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A novel interaction between human DNA polymerase η and MutLα

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ABSTRACT

Human DNA polymerase η (Polη) is the gene product underlying xeroderma pigmentosum variant, and plays principal roles in translesion DNA synthesis. Here, we identified human MLH1, an essential component of mismatch repair (MMR), as a Polη-interacting protein. The middle area residues, which include the little finger domain, of Polη are important for the interaction with MLH1. Polη also interacts with the MLH1/PMS2 heterodimer (MutLα). Co-immunoprecipitation analyses revealed that MutLα, and also MSH2 and MSH6, components of the MutSα heterodimer, form complexes with Polη in human cells. Although MutSα had been reported to interact with C-terminal residues of Polη, MutLα and MutSα co-precipitated with C-terminally truncated Polη, suggesting that MutSα can interact with Polη through MutLα. MMR proteins were more abundant in the Polη complex on the chromatin of S phase-synchronized cells than of asynchronous cells, suggesting that the interaction between Polη and MLH1 is involved in DNA replication.

Introduction

Most types of DNA damage block progression of replicative DNA polymerases [1]. Cells have several mechanisms to prevent replication blockage by DNA lesions. One way to circumvent these replication blocks is translesion synthesis (TLS). Human DNA polymerase η (Polη), the gene product responsible for the variant form of xeroderma pigmentosum (XP-V) [2,3], accomplishes error-free TLS past UV-induced cyclobutane pyrimidine dimers (CPDs) [4,5], and plays an important role in the prevention of UV-induced carcinogenesis [6]. Polη belongs to the Y-family of DNA polymerases, and has conserved domains, namely, palm, finger, thumb and little finger domains, in its N-terminus, and poorly conserved residues in the residual C-terminus [7]. Structural analyses of Y-family polymerases revealed that they have an extensive active site, which might impart the lesion bypass ability at the expense of loosing high fidelity DNA synthesis ability [7,8]. Recent studies showed that Polη is involved in somatic hypermutation of immunoglobulin genes as an error-prone DNA polymerase, and also in homologous recombination [8,9]. These results imply that cells have substantial mechanisms to regulate Polη appropriately.

Several proteins have been reported to interact with human Polη. Polη interacts with Rad18, which catalyzes monoubiquitylation of PCNA [10], and then with monoubiquitylated PCNA [11]. These interactions can trigger the lesion bypass by Polη. The interactions between Polη and RAD18, PCNA, and ubiquitin require the C-terminal amino acids of Polη [10–14]. Polη has also been reported to interact with other Y-family polymerases, Polι and REV1, through its C-terminal region, and to assist with the nuclear re-localization of these proteins in human cells [15,16]. It has also been demonstrated that the mismatch repair (MMR) proteins, MSH2, MSH3, and MSH6, interact with C-terminal residues of Polη [17].

MMR is an indispensable system in the maintenance of genomic stability, and defects in this system result in mutator phenotypes [18]. Multiple MutS and MutL homologues are known to play important roles in eukaryotic MMR. In human cells, MSH2 forms heterodimers with MSH6 (MutSα) and MSH3 (MutSβ). MutSα preferentially recognizes base–base mismatches and one or two nucleotide insertion/deletion (ID) mispairs, and MutSβ preferentially recognizes larger ID mispairs. MLH1 forms heterodimers with PMS1 (MutLβ), PMS2 (MutLα), and MLH3 (MutLγ). MutLα has been shown to play principal roles in MMR, MutLγ is thought to be predominantly involved in meiotic recombination, and the role of MutLβ is still uncertain [19–21].

Several reports suggest that MMR proteins have multiple roles in other cellular processes. MutLα and MutSα have been reported to act upstream of damage signaling protein kinases, which could trigger the DNA damage response [19–22], indicating that MMR proteins have crucial roles in DNA damage signaling pathways.

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MMR proteins are also reported to be involved in DNA recombination during mitosis [19,20]. It has also been reported that MutLα and MutLβ have regulatory roles in homologous recombination [23]. MutSα have been reported to contribute to the development of mutations in immunoglobulin genes, but MutLα may not [20]. It has been reported that MutLα interacts specifically with FANC-J, implicating MutLα in the interstrand crosslink repair pathway [24]. Thus, the MMR proteins are likely to have crucial regulatory roles in various kinds of DNA tolerance mechanisms.

