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Pediatric Brain Tumor Cell Lines

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Abstract

Pediatric brain tumors as a group, including medulloblastomas, gliomas and atypical teratoid rhabdoid tumors (ATRT) are the most common solid tumors in children and the leading cause of death from childhood cancer. Brain tumor-derived cell lines are critical for studying the biology of pediatric brain tumors and can be useful for initial screening of new therapies. Use of the appropriate brain tumor cell line for experiments is important, as results may differ depending on tumor properties, and can thus affect the conclusions and applicability as a model. Despite reports in the literature of over 60 pediatric brain tumor cell lines, the majority of published papers utilize only a small number of these cell lines. Here we list the approximately 60 currently-published pediatric brain tumor cell lines and summarize some of their central features as a resource for scientists seeking pediatric brain tumor cell lines for their research.

Keywords

ATRT; ependymoma; glioma; medulloblastoma; pediatric brain tumor cell lines

Pediatric brain tumors

Tumors of the central nervous system (CNS) comprise approximately 20% of all cancers in children up to 14 years of age and about 10% of tumors occurring among 15 to 19 year-olds, making them the most common solid tumors in children, and second in incidence only to leukemias [1]. Brain tumors are among the leading causes of death from childhood cancer and one of the leading causes of children's death from any disease. Table 1 lists the common pediatric brain tumors. Among pediatric brain tumors, gliomas and embryonal tumors are the most common, accounting for 53% and 16% in children ages 0-14 years, respectively [1]. A detailed description of pediatric brain tumors is provided elsewhere [2–4]. It is important to recognize that pediatric brain tumors are different from adult brain tumors in many respects, including the relative frequency and incidence of tumor types, molecular characteristics, biology, clinical behavior, and treatment approaches [5–7]. When conducting

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experiments related to pediatric brain tumors, it is therefore important to use cell lines and primary isolates that are as closely related to the tumor being studied as possible.

Models used to study pediatric brain tumors

Biology of human cancer can be studied using a number of tools, including direct use of tumors, and modeling in genetically engineered mice (GEMs), with each approach tailored for specific research purposes. Primary surgical tumor samples preserve a snapshot of the histology, complex composition, heterogeneity and microenvironment of the original tumors. Some surgical tumor samples may also be amenable to direct implantation and passaging in mice in attempt to preserve the *in vivo* growth characteristics of the primary tumor. However, direct passaging in mice is limited due to 1) its high costs, 2) risk that serial passaging in mice may confer characteristics unrelated to the original tumor due to acquisition of elemnts such as murine retroviruses [8], and 3) change in the composition of the original tumor, which include tumor cells and cells of the tumor microenvironment, that with subsequent passages incorporates elements from the mouse microenvironment.

When pure tumor cells are needed for experiments, the most frequently used are tumor cell lines, both primary and continuous. Tumors that are most amenable to growing as continuous cell lines are typically those which are fast growing, likely explaining the relative paucity of low-grade tumor cell lines. Cell lines are used in experiments *in vivo* and *in vitro* and are indispensible to researchers due to their relatively uniform nature, availability, ease of sharing between laboratories and relative ease of *in vitro* expansion, manipulation and experimentation. The Pediatric Preclinical Testing Program (PPTP) uses a panel of such cell lines, including a small number of pediatric brain tumor cell lines, to test drugs in pediatric cancers [9–13].

In vivo experimental models for pediatric brain tumors include subcutaneous and orthotopic intracranial xenografts in mice and genetically-engineered models. Subcutaneous xenografts are easier to initiate and monitor over time compared to intracranial ones, but are limited by being in the non-brain microenvironment. Experiments using intracranial orthotopic xenografts are more cumbersome to initiate, require a higher level of expertise, and monitoring of their growth requires specialized imaging. The advantage of intracranial models is that they grow in a brain microenvironment, albeit a mouse rather than human brain. Even the exact location of injection within the brain can affect the characteristics of resulting tumors . Another limitation of xenografts is that they require an immune compromised recepient to prevent rejection, which limits studies related to the tumor microenvironment. Genetically engineered models on the other hand, provide an immune competent microenvironment and can be modelled according to defined needs, although this may require extensive efforts [14–17]. Moreover, they allow both *de novo* growth of tumors, as well as transplantation of *ex vivo*-manipulated GEM tumor cells into transplant-compatible mice. Optimally, studies should choose models appropriate for the question being asked, and if possible, utilize more than one type of model. This review, intended to serve as a resource for researchers, will highlight continous cell lines from pediatric brain tumors.

