Immunhistologie

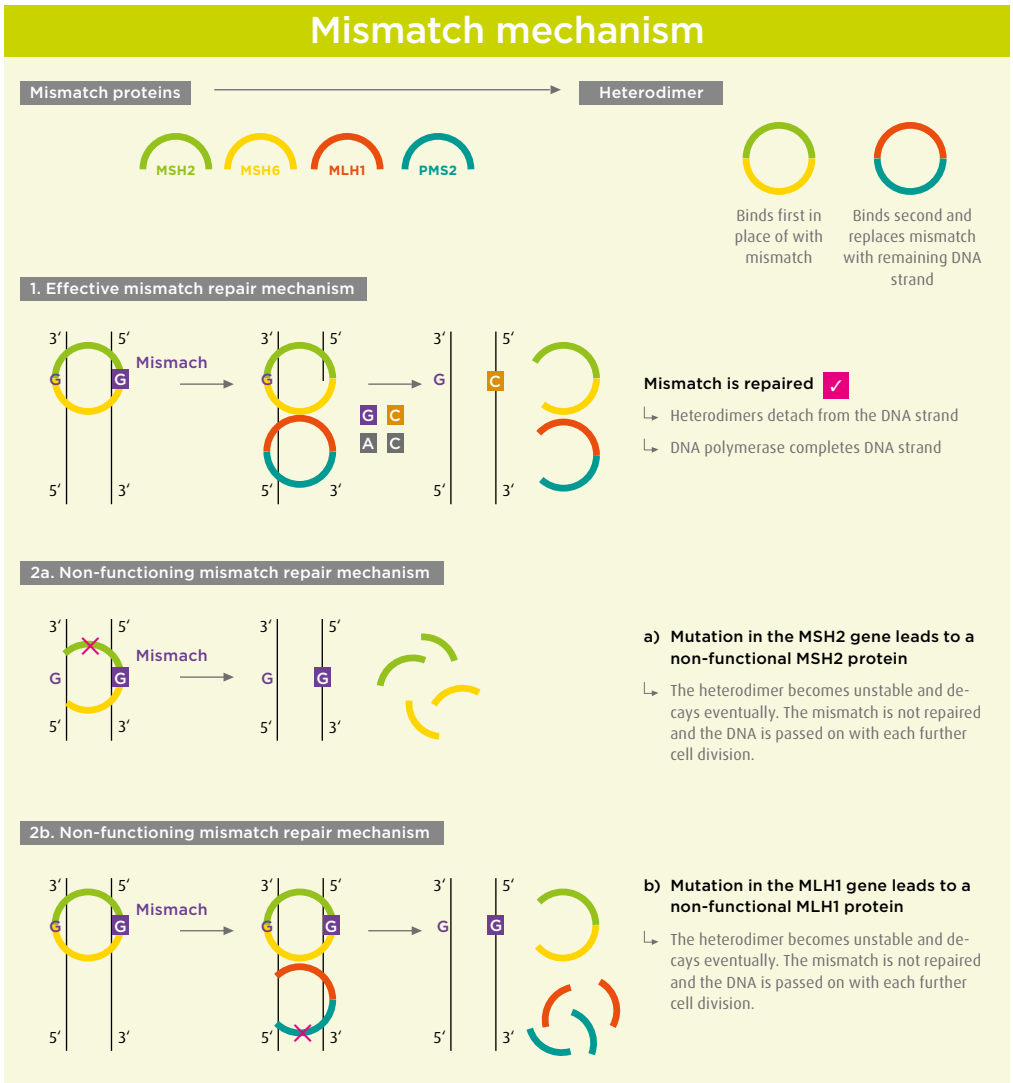
MMR-Proteine

Immunohistochemistry of DNA Mismatch Repair (MMR) Proteins

In the human body, an average of 50 to 70 billion new cells are formed every day. To ensure that no errors occur in the replication of DNA replication, there are various control and correction mechanisms that correct base pairings mismatches (mismatches) during the replication process.
One of these mechanisms is implemented with the help of the four DNA mismatch repair proteins (MMR): ▸ MLH1; ▸ MSH2; ▸ MSH6; ▸ PMS2

Two of these four proteins always form heterodimers: MSH2 with MSH6 and MLH1 with PMS2. If one of these proteins fails, e.g. due to a mutation, the heterodimers can no longer fulfill their function and the function and the defective base is not replaced. Thus, mismatch repair (MMR) no longer functions. The loss of one and/or of the four proteins can be caused either by germline mutation or by sporadic loss.