Here, we demonstrate that human Polη directly interacts with human MLH1, regardless of whether MLH1 occurs as a monomer or as a MutLα heterodimer with PMS2. In contrast with previously identified Polη-interacting proteins, including MutSα, which all interact with C-terminal residues of Polη, MLH1 associates with the middle part of Polη, which includes the little finger domain. We also found that Polη forms a complex with MMR proteins in human cells, and that this interaction is increased on the chromatin in S phase cells, suggesting the importance of this interaction during DNA replication.

Materials and methods

Full details are presented in Supplementary materials.

Two-hybrid assay. Two-hybrid assay was performed using the PROQUEST two-hybrid system (Gibco BRL) as described previously [16].

In vitro binding assay. For GST pull-down assays, GST-fused MLH1 proteins were immobilized on glutathione Sepharose, and then incubated with Polη. The bound proteins were eluted by SDS.

For detecting the interaction between Polη and MutLα, Polη was mixed with protein G Sepharose conjugated with a mouse monoclonal anti-Polη antibody, cl.5C6, and then incubated with MutLα. The bound proteins were eluted by SDS.

Immunoprecipitation assay from soluble cell extracts. Soluble materials from HeLa and HeLa/Polη cells were pretreated with mouse IgG-agarose and incubated with anti-FLAG M2 agarose. The bound proteins were eluted with the FLAG peptide.

For the experiments using FreeStyle 293-F cells, cells were transfected with constructs expressing Flag-tagged Polη, and analyzed 48 h after the transfection.

Chromatin immunoprecipitation assay. For the chromatin immunoprecipitation assays, formaldehyde was added into cultured medium of cells at a final concentration of 1%. After removing the soluble material, DNA was sheared by sonication. The solubilized material was pretreated with mouse IgG-agarose and then incubated with anti-HA agarose. The bound proteins were eluted by SDS.

Results

Polη interacts with MLH1 in vivo and in vitro

To identify Polη-interacting proteins, we performed yeast two-hybrid screening with full-length human Polη as bait, and obtained a clone containing the C-terminal residues (amino acids 473–756) of human MLH1, an essential component of mismatch repair (MMR). To identify which Polη domain binds with MLH1, we carried out two-hybrid assays using the C-terminal residues of MLH1 and a series of Polη deletion derivatives. As shown in Fig. 1A, the C-terminal residues of Polη (amino acids 509–713) were unable to interact with MLH1, whereas other truncated proteins tested were able to interact. All of the MLH1 interaction-positive fragments contained the entire little finger domain (amino acids 317–432). As a peptide consisting of amino acids 301–431 of Polη gave a very weak, but significant, positive signal (data not shown), we predict that the core residues for the interaction are situated in the little finger domain. Pull-down assays with full-length and truncated Polη proteins with GST-fused to full-length MLH1 or the C-terminal portion (amino acids 473–756) of MLH1 revealed that truncated Polη proteins consisting of amino acids 1–511, 301–713, and 301–511, as well as the full-length protein, interact with the GST-MLH1 proteins (Fig. 1B), while the N-terminus of Polη (amino acids 1–354) does not. From these results, we conclude that Polη and MLH1 interact directly through the C-terminus of MLH1 and the middle part of Polη, which contains the little finger domain.

MLH1 is known to interact with PMS2 through its C-terminus, forming MutLα, the functional heterodimer in MMR. Therefore, we next examined whether Polη interacts with the MutLα heterodimer, using purified Polη and MutLα proteins. Co-immunoprecipitation experiments with an anti-Polη antibody showed that both MLH1 and PMS2 co-precipitated with Polη (Fig. 1C). Although we could not exclude the possibility that PMS2 also directly interacts with Polη, this result indicates that Polη directly interacts with MutLα *in vitro*.

