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Membrane receptors in glioblastoma cancer stem cells (GSCs)

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Abstract

Glioblastoma multiforme is the primary tumor most commonly diagnosed in the central nervous system, characterized by being highly angiogenic, proliferative, infiltrative and lethal. Resistance to chemo and radiotherapy further complicates treatment and offer a poor prognosis for the patient. This is due to the fact that it has a subpopulation called gliblastoma stem cells (GSCs), although several membrane proteins involved in the regulation of differentiated tumor cells of non-GSCs glioblastoma are known, there are new specific receptors that have been described in GSCs and the role they play in the origin, maintenance and progression of the disease by downstream regulation of self-renewal, undifferentiated state maintenance and proliferation.

Glioblastoma, GSC, CSC self-renewal, undifferentiation and proliferation

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Introduction

Glioblastoma multiforme (GBM) is a tumor type that originates from glial cells in the central nervous system (CNS) and is considered one of the most aggressive CNS tumors. When its ontogeny begins from a low-grade astrocytoma it is considered secondary glioblastoma, and glioblastomas that are generated from "novo" are called primaries. Although therapeutic management includes immunotherapy, chemotherapy, radiotherapy and surgical resection, the patient remains at mortal risk due to relapses.[1]

This is due to a subpopulation called glioma cancer stem cells (GSCs), which have membrane receptors distinct from differentiated glioma tumor cells. The α6β1, CD90, TfR1 / 2 TLR4, DRD4 and PTPRZ1 receptors play an essential role in chemo and radio resistance, and they also participate to regulate immune system evasion, self-renewal, undifferentiated state maintenance and cell proliferation. It is important to know the downstream signaling of these specific GSCs receptors to better understand the maintenance and expansion mechanisms of GSCs with a view to proposing new therapeutic targets.[2-4]

Primary GBM accounts for 16% of malignant neoplasms in CNS, tumor incidence increases on the basis of age, affects on average 7.2 people per 100,000 adults (> 19) per year; the diagnosis in people aged 75-84 years has an annual incidence of 14.6 people per 100,000 and in children (age <19) to 0.8 per 100,000.[5] In Mexico there is no specific registry of primary neoplasms originating in the CNS. However, reports by GLOBOCAN on primary tumors that originate in the CNS, the incidence comprises 2,998 neoplasias, which is equivalent to 2.3% of malignant tumors.[6]

Cancer stem cells (CSCs)

Cancerous trocal cells were first isolated in 1994 by Bonnet and Dick et. al., being isolated from acute myeloid leukemia. The maintenance of undifferentiated state, self-renewal and proliferation of CSCs is mediated by a number of molecules including membrane receptors that regulate downstream signaling pathways linked to the activation of cell cycle regulatory genes, undifferentiation and Warburg effect. In addition, CSCs increase their survival and mitotic activity in hypoxic environments through the HIF-1α and HIF-2α proteins (Hypoxia-induced Factors 1 and 2). However, master receptors that play a key role in maintaining trunkiness are Notch, LRP5 / 6 (Low Density Lipoprotein 5 and 6 Receptor), FDZ5 (Receptor Fridzzled 5), CD133 (Cluster Differentiation 133) , Thy-1 or CD90 (Cluster of differentiation 90), EpCAM (epithelial cell adhesion molecule) and ABC Transporters.[7-18] The WNT ligand mediates the activation of one of the most important pathways in CSCs, the β-catenin / GS3K pathway in CSCs. In non-cancerous stem cells (non-CSCs), β-catenin is phosphorylated and polyubiquitinated subsequently to be sent to 20S proteasome degradation, this mechanism is orchestrated by a protein complex called "destructive complex" that has the activity of Axina, APC (adenomatous polyposis coli), GSK3β (glycogen synthase kinase 3β) and CKIα (casein kinase Iα).[19-20]

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In addition, cytoplasmic proteins such as aldehyde dehydrogenase, BCL2, γ-secretase, JNK (c-Jun N-terminal), STAT3 (signal transducer and transcription activator 3), PKCα (Protein cyanase C alpha), PLCγ phospholipase C-γ) and Smad4, which at the intracellular level play an important role in the activation of genes logged to the trunk, proliferation and survival. In addition, they have the expression of the factors of Yamanaka Oct-4 (Transcription Factor to Octamer 4), Sox2 (Sex Determining Region Y) - Klf4 (Kruppel-like Factor 4), Nanog of transcription Homeobox NANOG) and c-Myc (Viral Avian Myelocitomatosis Oncogen Homologus), which are indispensable for maintaining cell undifferentiation and a pluripotent state.[21-23]

Cancerous stem cells in glioblastoma (GSCs)

They were described in 2002 by Ignatova et. *al.* In addition, GSCs represent between 0.5% and 0.1% of the tumor mass in tumors obtained by surgical resection and 10% from primary cultures supplemented for the maintenance of truncation and pluripotency. They have the characteristic truncated surface receptors such as Notch, Shh, WNT and CD133 and also present the β-catenin / GS3K pathway in GSCs.[24-28] The key role of the CD133 receptor in chemoresistance has been demonstrated in in vitro assays because it downstream regulates the PI3K / AKT pathway (Phosphatidylinositol 3 kinase / Protein Kinase B).

