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Saccharomyces cerevisiae as a Model System to Study the Role of Human DDB2 in Chromatin Repair

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1. Introduction

Genetic and biochemical studies in *Saccharomyces cerevisiae* have made major contributions in elucidating the mechanism of several DNA repair pathways, including the nucleotide excision repair (NER) pathway that remove bulky DNA damage from the genome. Although NER is conserved from yeast to humans, there are differences in NER between yeast and humans. For example, no homolog of the human NER factor DNA damage-binding protein 2 (DDB2) has been identified in the budding yeast *S. cerevisiae*. Here, we present evidence suggesting that *S. cerevisiae* can be used to dissect the roles of DDB2 in initiating NER in chromatin.

Ultraviolet light (UV) is a well studied genotoxic stress that induces bulky DNA damage. These UV lesions are repaired by the NER pathway (Hanawalt, 2002; Sancar & Reardon, 2004). The particular lesions induced by UV irradiation have been characterized, namely, cyclobutane pyrimidine dimers (CPDs) and 6-4 photoproducts (6-4PPs). Both lesions result in the distortion of the DNA double helix, but 6-4PPs result in a greater distortion. Additionally, there are other minor differences between the two types of lesions. CPDs have been consistently shown to have higher incidence than 6-4PPs (Douki & Cadet, 2001). CPDs are induced both in nucleosome core and linker DNA, whereas 6-4PPs are formed with 6-fold greater frequency in linker DNA. In addition, 6-4PPs are repaired much faster than CPDs, as reviewed by Smerdon (Smerdon, 1991).

In humans, a defect in NER results in xeroderma pigmentosum (XP) and several other rare diseases (Kraemer et al., 2007). XP patients are extremely sensitive to UV light and have about 2000-fold higher incidence of sunlight induced skin cancers than the general population. NER lesion recognition is via protein interaction with the structural DNA changes that are induced. Other bulky DNA lesions repaired by NER include those induced by cigarette smoke, cisplatin treatment and a newly identified form of bulky oxidative DNA damage (Zamble et al., 1996; Setlow, 2001; Wang, 2008).

NER has been extensively studied and the basic mechanism is understood. It consists of three main steps: 1) lesion detection, 2) dual incision to remove an oligonucleotide containing the lesion and 3) repair synthesis to fill the gap. There are two sub-pathways of NER, termed transcription coupled repair (TC-NER) and global genome repair (GG-NER) (Hanawalt, 2002). TC-NER is responsible for repair of damage on the actively transcribed

strand; while GG-NER is responsible for repair in the remainder of the genome, including lesions on the non-transcribed strand of actively transcribed genes, as well as those in repressed or silent chromatin regions. Both TC-NER and GG-NER consist of all three steps, but, they differ in the lesion recognition step. In TC-NER the lesion is thought to be detected by pausing of RNA polymerase I or II (Conconi et al., 2002; Hanawalt, 2002; Fousteri & Mullenders, 2008). GG-NER, on the other hand, requires a specific lesion recognition hetero-dimeric protein complex, XPC-hRad23 (Xeroderma Pigmentosum complementation group C-human Rad23) in humans and Rad4-Rad23 (RADiation sensitive) in budding yeast (Wood 2010; Guzder et al., 1998; Jansen et al., 1998; Sugasawa, 2009). However, under certain *in vivo* circumstances, DDB2 is the pioneering damage recognition factor during GG-NER (Hwang et al., 1999; Nichols et al., 2000; Sugasawa, 2009). So far, no DDB2 homolog has been identified in the budding yeast (Fig. 1). Of note, the Rad16-Rad7 heterodimer, without a known human homolog, is required for GG-NER in the budding yeast.

