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Downregulation of Robust Acute Type I Interferon Responses Distinguishes Nonpathogenic Simian Immunodeficiency Virus (SIV) Infection of Natural Hosts from Pathogenic SIV Infection of Rhesus Macaques▽

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The mechanisms underlying the AIDS resistance of natural hosts for simian immunodeficiency virus (SIV) remain unknown. Recently, it was proposed that natural SIV hosts avoid disease because their plasmacytoid dendritic cells (pDCs) are intrinsically unable to produce alpha interferon (IFN-α) in response to SIV RNA stimulation. However, here we show that (i) acute SIV infections of natural hosts are associated with a rapid and robust type I IFN response *in vivo*, (ii) pDCs are the principal *in vivo* producers of IFN-α/β at peak acute infection in lymphatic tissues, and (iii) natural SIV hosts downregulate these responses in early chronic infection. In contrast, persistently high type I IFN responses are observed during pathogenic SIV infection of rhesus macaques.

A hallmark of pathogenic human immunodeficiency virus (HIV)/simian immunodeficiency virus (SIV) infections is persistent chronic activation of the immune system that is associated with (i) dysfunctions in cellular and humoral immunity, (ii) elevated levels of activation-induced cell death in all lymphocyte subsets, and (iii) failure to effectively control virus replication (reviewed in references 7 and 26). The chronic inflammatory environment in pathogenic HIV/SIV infection disrupts T-cell homeostasis through (i) suppression of regenerative bone marrow functions, (ii) reduction of thymic output, and (iii) structural and functional damage of peripheral lymphoid tissues (12). Indeed, it is now widely accepted that persistent chronic immune activation is a major driving force for $CD4^+$ T-cell depletion and AIDS progression (8, 12).

SIV infection of natural hosts such as sooty mangabeys (SMs), African green monkeys (AGMs), and mandrills is typically nonprogressive even though these "natural" infections share key features with pathogenic HIV infection of humans and SIV infection of rhesus macaques (RMs) including (i) chronic high levels of viremia, (ii) viral tropism for $CD4^+$ T cells, (iii) short half-lives of virus-infected cells, and (iv) severe acute depletion of mucosal $CD4^+$ T cells (10, 11, 22, 25, 28). A striking difference between nonpathogenic SIV infection in natural hosts and pathogenic HIV and SIV infections in humans and RMs, respectively, is the lower levels of immune activation during the chronic phase of infection observed in natural hosts (16, 25). While several groups have documented T-cell proliferation and immune activation during the acute phase of SIV infection in natural hosts (5, 11, 17, 20–22), it has recently been proposed that a key biologically distinguishing feature of SMs (and potentially other natural hosts of SIV) is a host species-specific attenuated innate immune response to infection that includes the lack of plasmacytoid dendritic cell (pDC) activation and type I interferon (IFN) production in response to SIV infection (19). This hypothesis is largely based on *in vitro* experiments, in which isolated peripheral blood pDCs from SMs were reported to show diminished Toll-like receptor (TLR)-7/9-mediated type I IFN responses to SIV RNA compared to pDCs from RMs, and limited *in vivo* studies, including longitudinal flow cytometric comparisons confined to the acute phase of infection, along with cross-sectional gene expression comparisons from a single time point during chronic infection. To further study these questions in a biologically relevant *in vivo* setting, we sought to (i) determine if pDCs in lymphatic tissues of natural hosts produce type I IFN during acute infection and (ii) determine if type I IFN responses are attenuated following SIV infection in SMs compared to RMs. In addition, we extended our analysis to a second widely studied SIV natural host, the African green monkey (AGM) (Table 1). Here we provide direct *in vivo*

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TABLE 1. Characteristics of animals whose data were used in this study