PI3K phosphorylates the AKT protein in T308 and DNA-PKcs phosphorylates S437 by promoting AKT-mediated IKKα (Kappa-B subunit kinase inhibitor) phosphorylation. Phosphorylation in IKKα interacts with IκB (Nuclear Factor Inhibitor Kappa-B subunit alpha kinase), phosphorylated IκB breaks its interaction with the IκB / NF-κB complex (nuclear factor kappa B) by freeing NF-κB in its active form, is translocated to the nucleus by interacting with the promoter of the MDR1 (Multiple Drug Resistance Protein 1) gene, which promotes its transcription into non-GSCs.[29-32] Although the activity of these receptors in non-GSCs is known, novel GSCs-specific receptors have also been described that also have tumorigenic activity such as radio resistance and chemotherapy. However, they not only confer these qualities, they also participate in mediating the survival, migration, dedifferentiation, self-renewal and proliferation GSCs.[33] Table 1 shows the main receptors of glioblastoma cancer stem cells and their location in two databases, to expand information.

Integrin alpha 6 subunit (ITGA6)

The membrane protein ITGA6 also known as α6β1, is overexpressed in astrocytoma, meningioma, neuroblastoma and glioblastoma, as opposed to healthy brain tissue.[34] However, its presence has been demonstrated in the subventricular zone (SVZ); this region of the brain is very important because it carries out embryonic and postnatal neurogenesis. This has led to the generation of the hypothesis about the possible site of origin of the GSCs.[35-36] Ligands interacting with ITGA6 are laminins and other extracellular matrix molecules. The presence of ITGA6 in GSCs was demonstrated in 2010 by Justin D.

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Lathia *et. al*. who determined that ITGA6 can be found concomitantly in cells with CD133 (+) and CD133 (-), in addition, by siRNA directed to ITGA6 determined that the silencing of it, compromised the auto-renewal and cellular motility of GSCs.[37] The ITGA6 protein is indispensable for the increase of proliferation and decrease of apoptosis in vitro and in vivo in glioblastoma, the silencing of ITGA6 allows for apoptosis in GSCs regulated by TNFα / TNF-R1 (Tumor Necrosis Factor alpha / Factor Receptor tumor necrosis 1), downstream activating the p38MAP / JNK pathway (38 / c-Jun N-terminal mitogen-activated protein kinase); and the inhibition of apoptosis is mediated by cFLIP (protein cell inhibitor of FLICE) is activated upstream by ITGA6, as high levels of cFLIP inhibit caspase-8 (apoptosis 8-related protein peptidase) which forms part of DISC (death-inducing signaling complex). In addition, ITGA6 increases in perivascular areas and regulates tumor migration by the downstream activation of laminin-111 and the anti-coagulation factor VIII, enhancing its angiogenic, proliferative and invasive capacity.[38-41] UniProt: P23229

Thy-1 cell surface antigen (THY1)

This protein is also known as CD90; was identified by tissue microarrays, analyzing varying degrees of tumor, CD90 expression was significantly higher in high grade tumors. Cells bearing CD90 (+) also co-expressed CD133 (+).[42] CD90 levels were highly expressed in GSCs but not the same in differentiated tumor cells, the self-renewal assay was performed to observe whether CD90 was in GSCs, CD90 (+) / CD133 (+) cell population required an equal amount of cells for the formation of neurospheres compared to CD90 (-) / CD133 (+) cells which required up to twice as much cell volume to form neurospheres and self-renewal.

CD90 is co-localized with CD31 in endothelial cells lining the tumor vasculature creating an angiogenic niche favoring the production of Notch by paracrine regulation of self-renewal of GSCs.[43-46] UniProt: P04216

Receptors 1 (TFRC) and Transferrin 2 (TFR2) and Ferritin Light Chain (FTL)