Polη and MutLα form a complex in human cells

Given that recombinant Polη and MutLα proteins interact in yeast cells and *in vitro*, we performed co-immunoprecipitation experiments to examine the interaction between endogenous proteins in human cells. Since we were unable to detect co-precipitated MMR proteins with endogenous Polη, probably due to an insufficient detection limit of the analysis, we employed HeLa cells overexpressing FLAG- and HA-tagged Polη (HeLa/Polη). Soluble extracts from the HeLa/Polη cells and the corresponding parental HeLa cells were used for immunoprecipitation with an anti-FLAG antibody. As shown in Fig. 2A, endogenous MLH1 and PMS2 proteins were observed in the precipitates from HeLa/Polη cells (lane 4), whereas only trace signals were observed from HeLa cells (lane 3), suggesting that Polη interacts with MutLα in human cells. MSH2 and MSH6 proteins, which consist of the mismatch recognition factor MutSα, were also detected in the precipitates from HeLa/Polη cells.

MutSα had been reported to associate with C-terminal residues (481–713) of Polη [17]. To analyze the modes of interaction between Polη and the MutLα and MutSα proteins, we performed co-precipitation experiments using a truncated version of Polη consisting of the 511 N-terminal-most amino acids (Polη(1–511)). In the *in vitro* pull-down assays with recombinant proteins, we confirmed that MSH2 and MSH6 proteins, MutSα components, were not co-precipitated with the Polη(1–511), while they were co-precipitated with full-length Polη (Supplemental Fig. 1). Then the Polη(1–511) tagged with FLAG and a nuclear localization signal was expressed in Human Embryonic Kidney (HEK) FreeStyle 293-F cells (Fig. 2B). Interestingly, in the pull-down assays with the cell extracts, MSH2 and MSH6 proteins were found to co-precipitate with the Polη(1–511) protein; however, the amount of co-precipitation was less than when using full-length Polη. In contrast, similar amounts of MLH1 and PMS2 were co-precipitated with Polη(1–511) and full-length Polη. These results suggest that MutLα interacts with the N-terminal-most 511 amino acids of Polη, and MutSα interacts with Polη in two modes, probably directly to the C-terminus of Polη and probably indirectly to the N-terminus residues through MutLα.

The interaction between Polη and mismatch repair proteins on the chromatin increases in the S phase of the cell cycle

As Polη and MMR proteins are expected to act on DNA, we then examined the interaction between these proteins on the chroma-

