

## REVIEW

## The role of MDA5 in the development of autoimmune disease

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## Abstract

IFNs protect us against infection from viral pathogens, but can also induce damaging inflammation and are associated with the development of autoimmune conditions. By dissecting the response that is mediated by different IFN-regulated genes, we hoped to identify targets that will enable us to preserve the defense against pathogens while minimizing immune disease. Toward this, several reports have identified that variability in the gene that encodes the melanoma differentiation-associated protein (MDA)-5 and other molecules in this pathway correlated with the risk of autoimmune diseases. The evidence for MDA5 activity as a cause of autoimmune disease is discussed.

## KEYWORDS

antiviral response, IFN, inflammation, interferonopathies, signaling pathways

## 1 | IFN ACTIVITY

IFNs constitute a critical component of our innate antiviral response. Detection of pathogen-associated molecules by innate immune pattern recognition receptors induces production of IFNs that are released from infected cells to bind to their cognate receptors on uninfected cells, to initiate an antiviral response. Of the three designated classes, both type I and III (or IFN- $\lambda$ s) IFNs are critical in the defense against viruses. These two classes of IFN bind separate receptor complexes, but induce an equivalent cellular response. Binding of type I or III IFNs to their respective receptors [constituted by the heterodimeric IFN- $\alpha/\beta$  receptor-1 and -2 (IFNAR1/2) or the IFN- $\lambda$  receptor 1 (IFNLR1) and IL10RB complex] activates the preassociated JAK-1 and tyrosine kinase 2. These kinases phosphorylate the receptors that lead to the recruitment and phosphorylation of the STATs. STAT heterodimers associate with IFN regulatory factor (IRF)-9 in the cytosol to form the IFN-stimulated gene factor (ISGF)-3 transcription factor.<sup>1,2</sup> ISGF3 translocates to the nucleus and interacts with the IFN-stimulated response element within gene promoters to induce more than 2000 genes.<sup>3</sup> The tissue-specific expression patterns of each

receptor governs their biologic consequences, with the epithelium-expressed type III IFNR associated with barrier defense, whereas the broadly expressed type I IFNR acts more globally.<sup>4</sup>

## 2 | IFN SIGNALING ASSOCIATED WITH IMMUNE DISEASE

In addition to this role in protecting against viral infection, IFN signaling is also associated with several immune diseases, including systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, type I diabetes, Graves disease, and psoriasis.<sup>5-11</sup> These diverse diseases share severe inflammation and autoimmunity that have been proposed to be consequences of IFN action, although the mechanism of this action is unknown. Accordingly, it has been proposed that there would be clinical benefit to repressing IFN signaling in these chronic conditions. Inhibitors such as the Ab anifrolumab (AstraZeneca, Gaithersburg, MD, USA), which blocks the type I IFN receptor, and small molecules, such as tofacitinib (National Institutes of Health, Bethesda, MD, USA; and Pfizer, New York, NY), which inhibit JAK-1 to block type I and III IFN signaling pathways, are currently in clinical trials. However, this strategy has risks. Immune regulation by IFNs is complex, and entirely blocking the response could be counterproductive. In some diseases, such as multiple sclerosis, IFN signaling ameliorates the pathologic course.<sup>12</sup> Notably, one of the major checkpoint inhibitors for T cells, programmed cell-death protein (PD)-1, is an IFN-induced gene.<sup>13</sup> Also, as this response is necessary to protect

Abbreviations: ADAR1, RNA-specific adenosine deaminase; CARD, caspase recruitment domain; DHX, DExH-box helicase; FADD, Fas-associated protein with death domain; I $\kappa$ B, inhibitor of  $\kappa$ B; IFIH, IFN induced with helicase C domain; IFNAR, IFN $\alpha/\beta$  receptor; IFNLR, IFN $\lambda$  receptor; IKK, I $\kappa$ B kinase; IL10RB, IL-10 receptor  $\beta$ ; IRF, IFN regulatory factor; ISGF, IFN-stimulated gene factor; LGP, laboratory of genetics and physiology; MAVS, mitochondrial antiviral signaling; MDA, melanoma differentiation-associated gene; PD, programmed cell-death protein; RIG, retinoic acid-inducible gene; RNF, ring finger protein 125; SUMO, small ubiquitin-like modifier; TANK, TRAF family member-associated NF $\kappa$ B activator

against viruses, inhibiting IFN signaling will increase vulnerability to infection. Indeed, individuals with genetic impairment of the IFN signaling pathway are vulnerable to fatal viral infections.<sup>14–17</sup> Accordingly, it would be imprudent to maintain patients on treatments that entirely block the IFN response. This risk could be avoided, or at least reduced, by using a more targeted therapeutic approach that would require a better understanding of the diverse functions of the separate IFN-regulated genes and their individual contributions to the immune response.