TFCR and TFR2 receptors are known as TfR1 / TfR2, and are commonly expressed in glioblastoma both in vitro and in vivo; are activated by interacting with Fe^{2+} and transferrin particles.[47] TFRC plays an important role in the chemoresistance and as surface marker of GSCs was determined by Mi Kyung et. al.[48] TFRC levels are high in GSCs, being activated induces the synthesis of FTH1 (Ferritin heavy chain 1) and FTL (light ferritin chain). FTL interacts with FTH1 and handles the processing and catabolism of the Fe^{2+}. It regulates downstream the STAT3 pathway, which phosphorylates FoxM1 (M1 Fork Box), favoring cell cycle activation in CSCs and GSCs. The presence of FoxM1 is regulated positively in different types of cancer and is also highly expressed in GSCs; also interacts with c-Myc enhancing cell proliferation, in GSCs. The STAT3 and FoxM1 proteins appear to be dependent on ferritin receptors, since the inhibition of TFRC promotes the generation of free radicals and reactive oxygen species that trigger the response of the antioxidant response elements (AREs). When the active AREs repress the activity of the ferritin, however, this is neutralized by the PIAS3 (E3 sumo-protein ligase) a protein repressor of STAT3 this generates a loop of self-regulation, in addition, TFRC compromises the proliferation, self- renewal and promotes the differentiation of GSCs both in vitro and in vivo and decreases their ability to form tumors in xenotransplants.[49-53]

ISSN:2410-4191

TFR2 promotes resistance to temozolomide since the silencing of TFR2 sensitizes the cells treated in culture with temozolomide, in addition, it activates downstream the ERK1 / ERK2 pathway (Kinase related to extracellular signaling 1 and 2) which is overexpressed in GBM and GSCs.[54, 55] UniProt: P02786; Q9UP52; P02792.

Protein tyrosine phosphatase Z1 receptor (PTPRZ1)

It was described during a microarray analysis in glioblastoma and differences between the expression levels of differentiated cells and GSCs were identified; the presence of the protein was corroborated by western blotting.[56-57] The PTPRZ1 receptor is highly expressed in glial progenitors and is responsible for regulating self-renewal.[58-59] M2 (type 2 macrophages) and TAMs (tumor associated macrophages) secrete PTN (pleotrophin) to stimulate GSCs through interaction with PTPRZ1. The PTPRZ1 protein mediates activation downstream of PI3K / AKT by promoting phosphorylation of serine 437 in AKT and phosphorylation in tyr 416 in Src cyanase, which belongs to the SFK (Src kinase family). The phosphorylation of AKT is carried out by Fyn kinase (FYN tyrosine protein cyanase) and Src (V-Src Avian sarcoma) are at the same time phosphorylated when the upstream signal is induced by PTPRZ1 because they share the same site of phosphorylation in Tyr416, its inhibition compromises the pluripotent state, proliferation and self-renewal.[60-65] UniProt: P23471

Toll-like receptor 4 (TLR4)

TLR4 is highly expressed in neuronal stem cells (NPCs), the absence of the TLR4 receptor potentiates neuronal differentiation and proliferation.[66-67] In GSCs TLR4 is inactive, because high levels of TLR4 inhibit proliferation; the decrease of TLR4 allows the maintenance of undifferentiated state and self-renewal. The TLR4 receptor mediates downstream phosphorylation of TBK1 (serine / threonine protein kinase 1) and interacts with RBBP5 (retinoblastoma binding protein 5) which inhibits its activity, thereby reducing the mRNA levels of SOX2, OCT4 and NANOG . The absence of TLR4 is vital for the maintenance of GSCs, proliferation and self-renewal, by activating the retinoblastoma binding protein 5 (RBBP5) that interacts with MLL1 (myeloid / lymphoid or mixed lineage leukemia) that is part of the protein complex WRAD (Romano-Ward Syndrome) and can modify the epigenome in GSCs. Alterations in MLL1 affect the epigenetic state in the promoter regions of the pluripotency genes SOX2, OCT-4, NANOG, where the methylation marks associated with the lysine 4-mediated transcriptional activation of $H3_{me}^{3}$ (histone 3 trimethylated).[68] UnitProt: O00206.

Dopamine D4 Receptor (DRD4)

The DRD4 receptor has recently been reported in glioblastoma and plays an important role in clonogenic potentiation. The DRD4 gene is not methylated in glioblastoma; however, inhibition of methylation favors the therapeutic efficacy of temozolomide in patients with GM. It reduces levels of adenylate cyclase and inhibits cAMP (cyclic AMP). Cells treated with DRD4 antagonists carry genes involved in DNA replication, cell cycle, and on the contrary, genes related to autophagy are activated.

