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The Musashi1 RNA-Binding Protein: A Critical Regulator in Glioblastoma

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1. Introduction

Musashi1 (Msi1) is an evolutionary conserved RNA-binding protein that plays important roles in neural stem cell maintenance, nervous system development, and tumorigenesis. In glioblastoma, Msi1 is found to be highly expressed and to control a network of cancer-related genes. In this chapter, we will review the participation of RNA-binding proteins in tumorigenesis and the role of Msi1 in stem cells and in glioblastoma. Furthermore, we will discuss the results of a study done with The Cancer Genome Atlas (TCGA) dataset to map genes highly correlated in expression with Msi1 as an avenue to understand its function in gliomagenesis.

2. Musashi1 and RNA-binding proteins

2.1 RNA-binding proteins

RNA-binding proteins (RBPs) are instrumental in RNA metabolism, from biogenesis to degradation affecting molecular processes associated with mRNA capping, 3' end formation, splicing, transport, localization, stability, and translation (**Figure 1**). RNA-binding proteins associate with target RNA ligands forming the so-called ribonucleoprotein complexes (RNPs). Changes that affect RBP expression and/or function, either temporally or spatially, can have a profound impact on the fate of their target RNAs.

Recent genomic analyses suggest that RNA-binding proteins target mRNAs that code for proteins of similar function, forming the so-called RNA operon (Keene, 2007). In this scenario, RNA-binding proteins coordinate the expression of newly synthesized transcripts in order to ensure the needs of the cells are met. This relationship is not linear and any particularly mRNA may be bound by many different RNA-binding proteins thus forming a higher order of regulation termed the RNA regulon. Since RNA-binding proteins regulate large subsets of mRNA, it is conceivable that changes in expression or function can have a profound impact on human disease.