Animal designation	Species	Virus	LN sample(s) (dpi)[a]	Source (reference[s])[b]
AG-2	AGM	SIVagm1	Pre, +7, +14, +28	NIH/LMM (9)
AG-3	AGM	SIVagmVer	Chronic	NIH/LMM (9)
AG-4	AGM	SIVagmVer	Chronic	NIH/LMM (9)
AG-8	AGM	SIVagm1	Pre, +7, +14, +28	NIH/LMM (9)
AG-10	AGM	SIVagmVer	Chronic	NIH/LMM (9)
AG-14	AGM	SIVagm1	Pre, +7, +14, +28	NIH/LMM (9)
AG-17	AGM	SIVagmVer	Chronic	NIH/LMM (9)
AG-19	AGM	SIVagm1	Pre, +7, +14, +28	NIH/LMM (9)
AG-21	AGM	SIVagmVer90	Pre, +7, +14, +28	NIH/LMM (9)
AG-22	AGM	SIVagmVer90	Pre, +7, +14, +28	NIH/LMM (9)
AG-24	AGM	SIVagmVer90	Pre, +7, +14, +28	NIH/LMM (9)
FBn	SM	SIVsmm	Chronic	Yerkes (2)
FBq	SM	SIVsmm	Chronic	Yerkes (2)
FFq	SM	SIVsmm	Chronic	Yerkes (2)
FFs	SM	SIVsmm	Pre, +7, +14, +30	Yerkes (5, 10)
FLh	SM		SIV negative	Yerkes (2)
FOz	SM		SIV negative	Yerkes (2)
FRs	SM	SIVsmm	Pre, +7, +14, +30	Yerkes (5, 10)
FSs	SM	SIVsmm	Pre, +7, +14, +30	Yerkes (5, 10)
FUv	SM	SIVsmm	Pre, +7, +14, +30	Yerkes (5, 10)
FWv	SM	SIVsmm	Pre, +7, +14, +30	Yerkes (5, 10)
FXn	SM	SIVsmm	Chronic	Yerkes (2)
FZr	SM		SIV negative	Yerkes (2)
04D169	RM		SIV negative	NIH/VRC
95084	RM	SIVmac239	Chronic	WNPRC (5, 6)
R268	RM	SIVmacE660	Chronic	UPitt
R437	RM	SIVmacE660	Chronic	UPitt
R443	RM	SIVmac239	Chronic	UPitt
R451	RM	SIVmac239	Chronic	UPitt
R453	RM	SIVmac239	Chronic	UPitt
R455	RM	SIVmac239	Chronic	UPitt
R457	RM	SIVmac239	Chronic	UPitt
R462	RM	SIVmac239	Chronic	UPitt
R472	RM	SIVmac239	Chronic	UPitt
R475	RM	SIVmac239	Chronic	UPitt
RCo8	RM	SIVmac239	Pre, +7, +14, +30	Yerkes (5)
RJi8	RM	SIVmac239	Chronic	Yerkes (5)
RJi9	RM	SIVmac239	Pre, +7, +14, +30, chronic	Yerkes (5)
RKb9	RM	SIVmac239	Pre, +7, +14, +30, chronic	Yerkes (5)
RM340	RM	SIVmac239	Pre, +7, +28	NCI-Frederick (5, 6)
RSq8	RM	SIVmac239	+14	Yerkes (15)
RWf7	RM	SIVmac239	Pre, +14	Yerkes (15)
RWu8	RM	SIVmac239	Chronic	Yerkes (5)

[a] Pre, preinfection.
[b] LMM, Laboratory of Molecular Microbiology; Yerkes, Yerkes National Primate Research Center; VRC, Vaccine Research Center; WNPRC, Wisconsin National Primate Research Center; UPitt, University of Pittsburgh.

evidence that during acute SIV infection RMs, SMs, and AGMs all mount a similarly robust type I IFN response and that a key distinguishing feature between nonpathogenic SIV infection of SMs and AGMs and pathogenic SIVmac infection of RMs is the timely resolution of this vigorous *in vivo* type I IFN response in natural hosts but not RMs, resulting in limited chronic activation of type I IFN-responsive pathways.