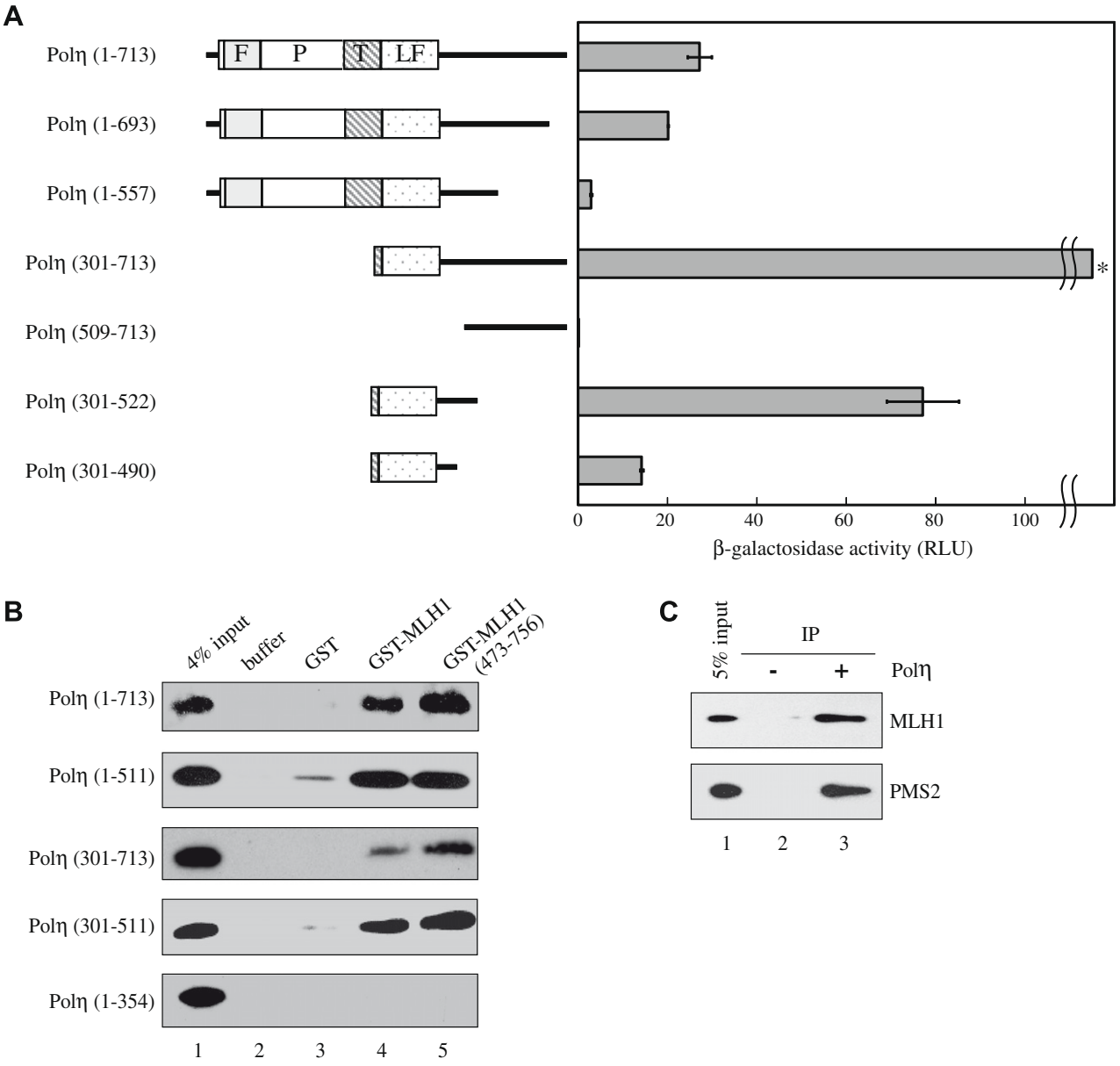

Fig. 1. Interaction between Polη and MLH1 in yeast cells and *in vitro*. (A) Interaction of Polη with MLH1 in a yeast two-hybrid assay. A series of truncated Polη mutants and C-terminal residues of MLH1 (amino acids 473–756) were expressed in yeast as fusion proteins with GAL4 DNA-binding and -activating domains, respectively. Results of quantitative β-galactosidase assays were plotted. Polη deletion mutants are schematically shown on the left. Light grey, white, striped, and dotted boxes represent finger (F), palm (P), thumb (T), and little finger (LF) domains, respectively. *The net value was 231.8 ± 29.7 RLU. (B) Interaction of Polη with MLH1 in a GST pull-down assay. Purified GST-fused full-length (lane 4) and the C-terminal residues (lane 5) of MLH1, and GST (lane 3) were immobilized on glutathione Sepharose, and mixed with purified full-length (amino acids 1–713) and truncated Polη proteins. Bound proteins were resolved by SDS–PAGE, and detected by Western blot analysis. A monoclonal anti-Polη antibody was used for detecting Polη(1–713), (301–713), and (301–511) and a monoclonal anti-penta-His antibody was used for detecting Polη(1–511) and (1–354). Mock experiments were performed without GST proteins (lane 2). Amounts equivalent to 4% inputs of each Polη derivative were loaded in lane 1. (C) Interaction between Polη and MutLα. The MutLα heterodimer was immunoprecipitated using an anti-Polη antibody in the presence (lane 3) or absence (lane 2) of the full-length Polη protein. Bound proteins were detected by Western blot analysis using anti-MLH1 and anti-PMS2 antibodies. Equivalent amounts to 5% inputs of MutLα were loaded in lane 1.