Toward this goal, there has been considerable progress in identifying genetic drivers of interferonopathies, a class of heterogeneous conditions that share elevated IFN signaling, severe inflammation, and autoimmunity, which are caused by monoallelic mutations.<sup>18</sup> Genome sequencing studies have identified several causal genes that encode regulators of type I IFN signaling or are effectors of the antiviral response. Two interferonopathies, the Singleton-Merten and Aicardi-Goutières syndromes, have been shown to be the result of gain-of-function mutations in the IFN-induced with helicase C domain 1 (*IFIH1*) gene that encodes the melanoma differentiation-associated gene (MDA)-5 protein.<sup>19,20</sup> Significantly, allelic variation in the *IFIH1* gene locus has also been associated with the risk of developing the autoimmune conditions type I diabetes and systemic lupus erythematosus.<sup>21,22</sup> As MDA5 activity induces IFNs and is itself induced by IFN, this genetic association suggests that the activity of MDA5 promotes the development of autoimmunity.

### 3 | MDA5 ACTIVITY

MDA5 is a cytoplasmic RNA receptor that senses RNA with a helicase domain and subsequently transmits a signal via its homotypic-interacting caspase recruitment domain (CARD).<sup>23</sup> Binding of RNA induces MDA5 to oligomerize, then to induce oligomerization of the adaptor mitochondrial antiviral signaling (MAVS) protein via the proteins' mutual CARDS. Oligomerization of MAVS activates IRF3 and -7, and the NF- $\kappa$ B transcription factors. This induces expression of the antiviral type I and III IFNs with inflammatory cytokines and induces cell death<sup>24</sup> (Fig. 1). The activity of MDA5 is advanced by another helicase, the laboratory of genetics and physiology 2 (LGP2, encoded by the *DHX58* gene).<sup>25</sup> This co-operation does not appear to be necessary for the activity of the related helicase, the retinoic acid-inducible gene (RIG)-I (encoded by the *DDX58* gene), which signals via the same MAVS adaptor and has also been identified as being mutated in patients with interferonopathies.<sup>26</sup>

