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LETTER TO THE EDITOR

Novel mechanisms of thrombo-inflammation during infection: the harmful impact of circulating histones

To the Editor,

We read with great interest the exhaustive review/state of the art by Colicchia et al. [1], in which the new data on thrombo-inflammation mechanisms were shown through the coordinate activation of platelets and neutrophils during bacterial and viral sepsis. We appreciate their careful review, and we wish to comment on some associated issues for integrating and updating the readers about the new biological and biochemical knowledge related to the harmful effects of circulating histones.

Ever increasingly important evidence highlights that histones (intranuclear positively charged proteins, associated with chromatin) show extranuclear/extracellular functions when extruded mainly by activated white blood cells and platelets during bacterial and viral infections [2,3]. In this respect, circulating histones have been demonstrated as inducers of cellular damage through cytotoxic proinflammatory effects, promoting monocyte activation and platelet aggregation, as well as finally acting as damage-associated molecular pattern molecules [2].

A growing number of recent studies underlined the involvement of circulating histones in inflammatory processes and infections (eg, bacterial and COVID-19-associated viral sepsis), shedding light on their roles as both molecular triggers and potential therapeutic targets [3]. Recently, increased levels of circulating histones were also correlated with worsening of several diseases, raising their usefulness to stratify patients at higher risk of morbidity/mortality [2,3].

Other than neutrophils [1], monocytes are well-recognized key players in innate immunity against pathogens [2]; monocyte activation is characterized by peculiar morphologic changes, mirroring cell heterogeneity and anisocytosis, and clinically quantified by the monocyte distribution width (MDW) test, a mathematical parameter based on the measurement of volume (by direct current impedance), conductivity (by radio frequency opacity), and scatter (by laser beam intracellular/intranuclear scatter) of monocyte population [4].

When monocytes overreact to increased levels of circulating histones (as during infection or injury by critical bacterial and viral sepsis) they kick up a cytokine storm [5], a hyperinflammatory reaction inducing a harmful vicious cycle leading patients to a higher risk of severe/critical conditions up-to death [3]. We recently demonstrated that histones trigger MDW changes [4], promoting also hyperinflammatory responses associated with a monocyte anisocytosis [5], mirroring those observed in bacterial and COVID-19-associated viral sepsis [4]. Moreover, we determined the role of circulating histones on the alteration of platelet indices (eg, count, mean platelet volume; platelet distribution width [PDW], and inflammatory cytokines [eg, Platelet-derived growth factor-BB, Regulated on Activation, Normal T cell Expressed and Secreted, transforming growth factor beta-1, beta-2 and beta-3]), revealing that circulating histones may significantly contribute to the thrombocytopenia and cytokine storm observed in COVID-19 and classical sepsis [5].

According to the outstanding focus on neutrophil-mediated platelet activation and the crucial interpretation of the novel mechanisms of thrombo-inflammation during infection by Colicchia et al. [1], as well as considering the novel emerging functions of histones as triggers of both hyperinflammation and monocyte and platelet alterations (determined by MDW and PDW), we would reinforce and integrate their conclusions [1], suggesting that the evaluation of MDW (as an index of activated and heterogenous monocyte populations), PDW (as an index of activated, aggregated and/or ballooning/giant platelets), and histone concentrations may provide a possible future tool to timely predict higher risk of worst outcome in patients with classic bacterial and COVID-19 sepsis.

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D.L. and C.D.F. drafted the manuscript. F.M. participated in the discussion and critical editing of the manuscript. All authors read and approved the final paper.

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