As pDCs are the major source of type I interferon (alpha/beta IFN [IFN-α/β]) produced in response to viral infections (18) and as pDCs migrate to inflamed lymphatic tissues (LT) through high-endothelium venules during viral and bacterial infections (3, 29), we studied pDC localization and IFN-α/β expression in peripheral lymph nodes (LN) early after SIV infection in RMs, SMs, and AGMs, analyzing IFN-α/β at the protein level by immunohistochemistry on lymphatic tissue sections. Although the limited availability of tissues from our sooty mangabey cohort limited our ability to perform detailed kinetic assessments of type I IFNs, each nonhuman primate species clearly showed an upregulation of IFN-α/β at 14 days postinfection (dpi) of the acute phase of infection with cells showing distinctively plasmacytoid morphology (putative pDCs) being the principal cell population producing these type I IFN proteins (Fig. 1A). Furthermore, type I IFN-α production colocalized with expression of the pDC marker CD123 (Fig. 1B). Although these data demonstrate that, at a time point around peak viral replication during the acute stage of SIV infection, pDCs of all three species are fully capable of producing type I IFNs, these data do not rule out the potential important contribution of other cell types as a source of type I IFNs in SIV infection.

Despite the clear demonstration of IFN expression by pDCs at the protein level following SIV infection in RMs, SMs, and