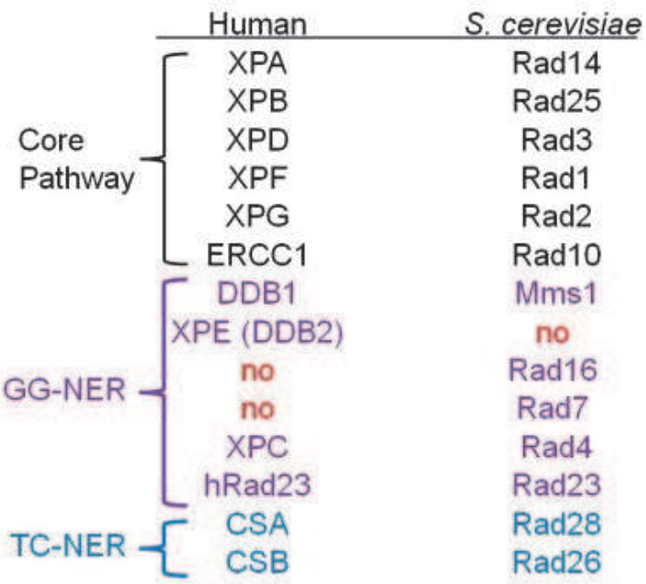

Fig. 1. Conservation of NER pathway between humans and the budding yeast *S. cerevisiae*. Of note, no DDB2 counterpart has been identified in *S. cerevisiae*. Likewise, humans don't have a homolog of the Rad16-Rad7 heterodimer that is essential for GG-NER in *S. cerevisiae*.

Several lines of evidence suggest that DDB2 plays a key role in **chromatin repair** of UV damage. It has been shown that DDB2 is responsible for the lesion detection by directly interacting with the damaged DNA (Tang, et al., 2000; Scrima et al., 2008). Additionally, DDB2 binds the lesion independent of XPC (Wakasugi et al., 2002). DDB2 can co-localize with both CPDs and 6-4 PPs *in vivo*, while XPC seems to bind 6-4 PPs efficiently, but not CPDs. This suggests the necessity of DDB2 in GG-NER is specific for CPD repair (Fitch et al., 2003). Importantly, it has been suggested that the observed high affinity of DDB2 for 6-4PPs aids in the targeting of XPC to 6-4PPs when low levels of damage are present (Nishi et al., 2009).

Additionally, DDB2 is in complex with the E3 ubiquitin ligase complex consisting of DDB1, Cul4 (CULlin 4) and ROC (Ring Of Cullins) (Jackson & Xiong, 2009). E3 ubiquitin ligases transfer ubiquitin to the target protein. DDB2 is thought to be the substrate receptor targeting the E3 ubiquitin ligase complex to DNA lesion sites to facilitate GG-NER. Of note, DDB1 and Cul4 have been shown to be in complex with other proteins, including CSA, a TC-NER specific protein (Jackson & Xiong, 2009). Consistent with its classification as an E3 ubiquitin ligase, XPC, histone H2A, H3, H4, and DDB2 itself have been identified as UV-dependent ubiquitination targets of the DDB1-DDB2 E3 ligase complex (Chen et al., 2001; Nag et al., 2001; Matsuda et al., 2005; Sugasawa et al., 2005; Kapetanaki et al., 2006; Wang et al., 2006). The UV-dependent mono-ubiquitination of histone H2A has been suggested to be involved in both chromatin relaxation and restoration (Kapetanaki et al., 2006; Zhu et al., 2009). Clearly, understanding the role of DDB2 in NER will yield important insights into the mechanisms of NER operation in the context of chromatin.

Chromatin is a hierarchal structure composed of DNA and protein. The core component is the nucleosome. It is a complex of 147 base pairs of DNA wrapped around the core histone octamer. The core histone octamer consists of four subunits, H2A, H2B, H3 and H4 in a 2:2:2:2 ratio (Luger et al., 1997; Kornberg & Lorch, 1999). The innate structure of chromatin restricts DNA protein interactions. ATP-dependent chromatin reconfiguration is an important mechanism to alleviate this tight association. Several groups have demonstrated a requirement for the ATP-dependent chromatin remodeling in chromatin repair (Jiang et al., 2010; Gong et al. 2006; Zhang et al. 2009a; Zhang et al. 2009b; Zhao et al. 2009; Lans et al. 2010; Sarkar et al. 2010). How DNA repair occurs in chromatin is an emerging question and has been discussed in several recent review articles (Osley et al., 2007; Nag & Smerdon, 2009; Waters et al., 2009; Zhang et al., 2009a; Jones et al., 2010).

