ScienceDirect

Developmental Cell

Available online 2 July 2025

In Press, Corrected Proof What's this?

Article

Therapeutic radiation drives leptomeningeal dissemination of medulloblastoma through an innate immune process

Carolina Nör [1 2 21], Kaitlin Kharas [1 2 3 21], Alex Rasnitsyn [1 2 4], Maria C. Vladoiu [1 2 3], Nam Woo Cho [5 6], Jacob S. Young [7], Felipe Nör [8], Ncedile Mankahla [1 2], Joonas Haapasalo [1 2], Kristiina Nordfors [1 2], Sara Rapic [9], Patryk Skowron [1 2], Raúl A. Suárez [1 2], Alexander T. Bahcheli [10 11], Oliver Ocsenas [4 10], Xin Chen [1 2], Shahrzad Bahrampour [1 2], Ali Momin [1 2], Lakshmikirupa Sundaresan [1 2], Winnie Ong [1 2 3], Liam D. Hendrikse [1 2 4], Namal Abeysundara [1 2], Kyle Juraschka [1 2 3], Michelle Ly [1 2 3], Jonelle G. Pallota [1 2], Tajana Douglas [1 2], Ning Huang [1 2], Hao Wang [1 2], Esta Mak [1 2], Lei Qin [1 2], Jessica Liu [1 2], Lily Shen [1 2], Betty Luu [1 2], Alex Manno [1 2], Sachin A. Kumar [1 2 3], Laura K. Donovan [1 2], Vernon Fong [1 2 3], Cory Richman [1 2 4], Craig Daniels [1 2 12 13], Livia Garzia [14], Jeremy N. Rich [15], Cynthia Hawkins [2 3], Xiaochong Wu [1 2 12 13], Ralph DaCosta [4 9], Jüri Reimand [4 10 11], Xi Huang [1 2 11], Vijay Ramaswamy [1 2 4 16 22] ✉, David R. Raleigh [5 7 22] ✉, Michael D. Taylor [1 2 3 4 12 13 17 18 19 20 22 23] ✉

[1] Developmental and Stem Cell Biology, Hospital for Sick Children, Toronto, ON, Canada
[2] Arthur and Sonia Labatt Brain Tumour Centre, Hospital for Sick Children, Toronto, ON, Canada
[3] Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada
[4] Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada
[5] Department of Radiation Oncology, University of California, San Francisco, San Francisco, CA, USA
[6] Department of Otolaryngology-Head and Neck Surgery, University of California, San Francisco, San Francisco, CA, USA
[7] Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA, USA
[8] Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry, Ann Arbor, MI, USA
[9] Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada
[10] Computational Biology Program, Ontario Institute for Cancer Research, Toronto, ON, Canada
[11] Department of Molecular Genetics, University of Toronto, Toronto, ON, Canada
[12] Texas Children's Cancer and Hematology Center, Houston, TX, USA
[13] Department of Pediatrics, Hematology/Oncology, Baylor College of Medicine, Houston, TX, USA
[14] Department of Surgery, Faculty of Medicine and Health Sciences, McGill University, Montreal, QC, Canada

[15] Hillman Cancer Center, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
[16] Division of Haematology/Oncology, Hospital for Sick Children, Toronto, ON, Canada
[17] Division of Neurosurgery, Hospital for Sick Children, Toronto, ON, Canada
[18] Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, TX, USA
[19] Department of Neurosurgery, Baylor College of Medicine, Houston, TX, USA
[20] Department of Neurosurgery, Texas Children's Hospital, Houston, TX, USA

Received 8 December 2024, Revised 23 March 2025, Accepted 9 June 2025, Available online 2 July 2025.