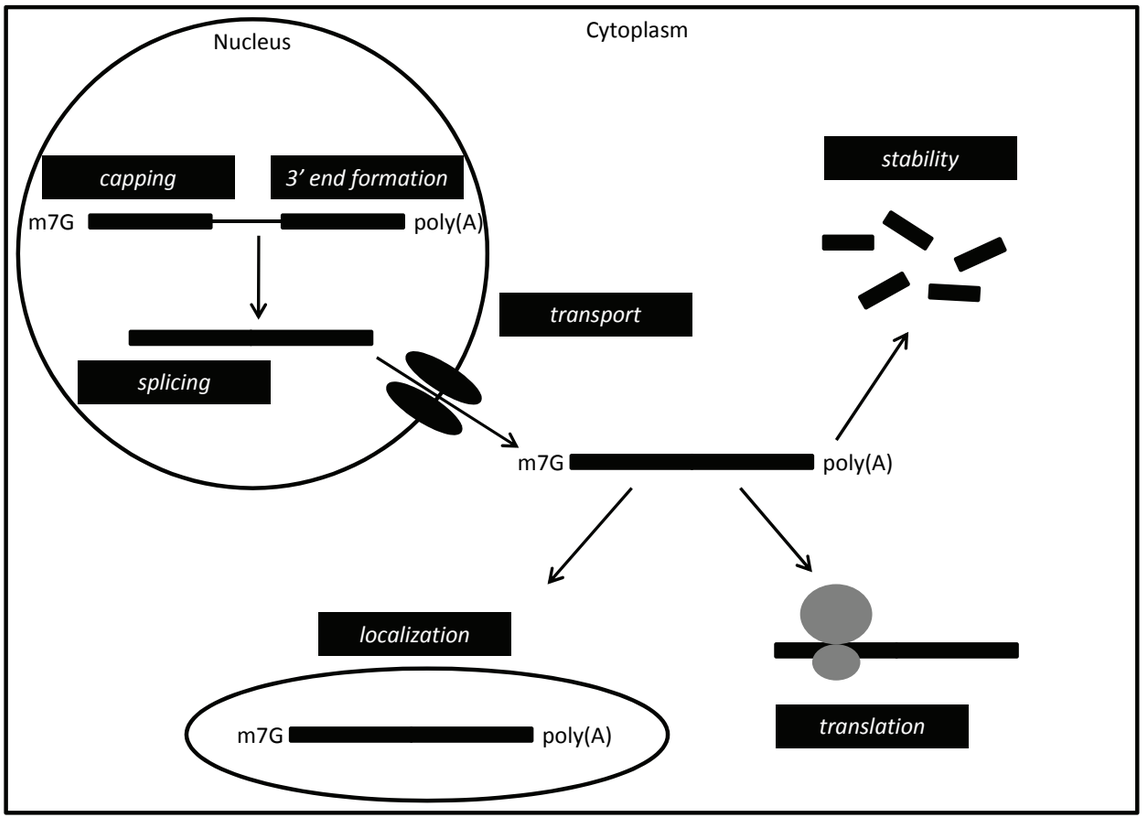

Fig. 1. RNA-binding proteins have diverse functions in RNA metabolism. A schematic of the life cycle of an mRNA and various functions, in black boxes, where RNA-binding proteins participate is shown. m7G denotes the 7-methylguanosine cap and poly(A) denotes the poly(A) tail of mRNAs.

2.2 RNA-binding proteins and cancer

RNA-binding proteins can regulate operons formed by mRNAs involved in cell proliferation, apoptosis, growth, angiogenesis, and invasion/metastasis, processes which, if dysregulated can lead to or potentiate cancer (Lukong et al., 2008). In recent times, the recognition of the impact RNA-binding proteins have on tumorigenesis has been emerging. For example, eIF4E is an important RNA-binding protein that acts downstream of the mTOR pathway (Wendel et al., 2007). This protein functions normally as a component of the translation initiation complex. When elevated, eIF4e contributes to tumor formation by increasing the translation of oncogenes and genes involved in cell proliferation.

It is estimated that the human genome encodes ~1000 different RNA-binding proteins. A recent study from our lab utilized a comprehensive *in silico* approach to analyze the expression pattern of RNA-binding proteins in normal and tumor tissues (Galante et al., 2009). In this study, we analyzed 383 RNA-binding proteins in 12 different tissue/tumor types. 53 proteins have been shown to be aberrantly expressed in at least two tumor types, with the majority of them being upregulated, suggesting that RNA-binding proteins may be oncogenic or potentiate certain characteristics in cancer. One example is Musashi1, whose increased expression pattern has been shown in malignancies such as glioblastoma,

medulloblastoma, breast, and colon cancer (Kanemura et al., 2001; Toda et al., 2001; Sureban et al., 2008; Wang et al., 2010).

2.3 The Musashi1 RNA-binding protein

Musashi (Msi) is an evolutionarily conserved RNA-binding protein (RBP) that controls translation through its interaction with specific motifs located in the 3′ untranslated region of target messenger mRNAs (Okano et al., 2005). Msi1 represses the translation of Numb (Imai et al., 2001), a negative regulator of Notch, $p21^{Cip1}$, an inhibitor of cyclin-dependent kinases (Battelli et al., 2006), and doublecortin (Dcx), a microtubule-binding protein involved in neural stem cell migration (Horisawa et al., 2009), but promotes the translation of Robo3, a receptor involved in axonal guidance (Kuwako et al., 2010). Additional targets for Msi1, many of which pertain to the cell cycle, apoptosis, proliferation and differentiation were identified by RIP-chip analysis (de Sousa Abreu et al., 2009). The ability of Msi1 to either positively or negatively control protein expression suggests the duality of its function in translation. Musashi1 inhibits translation through its interaction with poly (A)-binding protein (PABP), thus disrupting the formation of an active translation complex (Kawahara et al., 2008). The mechanism by which Msi1 activates translation is not yet known.

Msi1 was identified in *Drosophila* as a protein involved in sensory organ development and asymmetric cell division (Nakamura et al., 1994). In *Drosophila,* mutations in Musashi results in a double sensory shaft. The name Musashi is a tribute to the famous 17th century samurai, Miyamoto Musashi, who developed the two sword technique. In metazoans, Musashi has two paralogs, Msi1 and Msi2, which have similar RNA-binding properties (Sakakibara et al., 1996; Sakakibara et al., 2001; Sakakibara et al., 2002). