MYCN transcriptionally represses *CD9* to trigger an invasion-metastasis cascade in neuroblastoma

Johannes Fabian,[Aff1, $]
Corresponding Affiliation: [Aff1]

Desirée Opitz,[Aff1, $]

Kristina Althoff,[Aff2 Aff3]

Marco Lodrini,[Aff4]

Kathy Astrahantseff,[Aff4]

Barbara Hero,[Aff5]

Ruth Volland,[Aff5]

Anneleen Beckers,[Aff6]

Katleen de Preter,[Aff6]

Nitin S Patil,[Aff7 Aff8]

Mohammed L Abba,[Aff7 Aff8]

Theresa M Thole,[Aff4]

Jasmin Wünschel,[Aff4]

Annette Künkele,[Aff4]

Jamie Hu,[Aff1 Aff9]

Leonille Schweizer,[Aff10]

Gunhild Mechtersheimer,[Aff11]

Daniel R Carter,[Aff12]

Belamy B Cheung,[Aff12]

Odilia Popanda,[Aff13]

Andreas von Deimling,[Aff10 Aff14]

Kai-Oliver Henrich,[Aff15]

Frank Westermann,[Aff15]

Manfred Schwab,[Aff15]

Jan Koster,[Aff16]

Rogier Versteeg,[Aff16]

Glenn M Marshall,[Aff12 Aff17]

Frank Speleman,[Aff6]

Margot Zoeller,[Aff18]

Heike Allgayer,[Aff7 Aff8]

Matthias Fischer,[Aff5 Aff19]

Frank Berthold,[Aff5 Aff19]

Andreas E Kulozik,[Aff20]

Olaf Witt,[Aff1 Aff20]

Angelika Eggert,[Aff4]

Johannes H Schulte,[Aff2 Aff3 Aff21 Aff22]

Hedwig E Deubzer,[Aff4]

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Aff1
Clinical Cooperation Unit Pediatric ncology, German Cancer Research Center (DKFZ), INF 280, 69120 Heidelberg, Germany

Aff2
Department of Pediatric Hematology & Oncology, University Children's Hospital Essen, Hufeland Str. 55, 45147 Essen, Germany

Aff3
Translational Neurooncology, German Consortium for Translational Cancer Research (DKTK), Partner Site Essen/ Duesseldorf, Essen, Germany

Aff4
Department of Pediatric Hematology, Oncology & BMT, Charité - University Hospital Berlin, CVK, Augustenburgerplatz 1, 13353 Berlin, Germany

Aff5
Department of Pediatric Hematology and Oncology, University of Cologne, Kerpener Str. 62, 50937 Cologne, Germany

Aff6
Center for Medical Genetics Ghent (CMGG), Ghent University Hospital Medical Research Building (MRB), De Pinelaan 185, Ghent, Belgium

Aff7
Molecular Oncology of Solid Tumors Unit, DKFZ, INF280, 69120 Heidelberg, Germany

Aff8
Department of Experimental Surgery, Medical Faculty Mannheim, University of Heidelberg, Mannheim 68135, Germany

Aff9
Cornell University, 300 Day Hall, Ithaca, NY 14853, USA

Aff10
Department of Neuropathology, University of Heidelberg, INF 224, 69120 Heidelberg, Germany

Aff11
Department of Pathology, University of Heidelberg, INF224, 69120 Heidelberg, Germany

Aff12
Children's Cancer Institute, UNSW, Corner High & Botany Streets, Randwick, New South Wales 2031, Australia

Aff13
Division of Epigenomics and Cancer Risk Factors, DKFZ, INF 280, 69120 Heidelberg, Germany

Aff14
Clinical Cooperation Unit Neuropathology, DKFZ, INF280, 69120 Heidelberg, Germany

Aff15
Neuroblastoma Genetics, DKFZ, INF280, 69120 Heidelberg, Germany

Aff16
Department of Oncogenomics, Academic Medical Center, University of Amsterdam, Meibergdreef 15, PO Box 22700, 1105 AZ Amsterdam, The Netherlands

Aff17
Kids Cancer Centre, Sydney Children's Hospital Randwick, High Street, Randwick, New South

Wales 2031, Australia

Aff18
Experimental Surgery and Tumor Cell Biology, University of Heidelberg, INF 365, 69120 Heidelberg, Germany

Aff19
Center for Molecular Medicine Cologne, University of Cologne, Robert-Koch-Str. 21, 50931 Cologne, Germany

Aff20
Department of Pediatric Hematology and Oncology, University of Heidelberg, INF 430, 69120 Heidelberg, Germany

Aff21
Translational Neuro-Oncology, West German Cancer Center (WTZ), University Hospital Essen, University Duisburg-Essen, Hufeland Str. 55, 45147 Essen, Germany

Aff22
Center for Medical Biotechnology, University Duisburg-Essen, 45117 Essen, Germany

$
Author contributed equally with all other contributors.

Misc
Johannes Fabian, Desirée Opitz contributed equally to this work.

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The systemic and resistant nature of neuroblastoma metastasized to distant organs makes it largely incurable with current multimodal treatment. Clinical progression stems mainly from an increasing burden of metastatic colonization. Novel therapeutic perspectives may be won by blocking as yet poorly understood pathways triggering the migration-invasion-metastasis cascade in neuroblastoma. The CD9 cell surface glycoprotein was decoded as a major downstream player and direct target of the recently described *GRHL1* tumor suppressor in in-depth transcriptome analyses and ChIP-qRT-PCR. CD9 is known to facilitate carcinoma cell motility and metastasis. High-level CD9 expression in primary neuroblastomas correlated with patient survival and established markers for favorable disease. Low-level *CD9* expression was an independent risk factor for adverse outcome and predicted poor treatment response in patients with the worst outcome. MYCN and HDAC5 co-localized to the *CD9* promoter and repressed transcription. *CD9* expression was strongly reduced during progressive development of murine tumors in the *TH-MYCN* transgenic mouse model of neuroblastoma compared to expression in ganglia from wildtype mice, further supporting MYCN involvement in *CD9* transcriptional repression in neuroblastoma cells. We detected differential *CD9* methylation in 450K methylation array analyses of primary neuroblastomas, and *CD9* hypermethylation was associated with reduced *CD9* expression, supporting epigenetic regulation. Inducing CD9 expression in a SH-EP cell model inhibited migration and invasion in Boyden chamber assays. Enforced CD9 expression in neuroblastoma cells transplanted onto chicken chorioallantoic membranes strongly reduced metastasis to chicken embryo bone marrow. Combined treatment of neuroblastoma cells with inhibitors for

HDACs and DNA methyltransferase induced CD9 expression. Our results show CD9 is a critical and indirectly druggable mediator of neuroblastoma cell invasion and metastasis.