



Commentary

COVID-19 as a STING disorder with delayed over-secretion of interferon-beta

Jean-Marie Berthelot^{a,*}, Frédéric Lioté^b

^a Rheumatology Department, Nantes University Hospital, Hôtel-Dieu, Place Alexis-Ricordeau, 44093, Nantes Cedex 01, France

^b Rheumatology Department & Inserm UMR 1132 (centre Viggo Petersen), Hôpital Lariboisière, 2 rue Ambroise Paré, F-75010 Paris, Université de Paris, UFR de Médecine, F-75010 Paris, France



ARTICLE INFO

Article History:

Received 25 April 2020

Accepted 30 April 2020

Available online xxx

STING (stimulator of interferon (IFN) genes, encoded by *TMEM173*), is mainly a key adaptor molecule that links the sensing of cytosolic DNA, to the production of IFNs and NF κ B, but STING also senses infections by some RNA viruses (Fig. 1).

We believe that there are several arguments to suggest that polymorphisms of the STING pathway could be involved in the pathogenesis of COVID-19.

- (i) Fatal COVID-19 in children and familial cases strongly supports the contribution of genetic defects of the immune response, as already demonstrated for severe pneumonitis induced by other positive RNA viruses. Some of those genetic defects might lower the ability of infected cells to prevent viral invasion but others (or the same) could conversely induce a delayed over-response to self-molecules damaged by the extensive replication of the virus.
- (ii) Bats, the only flying mammals, have an increased capacity to co-exist with viruses, including coronaviruses. The high metabolic demand of flight causes much DNA damage, and the release of self-DNA into the cytoplasm [1]. Consequently, STING activation is dampened, due to the replacement of the highly conserved and functionally important serine residue S358. This STING mutation is associated with a much lower basal expression of IFN- β [1] (Fig. 1).
- (iii) During the first days of SARS-CoV infections several viral papain-like-proteases, contained within the nsp3 and nsp 16 proteins, interact with STING to inhibit its pathway and downstream IFN secretion. So far, similar data are not available for SARS-Cov-2, and there is no evidence yet that some SARS-CoV-2 proteins could later activate STING. However, in a second phase of COVID-19, damaged self-DNA could excessively activate STING, leading

to sudden IFN- β release and a cytokine storm following IRF-3 and NF κ B activation, respectively (Fig. 1). This human self-DNA can include oxidized mitochondrial DNA, like those enriched in neutrophil extracellular traps, since they stimulate type I IFN signalling through a pathway dependent on STING [2]. Neutrophil infiltration in pulmonary capillaries, with acute capillaritis and fibrin deposition, as well as extravasation of neutrophils into the alveolar space, have been observed in autopsy samples from the lung of COVID-19 patients. A feedback loop might ensue since IFN- β enhanced NETosis in other lung infections.

- (iv) Although early or preventive treatment by IFN α or β improved the outcomes of SARS-CoV and MERS-CoV infection in mice and in non-human primates, in humans survival rates in MERS were not increased, possibly because the drugs were given too late, when viral load was already high [3]. At this stage, IFN could have been detrimental by further enhancing the delayed innate immune response. Indeed, the delayed IFN- β response in some murine models of SARS is also associated with excessive influx of pathogenic inflammatory monocytes-macrophages and a much worse prognosis [4]. Similarly, in mice models of MERS, delayed IFN- β treatment failed to effectively inhibit pathogen replication, which was paradoxically increased following interferon injection [4], as also observed in a mice model of lung pseudomonas infection.
- (v) Previous description of a human gain-of-function STING mutation (p.N153S) causing immuno-disturbances and γ -herpes-viruses-induced pulmonary fibrosis in knock-in mice [5], fits with the hypothesis that over-activation of the STING pathway following viral infection can worsen pneumonitis rather than prevent it.
- (vi) The similarities between features of COVID-19 and SAVI (STING-associated vasculopathy with onset in infancy) syndrome [6], would fit with the possibility that delayed STING overstimulation, once self-DNA damage occurs in the infected cells, leads to a deleterious excess of IFN secretion and/or NF- κ B activation, and contributes to the most severe COVID-19 features. SAVI and end-stages of severe COVID-19 indeed share a prominent IFN-response-gene signature in the peripheral blood, and a variable combination of fever, pulmonary inflammation leading to interstitial lung disease, myositis, rashes, lymphopenia, and an inflammatory vasculopathy, sometimes leading to acral necrosis [6]. In SAVI syndrome, STING-induced endothelial-cell dysfunction instigates an inflammatory and vaso-occlusive process, and localizes it to

* Corresponding author.

E-mail address: jeanmarie.berthelot@chu-nantes.fr (J.-M. Berthelot).

