**Table I. Proposed mechanisms of histone-mediated cytotoxicity, inflammatory and procoagulant effects**

|  |
| --- |
| **Cytotoxicity*** Membrane disruption causing calcium influx and overload
* Toll-like receptor (mainly TLR 2, 4 and 9) signalling
 |
|  |
| **Inflammatory effects*** NFκB activation
* NLRP inflammasome activation
* Cytokine release
 |
|  |
| **Procoagulant effects*** Vascular endothelial damage
* Enhanced release of ultra-large multimers of von Willebrand factor
* Enhanced tissue factor expression on endothelial cells
* Increased thrombin generation
* Suppression of thrombomodulin-mediated protein C activation
* Enhanced platelet aggregation and disruption
* Enhanced polyphosphate release from platelets
* NETosis
* Increased clot resistance to fibrinolysis
 |