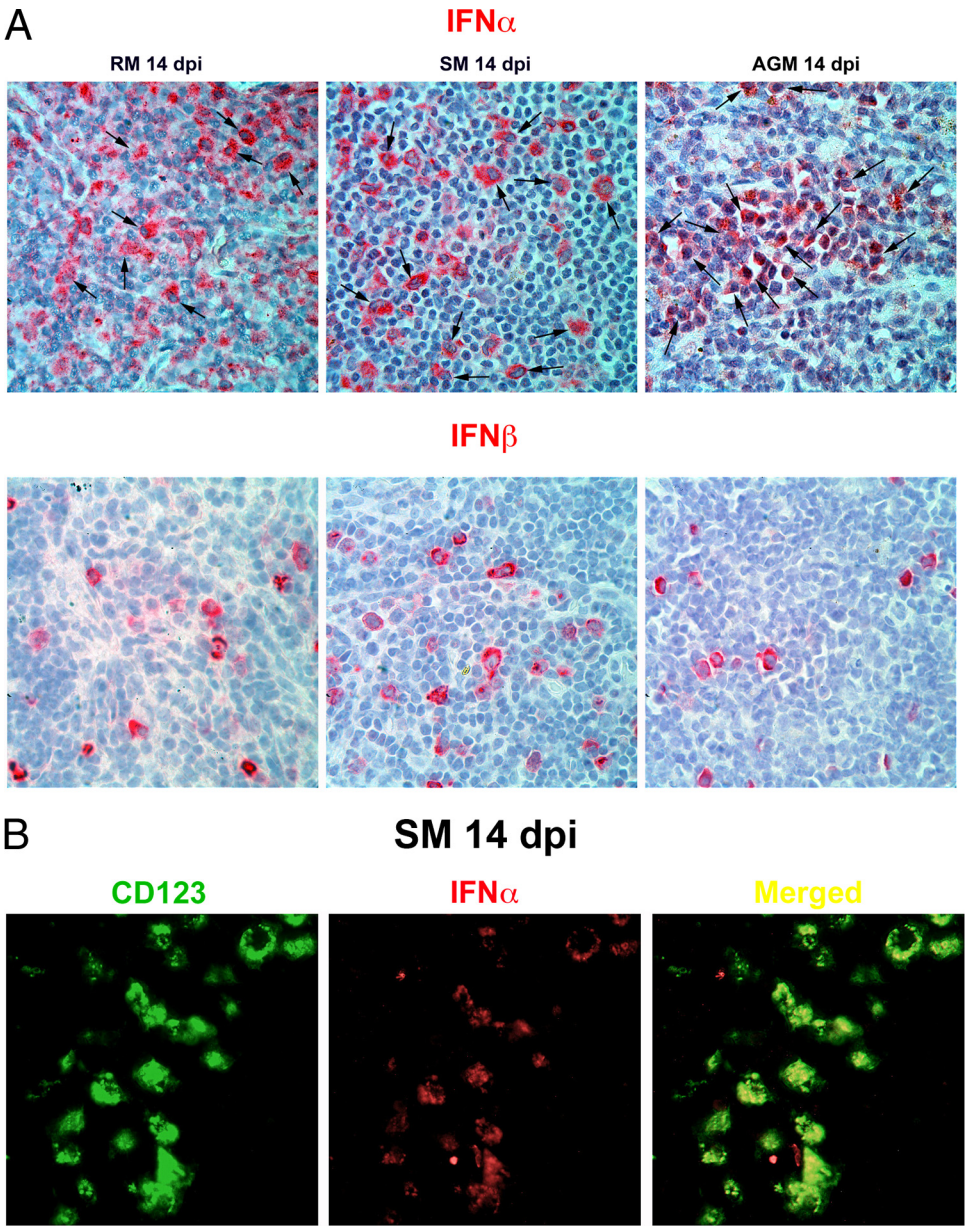

FIG. 1. *In vivo* IFN-α/β protein expression in pDCs during acute SIV infection of RMs, SMs, and AGMs. (A) Immunohistochemical staining (1,000×) of IFN-α (top panels) and IFN-β (bottom panels) in lymph node sections from animals 14 dpi. Arrows identify examples of IFN-α expression in cells with a clear plasmacytoid morphology, putative pDCs. Tissues were stained with antibodies to IFN-α (clones MMHA-2 and MMHA-3) or IFN-β (MMHB-16) (all from PBL InterferonSource) using the biotin-free MACH-3 polymer-ALP system (Biocare Medical), developed with Vulcan Fast Red (Biocare Medical) and counterstained with hematoxylin. (B) Immunofluorescent staining (400×) shows that $CD123^+$ pDCs (green) in SMs at 14 dpi do in fact express IFN-α protein (red), as the merged images clearly demonstrate colocalization (yellow).

AGMs, the presence of numerous variants of type I interferons and possible species-specific differences in immunoreactivity with available reagents rendered interpretation of quantitative analysis of type I interferon protein by immunohistochemistry potentially problematic. However, the biological activity of type I interferons can be assessed by measuring IFN-stimulated genes (ISGs), an approach which has been reported to be a more sensitive measure of type I IFN induction *in vivo* than either IFN mRNA or protein levels (23). Therefore, we focused our efforts and available tissues to study the kinetics and magnitude of interferon-dependent responses in lymph nodes by measuring two highly specific IFN-α/β-inducible effector molecules, myxovirus resistance protein A (MxA or Mx1) and interferon-stimulated gene 15 (ISG15), proteins with highly conserved sequences across species which showed excellent, consistent reactivity in preliminary experiments using our immunohistochemistry methods (4, 13, 24, 27) (Fig. 2A). Of note, to compare IFN-specific responses by SIV-infected SMs and RMs and HIV-infected humans in their study, Mandl et al. measured expression of mRNA for Mx1 (and other markers) in peripheral blood mononuclear cells (PBMC) by quantitative real-time reverse transcription-PCR (RT-PCR), but only at a

