana Falcón completed her PhD in Molecular Biology and Science at Autonomous University, Madrid. During her scientific career, she has studied molecular biology of several respiratory viruses of clinical significance as influenza virus, SARS-CoV and other coronaviruses. She has worked on virus reverse genetics, functional analysis of viral and cellular proteins, and molecular diagnosis of virus in clinical samples and on animal models to study viral pathogenesis. She is developing and coordinating an international multidisciplinary project including physicians, microbiologists, molecular virologists and bioinformatics. She is a Reviewer for several scientific journals and has trained PhD and master students.

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