Neurosphere cultures for generation of brain tumor cell lines

Pediatric brain tumor cell lines have been historically difficult to generate compared to pediatric tumors such as high risk neuroblastomas, of which a well-characterized panel of over a hundred cell lines is available for researchers [18, 19]. Pediatric brain tumor cell lines have been difficult to establish, with only five published prior to 1990 [20–24]. Over the next decade 20 additional pediatric brain tumor cell lines were published, with the remaining 46 published after the year 2000 (Table 2). Use of neurosphere culture [25], where cells are grown under non-adherent conditions and without fetal bovine serum, may further increase the success of establishing continuous cell lines from aggressive brain tumors, including those from pediatric patients [26, 27]. Neurosphere cultures are thought to better preserve the three-dimensional environment, decrease the incidence of further mutations and maintain cancer stem-like properties of tumor cells [28, 29]. However, neurosphere cultures also have some limitations [30]. These include 1) change in composition and properties of cells in neurospheres in response to culture conditions, cell density, frequency of passaging, number of passages, and relative spatial position of cells within the neurosphere, making it hard to compare between experiments and laboratories; 2) technical challenges of working with neurospheres due to cumbersome imaging, difficulty in genetic and therapeutic manipulation, and limitations in monitoring of individual cells; 3) inconsistent stem-like properties of cells in neurospheres [31]; 4) Not all brain tumor cell lines can form neurospheres. Consequently, laboratory work relies on a combination of models, depending on availability of cells, the needs of the experiment and the nature of the cells used.

Pediatric Brain Tumor Cell Lines

To facilitate access of researchers to available pediatric brain tumor cell lines, Table 2 summarizes cell lines reported in the literature and lists some of their essential information, including diagnosis, *in vivo* xenograft growth, and publication(s) describing them. Only a small number of pediatric brain tumor cell lines are available from central repositories such as ATCC or COG. Other lines can only be obtained by requisition from the publishing invesitigators, thus limiting their availiability to the research community. Table 2, which lists pediatric brain tumors and their sources, is intended to serve as a resource for scientists seeking pediatric brain tumor cell lines for their experiments.

Notes on specific cell lines

Medulloblastoma cell lines: Recently-accepted molecular-based classification divides medulloblastomas into four molecular subgroups: WNT, Sonic Hedgehog (SHH), Group 3 and Group 4, based on their mRNA expression profile. These subgroups also differ in epidemiology, clinical features and biology [32–34]. Molecular subgroup is assigned to a growing number of medulloblastoma cell lines (Table 3), and is important for research in medulloblastoma.

Of the medulloblastoma cell lines the most commonly published are D283MED, D341MED, D425MED, and UW228-2. DAOY, the most commonly reported, has been used in over 275 published papers over almost 30 years [20, 35]. The basis for the somewhat different microarray profile of DAOY cells is not known [36]. Increasingly, primary

low-passage surgical isolates of medulloblastoma are becoming available for researchers, although these typically are more difficult to work with than traditional cell lines. Two unique lines added recently are CHLA-01-MED and CHLA-01R-MED, derived from a primary medulloblastoma and its post-chemoradiotherapy recurrence. Over 25 other medulloblastoma cell lines are available from various sources. Their subgroup characterization will make them more useful and their use will likely become more widespread.