https://doi.org/10.1016/j.devcel.2025.06.016 ↗

Highlights

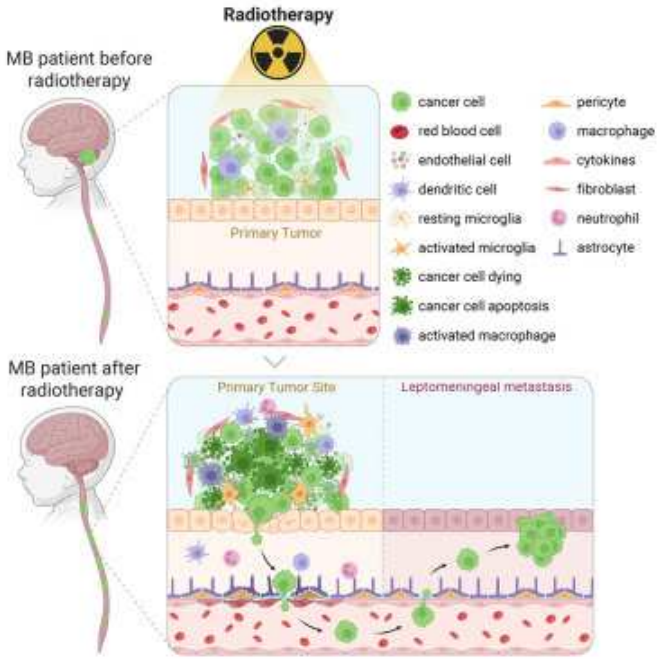
- Radiation induces inflammation and opens the blood-brain barrier in medulloblastoma
- Radiation drives medulloblastoma leptomeningeal dissemination *in vivo*
- An inflammatory agent induces leptomeningeal metastasis in medulloblastoma
- Dexamethasone prevents inflammation and the pro-metastatic effect of radiation

Summary

Leptomeningeal metastases are the most important source of morbidity and mortality for medulloblastoma patients. Radiation of the entire brain is highly effective in the treatment and/or prevention of medulloblastoma leptomeningeal metastases. Infants treated on clinical trials with focal tumor radiation recur metastatically, whereas infants treated with only chemotherapy relapse locally. In murine medulloblastoma model systems, provision of a single dose of radiation to the tumor drives leptomeningeal dissemination. An inflammatory response after radiation-induced tumor cell death recruits a variety of immune cells. Inflammation opens the local blood-brain barrier, allowing intravasation of medulloblastoma cells. Experimental induction of inflammation with lipopolysaccharide drives medulloblastoma leptomeningeal dissemination, whereas premedication with corticosteroids prevents both inflammation and the

pro-metastatic effect of radiation. In murine model systems, inflammation in the tumor microenvironment secondary to external beam radiation is both sufficient and necessary to drive leptomeningeal metastases.

Graphical abstract



Download: Download high-res image (230KB)

Download: Download full-size image

Introduction

Medulloblastomas metastasize almost exclusively to the leptomeninges, which consist of the pia mater, the arachnoid mater, and the blood vessels of the sub-arachnoid space.[1,2,3,4,5] Medulloblastoma metastases to the actual sub-pial substance of the brain proper or to systemic locations outside of the central nervous system (CNS) are extremely rare and usually only seen in highly treated patients.[6,7] The biological mechanisms behind medulloblastoma's specificity for the leptomeninges are currently unknown. It is uncertain whether medulloblastoma spreads from the primary tumor to the leptomeninges by shedding cells into the cerebrospinal fluid, followed by implantation after landing on the leptomeninges, or whether metastases occur after hematogenous dissemination followed by specific homing to the leptomeninges from the peripheral blood circulation.[8] A subset of medulloblastoma patients have leptomeningeal metastases on magnetic resonance imaging (MRI) at the time of presentation, with the best-known risk factor being the molecular subgroup affiliation of the primary tumor (group 3 > group 4 > Sonic Hedgehog (Shh) > Wingless (Wnt) medulloblastoma).[3,9,10] The presence of MRI-evident leptomeningeal metastases at diagnosis portends a very poor prognosis for affected children.[11,12]