tin. We previously showed, without using crosslinkers, that RAD18 and REV1 are co-precipitated with Polη from the chromatin fractions of HeLa/Polη cells [25]. However, in the same procedure, reliable signals of MMR proteins were not recovered with Polη from the chromatin fractions, suggesting that the interaction between Polη and MMR proteins is very labile and dynamic on the chromatin. Therefore, we performed immunoprecipitation experiments with the chromatin prepared from crosslinker-treated cells. As shown in Fig. 3A, Western blot analysis of the anti-HA immunoprecipitates showed that Polη associated with MLH1, PMS2, MSH2, and MSH6 on the chromatin (lane 4). To examine the effect of cell cycle status on the interaction between Polη and MMR proteins on the chromatin, HeLa/Polη cells were synchronized by the double thymidine block method, and released into a synchronous cell cycle. Most of the cells were in the G1/S boundary to early S phase, early to mid S phase, and late S or G2 phase at 0 h, 2 h, and 6 h after the release, respectively (Fig. 3C). As shown in Fig. 3B, compared to asynchronous cells, the amount of MLH1 and PMS2 proteins found in the Polη-associated fraction increased after synchronization (compare lanes 5 and 6), and further increased at 2 h, and decreased at 6 h after the release (lanes 7 and 8). The amount of MSH2 and MSH6 proteins that co-precipitated with Polη increased

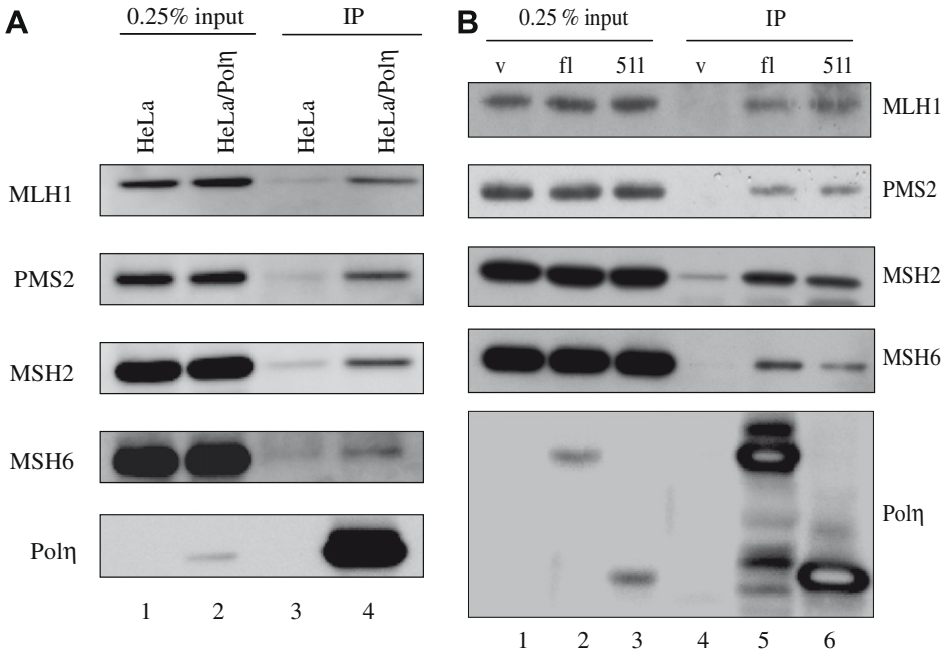

Fig. 2. Interaction between Polη and MMR proteins in human cells. (A) Interaction between Polη and MMR proteins in HeLa/Polη cells. Soluble proteins extracted from cells were immunoprecipitated with an anti-Flag antibody. The precipitated proteins from HeLa/Polη (lane 4) and parental HeLa (lane 3) cells were analyzed by Western blot analysis with antibodies for the indicated proteins. Equivalent amounts to 0.25% inputs of HeLa and HeLa/Polη were loaded in lanes 1 and 2, respectively. (B) Interaction between full-length and C-terminally-truncated Polη and MMR proteins in 293 cells. Anti-FLAG immunoprecipitation was performed with soluble extracts from FreeStyle 293-F cells that were transfected with vector alone (lane 4), expression constructs for the full-length Polη (lane 5), and Polη(1–511) (lane 6). Immunoprecipitated proteins were detected by Western blot analysis with antibodies against the indicated proteins.

at G1/S, compared to asynchronous cells, remained at high levels at 2 h after the release, and decreased at 6 h after the release. These results suggest that the interaction between Polη and MMR proteins is somehow regulated on the chromatin, responding to DNA replication status in human cells. Together with our observation that UV-irradiation of the cells did not alter the Polη-MMR protein interaction profiles (data not shown), we conclude that the interaction may be coupled to normal DNA replication, rather than to UV damage tolerance.