Glioma cell lines: There are fewer continuous cell lines from pediatric gliomas compared to medulloblastomas, despite glioma incidence being several fold higher than medulloblastomas in children. A possible explanation may be that most pediatric gliomas at diagnosis are low grade tumors, and as such, do not lend themselves to continuous growth in culture. Glioblastoma multiforme (GBM, WHO IV glioma), the most malignant of gliomas, grows readily under culture conditions, but is infrequent in children, possibly explaining the paucity of pediatric GBM cell lines. In adults on the other hand, GBMs constitutes about half of all gliomas, accounting for the many primary and continuous adult GBM cell lines available.

Atypical Teratoid Rhabdoid Tumors: Atypical teratoid rhabdoid tumors (ATRT) were recognized as a distinct entity in the late 1980's and beginning 1990's [37]. Typical to them is loss of expression of the *SMARCB1* (*INI1*) gene [38]. Prior to that period, these highly malignant and aggressive brain tumors of early childhood were frequently diagnosed as medulloblastomas or primitive neuroectodermal tumors (PNET). It is therefore possible that some earlier cell lines generated from medulloblastoma, PNET, or even pediatric GBM generated prior to reliable diagnosis of ATRT may have not been categorized as such. If doubt exists, examination of SMARCB1 expression or sequencing may answer the question. It is surprising that despite the relatively higher success of growth in culture of ATRTs, their proportion among pediatric brain tumors, and the increased research in the field, there is only a limited number of published ATRT cell lines (Table 2).

Other pediatric brain tumor cell lines—Other pediatric brain tumor cell lines are infrequent, probably owing to their lower incidence and the less extensive research efforts and grant funding opportunities devoted to them.

Summary—Pediatric brain tumor cell lines are invaluable for research. Depositing them in a central repository and sharing them among investigators is critical for enhancing research on pediatric brain tumors.

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Table 1:

Pediatric Brain Tumors, Summary

TUMORS IN THE BRAIN THAT ORIGINATED IN BRAIN-DERIVED CELLS:			
General Category		**Histological Type**	**Other names used:**
Gliomas	Astrocytoma	Pilocytic astrocytoma (WHO grade I) Astrocytoma (WHO grade II) Anaplastic astrocytoma (WHO grade III) Glioblastoma multiforme (WHO grade IV)	- Brain Stem Glioma (including diffuse intrinsic brain stem glioma, DIPG) - Tectal Glioma - Optic Glioma
	Ependymoma	Ependymoma Anaplastic ependymoma	
	Ganglioglioma	Ganglioglioma Anaplastic Ganglioglioma	
	Oligodendroglioma	Oligodendroglioma (WHO grade II) Anaplastic oligodendroglioma (WHO grade III) Glioblastoma multiforme (WHO grade IV)	
	Mixed gliomas	Oligoastrocytoma	
Non-gliomas	Embryonal tumors	Medulloblastoma	Previously called **infra**tentorial PNET
		PNET (primitive neuroectodermal tumor)	Previously called **supra**tentorial PNET
		AT/RT (atypical teratoid rhabdoid tumor)	
	Choroid plexus tumor	Choroid plexus papilloma Choroid plexus carcinoma	

TUMORS IN THE BRAIN WHICH ORIGINATED FROM CELLS EXTRINSIC TO BRAIN TISSUE:			
Germ Cell Tumors	Germinoma		
	Non-germinomatous germ cell tumors	Teratoma Yolk sac tumor Embryonal carcinoma Choriocarcinoma	
	Mixed malignant germ cell tumor		
Craniopharyngioma			
Meningioma	Meningioma Malignant meningioma		
Others			

Table 2:

Current available pediatric brain tumor cell lines in literature.

