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1 The unexpected role of the STING protein in lipid metabolism.

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5

6 1. STING, a central protein of the immune response associated with cytosolic nucleic 7 acids.

8 The innate immune system is the first line of defence against pathogens. One of the central
9 pathways for pathogen detection is the recognition of their nucleic acid content by intracellular
10 receptors. A large panel of receptors involved in the initiation of the innate immune response has been
11 described [1]. Their interaction with pathological nucleic acids leads to the activation of signalling
12 pathways that induce the production of inflammatory cytokines. This inflammatory response mobilises
13 effector cells of the adaptive immune system and is therefore a crucial step in the initiation,
14 maintenance and clatexoordination of immune responses.

15 Recently, a central pathway for the detection of cytosolic nucleic acids has been described
16 (Figure 1). This pathway was originally identified in immune cells as activated by cytosolic double-
17 stranded DNAs during viral or bacterial infections [2]. This pathway relies on the cyclic GMP-AMP
18 synthase (cGAS) receptor and the Stimulator of Interferon Genes (STING) adaptor protein. The cGAS
19 receptor recognises cytosolic nucleic acids, including double-stranded DNA (dsDNA), single-stranded
20 DNA (ssDNA) or DNA:RNA hybrids [3–5]. Binding of cGAS to cytosolic nucleic acids induces its activation
21 and the synthesis of 2'3'-cGAMP, a cyclic dinucleotide [6]. This secondary messenger interacts with the
22 adaptor protein STING, promoting the assembly of a signalosome in which STING serves as an anchoring
23 site for the various partners required for the induction of the inflammatory response. Those partners
24 notably include the protein TANK binding kinase 1 (TBK1) and the interferon regulatory factor 3 (IRF3)
25 and/or nuclear factor κ B (NF- κ B) transcript factors [7,8]. Activation of the cGAS-STING signalling axis is

26 characterised by the production of type I interferons, besides other pro-inflammatory cytokines and
27 chemokines. Thus, this signalling pathway is particularly critical in the response to pathogens, as the
28 production of type I interferons leads to the establishment of an antiviral state through induction of the
29 expression of interferon response genes.

30 Recent work suggests that cGAS and STING proteins, beyond their canonical function in innate
31 immunity, are also involved in various cellular processes such as the induction and maintenance of
32 senescence or the regulation of cell proliferation [9–11].

33 2. STING in fatty acid metabolism: an unexpected role.

34 In 2022, work performed by the team of Dr Nadine Laguette in Montpellier, revealed a central role
35 of STING in metabolic homeostasis [12](figure 2). Using a mouse model deleted for the STING protein
36 [13], this study showed that STING inhibits the fatty acid desaturase 2 (FADS2) enzyme essential for the
37 desaturation of dietary polyunsaturated fatty acids (PUFAs). Therefore, ablation or agonist-induced
38 degradation of STING led to increased FADS2 activity leading to the accumulation of PUFA derivatives
39 and driving increased thermogenic gene activation, which results in browning of white fat deposits *in*
40 *vivo*. PUFAs were also shown to bind STING and inhibit its activity. Modulation of PUFA production thus
41 regulates STING-dependent antiviral responses while contributing to the resolution of STING-associated
42 inflammation. Finally, this study also revealed that STING agonists can bind and modulate the enzymatic
43 activity of FADS2. Thus, this work demonstrates the existence of a negative regulatory loop between
44 STING and FADS2, opening many questions pertaining to their respective roles in human pathologies
45 presenting with a chronic STING-associated inflammation (Vila, Guha, et al., 2022).