Discussion

A novel interaction at the N-terminus of human Polη

In this study, we identified MLH1 as a novel human Polη interaction protein. Analysis of the binding domain of Polη that interacts with MLH1 suggests that the little finger domain is important for the interaction. Previous studies revealed that several proteins, such as PCNA, ubiquitin, and RAD18, interact with Polη directly, and promote cellular re-localization of Polη to perform TLS (10–14). Polι and REV1 are also reported to interact with Polη and to be guided to arrested replication forks at damaged DNA sites [15,26]. MMR proteins, MSH2, MSH3, and MSH6, are also reported to interact with Polη [17]. Importantly, all of these interactions target the C-terminal residues of Polη. In contrast, the MLH1 interaction domain of Polη locates in or very close to the catalytic domain of Polη, suggesting that the interaction with MLH1 might have different aspects from other interacting proteins. To the best of our knowledge, this is the first report of a protein–protein interaction involving the little finger domain of a Y-family polymerase.

Modes of interaction between Polη and MMR proteins

Although the Polη-interacting region of human MLH1 (amino acids 473–756) overlapped with the interaction regions for PMS2 [27], our observation that Polη directly interacts with MutLα strongly suggests that MLH1 interacts with Polη and PMS2 simultaneously. In addition to the MutLα components, we found MSH2 and MSH6, the MutSα components, in the fractions co-immunoprecipitated with Polη from human cells. Since MutSα and MutLα interact with each other and cooperatively function in MMR, it is possible that MutSα co-precipitates with Polη through interactions with MutLα. However, it has been demonstrated that MSH2, MSH3, and MSH6 directly interact with the C-terminal-most 233 amino acids of human Polη [17]. Considering our finding that reduced but still observable levels of MSH2 and MSH6 proteins co-immunoprecipitated with N-terminal-most 511 amino acids of Polη, it is likely that MutSα interacts with Polη in two modes, directly to the C-terminus of Polη and indirectly to the little finger domain, probably through MutLα.

Possible relevance of the interactions between Polη and MMR proteins

Msh2- and Msh6-deficient mice have been reported to show decreased A/T mutations in Ig genes, similar to Polη-deficient mice [28], and MutSα has been shown to interact with Polη [17]. These reports suggest the involvement of MutSα and Polη in the somatic hypermutation of Ig genes. In contrast, only modest alterations of the spectrum have been observed in Mlh1- and Pms2-deficient mice. Since MutSα has been reported to stimulate DNA synthesis by Polη on gapped DNA templates *in vitro* [17], we examined the effects of MutLα on Polη DNA synthesis activities with the same sequence context of templates, but neither stimulation nor inhibition was observed (data not shown). Thus, in contrast to the interaction with MutSα, the interaction between Polη and MutLα is likely to have another functional significance. We showed that the interaction between Polη and MMR proteins increased on the chromatin during S phase. As the best-known role of MMR is to correct errors during DNA replication, collaborative actions of Polη with MMR proteins could facilitate error-free DNA replica-

