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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 appropriate brain tumor cell lines for experiments is important, as results may differ depending on tumor properties, and can thus affect the conclusions and applicability of the 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. J. Cell. Biochem. 116: 218–224, 2015.

KEY WORDS: ATRT; EPENDYMOMA; GLIOMA; MEDULLOBLASTOMA; PEDIATRIC BRAIN TUMOR CELL LINES

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 15–19 year-olds, making them the most common solid tumors in children, and second in incidence only to leukemias [Ostrom, 2013]. 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 I 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 [Ostrom, 2013]. A detailed description of pediatric brain tumors is provided elsewhere [Mueller and Chang, 2009; Pfister et al., 2009; Dubuc, 2010]. 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 [Korshunov, 2010; Nishikawa, 2010; Paugh, 2010]. When conducting 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 elements such as murine retroviruses [Erdreich-Epstein, 2006]; and (3) changes in the composition of the original tumor, which include tumor cells and cells of the tumor microenvironment, that with subsequent passages incorporate 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.

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TABLE I. Pediatric Brain Tumors, Summary

General category		Histological type	Other names used
Tumors in the brain that originated in brain-derived cells			
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 PNET (primitive neuroectodermal tumor) AT/RT (atypical teratoid rhabdoid tumor)	Previously called infratentorial PNET Previously called supratentorial PNET
	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			

Tumors that are most amenable to growing as continuous cell lines are typically those which are fast growing and the most aggressive, likely explaining the relative paucity of low-grade tumor cell lines. Cell lines are used in experiments in vivo and in vitro and are indispensable 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 [Houghton, 2007; Tajbakhsh, 2008; Keir, 2010; Kang, 2011; Smith, 2012].

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 to 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 recipient 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 modeled according to defined needs, although this may require extensive efforts [Becher and Holland, 2006; Hambardzumyan, 2009; Rubin, 2009; Swartling, 2010]. Moreover, genetically engineered brain tumor models 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 continuous 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 [Keshelava, 2000; Loschmann, 2013]. Only five pediatric brain tumor cell lines were published prior to 1990 [Friedman, 1985; Jacobsen et al., 1985; Takeshita, 1987; Friedman, 1988; Yamada 1989]. Over the next decade 20 additional pediatric brain tumor cell lines were published, with the remaining 46 published after the year 2000 (Table II). Use of neurosphere culture [Reynolds et al., 1992], 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 [Hemmati, 2003; Erdreich-Epstein, 2014]. 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 [Galli, 2004; Singh, 2004].

