Proteomic Insights into Yellow Fever: Comparative Analysis of Blood Serum Profiles from Recovered and Fatal Cases During Brazil's 2016-2018 Outbreak

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Yellow fever (YF) is a severe viral hemorrhagic disease transmitted by mosquito bites. During Brazil\'s 2016-2018 outbreak, there were 2,154 confirmed cases, including 745 fatalities. Early symptoms include sudden fever, pain, headache, myalgia, increase in liver enzymes, leukopenia and proteinuria. Liver injury, jaundice, bleeding disorders, and acute kidney injury are critical features of the severe phase and are linked to high mortality. To better understand the progression of YF, we conducted a comparative proteomic analysis using pooled blood serum samples collected in Minas Gerais, Brazil, in January 2018. Samples were divided into three groups: Control (CG—serum from 10 healthy individuals), Recovered (RG—serum from 10 patients who had recovered from Yellow Fever), and Fatal (FG—serum from 8 fatal cases). Each sample was processed under two conditions: without acetonitrile depletion (non-depleted, SNDFA) and with acetonitrile depletion (depleted, SDFA). The samples were then digested with trypsin and analyzed using a timsTOF Pro 2 instrument (nLC-MS/MS). Data were processed with MSFragger, with a 1% FDR. The global proteome analysis identified 876 and 1,286 proteins under the SNDFA and SDFA conditions, respectively. After applying stringent criteria, the final protein numbers were 852 for SNDFA and 1,210 for SDFA. The FG exhibited a higher proportion of exclusive proteins compared to other groups, with 35% of exclusive proteins in SNDFA (301) and 51% in SDFA (617). This suggests a correlation between disease severity and alterations in protein profiles. These exclusive proteins included a significant number of immunoglobulins, as well as proteins involved in synthesis and degradation, oxidative stress, chaperones, and metalloproteinases. In contrast, the CG showed exclusive proteins related to transferases, extracellular matrix components, and housekeeping functions. In the RG, the exclusive proteins primarily comprised those associated with the complement system and immunoglobulins. Additionally, in the SNDFA, 339 proteins were shared among the groups, with 209 proteins upregulated in the FG and 196 in the RG compared to the CG. Notable upregulated proteins in these groups included Proteasome Subunit Alpha Type-1, Fructose-Bisphosphate Aldolase B, Catalase, L-Lactate Dehydrogenase A Chain, and Peroxiredoxin-2. These proteins play critical roles in proteolysis, removal of damaged or misfolded proteins, protection against hydrogen peroxide toxicity, and defense against oxidative stress. Conversely, in the SDFA, 313 proteins were shared, with 180 proteins upregulated in the FG and 165 in the RG. Noteworthy upregulated proteins in both the FG and RG compared to the CG included Macrophage Migration Inhibitory Factor, Trypsin-2, Hemoglobin, Insulin-like Growth Factor-Binding Protein 2, and Protein S100-A9. These proteins are involved in diverse functions such as the innate immune response, regulation of macrophage activity, inhibition of IGF-mediated growth, and modulation of inflammatory processes and immune responses. Our findings provide valuable insights into the protein profiles of YF patients compared to uninfected individuals, significantly advancing our understanding of disease pathogenesis. This data marks the initial phase of our study and lays the groundwork for further research, potentially contributing to the development of new therapeutic strategies for YF.

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