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It also increases the expression of genes involved in lipid biosynthesis. DRD4 antagonists increase the synthesis of LC3-1 / 2 (light chain proteins associated with 1/2 microtubules), which are markers of the autophagosome. They also increase p62 (nucleosporin) and LAMP1 (lysosome-associated membrane protein), both of which are key regulatory proteins for autophagy. The PDGFRβ-ERK1 / 2 signaling pathway (Factor Receptor derived from beta platelets and kinase related to extracellular signaling 1 and 2) is transactivated by DRD4, so the inhibition of DRD4 affects the phosphorylation of S6 in mTOR which leads to the induction of caspases 6/7 (apoptosis-related peptidase protein 6 and 7), cell cycle arrest followed by apoptosis.[69-70] UniProt: P21917

Receptor	Function	Ligands	Reference	UniProt[71]	neXtProt[72,73]
ITGA6	Self-renewal, proliferation, cell motility, angiogenesis, anti-apoptotic and biomarker.	Laminin-111 and extracellular matrix components.	37	P23229	NX_P23229
THY1	Self-renewal, biomarker, angiogenesis.	CD45 (Cluster of differentiation 45)	42	P04216	NX_P04216
TFRC1	Activation of the cell cycle, self-renewal, proliferation, undifferentiation, biomarker.	Fe^{3+} and Transferrin	47	P02786	NX_P02786
TFRC2	Biomarker, chemoresistance, activation of the ERK1/2 pathway.	Fe^{3+} and Transferrin	48, 55, 57	Q9UP52	NX_Q9UP52
PTPRZ1	Self-renewal, undifferentiation, proliferation.	Pleotrophin	60, 61,62	P23471	NX_P23471
TLR4	Self-renewal, proliferation, undifferentiation and activation of genes linked to pluripotency.	Absence of the receptor in GSCs.	69	O00206	NX_O00206
DRD4	Inhibition of autophagy, proliferation, undifferentiation, anti-apoptotic, transactivation of the PDGFRβ-ERK1/2 pathway, activation of mTOR.	Dopamine.	71	P21917	NX_P21917

Table 1 Principal recipients of glioblastoma cancer stem cells

Conclusion

Stem cells or glioma stem cells, GSCs, are capable of self-renewing in culture, and give rise to neurons and glia both in vivo and in vitro. Therefore, they are considered multipotential cells whose function is tissue replacement and regeneration; that for it to be carried out effectively requires complex processes involving targeted migration and growth that ensure connections at a distance.

Knowing the receptors described so far in the glioma stem cells allow to better describe the mechanisms involved in the origin, maintenance and progression of the disease, as shown in Figure 1; with the inherent unveiling of new therapeutic targets. This is a brief description of the main receptors of GSC, which allows the reader to have a first approach with these molecules and prepares them to delve into the molecular processes that are mediated by receptors of glioblastoma cancer stem cells.

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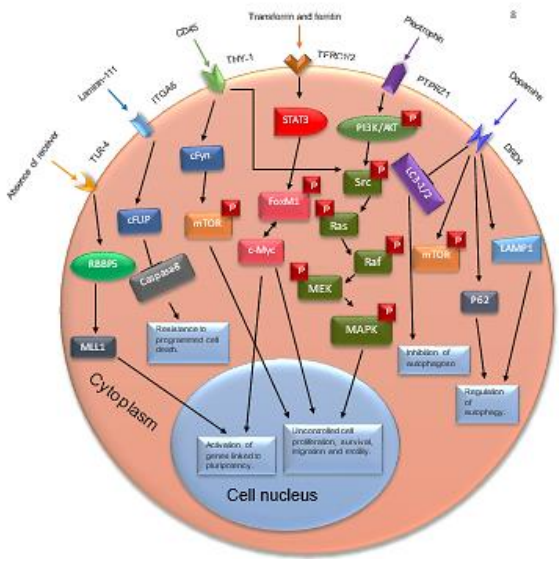

Figure 1 Scheme of GSCs with different membrane receptors, ligand and transduction of signals that exert downstream and at cytoplasmic and nuclear level

References

A. T. Collins, P. A. Berry, C. Hyde, M. J. Stower, and N. J. Maitland. Prospective identification of tumorigenic prostate cancer stem cells. Cancer Research 2005; 65: 10946-51.

Akihiro Inoue, Junya Tanaka, Hisaaki Takahashi, Shohei Kohno, Shiro Ohue, Akihiro Umakoshi, Katsuhiro Gotoh, Takanori Ohnishi. Blood vessels expressing CD90 in human and rat brain tumors. Neurophatology 2015; 36: 168-80.

Alessia Calzolari, Luigi Maria Larocca, Silvia Deaglio, Veronica Finisguerra, Alessandra Boe, Carla Raggi, Lucia Ricci Vitani, Francesco Pierconti, Fabio Malavasi, Ruggero De Maria, Ugo Testa, and Roberto Pallini. Transferrin Receptor 2 Is Frequently and Highly Expressed in Glioblastomas. Trans Oncol 2010; 3: 123-34.