Cell Line	Diagnosis	Age	Male/ Female	Year 1st Paper	Source	Tumorigenic *in vivo*	Neurosphere culture	Literature Citations	Ref
D283MED	Medulloblastoma	6 yr	M	1985	ATCC	Y	Y	***	[21];HTB-185
DAOY	+Medulloblastoma	4 yr	M	1985	ATCC	Y	Y	***	[22];HTB-186
D341MED	Medulloblastoma (metastasis from peritoneum)	3.5 yr	M	1988	ATCC	Y		***	[20];HTB-187
ONS-76	Medulloblastoma	2 yr	F	1989	JCRB	Y	Y	**	[23]
D384MED	Medulloblastoma	17 mo	M	1991		Y		**	[39]
D425MED	Medulloblastoma	5 yr	M	1991		Y		**	[39]
D458MED	Medulloblastoma			1991		Y		**	[39]
MHH-MED-1	Medulloblastoma	10 yr	M	1994		Y	Y	*	[40]
MHH-MED-2	Medulloblastoma	6 yr	F	1994		Y	Y	*	[40]
MHH-MED-3	Medulloblastoma	3 yr	F	1994		Y	Y	*	[40]
MHH-MED-4	Medulloblastoma	4 yr	M	1994		Y	Y	*	[40]
UW228-1	Medulloblastoma	9 yr	F	1995		Y	Y	**	[31]
UW228-2	Medulloblastoma	9 yr	F	1995		Y		***	[31]
UW228-3	Medulloblastoma	9 yr	F	1995		Y		**	[31]
UW443	Medulloblastoma	9yr	F	1995				*	[31]
D487MED	Medulloblastoma			1997		Y		**	[41]
UW402	Medulloblastoma			2001		N	Y	**	[42]
D556MED	Medulloblastoma	7 yr	F	2002		Y		**	[43]
D581MED	Medulloblastoma	2 yr	M	2002				**	[43]
D690MED	Medulloblastoma	2 yr	M	2002				**	[43]
D721MED	Medulloblastoma	16 yr	M	2002				**	[43]
UW426	Medulloblastoma			2004			Y	**	[44]
UW473	Medulloblastoma	5 yr	M	2005		N		**	[45]
Res256	Medulloblastoma	16 yr	M	2005		Y		**	[45]
Res262	Medulloblastoma			2008				*	[46]
nMED1	Medulloblastoma	41 mo		2011		Y	Y	**	[47]
nMED2	Medulloblastoma	127 mo		2011		Y	Y	*	[47]
Res300	Medulloblastoma			2012				*	[48]
CHLA-259	Medulloblastoma	14 yr	M	2012	COG	Y	Y	*	[49]
CHLA-01-MED	Medulloblastoma	8 yr	M	2012	ATCC	Y	Y	*	[27];CRL-3021
CHLA-01R-MED	Medulloblastoma (recurrent, pleural fluid metastases)	8 yr	M	2012	ATCC	Y	Y	*	[27];CRL-3034

Cell Line	Diagnosis	Age	Male/ Female	Year 1st Paper	Source	Tumorigenic *in vivo*	Neurosphere culture	Literature Citations	Ref
MED8A	Medulloblastoma			2012					[50]
HD-MB03	Medulloblastoma	3 yr	M	2012		Y		*	[51]
MB002	Medulloblastoma			2014				*	[52]
PFSK-1	PNET	22 mo	M	1992	ATCC	Y	N	**	[53];CRL-2060
MHH-PNET-5	PNET	5 yr	F	1994		Y	N	*	[40]
ncPNET1	PNET	61 mo		2011		Y	Y	*	[47]
Res286	PA	15 yr	M	2005				**	[45]
Res186	PA	3 yr	F	2005			N	**	[45]
Res199	PA	14 yr	F	2005				**	[45]
Res259	DA	4 yr	M	2005		Y	N	**	[45]
JHH DIPG1	DIPG			2012		Y	Y	*	[54]
UW467	AA	12 yr	M	2005				**	[45]
UW479	AA	13 yr	F	2005			N	**	[45]
CHLA-200	AA	12 yr	M	2012	COG	Y		*	[49]
CHLA-03-AA	AA	9 yr	F	2012	ATCC		Y	*	CRL-3035
CHLA-07-BSGBM	non-DIPG brain stem GBM	77 mo	F	2014			Y	*	[27]
SF188	GBM	8 yr	M	1997		Y	Y	***	[55]
KNS-42	GBM	16 mo	M	1987	JCRB	Y	Y	**	[24]
bGB1	GBM	43 mo		2011		Y	Y	*	[47]
D212MG	HGG			1997		Y		**	[41]
D456MG	HGG			1997		Y	Y	**	[41]
Res251	Astrocytoma	15 yr	M	2005				**	[45]
ATRT95	ATRT	3 yr	F	1998		Y		*	[56]
BT-12	ATRT	6 wk	F	2007		Y		**	[57]
BT-16	ATRT	2 yr	M	2007		Y		**	[57]
KCCF1	ATRT	Infant	M	2008				*	[58]
CHLA-266	ATRT	18 mo	F	2012	COG	Y	Y	*	[49]
CHLA-02-ATRT	ATRT	20 mo	M	2012	ATCC		Y	*	CRL-3020
CHLA-04-ATRT	ATRT	20 mo	M	2012	ATCC		Y	*	CRL-3036
CHLA-05-ATRT	ATRT	32 mo	M	2013	$ATCC		Y	*	[27]
CHLA-06-ATRT	ATRT	4 mo	F	2013	$ATCC		Y	*	[27]
D528EP	Ependymoma			1997		Y		*	[41]
D612EP	Ependymoma			1997		Y		*	[41]