2. *S. cerevisiae* as a model system to study DDB2-mediated GG-NER in chromatin

It has been demonstrated that DDB2 is the initial lesion detection factor in GG-NER (Tang et al., 2000; Wakasugi et al., 2002; Fitch et al., 2003b; Pines et al., 2009). Although it has been implicated in the recruitment of XPC to CPD sites (Fitch et al., 2003b); how DDB2 transfers these identified lesions to XPC remains controversial. It is believed that ubiquitination of DDB2 leads to its degradation at damage sites and this degradation is required for CPD repair. However, there are several lines of evidence disputing this model, including: 1) inhibition of ubiquitination-mediated DDB2 degradation in mouse via Cul4a ablation enhances CPD repair (Liu et al., 2009), 2) DDB2 degradation is not stimulated by either DNA binding or XPC association (Luijsterburg et al., 2007), and 3) crystal structures suggest that DDB2 and XPC can co-localize on the lesion (Min & Pavletich, 2007; Scrima et al., 2008). Therefore, we try to explore the budding yeast as a simplified, alternative model system to begin to dissect the role(s) of ubiquitination in DDB2-mediated GG-NER.

2.1 Galactose induced expression of DDB2 in *S. cerevisiae*

As discussed in the introduction, DDB2 has no homolog in budding yeast. However, conservation of the GG-NER pathway and interacting partners such as DDB1 are known (Zaidi et al., 2008). Therefore, we hypothesized that DDB2 would act in a physiological relevant manner in budding yeast GG-NER. We first cloned the DDB2 gene into a low copy number, galactose inducible yeast expression vector. The cloning results in a fusion protein;

DDB2 fused with V5His6 tag (Fig. 2A). Both the empty plasmid vector and the DDB2 containing plasmid were transformed into *S. cerevisiae*. As expected, when cells were grown in the presence of galactose, DDB2 protein was produced as identified by Western blot using both V5 and DDB2 antibodies (Fig. 2B and data not shown). No protein was detectable at the calculated molecular weight of DDB2 in the empty vector control using the same Western blot technique (Fig. 2B).

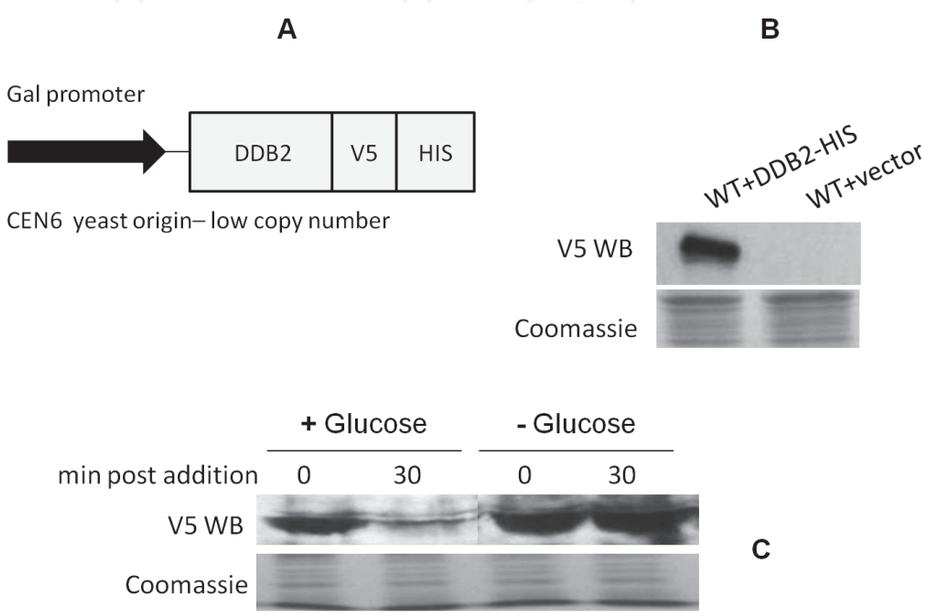

Fig. 2. Expression of DDB2-HIS in S. cerevisiae. (A) Schematic of DDB2 fusion cloned into pYCT/C2 expression vector. (B). Western blot (WB) using V5 antibody to detect expression of DDB2 containing or empty vector. (C) Glucose addition (4%) stops production of DDB2 detected by Western blot using V5 antibody, equal amount of total protein was verified using coomassie blue staining. BY4741 is the wild type (WT) strain used in these experiments.