Alvarado AG, Thiagarajan PS, Mulkearns-Hubert EE, Silver DJ, Hale JS, AlbaN TJ, Turaga SM, Jarrar A' Reizes O, Longworth MS, Vogelbaum MA, Lathia JD. Glioblastoma Cancer Stem Cells Evade Innate Immune Suppression of Self-Renewal through Reduced TLR4 Expression. Cell Stem Cell 2017; 20: 450-461.

Amy Bradshaw,Agadha Wickremsekera,Swee T. Tan,Lifeng Peng,Paul F. Davis and Tinte Itinteang. Cancer Stem Cell Hierarchy in Glioblastoma Multiforme. Frontiers in Surgery 2016; 3: 21.

An L, Li WW, Cheng GC. Fyn arrests swainsonine-induced apoptosis in 293T cells via Akt and its phosphorylation. Genet Mol Res 2015; 14: 5304-9.

Analysis of gene expression and chemoresistance of CD133+ cancer stem cells in glioblastoma. Molecular Cancer 2006; 5: 67.

Antonija Kreso and John E. Dick. Evolution of the Cancer Stem Cell Model. 2017. Cell 2014; 14: 275-291.

Asya Rolls, Ravid Shechter. Anat London, Yaniv Ziv, Ayal Ronen, Rinat Levy and Michal Schwartz. Toll-like receptors modulate adult hippocampal neurogenesis. Nat Cell Biol 2007; 9: 1081-8.

Arumugam and Mark P. Mattson. Toll-Like Receptor 3 Is a Negative Regulator of Embryonic Neural Progenitor Cell Proliferation. J Neurosci 2008; 28: 13978-84.

B. T. MacDonald, K. Tamai, and X. He. Wnt/β-catenin signaling: components, mechanisms, and diseases. Developmental Cell 2009; 17: 9–26.

ISSN:2410-4191

Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, Dewhirst MW, Bigner DD, Rich JN. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature 2006; 444: 756-60.

Bonnet D, Dick JE. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med 1997; 3: 730-7.

C. Delude. Tumorigenesis: testing ground for cancer stem cells. Nature. 2011; 480: 43–S45.

Cao Y, Lathia JD, Eyler CE, Wu Q, Li Z, Wang H, McLendon RE, Hjelmeland AB, Rich JN. Erythropoietin Receptor Signaling Through STAT3 Is Required For Glioma Stem Cell Maintenance. Genes Cancer 2010; 1: 50-61.

Cells for Cancer Treatment.. Stem Cells International 2017; ID: 2925869.

Claudia Capdevila, Lucía Rodríguez Vázquez, Joaquín Martí. Glioblastoma Multiforme and Adult Neurogenesis in the Ventricular-Subventricular Zone: A Review. J Cellular Physiology 2017; 232: 1596-1601.

Calzolari A, Oliviero I, Deaglio S, Mariani G, Biffoni M, Sposi NM, Malavasi F, Peschle C,

D. Friedmann Morvinski, E. A. Bushong, E. Ke. Dedifferentiation of neurons and astrocytes by oncogenes can induce gliomas in mice. Science 2012; 338: 1080-4.

David L. Schonberg, Tyler E. Miller, Qiulian Wu, William A. Flavahan, Nupur K. Das, James S. Hale, Christopher G. Hubert, Stephen C. Mack, Awad M. Jarrar, Robert T. Karl, Ann Mari Rosager, Anne M. Nixon, Paul J. Tesar, Petra Hamerlik, Bjarne W. Kristensen, Craig Horbinski, James R. Connor, Paul L. Fox, Justin D. Lathia, and Jeremy N. Rich.

Diwakar R Pattabiraman and Robert A. Weinberg. Tackling the cancer stem cells – what challenges do they pose?. Nat Rev Drug Discov. 2014 Jul; 13(7): 497–512.

Dominik S, Sebastian B. Paediatric and adult glioblastoma: multiform (epi) genomic culprits emerge. Nat Rev Cancer 2014; 14: 92–107.

Dolma S, Selvadurai HJ, Lan X, Lee L, Kushida M, Voisin V, Whetstone H, So M, Aviv T, Park N, Zhu X, Xu C, Head R, Rowland KJ, Bernstein M, Clarke ID, Bader G, Harrington L, Brumell JH, Tyers M, Dirks PB.Inhibition of Dopamine Receptor D4 Impedes Autophagic Flux, Proliferation, and Survival of Glioblastoma Stem Cells. Cancer Cell 2016; 29: 859-73.

DRD4 Selectively Promotes Glioblastoma Stem Cell Growth. Cancer Discov August 1 2016 6 (8) OF10-OF10; DOI:10.1158/2159-8290.CD-RW2016-117 American Association for Cancer Research.

Elena Codrici, Ana Maria Enciu, Ionela-Daniela Popescu, Simona Mihai and Cristiana Tanase. Glioma Stem Cells and Their Microenvironments: Providers of Challenging Therapeutic Targets. Stem cells int 2016; ID: 5728438.

