



Does the modification of serine 477 of DNA mismatch repair protein MLH1 play a role in cell proliferation?

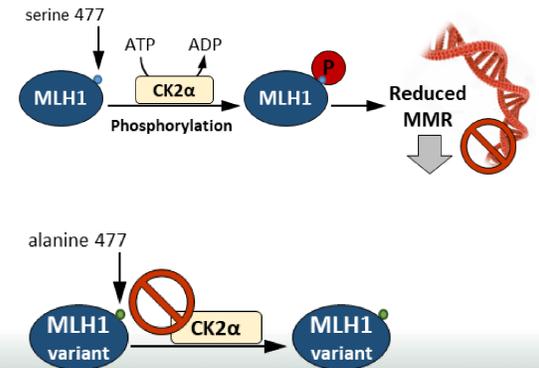
May-Britt Firnau, Angela Brieger

Medical Clinic I, Biomedical Research Laboratory, JWG University Hospital Frankfurt, Germany

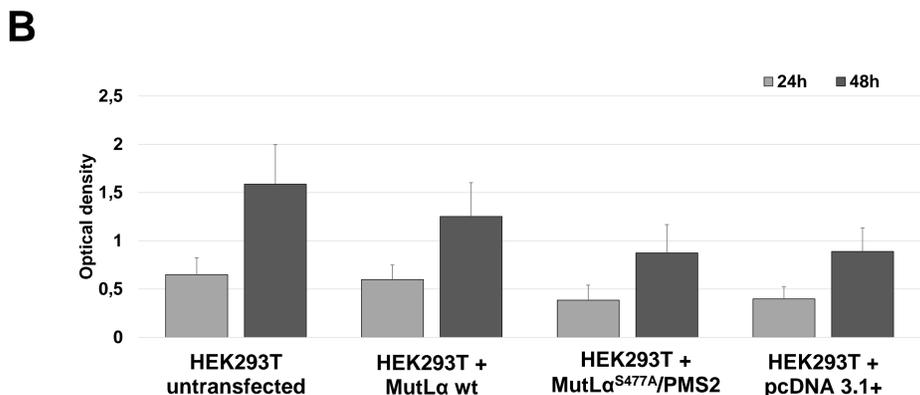
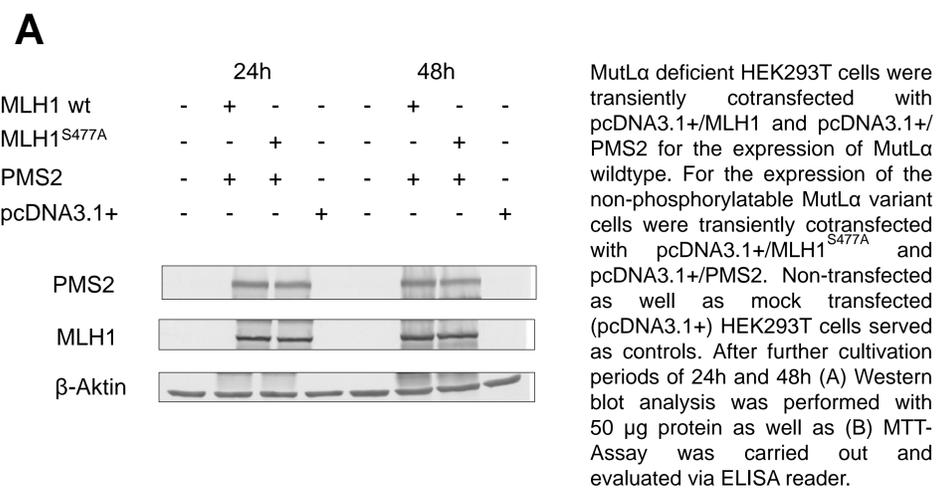
Introduction

MutL α , a heterodimer consisting of MLH1 and PMS2, is a key player of the DNA mismatch repair (MMR) system and of great importance to correct incorporation errors that occur during DNA replication. Previously, we identified that posttranslational phosphorylation of MLH1 at amino acid position serine 477 can switch off MMR activity in vitro. We also found that mutation of serine 477 prevented the posttranslational phosphorylation.

