Minireview

RecQ helicases: at the heart of genetic stability

Jennifer A. Cobb, Lotte Bjergbaek, Susan M. Gasser*

University of Geneva, Department of Molecular Biology, Quai Ernest-Ansermet 30, CH-1211 Geneva, Switzerland

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Abstract The checkpoint-mediated control of DNA replication is essential for maintaining the stability of the genome and preventing cancer in humans. The RecQ family of helicases has been shown to be important for the maintenance of genomic integrity in organisms ranging from bacteria to man. We propose that the RecQ homologue, Sgs1p, has an important function in the S-phase checkpoint response of budding yeast, where it may be both a 'sensor' for damage during replication and a 'resolvase' for structures that arise at paused forks. RecQ helicases may serve a unique function that integrates checkpoint proteins with the recombination and replication fork machinery.

Key words: Sgs1p; Checkpoints; DNA replication; DNA polymerase stability; RecQ helicases

1. Introduction

RecQ DNA helicases have been shown to be important for genome maintenance. The family of homologues includes the *Saccharomyces cerevisiae* gene *SGS1* [1,2] and at least five human genes, of which three are implicated in heritable diseases: *BLM* is mutated in Bloom's syndrome (BS, [3]), *WRN* is mutated in Werner's syndrome (WS; [4]), and *RECQL4* is mutated in Rothmund–Thomson syndrome (RTS; [5,6]. Although the human disorders associated with mutations in different RecQ helicase genes have distinct symptoms, a predisposition to cancer is common to all three. In yeast, *sgs1*-deficient cells exhibit several phenotypes similar to those described for cultured cells derived from BS or WS patients, including an increase in DNA recombination, enhanced chromosome missegregation, and a shortened life-span (meaning a reduction in the maximal number of cell divisions possible) [7,8]. Moreover, the expression of either the *BLM* or *WRN* cDNA in a yeast strain lacking Sgs1p suppresses certain of the mutant phenotypes in yeast [9], consistent with the notion that the RecQ helicase family has a conserved function necessary for the maintenance of genomic integrity.

All RecQ homologues tested to date unwind paired DNA, translocating in a 3′ to 5′ direction [10]. In addition, several have been shown to have a preference for forked or four-way DNA structures (e.g. Holliday junctions; [11]) or for G-quartet DNA [12]. Although this suggests that the helicases may function in recombination events, Sgs1p is clearly redundant with other helicases that serve to resolve reciprocal exchanges [13]. It has recently been shown that, in the absence of a proper checkpoint response, Holliday junction-like structures can also form at stalled replication forks [14]. Below we review data that place Sgs1p at the replication fork, where it may help to resolve aberrantly paired structures that form when replication fork progression is impaired [14,15]. The absence of this rescue pathway could account for the high rate of genomic rearrangements that is observed in cells lacking Sgs1p. In addition, genetic data argue that Sgs1p acts upstream of the crucial kinase activation step that activates the intra-S-phase checkpoint response [16].

2. S-phase checkpoints

DNA is replicated during the S-phase of the cell cycle, a time at which the genome is particularly vulnerable to mutagenic insult. To ensure an accurate duplication of the genome, eukaryotic cells have developed a surveillance and response network called the 'intra-S-phase checkpoint' [17]. When a sufficient amount of DNA damage accumulates, a signal-transducing pathway is activated, resulting in the phosphorylation of a range of proteins that either stabilise the replication fork, promote repair, or slow cell cycle progression.

Genetic analysis of several DNA damage checkpoint pathways has allowed classification of its components into 'sensors', which detect different sorts of damage, 'adaptors', which integrate and transmit the signal, and the 'effector kinases', which promote downstream functions [18] (see Fig. 1). Two aspects of this cascade appear to be unique to the intra-S-phase checkpoint. First, the level of signal required to activate the effector kinase is quite high; in other words, there is a 'damage threshold' for checkpoint activation in S-phase [19]. Secondly, enzymes directly involved in DNA replication (i.e. DNA polymerase ε, RFC, Dpb11p) are implicated in either the damage detection or signal generating step of the checkpoint response (reviewed in [20]). Recent data link RecQ helicases to components of the checkpoint pathway, and show that they may work together to stabilise polymerases at the fork and to promote repair of stalled or broken replication forks during DNA replication [16,21].