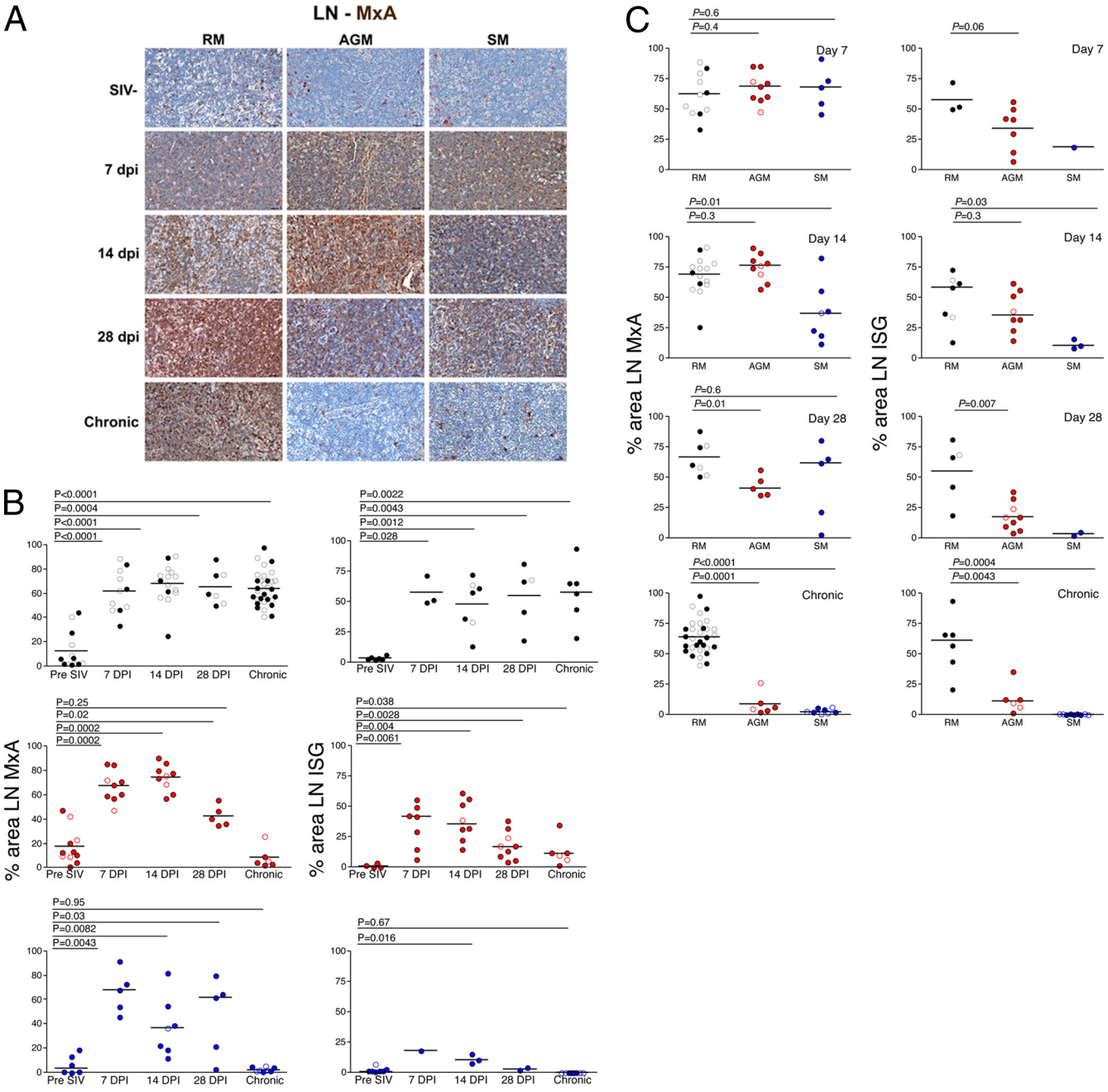

FIG. 2. Rapid and robust LN type I IFN responses in SIV-infected RMs, SMs, and AGMs that are promptly resolved in SMs and AGMs but not RMs. (A) Representative high-magnification (400×) images from the T-cell zone immunohistochemically stained for MxA, a specific type I IFN-responsive gene in RMs, AGMs, and SMs prior to and during the acute and chronic stage of SIV infection. (B and C) Quantitative image analysis of high-resolution whole-lymph-node scans immunohistochemically stained for MxA (left panels) and ISG15 (right panels) from SIV-infected RMs (black symbols), SMs (blue symbols), and AGMs (red symbols). Archived tissue sections were from three previous acute infection studies, in which we had collected lymph node biopsy specimens that spanned from preinfection time points through 30 days postinfection and into the chronic stage longitudinally (Table 1) (5, 9, 11, 15). In addition, we used cross-sectional tissue samples collected at various times during the chronic stage and from SIV-negative animals to add to our original data set (Table 1). Quantitative image analysis was performed on immunohistochemically stained, high-resolution whole-lymph-node tissue scans obtained from an Aperio ScanScope CS (Aperio Technologies, Inc.) to measure the protein expression levels of both MxA (anti-MxA antibody M143 generously provided by Georg Kochs, Universitätsklinikum Freiburg) and ISG15 (Sigma Prestige antibodies powered by Atlas antibodies) and shown kinetically for each nonhuman primate species (B) or at each time point showing comparative expression levels for all the species (C). Each circle represents a quantified lymph node section. For some animals there were multiple lymph nodes collected and measured and these are thus represented as separate independent data points. Additional lymph nodes from individual animals are indicated by unfilled plot symbols. Mann-Whitney nonparametric U tests were performed using Prism 4.0 software (Prism, San Diego, CA) with resulting *P* values shown.

single time point in chronic infection (19). Using quantitative image analysis tools to measure the protein expression levels for both MxA and ISG15 in high-resolution whole-lymph-node Aperio tissue scans, we found vigorous type I IFN responses to SIV infection during the acute stage of infection with similar kinetics and peaks in RMs and in SMs and AGMs, with these IFN-α/β-inducible responses mirroring viral replication patterns (Fig. 2B and C) (references 9 and 11 and data not shown).