Since MLH1 is involved in numerous MMR-independent cell processes, including the cell cycle control, we hypothesized that phosphorylation of MLH1 might alter the mediation of cell cycle-associated proteins and thus affects proliferation.

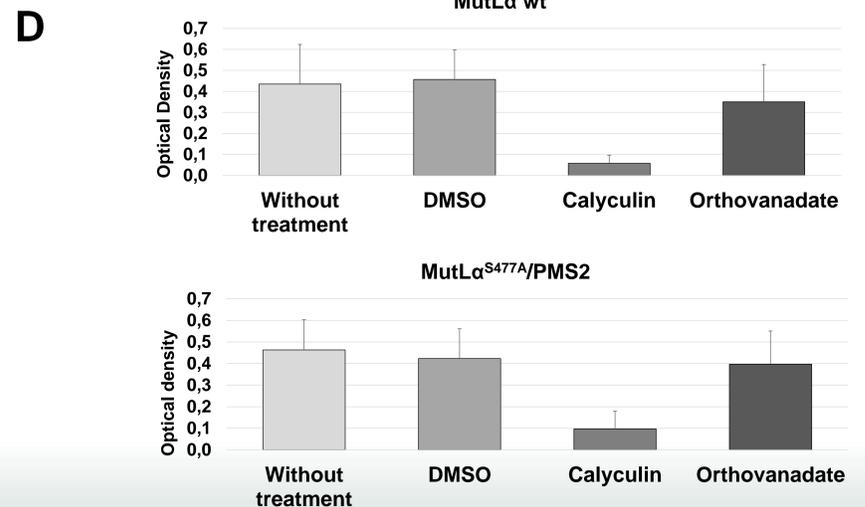
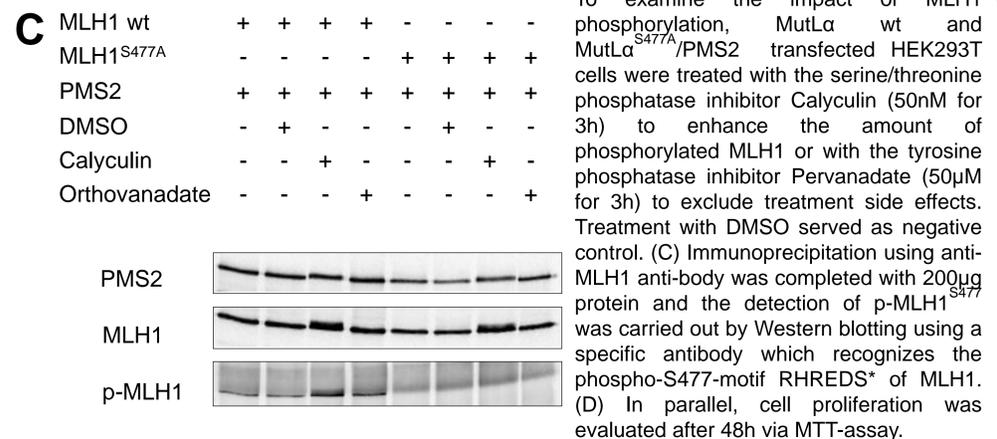


Investigation of the influence of different transfections on proliferation



Non-phosphorylatable MLH1^{S477A}/PMS2 overexpressing cells show less proliferation than MutL α wildtype overexpressing cells. The phosphorylation of MLH1 seems to play a role in cell proliferation.

Determination of the effect of phosphorylation of MLH1 on cell proliferation



Non-phosphorylatable MLH1^{S477A}/PMS2 overexpressing cells show slightly increased proliferation after Calyculin treatment compared to MutL α wildtype overexpressing cells.

Conclusion

In summary, significant differences of proliferation could be detected between the differently treated cells. Proliferation of Calyculin treated HEK293T cells overexpressing the non-phosphorylatable MutL α variant, however, was only weakly increased compared to cells overexpressing MutL α wildtype. Due to the fact that Calyculin and Orthovanadate are able to influence a multitude of signaling pathways, the role of MLH1 phosphorylation cannot be conclusively answered here. Further experiments are necessary to clarify the function of phosphorylated MLH1 in proliferation.