3. RecQ helicases and DNA replication

DNA replication does not proceed normally in the absence of RecQ helicases. Consistent with the high levels of BLM

*Corresponding author. Fax: (41)-22-702 6868.
E-mail address: susan.gasser@molbio.unige.ch (S.M. Gasser).

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helicase detected in S-phase, cultured cells lacking BLM have minor defects in DNA synthesis. Specifically, cells from BS patients have an abnormal profile of DNA replication intermediates [22], and retarded DNA-chain growth [23]. Furthermore, a second human homologue, the WRN helicase, has been shown to bind replication protein A [24], to co-fractionate on sucrose gradients with other replication proteins, and to co-precipitate with PCNA, a processivity factor for DNA polymerase δ [25].

Immunofluorescence studies show that in S-phase nuclei, the yeast Sgs1p helicase is present in numerous foci that coincide to a significant degree with sites of de novo DNA synthesis and with ORC, a six-protein complex essential for initiation of DNA replication [16]. These immunolocalisation data are supported by Chromatin immunoprecipitation (ChIP) experiments that detect Sgs1p at an early-firing origin, ARS305, at the beginning of S-phase (J.A. Cobb, unpublished results). Not only is Sgs1p located at the replication fork, but its abundance is cell-cycle regulated, and both *SGS1* transcript [26] and protein [16] levels peak in S-phase. Thus, Sgs1p is properly positioned to function at the replication fork. Surprisingly, in *sgs1*-deficient yeast cells, it appears that replication forks progress faster than in wild-type cells, rather than moving more slowly, possibly due to a lack of coordination between leading and lagging strand polymerases (J.A. Cobb et al., submitted, and Pasero, P., personal communication). This is also true when monitoring replication intermediates in the presence of hydroxyurea: *sgs1* cells again show an increased rate of fork movement (J.A. Cobb et al., submitted). This contrasts with fork behaviour in *rad53* cells exposed to HU, which collapse into a terminal structure that is unable to recover or re-initiate DNA synthesis after drug treatment [15].

4. 'Sensors' and S-phase damage signals

Members of the DNA-dependent protein kinase-like family (DNA-PK), which includes human ATM and ATR and *S. cerevisiae* Mec1p, have been defined as 'sensors' for checkpoint activation and as signalling kinases that activate the effector kinases Rad53p (hCHK2) and Chk1p (hCHK1, Fig. 1). Kinase activation is, indeed, the central regulatory event of the checkpoint transduction pathway [18,20]. Identification of the primary signal(s) that activate the kinase response is primordial to understanding the checkpoint response.

Although types of primary damage lead to checkpoint activation, it is still unclear whether the cell is able to recognise distinct DNA lesions, or if the primary damage generates a subset of common structures, which are in turn signals for checkpoint activation. A large variety of specialised sensors would be required if primary damage were responsible for Mec1p activation, while the cell might use a more limited number of factors if the signal were based on common generated structures. For example, the processing of primary damage could produce common intermediates such as DNA breaks, extended regions of ss DNA, or unique fold-back structures. Indeed, it has been proposed that ss DNA coated by replication protein A (RPA, the eukaryotic ss DNA-binding protein), which is generated during various repair processes such as non-homologous end-joining, nucleotide excision repair, base excision repair, and homologous recombination, could itself be a signal for the checkpoint response (for review [27]).

During the intra-S-phase checkpoint response, specific enzymes of the replication machinery, *RFC5* [28], *POL2* [29] and *DPB11* [30–32], appear also to be involved in checkpoint activation as sensors of DNA replication fork progression [18]. Dpb11p interacts with DNA pol ε and is required both for replication and for full arrest in response to HU [30–33]. Rfc5p is a subunit of replication factor C that binds to gapped DNA and recruits proliferating cell nuclear antigen (PCNA), which in turn recruits DNA pol δ and pol ε. Rfc1p is also required for Rad53 phosphorylation, and probably acts early on in the DNA damage recognition response process [28]. DNA pol ε is essential for viability and normal chromosomal DNA replication, yet deletion studies have shown that its N-terminal catalytic domain is not needed for these functions. The C terminus, on the other hand, which is important for a proper checkpoint response, is indispensable [29]. Thus, while DNA pol δ and ε may serve redundant roles as the leading strand polymerase, it appears that DNA pol ε alone can act as a sensor for DNA damage at the fork. It is not clear, however, exactly what these enzymes detect nor how they transmit signals to the checkpoint kinases.