Importantly, at 7 dpi all nonhuman primate species showed equivalent levels of MxA responses (Fig. 2C). It is not entirely clear why SMs showed statistically lower expression of MxA at 14 dpi and similar levels at 28 dpi compared to those in RMs; however, this may be due to the low numbers of animals that were available for this study. Furthermore, these data show that AGMs begin to downregulate MxA responses by 28 dpi, whereas only two SMs had attenuated this response at this time point (Fig. 2C). However, by the chronic stage of infection (ranging from 4 to 16 months postinfection) both AGMs and SMs showed completely attenuated type I IFN MxA responses, in stark contrast to RMs, which maintained high levels of MxA at all time points (Fig. 2). The striking difference between nonpathogenic SIV infection of SMs and AGMs and pathogenic infection of RMs, and likely human HIV infection, was not a relative or absolute inability of natural hosts to mount a type I IFN response or a functional block of pDC production of IFN-α/β proteins in response to SIV *in vivo* (Fig. 1 and 2), but the relatively rapid downregulation of these responses during the transition to chronic infection, despite ongoing viral replication (Fig. 2). Given the quantifiably lower ISG15 protein expression levels during acute infection in AGMs and SMs, in contrast to MxA (Fig. 2C), it is still possible that natural hosts respond in a qualitatively distinct way to type I IFNs produced rapidly following SIV infection compared to RMs, or alternatively resident lymph node cell populations have divergent sensitivities to type I IFNs. However, the presented data are fully consistent with the observation of a strong upregulation of type I interferon-stimulated genes (ISGs) during acute SIV infection of AGMs and SMs as measured by microarray analysis (1, 14, 17).

Together, these data unequivocally demonstrate that SMs and AGMs mount robust type I IFN responses to acute SIV infection and have functional IFN-α/β-producing pDCs *in vivo*. However, in contrast to pathogenic infection of RMs, SIV-infected SMs and AGMs resolve these innate immune responses in the transition to chronic infection. While these data do not address whether or not the observed robust type I IFN response and upregulation of ISGs in SMs and AGMs occur via a TLR-7/9-dependent or -independent mechanism, we conclude that a muted IFN-α response by pDCs is neither a feature of nor a requirement for nonpathogenic SIV infection in SMs or AGMs.

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