Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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How NETosis could drive "Post-COVID-19 syndrome" among survivors

The extensive world propagation of SARS-CoV-2 with millions of cases of COVID-19 and its high severity and mortality rates is an unprecedented situation. Initially focused on the inhibition of virus replication based on virus- induced pathogenesis, the weak efficiency of antiviral drugs and the predominant hyperinflammatory symptoms is reorienting the pathophysiology through an immunopathogenesis. Acute respiratory distress syndrome associated with lung, heart, liver and kidney damage, thrombosis and disseminated intravascular coagulation, crosstalk for hyperactivation with complement system proteins and platelets, adaptive immune response disorientation and immune-crippling cytokine storm could all be neutrophil-driven during COVID-19 [1–6].

After a grueling stay in resuscitation units, patients recovering from severe forms of COVID-19 experience after few days or weeks of remission, long and painful convalescence. This evolution can be interspersed with residual systemic inflammatory symptoms and sequelaes. COVID-19 survivors suffer from headaches, asthenia, arthromyalgia, tissue lesion sequelaes (lung, heart, and skin) and neuropsychopathologies. Other viral immune-driven diseases share with COVID-19 its features of hyperinflammatory immune response, coagulation disorders, and painful convalescence. In fact, such post-infection remnant inflammation and autoimmune-like relapse with rheumatoid arthritis, arthromyalgia, spondyloarthritis and uveitis has been described for Ebola virus disease [7–9], and to a lesser degree Dengue fever [10,11] and West Nile fever [12,13]. In Wilson HW research, Post-Ebola Syndrome is reported among survivors during the first 1–12 weeks after being discharged from hospitalization. The frequency is estimated at 90 % of Ebola survivors mainly among women (67 %). The detection of auto- antibodies (anti-nuclear antibodies, anti−CCP, rheumatoid factor) in the blood of survivors strongly suggest residual autoreactive participation to inflammation and tissue lesions [14]. More concerning are the observed Post-Ebola sequelaes such as secondary amenorrhea, alopecia, blindness and deafness, which seem to be associated with more permanent immune-driven damages.

Another intriguing similarity is that growing evidence suggests that SARS-CoV-2, like Ebola or Dengue, seems to trigger neutrophil-induced immunopathogenesis. Severe COVID-19 cases develop priming of neutrophils which matches a hyperinflammation state and severity in disease [15] : Analysis of haematologic parameters reveals that important neutrophilia [16,17], high neutrophils to lymphocytes ratio – NLR [15, 17] and Systemic Inflammation index (SII) are correlated with severe expression of COVID-19 and higher rate of mortality during hospitalization [18–20]. NLR and SII are together considered accurate haematologic markers of systemic inflammation. COVID-19 severity is also associated with neutrophil over-expression of Neutrophil Extracellular Traps - NETs [1,6,21,22]. NETs release (NETosis) is a powerful mechanism of microbial destruction whereby neutrophils die and release digestive granules containing neutrophil elastase (NE) and myeloperoxidase (MPO) [23]. The concomitant and inflammatory release of auto-antigens from dying neutrophils is increasingly a hallmark of autoimmune processes. As foreseen, NETosis participates in several tissue-specific and systemic autoimmune diseases [24] : systemic lupus erythemosus, antineutrophil cytoplasmic antibodies (ANCA) Vasculitis (AVV), rheumatoid arthritis, antiphospholipid syndrome, multiple sclerosis…

In fact, NETosis is a singular immune response whereby immune cells, mainly neutrophils, are empowered to expel nuclear and cytoplasmic proteins in tissues and in the blood [23] [24]. Externalized neutrophil granule proteins, namely NE and MPO, are able to protectively lyse pathogens, yet also induce tissue damages. During this process neutrophils on one hand release several hidden auto-antigens as substrates for immunization, drive tissue damage and tissue-specific auto-antigens externalization; and on the other hand release danger-associated molecular patterns (DAMPs) that induce, perpetuate or increase cell damage based inflammation and immune stimulation. The efficient and quick clearance of those immune-unbeknown self--antigens through efferocytosis greatly contributes to maintain the tissue tolerance and/or the limitation of inflammation-related tissue damages [25,24]. This happens when NETosis is excessive and is inefficiently cleared by regular efferocytosis. Infection-induced systemic inflammatory response syndrome (SIRS) is a particular situation giving immune cells the *quitus* to activate and eradicate the pathogens. This license to activation, the bystander activation, is not contained to protective effectors but also to other immune effector cells and even autoreactive B et T cells [26]. Bystander activation then operates to facilitate the activation of autoreactive cells and this ends normally without long-lasting autoimmune disease through resolution of the SIRS, cleaning of tissue damages and NETs, and finally suppressive brake by inducible regulatory cells.

So, if NETosis is confirmed as the leading cause of severe and fatal evolution of COVID-19 as several research teams envision [1,6,21,22] we must be prepared to observe a resurgence of a non- infectious inflammatory illness among convalescents : the" Post−COVID-19 Syndrome". Based on post-Ebola syndrome observations, women should be more at risk to develop this autoimmune-like syndrome [14]. Beyond clinical symptoms follow-up, biomarkers should be identified, monitored and extended to autoimmune marker exploration. The contemporaneous and residual neutrophil-induced inflammation and low-grade systemic inflammation state among convalescents should predict the eventual conversion to Post−COVID-19 Syndrome: hs-CRP, NE and MPO titrations, with sera remnant NETs – [27]. The titration and follow-up of several autoantibodies will strengthen the exploration when symptoms or biological disturbances appear. Anti-nuclear antibodies such as anti-histone, together with anti-neutrophil cytoplasmic antibody –

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ANCA [28], anti-cyclic citrullinated peptide [29], rheumatoid factor [14], and anti-NET antibodies – ANETA [30] are good candidates. Therapies controlling NETosis, NETs clearance and neutrophil recruitment should also be considered for management during a COVID-19 episode and for recovered convalescents [3,31]. Post−COVID-19 Syndrome should be considered as a full clinical entity with epidemiologic, ethical and socio-economic impact requiring official consideration in the COVID-19 treatment and social care strategy.

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