To access the efficacy of the galactose induction 4% glucose was added to the media. Rapid shut down of the galactose inducible promoter is presumed due to the significant decrease in DDB2 protein levels 30 min post addition of glucose (Fig. 2C). This observed decrease in DDB2 protein levels is likely due to normal protein turnover in the absence of nascent DDB2 transcription and subsequent translation. These data confirm that DDB2 is expressed in *S. cerevisiae* cells under the control of the galactose promoter.

2.2 DDB2 suppresses UV sensitivity of Δ*rad26* cells

Next we identified genetic background in which a DDB2-dependent phenotype could be observed. We screened several yeast strains in which various NER proteins were deleted. The strains tested were Δ*rad7* and Δ*rad16* in which only TC-NER is active, Δ*rad26* in which only GG-NER is active, and Δ*rad1* in which the core pathway is defective and therefore there is no active NER. The spotting assay was used to determine DDB2 dependent suppression of UV sensitivity. Clearly, DDB2 expression suppresses the UV sensitive phenotype of Δ*rad26* cells (Fig. 3A). Survival curve experiments verified these findings (Data not shown).

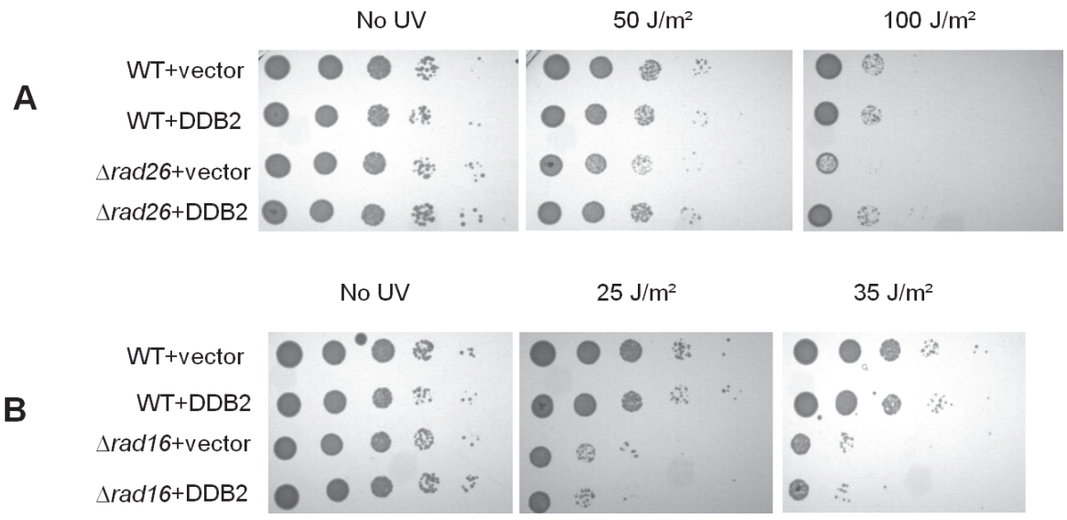

Fig. 3. DDB2 expression suppresses UV sensitivity of Δ*rad26* mutant, but not Δ*rad16* mutant. BY4741 (WT) cells expressing DDB2 or empty vector were diluted 1/10 and plated on galactose media. Cells were exposed to UV irradiation at dose indicated and grown in dark at 30 °C for 48 hours. Δ*rad26* (A). Δ*rad16* (B).

As discussed in the introduction, both DDB2 and Rad16 are necessary for lesion identification *in vivo* and are part of E3 ubiquitin ligase complexes (Verhage et al., 1994; Mueller & Smerdon, 1995; Shiyanov et al., 1999; Tang et al., 2000; Wakasugi et al., 2002; Fitch et al., 2003b; Groisman et al., 2003; Ramsey et al., 2004; Pines et al., 2009). Therefore, it was surprising that DDB2 was unable to suppress the Δ*rad16* UV sensitive (Fig. 3B). Our data suggest that despite similarities in their biochemical properties, on a gross functional level DDB2 and Rad16 are not analogs. It should be noted that Rad16 has also been implicated in post-incision processes (Reed et al., 1998) while DDB2 has not. It is therefore plausible that DDB2 and Rad16 have analogus functions in the lesion identification step of GG-NER, but this post-incision function of Rad16 is unable to be rescued by DDB2 expression.
In addition, we found that DDB2 was not able to significantly suppress UV sensitivity of any other knockout strains, including Δ*rad7* cells (data not shown). These data are consistent with no known DDB2 homolog in budding yeast. The observed DDB2-dependent suppression of TC-NER deficient UV sensitivity is consistent with reported DDB2 stimulation of GG-NER (Wakasugi et al., 2001; Wakasugi et al., 2002).