Genetic data from yeast also implicate Sgs1p as a 'sensor' protein involved in signalling the S-phase checkpoint response [16,21]. In budding yeast, *sgs1*-deficient yeast cells show hypersensitivity to hydroxyurea and to DNA damage by MMS, uniquely in S-phase. Sgs1p functions in the same epistasis group as DNA pol ε (*POL2* [16,29]) to activate Rad53p in the presence of hydroxyurea, and this signalling pathway acts in parallel to that of Rad17p and Rad24p, which respond primarily to ss or ds breaks [16,21]. Cells must lose both Sgs1p and Rad24p to fully compromise Rad53p phosphorylation on HU, and allow uncontrolled progression of S-phase.

We propose that Sgs1p is involved in the creation of the signal for checkpoint activation, perhaps by resolving aberrantly paired double helices, to generate or maintain ss DNA for RPA binding. During normal replication fork progression the lagging strand has regions of ss DNA of roughly 100 nt that are normally coated by RPA [14]. Recent electron microscopic analyses shows that a stalled replication fork in yeast accumulates roughly 100 nt of additional ss DNA when a *rad53* mutant is exposed to hydroxyurea [14]. If the extended ss stretch also occurs in wild-type cells, then it is possible that the additional RPA/ss DNA complex itself acts in a dose-dependent manner to override the S-phase threshold of tolerance and activate Rad53p. In this respect, RecQ helicases could be involved in the resolution of fold-back or 'chickenfoot' structures that form due to the regression of stalled replication forks, to produce ss DNA for RPA binding. This would implicate Sgs1p directly in the generation of the checkpoint activating signal. Further support for this model is based on the observation that Sgs1p, like the WRN helicase, interacts with the large subunit of the RPA (J.A. Cobb, unpublished results). Alternatively, the aberrant DNA structures that form at stalled or broken forks may themselves be recognised by Sgs1p and the complex may activate the checkpoint pathway.

5. 'Effector kinases' and downstream targets

In the signal-transducing pathway 'effector kinases' are downstream of 'sensors' and 'adaptors' (see Fig. 1), acting on the targets of the checkpoint response [18]. In *S. cerevisiae*,

