

The pathogenesis of microsatellite unstable colorectal cancer and
the evaluation of novel diagnostic and therapeutic options

Forum Moderne Pathologie

Forum Modern Pathology

Schriftenreihe des Pathologischen Instituts
der Universitätsklinik Heidelberg

herausgegeben von
Prof. Dr. Peter Schirmacher

Band 15

Matthias Johannes Kloor

**The pathogenesis of microsatellite unstable
colorectal cancer and the evaluation of
novel diagnostic and therapeutic options**

Shaker Verlag
Aachen 2012

Bibliographic information published by the Deutsche Nationalbibliothek

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available in the Internet at <http://dnb.d-nb.de>.

Zugl.: Heidelberg, Univ., Habil.-Schr., 2011

Copyright Shaker Verlag 2012

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the publishers.

Printed in Germany.

ISBN 978-3-8440-1346-7

ISSN 1863-7515

Shaker Verlag GmbH • P.O. BOX 101818 • D-52018 Aachen

Phone: 0049/2407/9596-0 • Telefax: 0049/2407/9596-9

Internet: www.shaker.de • e-mail: info@shaker.de

Institut für Pathologie
Abteilung für Angewandte Tumoriologie
(Ärztlicher Direktor: Prof. Dr. Magnus von Knebel Doeberitz)

The pathogenesis of microsatellite unstable colorectal cancer and the evaluation of novel diagnostic and therapeutic options

Habilitationsschrift
zur Erlangung der Venia Legendi
für das Fach
Angewandte Tumoriologie
der Medizinischen Fakultät Heidelberg
der Ruprecht-Karls-Universität

Vorgelegt von
Dr. med. Matthias Johannes Kloor
aus Landau in der Pfalz

2011

Original publications included in this work:

Publications as a first or senior author:

Buckowitz A, Knaebel HP, Benner A, Bläker H, Gebert J, Kienle P, von Knebel Doeberitz M, and **Kloor M**: Microsatellite instability in colorectal cancer is associated with local lymphocyte infiltration and low frequency of distant metastases.
Br J Cancer 2005; 92: 1746-1753

Findeisen P, **Kloor M**, Merx S, Sutter C, Woerner S, Dostmann N, Benner A, Dondog B, Pawlita M, Dippold W, Wagner R, Gebert J, von Knebel Doeberitz M: T25 Repeat in the 3'Untranslated Region of the CASP2 Gene: A Sensitive and Specific Marker for Microsatellite Instability in Colorectal Cancer.
Cancer Res 2005; 65: 8072-8078 *shared first authorship*

Kloor M, Becker C, Benner A, Woerner S M, Gebert J, Ferrone S, von Knebel Doeberitz M: Immunoselective Pressure and Human Leukocyte Antigen Class I Antigen Machinery Defects in Microsatellite Unstable Colorectal Cancers.
Cancer Res 2005; 65: 6418-6424

Woerner SM, **Kloor M**, Mueller A, Rueschoff J, Friedrichs N, Buettner R, Buzello M, Kienle P, Knaebel HP, Kunstmann E, Pagenstecher C, Schackert HK, Moslein G, Vogelsang H, von Knebel Doeberitz M and Gebert JF: Microsatellite instability of selective target genes in HNPCC-associated colon adenomas.
Oncogene 2005; 24: 2525-2535 *shared first authorship*

Kloor M, Schwitalla Y, von Knebel Doeberitz M, Wentzensen N: Tetranucleotide repeats in coding regions: no evidence for involvement in EMAST carcinogenesis.
J Mol Med 2006; 84:329-333.

Kloor M, Michel S, Buckowitz B, Ruschoff J, Buttner R, Holinski-Feder E, Dippold W, Wagner R, Tariverdian M, Benner A, Schwitalla Y, Kuchenbuch B, von Knebel Doeberitz M. Beta2-microglobulin mutations in microsatellite unstable colorectal tumors.
Int J Cancer 2007; 121:454-458.