2.3 DDB2 mutations abrogate its ability to suppress Δ*rad26* UV sensitivity

To assess if DDB2 is functioning in a physiologically relevant manner, we first examined the phenotypic effects of mutant DDB2 on DDB2-dependnet suppression of Δ*rad26* UV sensitive phenotype. Several DDB2 mutations identified in XPE patients are known to interfere with its ability to function properly in GG-NER. It has been reported that a point mutation changing lysine 244 to glutamic acid (DDB2 K244E) results in inability of DDB2 to make contact with DNA lesions (Scrima et al., 2008) (Fig. 4A). However, this mutation does not alter the ability of DDB2 to interact with DDB1 in the Cul4a E3 ubiquitin ligase complex, therefore its role in ubiquitination is not altered. When this damage recognition deficient mutant DDB2 was introduced into Δ*rad26* cells, it was unable to suppress Δ*rad26* UV sensitivity (Fig. 5). This suggests that the observed DDB2-conferred UV resistance is linked to its function in DNA damage detection.

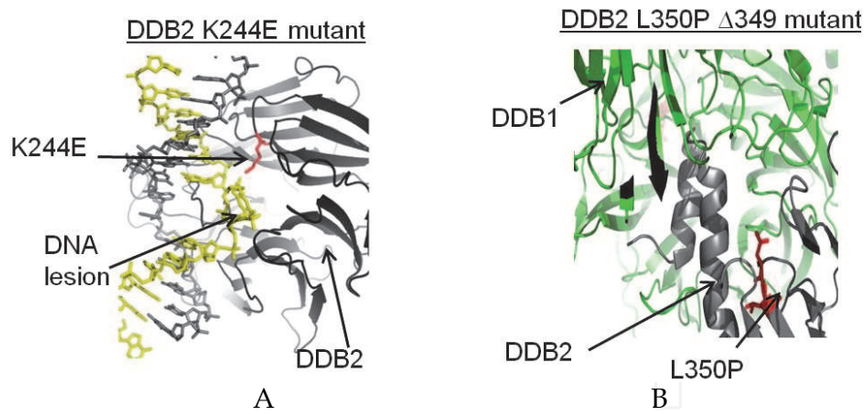

Fig. 4. Crystal structure of DDB2 mutations modified from crystal structure solved by Scrima et al. (A) Lysine to glutamic acid substitution at aa 244 predicted to effect DDB2 DNA interaction. Red residue indicates site of mutation. Yellow indicates damaged DNA strand. (B) Deletion of aa 349 and substitution of proline for leucine at aa 350. This mutation is predicted to effect the DDB2 DDB1 interaction. Red indicates site of mutation. Mutant DDB2 was constructed by site directed mutagenesis.

Another mutation that affects DDB2's function prevents the interaction with its in vivo partner DDB1 (Nichols et al. 2000). This mutation was also constructed and is a complex mutation, consisting of both a deletion of amino acid 349 and a proline substitution for leucine at amino acid 350 (DDB2 L350P) (Fig. 4B). Like DDB2 K244E, this mutation also abrogated DDB2's ability to suppress UV sensitivity in Δ*rad26* cells (Fig. 5). These data suggest DDB2-conferred UV resistance is dependent on a conserved interacting partner.