46 Interestingly, alleles of STING not competent for the induction of interferon responses have been
47 documented in human populations. These include the STING HAQ allele that bears 3 amino acid
48 substitutions: R71H-I229A-R292Q [15]. Analysis of STING haplotypes revealed a high prevalence of the
49 HAQ allele in East Asian populations, compared to sub-Saharan African populations while sub-Saharan
50 African populations show a high prevalence of an AQ allele (G230A, R293Q) which is competent for the

51 recognition of cyclic dinucleotides and the induction of interferon responses [16]. The authors propose
52 that these STING alleles (HAQ and AQ) underwent natural selection during migration out of Africa
53 50,000~70,000 years ago. Using mouse models expressing the HAQ or AQ human STING alleles, they
54 showed that AQ mice store less lipid than HAQ mice, while displaying improved fatty acid oxidation.
55 Furthermore, the visceral white adipose tissue of HAQ mice was infiltrated by regulatory T cells and anti-
56 inflammatory macrophages, unlike that of AQ mice. Thus, the HAQ haplotype promotes fat storage,
57 while the AQ haplotype promotes immune tolerance. The study by Vila et al showed that the HAQ allele
58 of STING strongly interacts with FASD2 [12], which is consistent with the description of a prominent role
59 of this allele in fatty acid metabolism [16]. Thus, the study of the evolution of STING haplotypes suggests
60 that the function of STING in modulating fatty acid metabolism may have been critical during human
61 migration out of Africa.

62 In support of this hypothesis, work in *Drosophila* [17] confirmed the conservation of the functional
63 link between STING and fatty acid metabolism. The authors showed that the *Drosophila* STING
64 orthologue interacts with enzymes involved in the biosynthesis of long-chain fatty acids such as acetyl-
65 CoA carboxylase (ACC) and fatty acid synthetase (FASN) within a multiprotein complex. Furthermore,
66 absence of STING in *Drosophila* led to decreased lipid storage and decreased expression of genes related
67 to lipid metabolism. Thus, absence of STING increased sensitivity to food deprivation and oxidative
68 stress in *Drosophila*. These results showing profound lipid metabolism alteration in *Drosophila* support
69 a conserved role for STING in the regulation of lipid metabolism.

70 3. Regulation of lipid metabolism by STING: a link to innate immune regulation?

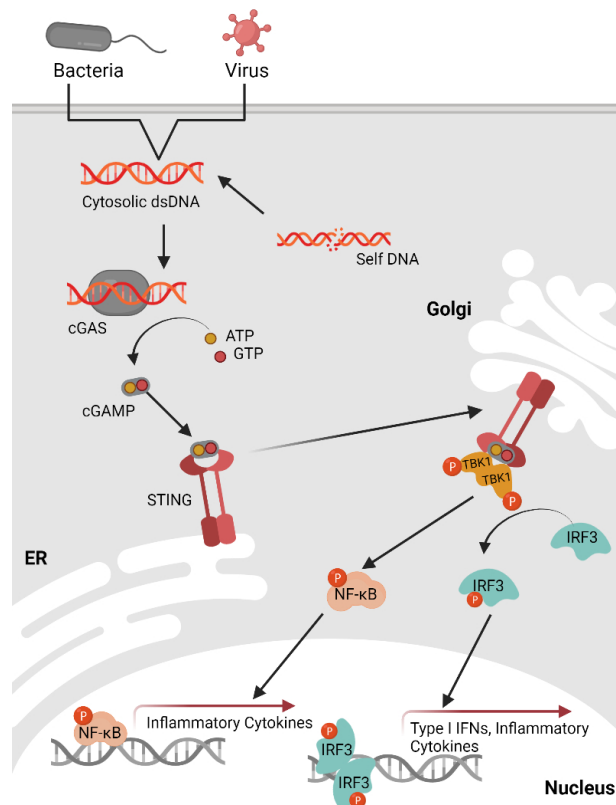
71 Although the role of STING in host defence mechanisms against pathogens is well established, these
72 recent findings on the link between STING and fatty acid metabolism demonstrate that this protein has
73 important functions beyond the detection of cytosolic nucleic acids. Evolutionary analysis of STING
74 suggests that the modulation of lipid metabolism is ancient, conserved and may be the primordial
75 function of STING.

76 Metabolic pathways that interact with STING, such as those leading to the production of PUFAs, are
77 also involved in the control of STING-independent inflammatory responses. Indeed, while PUFAs can
78 directly inhibit STING [12], they can also be processed into lipid mediators (oxylipins) that possess,
79 among others, immunomodulatory properties [18]. Thus, it can be hypothesised that STING alleles
80 expressed in organisms lacking an interferon signalling pathway could participate to the control of
81 inflammatory responses by regulating the generation of these lipid metabolites.

82 Altogether, these recent studies [12,16,17] highlight a tight link between innate immunity and lipid
83 metabolism, paving the way for research into the role of metabolic alterations in human pathologies
84 associated with aberrant STING activation [19]. Those notably include cancer, where a crucial role of a
85 functional cGAS-STING axis has been recently shown to be essential for driving tumour immunogenicity
86 [20,21]. The role of STING-dependent metabolic regulation remains to be investigated in this context.

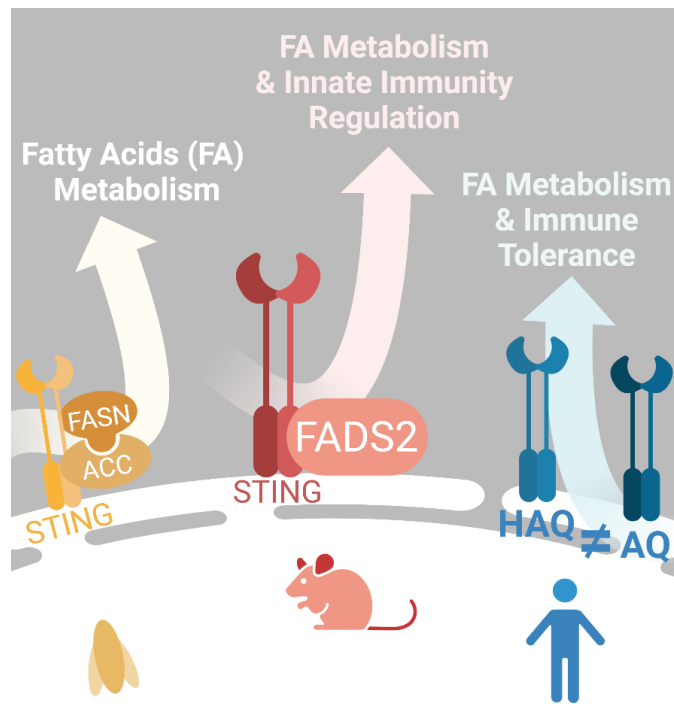
87 Conflicts of interest: Authors have no conflict of interest to declare.

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91 Figure 1: Overview of the cytosolic DNA sensing via the cGAS-STING pathway. dsDNA presence in the
 92 cytosol can result from pathogen infection or self-DNA after cellular stress. GAS binds dsDNA leading to
 93 cGAS activation and synthesis of 2,3'-cGAMP from ATP and GTP. cGAMP binds to ER-resident STING, this
 94 binding will trigger STING translocation to the Golgi apparatus. In the Golgi, STING binds to and activates
 95 TBK1 (by autophosphorylation) as well as the transcription factor NF-κB via IKK. TBK1 then
 96 phosphorylates IRF3 which undergoes dimerization and translocates to the nucleus to induce
 97 transcription of type I IFNs and several inflammatory chemokines. NF-κB induces transcription of
 98 inflammatory cytokines.



99

100 Figure 2: STING plays a role in lipid metabolism. Convergent data in 2022 showed that STING regulates
 101 lipid metabolism. In *Drosophila*, STING form a multi-protein complex with two enzymes involves in long-
 102 chain fatty acid synthesis FASN and ACC. In mouse STING regulates the activity of the lipid desaturase
 103 FADS2 modulating the synthesis of long-chain polyunsaturated fatty acid. The production of those lipid
 104 species will in turn modulate STING activity and narrow its activation in presence of its agonist cGAMP.
 105 In human populations several alleles exist and were already known to be more or less potent in the
 106 induction of IFN response. The study of AQ and HAQ alleles showed that they also differ in lipid
 107 metabolism modulation as HAQ promotes more fat storage than AQ.

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