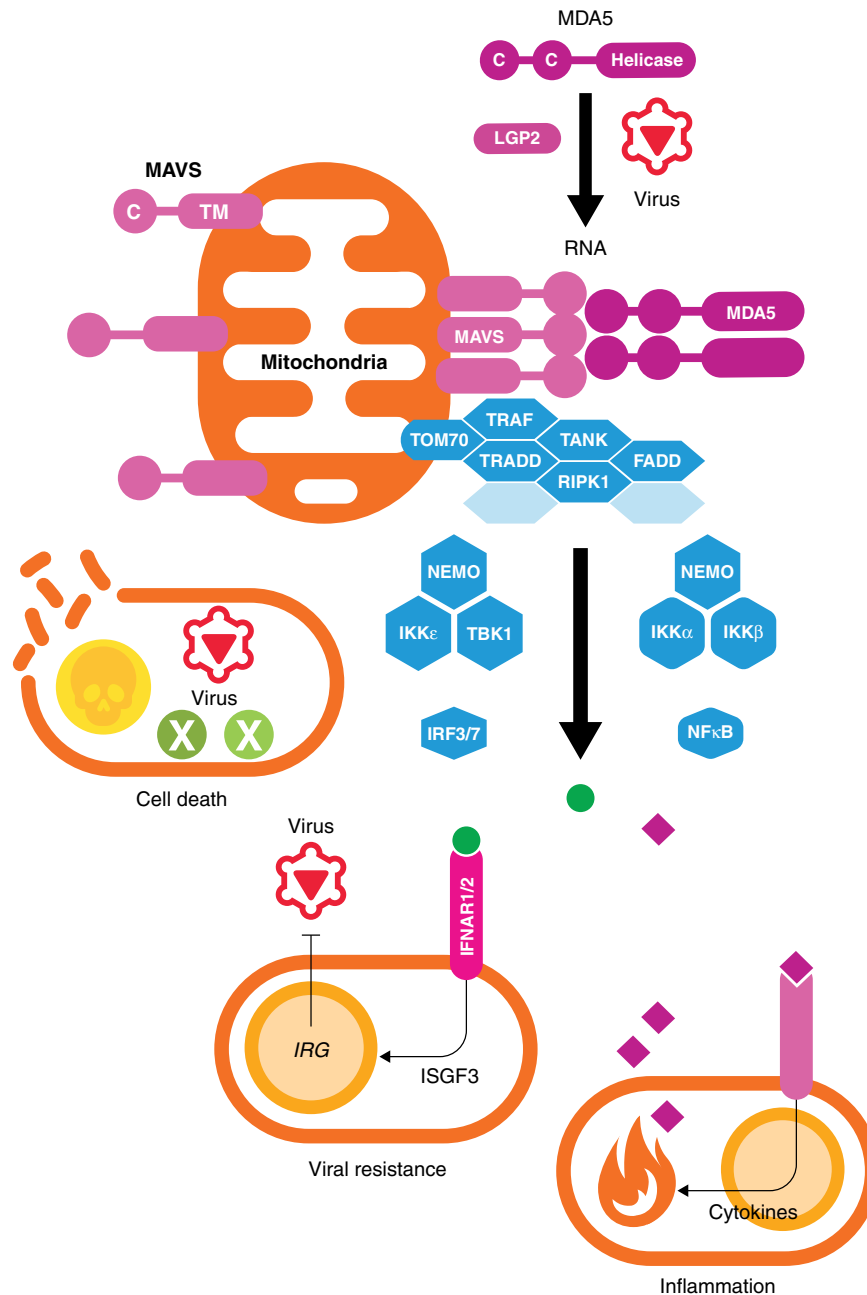
All three helicases, MDA5, LGP2, and RIG-I, have overlapping but distinct affinity for different types of RNA. MDA5 and LGP2 have higher affinity for duplex RNA, whereas RIG-I has greater affinity for single-stranded RNA with a 5' phosphate group. These RNAs are characteristic of viral replicative intermediates. However, these nucleic acids, particularly duplex RNA, are also produced endogenously and so must be tightly regulated to prevent autoactivation of the helicases. Correspondingly, IFN signaling, which induces the expression of MDA5, also induces the RNA-specific adenosine deaminase (ADAR)-

1, which edits endogenous RNAs to prevent auto-activation of MDA5. The functional interdependence of these two gene products is evident by their ability to rescue the fatal consequences of deleting *Adar1* by also ablating *Ifih1* in mice.<sup>27</sup> Loss-of-function mutations in ADAR1 have also been identified as causing Aicardi-Goutières syndrome.<sup>28</sup> The fatality of ADAR1 deficiency also depends on a second IFN-regulated gene, RNase L.<sup>29</sup> RNase L, with its cofactor 2'-5'-oligoadenylate synthase 1, produces RNA that activates MDA5.<sup>30</sup> Notably, gain-of-function mutations in 2'-5'-oligoadenylate synthase-1 have also been identified in patients with type I diabetes.<sup>31</sup> This genetic variance in *IFIH1* and genes that encode regulators of MDA5 in patients with autoimmune disease bolsters the case for a direct role for MDA5 activity in autoimmunity.