Cell Line	Diagnosis	Age	Male/ Female	Year 1st Paper	Source	Tumorigenic *in vivo*	Neurosphere culture	Literature Citations	Ref
Res196	Ependymoma	4 yr	M	2005				**	[45]
Res253	Ependymoma	7 yr	M	2005				**	[45]
Res254	Ependymoma	12 yr	M	2005				**	[45]
BXD-1425EPN	Ependymoma	9 yr	M	2010		Y	Y	*	[59]
nEPN1	Ependymoma	162 mo		2011		Y	Y	*	[47]
nEPN2	Ependymoma	41 mo		2011		Y	Y	*	[47]
Res280	ODG	18 yr	F	2005				*	[45]
nOLIG1	ODG	78 mo		2011		Y	Y	*	[47]

Abbreviations:

AA: Anaplastic Astrocytoma

DA: Diffuse Astrocytoma

DIPG: Diffuse Intrinsic Pontine Glioma

GBM: Glioblastoma Multiforme

HGG: high grade glioma

MBL: medulloblastoma

PA: Pilocytic Astrocytoma

PNET: Primitive Neuroectodermal Tumor

ATCC: American Type Culture Collection

COG: Children's Oncology Group, cell line repository (http://www.cogcell.org/)

JCRB: Japanese Collection of Research Bioresources

§: Deposited at ATCC but not yet released (as of August 2014); until released, available from Dr. Anat Erdreich-Epstein.

*** > 50 publications used this cell line;

** > 5 publications used this cell line;

* < 5 publications used this cell line. Number of publications for each cell line was derived from review of papers identified through search of PubMed and Google Scholar.

+ Microarray profile of DAOY may be different than other medulloblastoma cell lines [36].

Table 3:

Currently- published molecular subgroups and genetic alterations for medulloblastoma cell lines

Cell Line	Histology of primary tumor	Grouping	p53 status	*MYC* Amplification	Other	Reference
ONS76		SHH	WT	No		[50, 60]
UW426		SHH	WT			[60]
DAOY		SHH	Mutated	No	Near tetraploid	[20, 35, 36, 60]
UW228		SHH	Mutated			[60]
CHLA-01-MED	Large cell	Group 4		Yes		[27]
D283MED		Group 3	WT	Yes	Diploid	[20, 52]
D341MED		Group 3	WT	Yes	Diploid	[20, 61]
D384MED		Group 3		Yes		[52]
D425MED		Group 3	WT	Yes	OTX2 amplification	[62–64]
D487				Yes	OTX2 amplification	[64, 65]
D458		Group 3		Yes	OTX2 amplification	[52, 64]
D556		Group 3		Yes		[52, 65]
MED8A		Group 3	WT	Yes	*PVT1-MYC* fusion	[50, 66]
HD-MB03	Large cell	Group 3		Yes	17q [i(17q)]	[51]
MB002	Large cell	Group 3		Yes		[52]