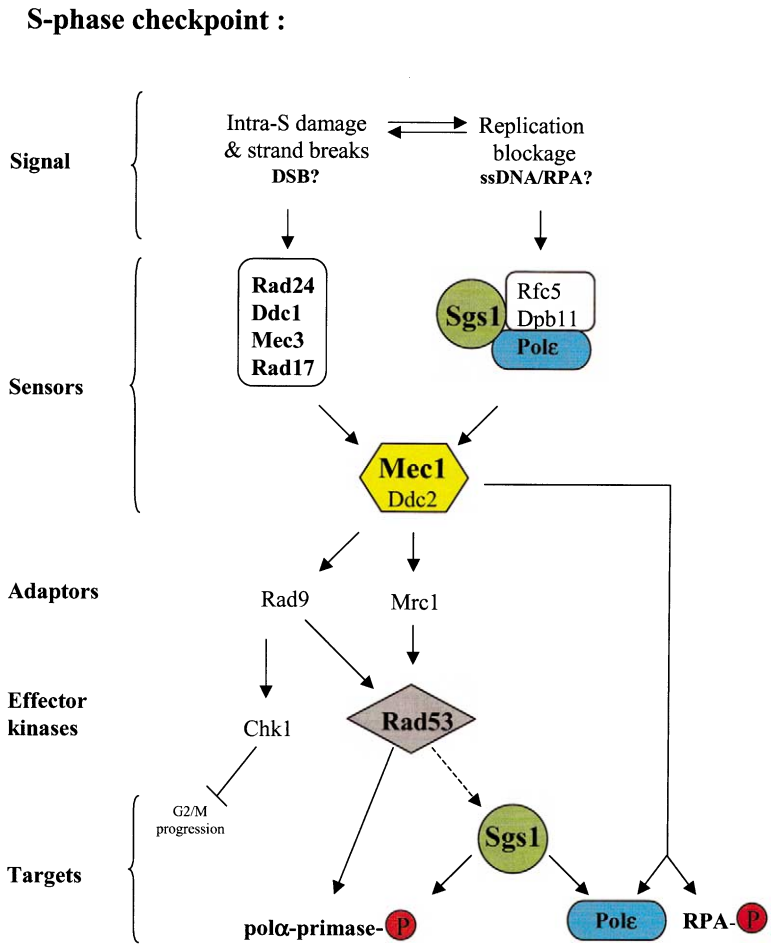

Fig. 1. S-phase checkpoint response pathway in *S. cerevisiae*. A checkpoint signal during replication is transmitted through a kinase network resulting in the suppression of cell cycle progression, down regulation of late-firing origins, and the arrest of replication polymerases until DNA damage can be repaired. Sgs1p is a RecQ helicase which plays an integral role in the intra-S-phase checkpoint. It functions as a sensor in the same epistasis group as DNA pol ε, and is required for the full activation of Rad53, particularly in cells lacking the Rad24p pathway of activation. Sgs1p helps ensure the functional integrity of the DNA pol α–primase complex and DNA pol ε during the checkpoint response.

Mec1p activates the effector kinase Rad53p by phosphorylation in response to a replication block [34,35]. One important outcome of Rad53p activation is the suppression of initiation from late-firing origins [36].

Rad53p is also involved in the stabilisation of replication forks in the presence of damage [15,37]. Cells treated with HU allow initiation from early-firing origins of replication, while late origins are repressed by the intra-S-phase checkpoint. When the block is removed, replication is allowed to continue from forks stabilised near early origins, rather than having to reassemble the replication machinery and re-initiate. Mutants lacking *mec1* or *rad53*, on the other hand, experience replication fork catastrophe or collapse [15,37]. Thus the checkpoint response maintains the integrity of a stalled fork at least in part by preventing replisome disruption. A recent study by Sogo et al. [14] further supports this hypothesis by showing that *rad53* cells treated with HU accumulate extensive single-stranded gaps, hemi-replicated intermediates, and Holliday junctions formed presumably through fork reversal.

It is not clear how the activation of Rad53p kinase stabilises a stalled fork, yet it appears likely that the replication machinery itself is a target of checkpoint kinases. Indeed, RPA is modified by Mec1p [38], and the DNA pol α–primase complex is a target of Rad53p [39]. The Rad53p-dependent phosphorylation of pol α–primase negatively regulates its activity, preventing priming downstream of chromosomal lesions and slowing replication to provide sufficient time for repair. Consistently, ChIP experiments show that Sgs1p is crucial for pol α–primase stabilisation at a stalled replication fork once the checkpoint has been activated (J.A. Cobb et al., submitted). This may be achieved through a direct interaction of Sgs1p with RPA, or perhaps by resolving 'chickenfoot' structures to produce ss DNA for RPA/pol α binding. A third possibility is that Sgs1p simply helps recruit Rad53p to the stalled fork to modify the replication machinery. In support of this model, immunostaining studies show a significant co-localisation of Sgs1p and Rad53p at sites of DNA replication [16], and preliminary studies indicate that Sgs1p interacts in vitro and in two-hybrid assays with the FHA domains of Rad53p (C. Frei et al., unpublished results).

In cells lacking Mec1p, DNA pol ε becomes completely dissociated from the stalled replication fork during HU treatment, whereas in the absence of *sgs1* DNA pol ε is not completely lost from the fork but is detected downstream of the stalled DNA pol α (J.A. Cobb et al., submitted). This suggests that the rate of pol ε progression is faster than in wild-type cells on HU, perhaps due to a lack of coordination of DNA pol ε and pol α during the checkpoint response. Because the