The activity of RIG-I and MDA5 is also regulated by various posttranslational modifications. Ubiquitin and ubiquitin-like molecules have been shown to play a decisive role in this pathway. Lysine 63-linked polyubiquitination is essential for MDA5 and RIG-I activity.<sup>32–35</sup> Alternatively, lysine 48-linked ubiquitination of RIG-I, MDA5, and the adaptor MAVS regulates their degradation.<sup>36</sup> As the activity of MDA5 and RIG-I induce IFN production and are themselves induced by IFN signaling, the IFN response must counter the activity of these helicases to prevent escalating inflammation. The balance of this regulation, which first induces then degrades the helicases to limit their activity, is critical in the context of autoimmune conditions that are associated with sustained, high levels of type I IFNs. Consistent with this finding, the ubiquitin ligase that mediates lysine 48 conjugation is the IFN-regulated ring finger protein (RNF)-125. Moreover, RNF125 activity is promoted by the ubiquitin-like, IFN-stimulated gene 15.<sup>37,38</sup> RIG-I and other proteins in this pathway, including the NF- $\kappa$ B and the IRF3 and -7 transcription factors,<sup>39</sup> are modified by the small ubiquitin-like modifier (SUMO).<sup>40</sup> The expression of the SUMO paralogues is also IFN inducible.<sup>41</sup> A loss-of-function mutation in SUMO4 has been associated with increased risk of type I diabetes.<sup>42</sup> In addition, the activity of both helicases is suppressed by phosphorylation.<sup>43–46</sup> Members of the PKC family have been demonstrated to phosphorylate RIG-I.<sup>44</sup> Consistent with coupling of the induction and control of helicase activity, members of this kinase family are activated by IFN signaling.<sup>47–49</sup> This balancing, which first induces then inhibits and degrades these helicases to limit their activity, is most likely critical for the outcome of autoimmune diseases that are associated with sustained, high levels of type I IFNs.

### 4 | MDA5 ACTIVITY IN AUTOIMMUNE CONDITIONS

Although interferonopathies are informative in identifying causal mutations, most autoimmune diseases develop in previously healthy individuals and so are not a consequence of a conspicuous functional mutation. Therefore, the association of *IFIH1* with type I diabetes is revealing.<sup>50</sup> Polymorphisms within the *IFIH1* locus have been shown to correlate with the risk of developing type I diabetes. In this instance, minor alleles in the population were associated with a



**FIGURE 1 MDA5 signaling.** MDA5, in conjunction with LGP2, associates with duplex RNA via the molecule's helicase domain, which promotes the oligomerization of the protein's N-terminal CARDs (C). MDA5 oligomers then complex with the CARD of the adaptor protein MAVS, which is anchored to the mitochondria by its transmembrane domain (TM), inducing oligomerization of MAVS and formation of a signaling complex that includes: mitochondrial translocase of outer membrane 70 (TOM70); TNFR-associated factor (TRAF)-2, -3, and -7; TRAF family member-associated NF $\kappa$ B activator (TANK); TNF receptor type-1-associated DEATH domain (TRADD); receptor-interacting serine/threonine-protein kinase (RIPK)-1; and Fas-associated protein with death domain (FADD). This complex then engages the NF $\kappa$ B essential modulator (NEMO) to activate the I $\kappa$ B kinases (IKK)- $\alpha$  and - $\beta$ , which phosphorylate the inhibitory I $\kappa$ B $\alpha$  to free the NF $\kappa$ B transcription factor or activate the TANK-binding kinase (TBK)-1 and IKK $\epsilon$ , to activate the IRF-3 and -7 transcription factors. This signaling directly promotes cell death in the affected cells and induces antiviral IFNs and inflammatory cytokines that, upon binding of their cognate receptors, elicit an antiviral state more broadly and recruit immune cells to the site of infection

reduced risk of developing type I diabetes relative to the dominant *IFIH1* allele.<sup>51</sup> It was initially found that the separate alleles were expressed at different levels,<sup>52</sup> and subsequent analysis by others and us has demonstrated that the products of the different *IFIH1* alleles vary in their activity, causing reduced autoregulation through IFN signaling.<sup>53</sup> This diminished activity probably accounts for the reduced

frequency of the minor alleles in the population, in the face of selective pressure from infectious viruses, which demands a strong immune response. It also indicates that a more robust MDA5-dependent immune response predisposes toward development of autoimmune disease. This is in keeping with the pathophysiology in type I interferonopathies that are caused by constitutively active mutant MDA5.

Pertinent to the objective of identifying targeted therapies for autoimmune conditions, the preceding discussion raises the question of whether MDA5 activity directly promotes autoimmunity or if it functions indirectly by promoting IFN production. It has been demonstrated that forced expression of type I IFN in murine  $\beta$  cells induced their immune destruction.<sup>54</sup> This finding was corroborated in the nonobese diabetic murine model of type I diabetes.<sup>55</sup> However, it was subsequently shown that ablating IFN signaling did not protect  $\beta$  cells in this model, whereas diminishing *IFIH1* expression was protective.<sup>56,57</sup> These findings suggest that the pathophysiology of the IFN response is related to the activity of MDA5. Accordingly, identifying activators of MDA5 and the ensuing response may also determine drivers of autoreactivity.

