ABSTRACT

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Mechanosensitive brain tumor cells construct blood-tumor barrier to mask chemosensitivity.

Chen X(1), Momin A(2), Wanggou S(3), Wang X(1), Min HK(2), Dou W(4), Gong Z(4), Chan J(2), Dong W(2), Fan JJ(2), Xiong Y(3), Talipova K(1), Zhao H(3), Chen YX(5), Veerasammy K(5), Fekete A(6), Kumar SA(1), Liu H(7), Yang Q(7), Son JE(8), Dou Z(9), Hu M(1), Pardis P(1), Juraschka K(1), Donovan LK(1), Zhang J(1), Ramaswamy V(1), Selvadurai HJ(1), Dirks PB(2), Taylor MD(10), Wang LY(11), Hui CC(9), Abzalimov R(5), He Y(5), Sun Y(4), Li X(12), Huang X(13).

Author information:
(1)Program in Developmental and Stem Cell Biology, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; Arthur and Sonia Labatt Brain Tumour Research Centre, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada.
(2)Program in Developmental and Stem Cell Biology, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; Arthur and Sonia Labatt Brain Tumour Research Centre, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; Department of Molecular Genetics, University of Toronto, Toronto, ON M5S 3E1, Canada.
(3)Program in Developmental and Stem Cell Biology, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; Arthur and Sonia Labatt Brain Tumour Research Centre, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; Department of Neurosurgery, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China; Hunan International Scientific and Technological Cooperation Base of Brain Tumor Research, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China.
(4)Department of Mechanical and Industrial Engineering, University of Toronto, Toronto, ON M5S 3G8, Canada.
(5)Advanced Science Research Center at the Graduate Center, City University of New York, New York, NY 10031, USA.
(6)Program in Neurosciences and Mental Health, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada.
(7)Department of Neurosurgery, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China; Hunan International Scientific and Technological Cooperation Base of Brain Tumor Research, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China.
(8)Program in Developmental and Stem Cell Biology, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada.
(9)Program in Developmental and Stem Cell Biology, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; Department of Molecular Genetics, University of Toronto, Toronto, ON M5S 3E1, Canada.
(10)Program in Developmental and Stem Cell Biology, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; Arthur and Sonia Labatt Brain Tumour Research Centre, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; Department of Surgery, University of Toronto, Toronto, ON M5S 3E1, Canada; Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON M5S 3E1, Canada.
(11)Program in Neurosciences and Mental Health, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; Department of Physiology, University of Toronto, Toronto, ON M5S 1A8, Canada.
(12)Department of Neurosurgery, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China; Hunan International Scientific and Technological Cooperation Base of Brain Tumor Research, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China. Electronic address: lxjneuro@csu.edu.cn.
(13)Program in Developmental and Stem Cell Biology, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; Arthur and Sonia Labatt Brain Tumour

Research Centre, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; Department of Molecular Genetics, University of Toronto, Toronto, ON M5S 3E1, Canada. Electronic address: xi.huang@sickkids.ca.

Major obstacles in brain cancer treatment include the blood-tumor barrier (BTB), which limits the access of most therapeutic agents, and quiescent tumor cells, which resist conventional chemotherapy. Here, we show that Sox2+ tumor cells project cellular processes to ensheathe capillaries in mouse medulloblastoma (MB), a process that depends on the mechanosensitive ion channel Piezo2. MB develops a tissue stiffness gradient as a function of distance to capillaries. Sox2+ tumor cells perceive substrate stiffness to sustain local intracellular calcium, actomyosin tension, and adhesion to promote cellular process growth and cell surface sequestration of β-catenin. Piezo2 knockout reverses WNT/β-catenin signaling states between Sox2+ tumor cells and endothelial cells, compromises the BTB, reduces the quiescence of Sox2+ tumor cells, and markedly enhances the MB response to chemotherapy. Our study reveals that mechanosensitive tumor cells construct the BTB to mask tumor chemosensitivity. Targeting Piezo2 addresses the BTB and tumor quiescence properties that underlie treatment failures in brain cancer.

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