Current standard therapy for non-infantile medulloblastoma is maximal safe neurosurgical resection, followed by craniospinal radiotherapy, and ending with cytotoxic chemotherapy.[3] Of these current therapies, radiation is by far the most efficacious at treating medulloblastoma and at preventing leptomeningeal recurrence of medulloblastoma post standard therapy. Children under the age of 3 or 4 years are not administered craniospinal radiation due to the severe deleterious effects on growth, the endocrine system, and the development of the infant brain. Humans of any age who are treated with craniospinal radiation suffer secondary effects of the radiation on the CNS, effects that are often highly impactful on the patient's quality of life and that tend to worsen progressively with age.[13] Regardless of their metastatic status at presentation, many patients will have no evidence of disease on their MRI scan at the end of therapy. A subset of patients with no evidence of disease on their MRI post therapy will then recur over time, with the vast majority of recurrences being leptomeningeal metastases.[7,14,15] The specific cellular and/or molecular mechanisms by which initially non-metastatic medulloblastoma disseminates or by which leptomeningeal metastases recur after therapy are currently obscure.

There are currently no biological targeted agents or immunotherapies approved for the treatment of either primary medulloblastoma (of any subgroup) or metastatic medulloblastoma. Genomic comparison of medulloblastoma primary tumors and their metastases from both human children and genetically engineered mouse models (GEMMs) has demonstrated that the transcriptome and genetics of leptomeningeal metastases are highly divergent from that of their matched primary tumor and strongly suggests that any biologically based therapies are less likely to simultaneously work in both the primary tumor and the metastatic tumor compartment.[16,17] Despite the fact that the vast majority of medulloblastoma deaths are secondary to metastatic disease, almost all of the published literature on the biology of medulloblastoma focuses exclusively on the primary tumor.

Although infants with medulloblastoma are not treated with craniospinal radiation, in some clinical treatment protocols, the local tumor bed in the posterior fossa is treated with focal irradiation.[18,19,20,21] We anecdotally observed—based on prior clinical trials as well as analysis of patients within the MAGIC consortium—that although local tumor radiation does not demonstrably increase progression-free survival, it does appear to shift the recurrence pattern from local tumor bed recurrence to metastatic leptomeningeal recurrence. In our animal models of medulloblastoma, radiation kills the medulloblastoma cells with great efficacy. This results in an inflammatory microenvironment that disrupts the local blood-brain barrier (BBB), allowing both the influx of activated immune cells and the intravasation of medulloblastoma cells. This inflammatory cascade culminates in an increased incidence of leptomeningeal metastases. The possibility that treatment is associated with leptomeningeal dissemination offers an opportunity to develop strategies to contemporaneously block leptomeningeal dissemination due to radiation-induced inflammatory tumor cell death and, therefore, to perhaps increase the long-term survival rate for medulloblastoma patients.

Section snippets

Patterns of relapse after radiotherapy

Standard therapy for most children with medulloblastoma over the age of 3 years includes irradiation of the entire brain and spinal cord. Children under 3 years do not receive craniospinal radiation due to its devastating effects on the developing nervous system. A subset of infants in medulloblastoma clinical trials have been treated with focal tumor irradiation as opposed to being treated with cytotoxic chemotherapy alone. Most infants with medulloblastoma have Shh tumors, a minority have …

Discussion

Most of the deaths among medulloblastoma patients are secondary to metastatic disease. The worst of the morbidity among medulloblastoma survivors is secondary to treatment of leptomeningeal metastatic disease or prophylaxis against metastatic disease.[13] Future efforts to increase long-term survival, and to increase the quality of life for medulloblastoma patients, will necessarily focus on the metastases. Clinical material from actual medulloblastoma metastases is difficult to obtain as there …

Lead contact

Further information and requests for resources and reagents should be directed to, and will be fulfilled by, the lead contact, Michael D. Taylor (michael.taylor@bcm.edu ↗). …

Materials availability

This study did not generate new unique reagents. …

Data and code availability

Both bulk and single-cell RNA-seq data have been deposited at GEO and are publicly available as of the date of publication, with the accession numbers GEO: GSE266047 and GEO: GSE266048 ↗, respectively. Original code was not generated as part of this study, but details on analysis …

Acknowledgments

C.N. was supported by the National Council for Scientific and Technological Development (CNPQ 201001/2014-4), the Brain Tumour Foundation of Canada William Donald Nash Brain Tumour