▸ **Fig. 1** (according to Zhao *et al.* Journal of Hematology & Oncology, 2019)



▸ **Literatur**

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[2] Garg K *et al.* Selection of Endometrial Carcinomas for DNA Mismatch Repair Protein Immunohistochemistry Using Patient Age and Tumor Morphology Enhances Detection of Mismatch Repair Abnormalities. Am J Surg Pathol 33: 925-933, 2009

[3] Modica I *et al.* Utility of Immunohistochemistry in Predicting Microsatellite Instability in Endometrial Carcinoma. Am J Surg Pathol 31: 744-751, 2007

[4] Bellizzi A *et al.* Colorectal Cancer Due to Deficiency in DNA Mismatch Repair Function A Review. Adv Anat Pathol 16: 405-417, 2009

[5] Shia J *et al.* Immunohistochemistry as First-line Screening for Detecting Colorectal Cancer Patients at Risk for Hereditary Nonpolyposis Colorectal Cancer Syndrome. Am J Surg Pathol 33: 1639-1645, 2009

[6] Quick Handbook for Surgical Pathologists, Chapter 2, Springer Verlag, 2011

[7] Zhao *et al.* Mismatch repair deficiency/microsatellite instability-high as a predictor for anti-PD-1/PD-L1 immunotherapy efficacy. J Hem & Onc 12:54, 2019

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A defective MMR leads to instability of the microsatellites (small repetitive DNA sequences) – MSI. The degree of instability can be determined by PCR. However, compared to MSI testing by PCR, immunohistochemical determination of the MMR proteins has the significant advantage that the defective protein is clearly detected. Thus, germline mutations and the risk of developing further tumors can be identified. The screening can be extended to other family members to predict their risk of developing Lynch syndrome (HNPCC) or endometrial cancer, for example. [1, 2, 3, 4, 5]

From the paired occurrence of the four MMR proteins result in five possible staining patterns, in which the nuclei are stained – or not stained in the absence of the protein. The staining patterns are caused by the fact that, depending on which protein is defective, both proteins may not be stained: MLH1 and PMS2 form the MutLα heterodimer. If the loss is in MLH1 (the dominant partner) located, PMS2 will also not be detected. If however, there is a loss of PMS2, MLH1 will continue to stain.

The situation is similar for MSH2 and MSH6 (MutSα). Here, MSH2 is the dominant partner. In the case of a loss of MSH2, MSH6 is also not detected. In the case of loss of MSH6, however, MSH2 is still stained [6].

Interpretation of immunohistochemical staining of DNA MMR proteins*

MLH1	PMS2	MSH2	MSH6	Interpretation IHC	Implication regarding germ cell mutation (Lynch syndrome) vs. sporadic loss.
+	+	+	+	No defects (all DNA MMR proteins expressed)	No evidence of defective MMR by ICH
-	-	+	+	MLH1 defect	~ 90% sporadic loss (hypermethylation of promoter) ~ 10 % germline mutation
+	-	+	+	PMS2 defect	Germline mutation is the most common mechanism for gene inactivation (only very few cases of MLH1 mutation results in this staining pattern)
+	+	-	-	MSH2 defect	Germline mutation is the most common mechanism for gene inactivation**
+	+	+	-	MSH6 defect	Germline mutation is the most common mechanism for gene inactivation

* after Hatch SB et al. Clin Cancer Res 11:2180-2187, 2005
+ invasive adenocarcinoma retains nuclear expression (expression may be patchy or weak)
- complete loss of nuclear staining by invasive adenocarcinoma (patchy expression is not assessed)
** Recent data show that loss of MSH2 can be caused by either inherited mutation of the MSH2 gene or inherited deletion of the 3' end of the EPCAM gene leading to inactivation of the adjacent MSH2 gene by initiation of methylation of its promoter.

Note: Epithelial cells in normal tissue, lymphocytes and stromal cells can be used as internal positive controls, which in any case must show a positive immune response.

The following table shows the exact gene information of the MMR proteins.

Gen information

Gen	Bezeichnung	Synonyme	Gen-ID	Gen-Lokalisation
MLH1	MutL homolog 1	COCA2, FCC2, HNPCC, HNPCC2, hMLH1	MIM120436	3p22.2
MSH2	MutS homolog 2	COCA1, FCC1, HNPCC, HNPCC1, LCFS2	MIM609309	2p21
MSH3	MutS homolog 3	DUP, MRP1	MIM600887	5q14.1
MSH6	MutS homolog 6	GTBP, GTMBP, HSAP, p160, HNPCC5	MIM609309	2p16.3
PMS2	PMS2 postmeiotic segregation increased 2 (S. cerevisiae)	HNPCC4, H_DJ0042M02.9, PMSL2, MLH4	MIM600259	7p22.1

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