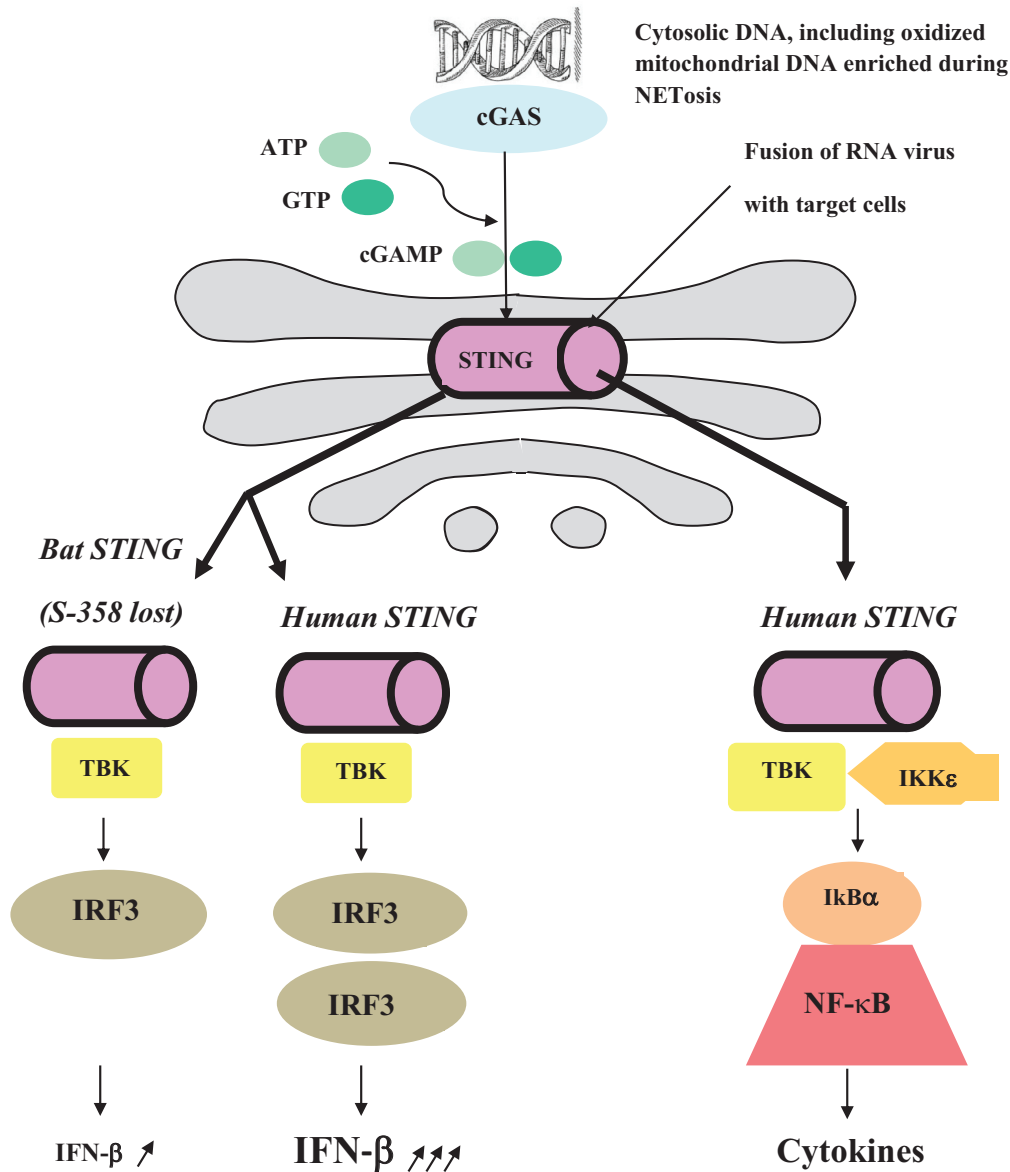


Fig. 1. STING activation in bats and humans. STING is a key adaptor molecule that links the sensing of cytosolic DNA, derived from foreign triggers or from self-DNA, to the production of IFNs and NFκB. However, fusion between RNA viral envelopes and target cells also specifically stimulates a type I IFN response which is dependent on STING, but independent of DNA, RNA and viral capsid. STING, which is part of the complex cGAS/STING, localizes to the endoplasmic reticulum membrane in basal conditions, and is activated by cGAMP. When cGAS (GMP-AMP cyclic synthetase) encounters its cognate PAMPs or DAMPs (mostly viral or bacteria double strand DNA, but also damaged self-DNA not effectively digested/cleared, and some bacterial cyclic dinucleotides) it transforms them in cGAMP. It also elicits translocation of STING toward the endoplasmic reticulum-Golgi intermediate compartment, wherein STING engages TBK1 to eventually activate either IRF3 and/or NF-κB and orchestrate type I IFNs and/or cytokines production, respectively. In bats, STING-dependent IFN-beta activation is dampened due to the replacement of the highly conserved and functionally important serine residue S358 of STING [1].

the vessels [6]. The unusual vasculopathy observed in COVID-19, but not in SARS and MERS, might similarly result from over-activation of STING following infection by SARS-Cov-2 in some hosts with genetic polymorphisms of STING. However, the possible link between COVID-19 and SAVI is not yet substantiated by the demonstration of overexpression of STING in lung and endothelial cells from COVID-19 patients, and mechanisms other than STING activation could also contribute to the combination of interstitial lung disease and inflammatory vasculopathy in COVID-19.