Research Fellow, and the Swifty Foundation. M.D.T. is a CPRIT Scholar in Cancer Research (CPRIT – RR220051). M.D.T. is supported by the NIH (R01NS106155, R01CA159859, and R01CA255369), The Pediatric Brain Tumour Foundation, The Terry Fox Research Institute, The Canadian Institutes of Health Research, The Cure Search …

Author contributions

Conceptualization, C.N. and M.D.T.; data curation, A.R., M.C.V., C.N., and V.R.; formal analysis, C.N., K.K., A.R., V.R., M.C.V., L. Sundaresan, N.W.C., J.S.Y., F.N., S.R., A.T.B., O.O., X.C., and S.B.; funding acquisition, M.D.T., C.D., and C.N.; investigation, C.N., K.K., A.R., M.C.V., V.R., N.W.C., J.S.Y., F.N., S.R., X.C., and S.B.; methodology, M.D.T., C.N., L.G., J.N.R., and X.W. project administration, M.D.T., C.D., and X.W.; resources, C.N., K.K., P.S., R.A.S., N.M., J.H., K.N., S.K., …

Declaration of interests

The authors declare no competing interests. …

Key resources table

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
Ki67	Abcam	Ab15580
Cleaved Caspase3	Cell Signaling	9661
MHCII	Becton Dickinson	556999
Ly6B	Serotec	MCA771GA
CD68	Abcam	Ab125212
IBA1	Abcam	Ab153496
^{89}Y CD45	Biolegend	103102
^{111}Cd CD3	Biolegend	100202
^{112}Cd CD64	Biolegend	139302
^{113}In Ter119	Biolegend	116202
^{114}Cd CD8	Biolegend	100702
^{116}Cd CD4	Biolegend	100506
^{139}La Ly6G	Biolegend	127626
^{140}Ce KLRG1	BD biosciences	562190
^{141}Pr Granzyme B	Biolegend	372202

REAGENT or RESOURCE	SOURCE	IDENTIFIER
^{142}Nd CD49b	Biolegend	103501
^{143}Nd CD11c	Biolegend	117341
^{144}Nd CD206	Biolegend	141702
^{145}Nd CD27		

...

...

...

Recommended articles

References (65)

L. Garzia *et al.*
A Hematogenous Route for Medulloblastoma Leptomeningeal Metastases
Cell (2018)

V. Ramaswamy *et al.*
Recurrence patterns across medulloblastoma subgroups: an integrated clinical and molecular analysis
Lancet Oncol. (2013)

G.W. Robinson *et al.*
Risk-adapted therapy for young children with medulloblastoma (SJYC07): therapeutic and molecular outcomes from a multicentre, phase 2 trial
Lancet Oncol. (2018)

A. Boire *et al.*
Complement Component 3 Adapts the Cerebrospinal Fluid for Leptomeningeal Metastasis
Cell (2017)

O.A. Martin *et al.*
Mobilization of viable tumor cells into the circulation during radiation therapy
Int. J. Radiat. Oncol. Biol. Phys. (2014)

Y.C. Zhou *et al.*
Ionizing radiation promotes migration and invasion of cancer cells through transforming growth factor-beta-mediated epithelial-mesenchymal transition
Int. J. Radiat. Oncol. Biol. Phys. (2011)

E.M. Thompson *et al.*
Prognostic value of medulloblastoma extent of resection after accounting for molecular subgroup: a retrospective integrated clinical and molecular analysis
Lancet Oncol. (2016)

E.A. Lumpkin *et al.*
Math1-driven GFP expression in the developing nervous system of transgenic mice
Gene Expr. Patterns (2003)

F.M.G. Cavalli *et al.*
Intertumoral Heterogeneity within Medulloblastoma Subgroups
Cancer Cell (2017)

Y. Hao *et al.*
Integrated analysis of multimodal single-cell data
Cell (2021)

View more references

Cited by (0)

21 These authors contributed equally

22 Senior author

23 Lead contact

View full text