TABLE II. 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	Reference
D283MED	Medulloblastoma	6 yr	M	1985	ATCC	Y	Y	***	[Friedman et al., 1985]; HTB-185
DAOY	+Medulloblastoma	4 yr	M	1985	ATCC	Y	Y	***	[Jacobsen et al., 1985]; HTB-186
D341MED	Medulloblastoma (metastasis from peritoneum)	3.5 yr	M	1988	ATCC	Y		***	[Friedman et al., 1988]; HTB-187
ONS-76	Medulloblastoma	2 yr	F	1989	JCRB	Y	Y	**	[Yamada et al., 1989]
D384MED	Medulloblastoma	17 mo	M	1991		Y		**	[He et al., 1991]
D425MED	Medulloblastoma	5 yr	M	1991		Y		**	[He et al., 1991]
D458MED	Medulloblastoma			1991		Y		**	[He et al., 1991]
MHH-MED-1	Medulloblastoma	10 yr	M	1994		Y	Y	*	[Pietsch et al., 1994]
MHH-MED-2	Medulloblastoma	6 yr	F	1994		Y	Y	*	[Pietsch et al., 1994]
MHH-MED-3	Medulloblastoma	3 yr	F	1994		Y	Y	*	[Pietsch et al., 1994]
MHH-MED-4	Medulloblastoma	4 yr	M	1994		Y	Y	*	[Pietsch et al., 1994]
UW228-1	Medulloblastoma	9 yr	F	1995		Y	Y	**	[Keles et al., 1995]
UW228-2	Medulloblastoma	9 yr	F	1995		Y		***	[Keles et al., 1995]
UW228-3	Medulloblastoma	9 yr	F	1995		Y		**	[Keles et al., 1995]
UW443	Medulloblastoma	9 yr	F	1995				*	[Keles et al., 1995]
D487MED	Medulloblastoma			1997		Y		**	[Hare et al., 1997]
UW402	Medulloblastoma			2001		N	Y	**	[Dimitroulakos et al., 2001]
D556MED	Medulloblastoma	7 yr	F	2002		Y		**	[Aldosari et al., 2002]
D581MED	Medulloblastoma	2 yr	M	2002				**	[Aldosari et al., 2002]
D690MED	Medulloblastoma	2 yr	M	2002				**	[Aldosari et al., 2002]
D721MED	Medulloblastoma	16 yr	M	2002				**	[Aldosari et al., 2002]
UW426	Medulloblastoma			2004			Y	**	[Yokota et al., 2004]
UW473	Medulloblastoma	5 yr	M	2005		N		**	[Bobola et al., 2005]
Res256	Medulloblastoma	16 yr	M	2005		Y		**	[Bobola et al., 2005]
Res262	Medulloblastoma			2008				*	[Kongkham et al., 2008]
nMED1	Medulloblastoma	41 mo		2011		Y	Y	**	[Hussein et al., 2011]
nMED2	Medulloblastoma	127 mo		2011		Y	Y	*	[Hussein et al., 2011]
Res300	Medulloblastoma			2012				*	[Sikkema et al., 2012]
CHLA-259	Medulloblastoma	14 yr	M	2012	COG	Y	Y	*	[Xu et al., 2012]
CHLA-01-MED	Medulloblastoma	8 yr	M	2012	ATCC	Y	Y	*	[Erdreich-Epstein et al., 2014]; CRL-3021
CHLA-01R-MED	Medulloblastoma (recurrent pleural fluid metastases)	8 yr	M	2012	ATCC	Y	Y	*	[Erdreich-Epstein et al., 2014]; CRL-3034
MED8A	Medulloblastoma			2012				*	[Northcott et al., 2012]
HD-MB03	Medulloblastoma	3 yr	M	2012		Y		*	[Milde et al., 2012]
MB002	Medulloblastoma			2014				*	[Sengupta et al., 2014]
PFSK-1	PNET	22 mo	M	1992	ATCC	Y	N	**	[Fults et al., 1992]; CRL-2060
MHH-PNET-5	PNET	5 yr	F	1994		Y	N		[Pietsch et al., 1994]
ncPNETI	PNET	61 mo		2011		Y	Y	*	[Hussein et al., 2011]
Res286	PA	15 yr	M	2005				**	[Bobola et al., 2005]
Res186	PA	3 yr	F	2005			N	**	[Bobola et al., 2005]
Res199	PA	14 yr	F	2005				**	[Bobola et al., 2005]
Res259	DA	4 yr	M	2005		Y	N	**	[Bobola et al., 2005]
JHH DIPG1	DIPG			2012		Y	Y	*	[Hutt et al., 2012]
UW467	AA	12 yr	M	2005				**	[Bobola et al., 2005]
UW479	AA	13 yr	F	2005			N	**	[Bobola et al., 2005]
CHLA-200	AA	12 yr	M	2012	COG	Y		*	[Xu et al., 2012]
CHLA-03-AA	AA	9 yr	F	2012	ATCC		Y	*	CRL-3035
CHLA-07- BSGBM	non-DIPG brainstem GBM	77 mo	F	2014			Y	*	[Erdreich-Epstein et al., 2014]
SF188	GBM	8 yr	M	1997		Y	Y	***	[Trent et al., 1986]
KNS-42	GBM	16 mo	M	1987	JCRB	Y	Y	**	[Takeshita et al., 1987]
bGB1	GBM	43 mo		2011		Y	Y	*	[Hussein et al., 2011]
D212MG	HGG			1997		Y		**	[Hare et al., 1997]
D456MG	HGG			1997		Y	Y	**	[Hare et al., 1997]
Res251	Astrocytoma	15 yr	M	2005				**	[Bobola et al., 2005]
ATRT95	ATRT	3 yr	F	1998		Y		*	[Yachnis et al., 1998]
BT-12	ATRT	6 wk	F	2007		Y		**	[D′Cunja et al., 2007]
BT-16	ATRT	2 yr	M	2007		Y		**	[D′Cunja et al., 2007]
KCCF1	ATRT	Infant	M	2008				*	[Narendran et al., 2008]
CHLA-266	ATRT	18 mo	F	2012	COG	Y	Y	*	[Xu et al., 2012]