## 5 | ENVIRONMENTAL TRIGGERS OF AUTOREACTIVITY

Although there is a genetic component, there is also evidence that environmental factors affect the development of type I diabetes and other autoimmune conditions. Correlations with seasonality and the epidemic nature of outbreaks, as well as associations with specific infectious events, have led to the proposition that viral infection is a trigger for type I diabetes.<sup>23,58,59</sup> In this light, the association of the antiviral MDA5 in autoimmunity identifies a primary immune responder. Our work has shown that activation of MDA5 by a viral agent may be etiological for type I diabetes.<sup>53</sup> An analysis of tissue-specific immune responses in mice to rotavirus, which causes enteric infections that have been associated with type I diabetes, showed that MDA5 is critical for the antiviral response in the pancreas, but not in other tissues.<sup>53</sup> This finding identifies conformity between MDA5 activity and tissue-specific autoimmunity in type I diabetes and corresponds with the pathophysiology associated with excess MDA5 activity in humans, where patients with gain-of-function mutations in MDA5 develop multiorgan autoimmunity.<sup>50,59</sup> It has been shown that increasing MDA5 levels in transgenic mice accelerates the production of class-switched autoantibodies in a lupus-susceptible background.<sup>60</sup> Reducing the expression of MDA5 through heterozygosity equivalently increases the regulatory T cell response compared to effector T cells at sites of autoimmunity.<sup>56</sup> A mechanism by which MDA5 activity may regulate lymphocytes is suggested by a report that its cofactor LGP2 controls peripheral T cell expansion and survival during viral infection.<sup>61</sup> Because LGP2 lacks a CARD, it cannot associate with MAVS, and so its function has been assessed from the perspective of its effect on MDA5 activity. The obverse regulation could link MDA5 with autoimmunity through its control of LGP2-dependent T cell survival.

A variety of mechanisms have been proposed for how viral infection may advance autoimmunity. A leading concept is that establishment of a persistent viral infection leads to ongoing inflammation and immune stimulation that breaks immune tolerance. However, the risk of type I diabetes is associated with increased MDA5 activity, which appears to reduce the likelihood of viral persistence. Also, persistent infection leads to exhausted T cells.<sup>62–67</sup> In fact, exhaustion of cytotoxic T cells

is a likely prerequisite for viral persistence. However, the presence of exhausted T cells in patients with autoimmune diseases correlates with a more favorable prognosis.<sup>68</sup> In addition, mice ablated for the IFN-regulated PD-1, which is important for establishing T cell exhaustion, develop severe spontaneous autoimmune diseases.<sup>69</sup> Although elevated in many autoimmune conditions, IFN signaling has not been shown to recover T cell function in patients with persistent viral infection. Rather, an earlier reduction in viral infection, as expected with higher MDA5 activity, preserves T cell activity.<sup>70</sup> Accordingly, the MDA5-dependent response increases inflammation and cell death and promotes the cell-mediated immune response. Nonetheless, the low incidence of autoimmunity in the population means that the activity of the major MDA5 allele is not sufficient to break self-tolerance.

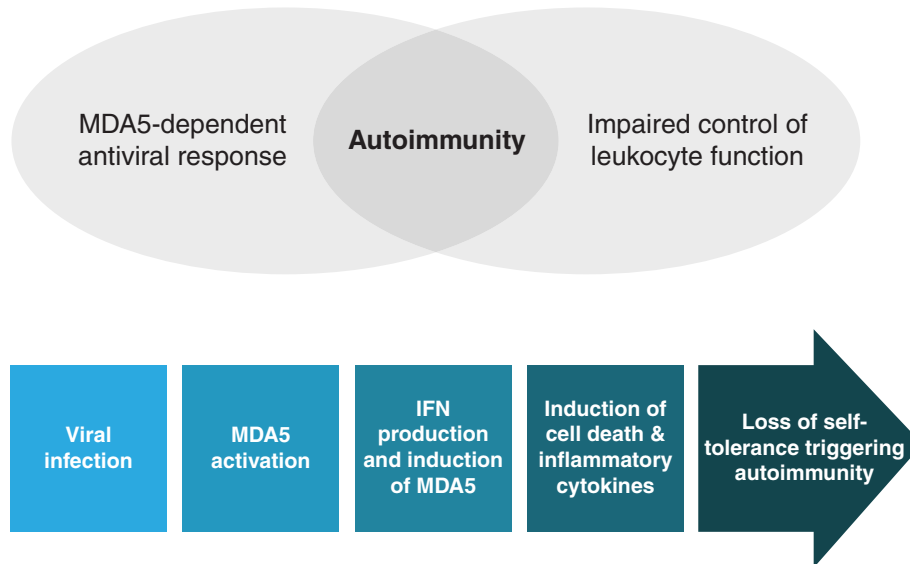
## 6 | AUTOIMMUNITY IS A MULTIFACTORIAL DISORDER