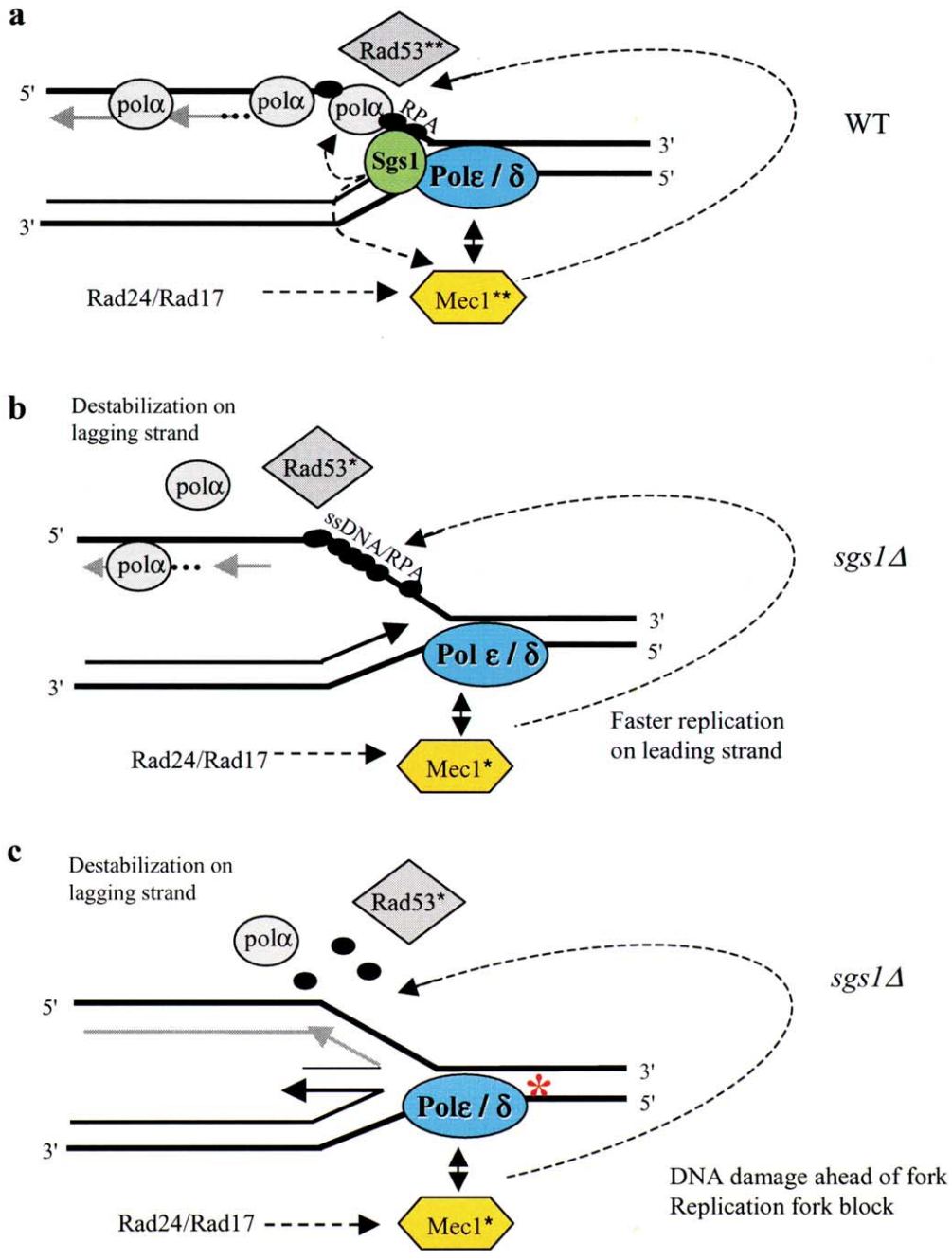

Fig. 2. A model for Sgs1p at a replication fork. A: In wild-type cells Sgs1p is present at a replication fork and will function to reverse hairpin structures or possibly 'chickenfoot' structures that arise when polymerases stall for extended periods of time, to maintain the ss DNA that binds RPA and DNA pol α. During replication fork stalling the stabilisation of polymerases is also strongly dependent on the activation of Rad53p kinase by the ATR homologue Mec1p. We propose that Sgs1p can stabilise the DNA pol α–primase complex on ssDNA so that it is recognised as a substrate for Rad53p and/or that Sgs1p may help recruit Rad53p to the fork. Mec1p and/or Sgs1p may also directly act to keep DNA pol ε from advancing along the leading strand. B: In *sgs1Δ* cells DNA pol α is destabilised at the fork and DNA pol ε moves faster, events that are likely to result in the accumulation of atypical ssDNA gaps and potential double-stranded breaks. These situations are highly recombinogenic, which is one of the hallmarks of an *sgs1* deletion strain. C: If there is DNA damage ahead of the fork or if a destabilised replication fork stalls for long periods of time, the leading and lagging strand may pair, accumulating Holliday junction-like structures through fork reversal. This phenotype is observed in *rad53* cells [14]. Sgs1p could also function as a branch migration enzyme downstream of Rad53p, to reverse these structures.

stabilisation of DNA pol ε may be a direct result of phosphorylation by the activated checkpoint kinases, the faster rate observed in *sgs1Δ* cells may result from a defect in signalling checkpoint activation. Intriguingly, recent studies have also indicated that Mec1p also helps promote replication fork progression during a normal, unchallenged S-phase [40].

6. A model for Sgs1p at the replication fork

We propose a model for Sgs1p action in the S-phase checkpoint response, both as a 'sensor' for damage during replication and a 'resolvase' for structures that arise at paused forks, such as the four-way 'chickenfoot' structure (Fig. 2a). The

action of Sgs1p may serve to maintain the proper amount and integrity of ss DNA that is necessary for the binding of RPA–DNA pol α complexes. Sgs1p would thus function by detecting (or resolving) aberrant DNA structures, and would thus contribute to the full activation of Mec1p and Rad53p. Its ability to bind both the large subunit of RPA (Rpa1p; J.A. Cobb et al., unpublished results) and the RecA-like protein Rad51p [41], place it in a unique position to resolve inappropriate fork structures that can occur when either the leading or lagging strand synthesis is stalled.