Table 2. (*Continued*)

Cell Line	Diagnosis	Age	Male/ Female	Year 1st Paper	Source	Tumorigenic in vivo	Neurosphere culture	Literature citations	Reference
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	*	[Erdreich-Epstein et al., 2014]
CHLA-06- ATRT	ATRT	4 mo	F	2013	§ATCC		Y	*	[Erdreich-Epstein et al., 2014]
D528EP	Ependymoma			1997		Y		*	[Hare et al., 1997]
D612EP	Ependymoma			1997		Y		*	[Hare et al., 1997]
Res196	Ependymoma	4 yr	M	2005				**	[Bobola et al., 2005]
Res253	Ependymoma	7 yr	M	2005				**	[Bobola et al., 2005]
Res254	Ependymoma	12 yr	M	2005				**	[Bobola et al., 2005]
BXD-1425EPN	Ependymoma	9 yr	M	2010		Y	Y	*	[Yu et al., 2010]
nEPN1	Ependymoma	162 mo		2011		Y	Y	*	[Hussein et al., 2011]
nEPN2	Ependymoma	41 mo		2011		Y	Y	*	[Hussein et al., 2011]
Res280	ODG	18 yr	F	2005				*	[Bobola et al., 2005]
nOLIG1	ODG	78 mo		2011		Y	Y	*	[Hussein et al., 2011]

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].

However, neurosphere cultures also have some limitations [Jensen and Parmar, 2006]. 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 [Keles, 1995]; and (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 II 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 (Children's Oncology Group). Other lines can only be obtained by requisition from the publishing invesitigators, thus limiting their availiability to the research community. Table II, 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 [Northcott, 2011; Kool, 2012; Taylor, 2012]. Molecular subgroup is assigned to a growing number of medulloblastoma cell lines (Table III), 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 [Friedman, 1988; Raffel, 1993]. The basis for the somewhat different microarray profile of DAOY cells is not known [Weeraratne, 2012]. 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-chemo-radiotherapy 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 (Table II).

GLIOMA CELL LINES

There are fewer continuous cell lines from pediatric gliomas compared to medulloblastomas, despite glioma incidence being

TABLE III. 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		[Northcott et al., 2012; Triscott et al., 2013]
UW426		SHH	WT			[Triscott et al., 2013]
DAOY		SHH	Mutated	No	Near tetraploid	[Friedman et al., 1988; Raffel et al., 1993; Weeraratne et al., 2012; Triscott et al., 2013]
UW228		SHH	Mutated			[Triscott et al., 2013]
CHLA-01-MED	Large cell	Group 4		Yes		[Erdreich-Epstein et al., 2014]
D283MED		Group 3	WT	Yes	Diploid	[Friedman et al., 1988; Sengupta et al., 2014]
D341MED		Group 3	WT	Yes	Diploid	[Friedman et al., 1988; Bigner et al., 1990]
D384MED		Group 3		Yes		[Sengupta et al., 2014]
D425MED		Group 3	WT	Yes	OTX2 amplification	[Zurawel et al., 2000; Bunt et al., 2011; Bunt et al., 2012]
D487				Yes	OTX2 amplification	[Zurawel et al., 2000; Boon et al., 2005]
D458		Group 3		Yes	OTX2 amplification	[Zurawel et al., 2000; Sengupta et al., 2014]
D556		Group 3		Yes		[Boon et al., 2005; Sengupta et al., 2014]
MED8A		Group 3	WT	Yes	*PVT1-MYC* fusion	[Northcott et al., 2012; Zindy et al., 2014]
HD-MB03	Large cell	Group 3		Yes	17q [i(17q)]	[Milde et al., 2012]
MB002	Large cell	Group 3		Yes		[Sengupta et al., 2014]

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 1990s [Biegel, 1990]. Typical to them is loss of expression of the *SMARCB1* (*INI1*) gene [Biegel, 1999]. 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 from medulloblastoma, PNET, or even pediatric GBM that were generated prior to reliable diagnosis of ATRT may have not been categorized as such. If doubt exists, SMARCB1 analysis 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 II).

OTHER PEDIATRIC BRAIN TUMOR CELL LINES

Other pediatric brain tumor cell lines are infrequent, possibly 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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