François Autelitano, Denis Loyaux, Sébastien Roudières, Catherine Déon Frédérique Guette, Philippe Fabre, Qinggong Ping, Su Wang, Romane Auvergne, Vasudeo Badarinarayana, Michael Smith, Jean Claude Guillemot, Steven A. Goldman, Sridaran Natesan, Pascual Ferrara and Paul August. Identification of Novel Tumor-Associated Cell Surface Sialoglycoproteins in Human Glioblastoma Tumors Using Quantitative Proteomics. PloS one 2014; 9: e110316.

Gang Wu, Alberto Broniscer. Somatic Histone H3 Alterations in Paediatric Diffuse Intrinsic Pontine Gliomas and Non-Brainstem Glioblastomas. Nat Genet 2012; 44: 251–253.

Glioblastoma Stem-like Cells. Cancer Cell 2015; 28: 441-55.

Gong AH, Wei P, Zhang S, Yao J, Yuan Y, Zhou AD, Lang FF, Heimberger AB, Rao G, Huang S. FoxM1 Drives a Feed-Forward STAT3-Activation Signaling Loop That Promotes the Self-Renewal and Tumorigenicity of

Glioblastoma Stem-like Cells. Cancer Res. 2015.

Gingras MC, Roussel E, Bruner JM, Branch CD, Moser RP. Comparison of cell adhesion molecule expression between glioblastoma multiforme and autologous normal brain tissue. J Neuroimmunol 1995; 57: 143-53.

G Xi, E Hayes1 , R Lewis, S Ichi, B Mania Farnell, K Shim, T Takao, E Allender, CS Mayanil, and T Tomita. CD133 and DNA-PK regulate MDR1 via the PI3K- or Akt-NF-κB pathway in multidrug-resistant glioblastoma cells in vitro. Nature 2015; 35: 5576.

Huang P, Rani MR, Ahluwalia MS, Bae E, Prayson RA, Weil RJ, Nowacki AS, Hedayat H, Sloan AE, Lathia JD, Rich JN, Tipps R, Gladson CL. Endothelial expression of TNF receptor-1 generates a proapoptotic signal inhibited by integrin α6β1 in glioblastoma. Cancer Res 2012; 72: 1428-37.

He J, Liu Y, Xie X, Zhu T, Soules M, DiMeco F, Vescovi AL, Fan X, Lubman DMJ. Identification of cell surface glycoprotein markers for glioblastoma-derived stem-like cells using a lectin microarray and LC-MS/MS approach. Proteome Res 2010; 9: 2565–2572.

H. Clevers. Wnt/β-catenin signaling in development and disease. Cell 2006; 127: 469-80.

INEGI (2012) Estadísticas de Mortalidad. Cubos dinámicos y CONAPO 2012. Proyecciones de la Población de México 2010-2050.

Ignatova TN, Kukekov VG, Laywell ED, Suslov ON, Vrionis FD, Steindler DA. Human cortical glial tumors contain neural stem-like cells expressing astroglial and neuronal markers in vitro. . 2002 Glia; 39: 193-206.

Iwasaki K, Hailemariam K, Tsuji Y. PIAS3 interacts with ATF1 and regulates the human ferritin H gene through an antioxidant-responsive element. J Biol Chem 2007; 282: 22335-43.

J. Chen, Y. Li, T. S. Yu. A restricted cell population propagates glioblastoma growth after chemotherapy. Nature 2012; 488: 522–526.

Jeffrey Koury, Li Zhong and Jijun Hao Targeting Signaling Pathways in Cancer Stem

Jintang He, Yashu Liu, Xiaolei Xie, Thant Zhu, Mary Soules, Francesco DiMeco, Angelo L. Vescovi, Xing Fan and David M. Lubman. Identification of cell surface glycoprotein markers for glioblastoma-derived stem-like cells using a lectin microarray and LC-MS/MS approach. J Proteome Res 2010; 9: 2565-72.

Justin D. Lathia, Eitan Okun, Sung-Chun Tang, Kathleen Griffioen, Aiwu Cheng, Mohamed R. Mughal, Gloria Laryea, Pradeep K. Selvaraj, Charles ffrench Constant, Tim Magnus, Thiruma V.

Jintang Hel ,Yashu Liu, Thant Zhu, Jianhui Zhu, Francesco DiMeco, Angelo L. Vescovi, Jason A. Heth, Karin M. Muraszko , Xing Ventilador and David M Lubman. CD90 is Identified as a Candidate Marker for Cancer Stem Cells in Primary High-Grade Gliomas Using Tissue Microarrays. Moll Cell Proteomics 2012; 11: M111.010744.