We also propose that Sgs1p provides stability to the lagging strand replication machinery after the checkpoint response has been activated. Whereas DNA pol ε appears to move faster in *sgs1*-deficient cells, DNA pol α is simply destabilised at the fork. These events are likely to result in the accumulation of atypical ss DNA gaps and potential ds breaks (Fig. 2b). Interestingly, *rad53* cells exhibit replication intermediates with long ss DNA regions, and accumulate Holliday junctions through fork reversal [14]. If Sgs1p functions as a reverse branch migration enzyme downstream of Rad53p at the fork to resolve such structures (Fig. 2c), then Sgs1p may itself require Rad53p kinase for full activity in the presence of HU, possibly being itself a target of checkpoint kinases. To see if reversed fork structures would persist in the absence of Sgs1p, replication intermediates formed in response to replication blocks should be analysed using in vivo psoralen cross-linking and electron microscopy in *sgs1Δ* cells as described in Sogo et al. [14]. To explain the phenotypes of the *sgs1* mutant, we propose that Sgs1p itself can either stabilise the RPA–DNA pol α–primase complex on ss DNA so that it is recognised as a substrate for Rad53p, or that Sgs1p helps to directly recruit Rad53p to the fork. In both cases, the RecQ helicase would function at a unique point during DNA synthesis to integrate checkpoint proteins, recombination, and replication fork integrity.

The role of BLM and WRN in the S-phase checkpoint is less clear in mammalian cells, but several studies show that the ATM protein kinase phosphorylates WRN in vitro and co-localises with the helicase and RPA in meiotic cells [42–44]. More recently, Werner protein was shown to co-localise with RPA in discrete nuclear foci upon replication arrest [45]. Moreover, the WRN helicase was reported to interact in vitro and in vivo with p53, a protein that is essential for the proper response to damaged DNA [46,47]. This interaction may be physiologically significant, since p53-mediated apoptosis is attenuated in cultured WS cells [48,49]. Finally, the BLM protein has been shown to co-localise with ATM and with other DNA repair proteins in a large complex called BASC (BRCA-1 associated genome surveillance complex) when cells are treated with agents that interfere with DNA synthesis [50]. While these are suggestive observations, further work is needed to identify the ways in which RecQ helicases integrate checkpoint activation and checkpoint response.

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