Woerner SM, **Kloor M**, Schwitalla Y, Youmans H, von Knebel Doeberitz, M., Gebert J, Dihlmann S: The putative tumor suppressor AIM2 is frequently affected by different genetic alterations in microsatellite unstable colon cancers.
Genes Chromosomes Cancer 2007; 46:1080-9. *shared first authorship*

Michel S, Benner A, Tariverdian M, Wentzensen N, Hoefler P, von Knebel Doeberitz M, **Kloor M**: Microsatellite instability is associated with a dense infiltration with regulatory T cells in colorectal cancer.
Br J Cancer 2008; 99:1867-1873.

Michel S, **Kloor M**, Singh S, Gdynia G, Roth W, von Knebel Doeberitz M, Schirmacher P, Bläker H. Coding microsatellite instability analysis in microsatellite unstable small intestinal adenocarcinomas identifies MARCKS as a common target of inactivation.

Mol Carcinog 2010;49(2):175-82. *shared first authorship*

Michel S, Linnebacher M, Alcaniz J, Voss M, Wagner R, Dippold W, Becker C, von Knebel Doeberitz M, Ferrone S, **Kloor M**: Lack of HLA class II antigen expression in microsatellite unstable colorectal carcinomas is caused by mutations in HLA class II regulatory genes.
Int J Cancer 2010;127(4):889-98.

Reuschenbach M, **Kloor M**, Morak M, Wentzensen N, Germann A, Garbe Y, Tariverdian M, Findeisen P, Neumaier M, Holinski-Feder E, von Knebel Doeberitz M: Serum antibodies against frameshift peptides in microsatellite unstable colorectal cancer patients with Lynch syndrome.
Fam Cancer 2010;9(2):173-9.

Publications as a coauthor:

Eckert A, **Kloor M**, Giersch A, Ahmadi R, Herold-Mende C, Hampl JA, Heppner FL, Zoubaa S, Holinski-Feder E, Pisch T, Wiestler OD, von Knebel Doeberitz M. et al.: Microsatellite instability in pediatric and adult high-grade gliomas.
Brain Pathol 2007; 17(2):146-150.

Schwitalle Y, **Kloor M**, Eiermann S, Linnebacher M, Kienle P, Knaebel HP, Tariverdian M, Benner A, von Knebel Doeberitz M: Immune Response Against Frameshift-Induced Neopeptides in HNPCC patients and healthy HNPCC mutation carriers
Gastroenterology 2008; 134:988-97.

Roeckel N, Woerner SM, **Kloor M**, Yuan YP, Patsos G, Gromes R, Kopitz J, Gebert J. High frequency of LMAN1 abnormalities in colorectal tumors with microsatellite instability.
Cancer Res 2009 Jan 1;69(1):292-9.

Table of Contents

Introduction	5
Discovery of microsatellite instability in colorectal cancer	6
Microsatellite instability and Lynch syndrome	7
The molecular consequences of mismatch repair deficiency	8
Microsatellite instability in sporadic colorectal cancer	9
Molecular pathogenesis and progression of microsatellite-unstable cancers	10
Microsatellite instability analysis in routine diagnostic procedures	11
Clinical and immunological characteristics of MSI-H CRCs	13
Infiltration with immune cells	13
Part I	
Identification of microsatellite mutations relevant for the development of MMR-deficient tumors	14
Coding microsatellite instability in colorectal adenomas	16
Establishment of a novel marker set for MSI analysis	18
Microsatellite instability and target gene inactivation in extracolonic tumors	20
Inactivation of cMS-bearing target genes AIM2 and LMAN1 in MSI-H CRC	22
Absence of coding tetranucleotide instability in EMAST tumors	23
Part II	
Characterization of clinical and immunological properties of MSI-H CRC	25
Prognosis and local immune infiltration in MSI-H CRC patients	25
Frameshift peptide-specific cellular immune responses in Lynch syndrome	27
Humoral FSP-specific immune responses in MSI-H CRC patients and Lynch syndrome	28
Part III	
Immune evasion and metastasis formation in MSI-H CRC	31
Alterations of HLA class I-mediated antigen presentation in MSI-H CRC	31
Beta2-Microglobulin mutations and metastasis formation in MSI-H CRC	32
HLA class II antigen expression and immune evasion in MSI-H CRC	36
High density of FOXP3-positive T cells in MSI-H CRC	38
Summary and Conclusions	41
References	44
Appendix	52
Curriculum vitae	
Bibliography	
Acknowledgements	