(vii) STING is mostly expressed in humans in three subsets of cells: lung alveolar epithelial cells, endothelial cells, and spleen cells. Interestingly, they are also the most important cells in COVID-19 pathogenesis.

(viii) Last but not least, overload of the STING pathway with ageing and metabolic disorders could also explain why severity of COVID-19 is associated with age, obesity or diabetes. One of the mechanisms of “inflamm-aging” is IFN over-response following activation of the STING pathway (up-regulated in senescent cells in response to either aberrant cytoplasmic chromatin and/or deficient mitochondrial DNA) [7]. Interestingly, STING polymorphisms are associated with increased or decreased risks of ageing-related diseases, and STING p.R293Q protects both from inflamm-aging and obesity-associated cardiovascular disease in advanced age subjects [8]. The-STING pathway also contributes to insulin resistance, and the development of non-alcoholic fatty liver disease. STING is now recognized as a key player in mediating obesity-induced chronic

low-grade inflammation and is stimulated under obesity conditions [9]. Delayed over-activation of the STING pathway might account for the frequency and severity of myocardial infarction in both COVID-19 and aged people.

Assessment of STING polymorphisms might help to detect and protect people with the greatest risks of severe COVID-19. Such assessments should be quickly feasible in research since the human *TMEM173* gene has great heterogeneity and population stratification, and numerous STING polymorphisms have already been described, which differ between East-Asians and Europeans [10].

Moreover, a better understanding of the mechanisms for STING-pathway over-activation, and how it leads to diffuse endothelial-cell dysfunction and vaso-occlusive process, could help and find efficient treatments for COVID-19, either by lowering activation of the STING pathway (pharmaceutical companies have already developed STING targeting immunotherapies) [10], or by antagonizing over-secretion of cytokines like IL-6 or over-expression of STAT1/2, downstream of STING over-activation.

Author Contributions

Jean-Marie Berthelot wrote the first draft of the article, which was extensively corrected by Frédéric Lioté.

Declaration of Competing Interest

None.

Funding source

None.

References

- [1] Xie J, Li Y, Shen X, Goh G, Zhu Y, Cui J, et al. Dampened STING-Dependent Interferon Activation in Bats. *Cell Host Microbe* 2018;23:297–301 e4. doi: [10.1016/j.chom.2018.01.006](https://doi.org/10.1016/j.chom.2018.01.006).
- [2] Lood C, Blanco LP, Purmalek MM, Carmona-Rivera C, De Ravin SS, Smith CK, et al. Neutrophil extracellular traps enriched in oxidized mitochondrial DNA are interferogenic and contribute to lupus-like disease. *Nat Med* 2016;22:146–53.
- [3] Shalhoub S, Farahat F, Al-Jiffri A, Simhairi R, Shamma O, Siddiqi N, et al. IFN-alpha 2a or IFN-beta1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. *J Antimicrob Chemother* 2015;70:2129–32. doi: [10.1093/jac/dkv085](https://doi.org/10.1093/jac/dkv085).
- [4] Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol* 2017;39:529–39. doi: [10.1007/s00281-017-0629-x](https://doi.org/10.1007/s00281-017-0629-x).
- [5] Bennion BG, Ingle H, Ai TL, Miner CA, Platt DJ, Smith AM, et al. A Human Gain-of-Function STING Mutation Causes Immunodeficiency and Gammaherpesvirus-Induced Pulmonary Fibrosis in Mice. *J Virol* 2019;93 pii: e01806-18. doi: [10.1128/JVI.01806-18](https://doi.org/10.1128/JVI.01806-18).
- [6] Liu Y, Jesus AA, Marrero B, Yang D, Ramsay SE, Sanchez GAM, et al. Activated STING in a vascular and pulmonary syndrome. *New Engl J Med* 2014;371:507–18. doi: [10.1056/NEJMoa1312625](https://doi.org/10.1056/NEJMoa1312625).
- [7] West AP, Khoury-Hanold W, Staron M, Tal MC, Pineda CM, Lang SM, et al. Mitochondrial DNA stress primes the antiviral innate immune response. *Nature* 2015;520:553–7. doi: [10.1038/nature14156](https://doi.org/10.1038/nature14156).
- [8] Hamann L, Szved M, Mossakowska M, Chudek J, Puzianowska-Kuznicka M. First evidence for STING SNP R293Q being protective regarding obesity-associated cardiovascular disease in age-advanced subjects - a cohort study. *Immun Ageing* 2020;17:7. doi: [10.1186/s12979-020-00176-y](https://doi.org/10.1186/s12979-020-00176-y).
- [9] Bai J, Liu F. The cGAS-cGAMP-STING Pathway: a Molecular Link Between Immunity and Metabolism. *Diabetes* 2019;68:1099–108. doi: [10.2337/dbi18-0052](https://doi.org/10.2337/dbi18-0052).
- [10] Patel S, Jin L. *TMEM173* variants and potential importance to human biology and disease. *Genes Immun* 2019;20:82–9. doi: [10.1038/s41435-018-0029](https://doi.org/10.1038/s41435-018-0029).