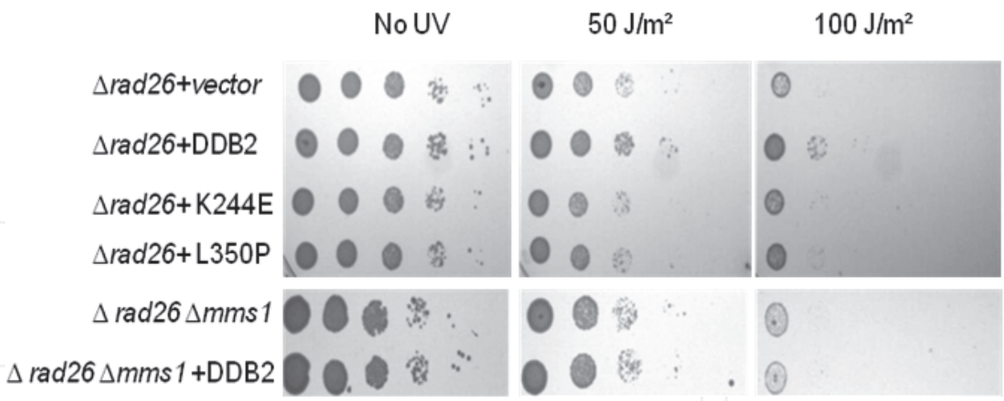

Fig. 5. DDB2 mutations and deletion of Mms1 (DDB1 homolog) abrogate suppression of UV sensitivity in Δ*rad26* cells.

Although Mms1 has been identified as the budding yeast DDB1 homolog (Zaidi et al., 2008), there are no reports of it being involved in NER. However, our previous observation suggesting DDB2 function requires a conserved interacting partner prompted us to test DDB2 function in the absence of Mms1. To test this, wild type DDB2 was expressed in the Δ*rad26*Δ*mms1* double mutant and UV sensitivity was accessed by spotting assays. Indeed, this reciprocal experiment verified that Mms1 is necessary for DDB2-dependent suppression of UV sensitivity (Fig. 5).

Taken together, these data suggest that exogenously expressed DDB2 is acting in a physiologically relevant manner. Additionally, our findings indicate that the DNA damage recognition function of DDB2 is essential for the observed suppression of UV sensitivity. We also found that DDB2 function is dependent on interaction with Mms1, a subunit of an E3 ubiquitin ligase. These observations are consistent with what is reported for DDB2 function in human cells.

3. Conclusion

Studies in *Saccharomyces cerevisiae* have made major contributions to our understanding of NER. Here, we present evidence suggesting that *S. cerevisiae* can be used to dissect the roles of human DDB2 in initiating NER in chromatin. Since DDB2 functions are regulated by the ubiquitin pathway and DDB2 itself is a component of an E3 ligase, it will be interesting to explore the regulation of DDB2 functions by ubiquitination, using yeast mutants with defects in various steps of the ubiquitin pathway.

Ubiquitination is a well studied post-translational modification and recent data suggest multiple fates of ubiquitin modified proteins (Sadowski & Sarcevic, 2010). It will be important to determine if ubiquitination of DDB2 promotes its degradation or controls DDB2 association with chromatin. The budding yeast system described here will also provide an alternative system to screen the effect(s) of various DDB2 lysine mutations to determine which amino acid residue(s) is modified. Additionally, as reviewed by Kirkin et al., ubiquitin signaling is altered in many cancers (Kirkin and Dikic 2010), suggesting a potential role of ubiquitination in regulating DNA binding proteins such as transcription factors and repair proteins. Therefore, it will be interesting to determine what, if any, role ubiquitination plays in the chromatin association of other DNA binding proteins, specifically transcription factors and repair proteins. The utilization of the budding yeast model system will facilitate deciphering such questions.

4. Acknowledgment

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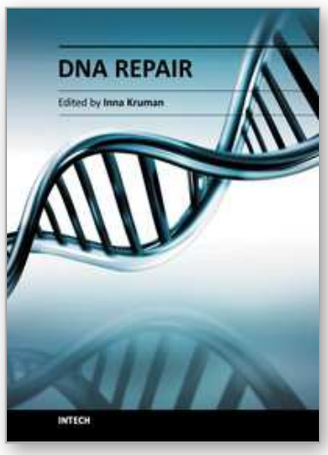

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The book consists of 31 chapters, divided into six parts. Each chapter is written by one or several experts in the corresponding area. The scope of the book varies from the DNA damage response and DNA repair mechanisms to evolutionary aspects of DNA repair, providing a snapshot of current understanding of the DNA repair processes. A collection of articles presented by active and laboratory-based investigators provides a clear understanding of the recent advances in the field of DNA repair.

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