Karine Loulier, Justin D. Lathia. b1 Integrin Maintains Integrity of the Embryonic Neocortical Stem Cell Niche. PloS Biology 2009; 7: 1000176.

Kim E, Kim M, Woo DH, Shin Y, Shin J, Chang N, Oh YT, Kim H, Rheey J, Nakano I, Lee C, Joo KM, Rich JN, Nam DH, Lee J. Phosphorylation of EZH2 activates STAT3 signaling via STAT3 methylation and promotes tumorigenicity of glioblastoma stem-like cells. Cancer Cell 2013; 23: 839-52.

Liu G, Yuan X, Zeng Z, Tunici P, Ng H, Abdulkadir IR, Lu L, Irvin D, Black KL, Yu JS. Vescovi AL, Galli R, Reynolds BA. Brain tumour stem cells. Nat Rev Cancer 2006; 6: 425-36.

Liss Nurrul Abdullah and Edward Kai-Hua Chow. Mechanisms of chemoresistance in cancer stem cells. Clin Transl Med 2013; 2: 3.

Li Z, Bao S, Wu Q, Wang H, Eyler C, Sathornsumetee S, Shi Q, Cao Y, Lathia J, McLendon RE, Hjelmeland AB, Rich JN. Hypoxia-inducible factors regulate tumorigenic capacity of glioma stem cells. Cancer Cell 2009; 15: 501–513.

Lathia JD, Gallagher J, Heddleston JM, Wang J, Eyler CE, Macswords J, Wu Q, Vasanji A, McLendon RE, Hjelmeland AB, Rich JN. Integrin alpha 6 regulates glioblastoma stem cells. Cell Stem Cell 2010; 6: 421-32.

Mi Kyung Kang and Soo Kyung Kang. Tumorigenesis of Chemotherapeutic Drug-Resistant Cancer Stem-Like Cells in Brain Glioma. Stem Cells Dev 2007; 16: 837-47.

Miao H, Gale NW, Guo H, Qian J, Petty A, Kaspar J, Murphy AJ, Valenzuela DM, Yancopoulos G, Hambardzumyan D, Lathia JD, Rich JN, Lee J, Wang B. EphA2 promotes infiltrative invasion of glioma stem cells in vivo through cross-talk with Akt and regulates stem cell properties. Oncogene 2015; 34: 558-67.

N. D. Marjanovic, R. A. Weinberg, and C. L. Chaffer. Cell plasticity and heterogeneity in cancer. Clinical Chemistry 2013; 59: 1168–179.

NexTprot. Gaudet P, Michel PA, Zahn-Zabal M, Britan A, Cusin I, Domagalski M, Duek PD, Gateau A, Gleizes A, Hinard V, Rech de Laval V, Lin JJ, Nikitin F, Schaeffer M, Teixeira D, Lane L, Bairoch A. The neXtProt knowledgebase on human proteins: 2017 update. Nucl. Acids Res. first published online November 29, 2016 doi:10.1093/nar/gkw1062.

Pacini N and Borziani F. Cancer stem cell theory and the warburg effect, two sides of the same coin?. 2014. Int J Mol Sci.

Preferential Iron Trafficking Characterizes Delamarre E, Taboubi S, Mathieu S, Bérenguer C, Rigot V, Lissitzky JC, Figarella Branger D, Ouafik L and Luis J. Expression of Integrin α6β1 Enhances Tumorigenesis in Glioma Cells. Am J Pathol 2009; 175: 844-55.

Previtali S, Quattrini A, Nemni R, Truci G, Ducati A, Wrabetz L, Canal N Alpha6 beta4 and alpha6 beta1 integrins in astrocytomas and other CNS tumors. J Neuropathol Exp Neurol 1996; 55:4 56-65.

R. M. Bachoo, E. A. Maher, K. L. Ligon. Epidermal growth factor receptor and Ink4a/Arf: convergent mechanisms governing terminal differentiation and transformation along the neural stem cell to astrocyte axis. Cancer Cell 2002; 1: 269-77.

S. K. Singh, C. Hawkins, I. D. Clarke et al., "Identification of human brain tumour initiating cells. Nature 2004; 432: 396-401.

S. Schwitalla. Tumor cell plasticity: the challenge to catch a moving target. Journal of Gastroenterology 2014; 49: 618–627.

Shi Y, Ping YF, Zhou W, He ZC, Chen C, Bian BS, Zhang L, Chen L, Lan X, Zhang XC, Zhou K, Liu Q, Long H, Fu TW, Zhang XN, Cao MF, Huang Z, Fang X, Wang X, Feng H, Yao XH, Yu SC, Cui YH, Zhang X, Rich JN, Bao S, Bian XW. Tumour-associated macrophages secrete pleiotrophin to promote PTPRZ1 signalling in glioblastoma stem cells for tumour growth. Nat Commun. 2017; 8: 15080.