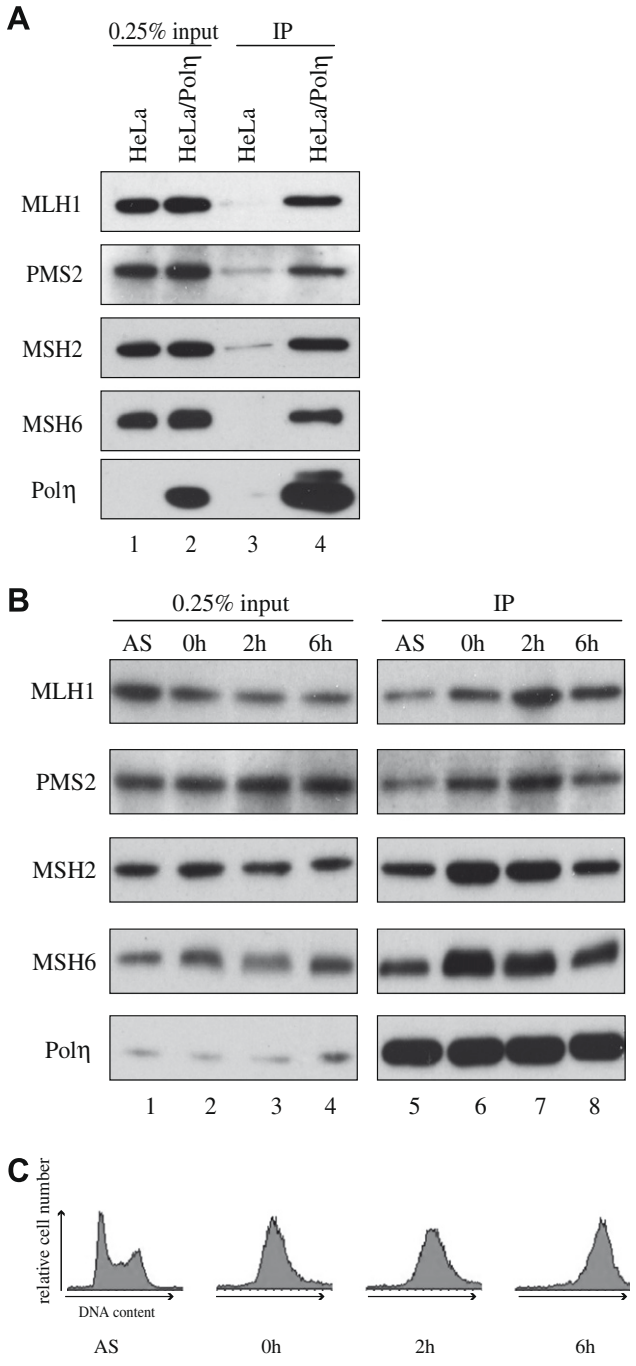

Fig. 3. Interaction between Polη and MMR proteins on the chromatin. (A) Interaction in asynchronous cells. HeLa/Polη (lane 4) and parental HeLa (lane 3) cells were crosslinked with formaldehyde, chromatin-bound materials were prepared and subjected to immunoprecipitation with an anti-HA antibody, and samples were analyzed by Western blot analysis with antibodies against the indicated proteins. Equivalent amounts to 0.25% inputs of HeLa and HeLa/Polη cells were loaded in lane 1 and 2, respectively. (B) Effects of cell cycle stage on the interaction between Polη and MMR proteins on the chromatin. HeLa/Polη cells were synchronized by the double thymidine block method and released. Chromatin fractions were prepared from synchronized cells 0, 2, and 6 h after the release and from asynchronous (AS) cells, and immunoprecipitations were performed with an anti-HA antibody followed by Western blot analysis with antibodies against the indicated proteins (lanes 5–8). Equivalent amounts to 0.25% inputs of corresponding samples were loaded in lanes 1–4. (C) Cell cycle profiles. A portion of cells used in (B) were subjected to FACS analysis.

tion. Although Polη catalyzes accurate TLS past *cis-syn* thymine dimers, Polη often incorporates incorrect nucleotides opposite some DNA lesions [8]. Therefore, it is conceivable that the interaction between TLS and MMR guarantees accurate replication of DNA, which is continuously afflicted with lesions.

Besides MMR, MMR proteins are known to play important roles in the DNA damage signaling pathways [19–22]. A recent study suggests that Polη also participates in the DNA damage signaling pathway, since Polη knockdown in human cells impairs the phosphorylation of CHK2 by ATM after exposure to camptothecin or ionizing radiation [29]. Thus, the Polη–MutLα interaction may contribute to the checkpoint signaling pathway during the S phase. It is our ongoing focus to decipher the precise modes of interaction between Polη and MMR proteins, and to determine their physiological relevance in cells.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbrc.2009.08.090.

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