CHIKV infection induces a viral immune response, platelet activation and persistent inflammatory process in chronic and non-chronic patients

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Despite thrombocytopenia not being predominant in CHIKF, it is known that platelets play a predominant role in the inflammatory process and participate in numerous immune-physiological mechanisms of defense and host-pathogen interaction in viral diseases. Previously, we have demonstrated an increase in platelet activation and involvement of the inflammasome in individuals infected with CHIKV, suggesting that this activation may predict the development of chronicity. We also show that the platelet proteome of DENV-infected patients presents novel pathways of platelet activation and immunoregulation. Taken together, our data suggest inflammatory profile, which could lead to potential consequences for the progression and severity in arboviruses. Here, we aimed to assess the differences between CHIKV and DENV through platelet proteomics. To this end, platelet samples isolated from the blood of patients affected by acute CHIKV (n=9), controls (n=9) and DENV (n=6). All samples were analyzed by LC-MS/MS (Orbitrap QExactive Plus), by DDA approach. 350 proteins were upregulated in CHIKV and 312 proteins were downregulated. The enrichment pathway terms were mainly viral infection pathway, adaptive immune system, neutrophil degranulation and vesicle-mediated transport. The biological processes indicate subsets linked to lipid biosynthetic process, regulation of viral genome replication, vesicle-mediated transport, interferon signaling, among others. In addition, the participation of proteins related to the viral immune response (IFITs) and the platelet activation process was also evidenced. To evaluate the particularities of CHIKV, we revisited the proteome of DENV. From 3809 proteins identified, 750 (19.69%) are exclusive to the CHIKV group while 131 (3,4%) are exclusive to the DENV group. Statistically, 618 proteins are upregulated in CHIKV and 465 are upregulated in DENV. PCA demonstrates a clear distinction between them. Moreover, some biological process such as hemostasis and vesicle-mediated transport were identified in common for both infections, while others such as metabolism of lipids, oxidoreductase activity, protein catabolic process, lipid biosynthetic process and Ub-specific processing proteases were enriched exclusively in CHIKF. Moreover, we stratified the CHIKV plasma cohort into who developed chronicity (n=6) six months after infection and patients who had only the acute infection of the disease (n=6) and performed LC-MS/MS (Orbitrap Exploris 480), by DIA. On average 501 proteins were identified by sample. Proteins such as SAA1, VWF, PZP, CRP and FN1 are up-regulated in the group of chronic patients compared to non-chronic patients. PCA analysis also distinguishes the groups, with stratification between chronic, non-chronic and control, which suggests alterations in the proteome

correlate with their clinical condition. We believe that these analyses together can provide us with important information about the molecular events that culminate in the persistence of inflammation in CHIKF, and the differences between this infection and dengue, pointing to potential biomarkers.

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