It has been demonstrated that overexpressing MDA5 in mice does not induce autoimmunity, unless combined with genetic backgrounds that have an increased susceptibility for autoimmune disorders.<sup>60</sup> This finding reflects the need for an activating stimulus, such as defective nucleic acid regulation.<sup>28,71</sup> It also points to a failure to down-regulate MDA5 activity and, likely, additional immune dysfunction. Candidate causal genes in type I diabetes, identified by genome-wide association studies, appear to act at both the  $\beta$ -cell and the immune system level. To date, functional changes in 5 candidate causal genes have been distinguished through nonsynonymous polymorphisms within the gene open reading frames. In addition to *IFIH1*, these genes are the protein tyrosine phosphatase and associated tyrosine kinase 2, nonreceptor type 22, cathepsin H, and fucosyltransferase.<sup>72–75</sup> These genes constitute elements of the antimicrobial response, supporting the proposition that the pathophysiology that causes type I diabetes and other autoimmune conditions is instituted by the innate immune response to infection.

Additional nucleotide polymorphisms that correlate with the risk of autoimmune disease have been identified that are less evidently functional, as they occur in genetic loci outside of the protein-coding sequence. In many instances, this variance occurs in genetic loci associated with lymphocyte function. Examples include polymorphisms in the human leukocyte antigen variants *-DQA1*, *-DQB1* and *-DRB1*, *CCR-5*, cytotoxic T-lymphocyte-associated protein 4, hepatic NF-1 $\alpha$ , and IL-2R $\alpha$ .<sup>76–80</sup> Although the gene products are unchanged, this variance may still affect cell function by altering gene expression. It is plausible that abnormal lymphocyte function combines with the immune pathology induced by MDA5 activity to promote the loss of tolerance to self-antigen.

## 7 | CONCLUDING REMARKS

Population studies of the incidence of autoimmune conditions and case studies of patients with interferonopathies have identified



**FIGURE 2** Autoimmunity is a multifactorial disorder that may be initiated by the antiviral response. It is proposed that autoimmunity is a consequence of a robust innate immune response in individuals who have diminished immune homeostasis. Environmental triggers, such as viral infection activate MDA5, which induces the expression of IFNs, further increasing the levels of MDA5 and inducing inflammatory cytokines that disseminate the immune response. Subsequent infections, endogenous stimuli or a failure to arrest MDA5 activity induce cell death, which produces self-antigen that in combination with inflammatory cytokines advances the development of autoreactivity by recruiting and priming the cell-mediated immune response

specific genetic alterations associated with autoimmunity. Heightened MDA5 activity and defects in factors that repress MDA5 function have been identified as equivalent features of several different autoimmune conditions. Findings by us and others have established a functional link between MDA5 activity and conditions that may promote the development of autoimmunity. It is proposed that selective pressure from infectious viruses has prioritized acute antiviral resistance over regulation of immune homeostasis. Because of this, MDA5-induced cell injury is associated with increased risk of developing autoimmunity. The risk is heightened in susceptible individuals who have reduced control of this pathway and their leukocyte function (Fig. 2). Confirmation of this proposition will advance our understanding of the specific mechanisms that cause autoimmunity and may allow us to target the IFN response more precisely for therapeutic intervention in autoimmune diseases or, alternatively, may promote immune therapy.

#### AUTHORSHIP

A.J.S. wrote the paper.

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#### DISCLOSURES

The authors declare no conflicts of interest.

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