Stieber D, Golebiewska A, Evers L, Lenkiewicz E, Brons NH, Nicot N, Oudin A, Bougnaud S, Hertel F, Bjerkvig R, Vallar L, Barrett MT, Niclou SP. Glioblastomas are composed of genetically divergent clones with distinct tumourigenic potential and variable stem cell-associated phenotypes. Acta Neuropathol 2014; 127: 203-19.

Sim FJ, McClain CR, Schanz SJ, Protack TL, Windrem MS, Goldman SA. CD140 a identifies a population of highly myelinogenic, migration-competent and efficiently engrafting human oligodendrocyte progenitor cells. Nat Biotechnol 2011; 29: 934-41.

Shen Q, Wang Y, Kokovay E, Lin G, Chuang SM, Goderie SK, Roysam B, Temple S. Adult SVZ stem cells lie in a vascular niche: a quantitative analysis of niche cell-cell interactions. Cell Stem Cell 2008; 3: 289-300.

Singh SK, Clarke ID, Hide T, Dirks PB. Cancer stem cells in nervous system tumors. Oncogene 2004; 23: 7267-73.

Science PubMed: 25613900 DOI: 10.1126/science.1260419. In: http://www.proteinatlas.org/

T. Lapidot, C. Sirard, J. Vormoor. A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. Nature 1994; 367:645 – 648.

Tang X, Feng Y, Ye K. Src-family tyrosine kinase fyn phosphorylates phosphatidylinositol 3-kinase enhancer-activating Akt, preventing its apoptotic cleavage and promoting cell survival. Cell Death Differ 2007; 14: 368-77.

Testa U. Transferrin receptor 2 is frequently expressed in human cancer cell lines. Blood Cells Mol Dis 2007; 39:82-91.
Y. Komiya and R. Habas. Wnt signal transduction pathways. . Organogenesis 2008; 4: 68-75.

Takahashi K., Tanabe K., Ohnuki M. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007; 30: 861-72.

The Human Protein Atlas. Uhlén M et al, 2015. Tissue-based map of the human proteome.

UniProt: the universal protein knowledgebase. Nucleic Acids Res. 45: D158-D169 (2017).

Wei Y, Jiang Y, Zou F, Liu Y, Wang S, Xu N, Xu W, Cui C, Xing Y, Liu Y, Cao B, Liu C, Wu G, Ao H, Zhang X, Jiang J. Activation of PI3K/Akt pathway by CD133-p85 interaction promotes tumorigenic capacity of glioma stem cells. Proc Natl Acad Sci U S A 2013; 110: 6829-34.

ISSN:2410-4191

Xiaosi Han, Wenbin Zhang, Xiuhua Yang, Crystal G. Wheeler, Catherine P. Langford, Lu Wu, Natalia Filippova, Gregory K. Friedman, Qiang Ding, Hassan M. Fathallah-Shaykh, G. Yancey Gillespie, And Role Of Src Family Kinases In Growth And Migration Of Glioma Stem Cells. Int J Oncol 2014; 45: 302-10.

Xiwei Wu, Tibor A. Rauch, XueyanZhong. CpG island hypermethylation in human astrocytomas. Cancer Res 2010; 70: 2718–2727.

Zhao D, Pan C, Sun J, Gilbert C, Drews-Elger K, Azzam DJ, Picon-Ruiz M, Kim M, Ullmer W, El Ashry D, Creighton CJ, Slingerland JM. VEGF drives cancer-initiating stem cells through VEGFR-2/Stat3 signaling to upregulate Myc and Sox2. Oncogene 2015; 34: 3107-19.

Sim FJ, Lang JK, Waldau B, Roy NS, Schwartz TE, Pilcher WH, Chandross KJ, Natesan S, Merrill JE, Goldman SA. Complementary patterns of gene expression by human oligodendrocyte progenitors and their environment predict determinants of progenitor maintenance and differentiation. Ann Neurol 2006; 59: 763-79.

Zhu TS, Costello MA, Talsma CE, Flack CG, Crowley JG, Hamm LL, He X, Hervey Jumper SL, Heth JA, Muraszko KM, DiMeco F, Vescovi AL, Fan X. Endothelial cells create a stem cell niche in glioblastoma by providing NOTCH ligands that nurture self-renewal of cancer stem-like cells. Cancer Res 2011; 71: 6061-72.

Zhou W, Ke SQ, Huang Z, Flavahan W, Fang X, Paul J, Wu L, Sloan AE, McLendon RE, Li X, Rich JN, Bao S. Periostin secreted by glioblastoma stem cells recruits M2 tumour-associated macrophages and promotes malignant growth. Nat Cell Biol 2015; 17:170-82.

ISSN:2410-4191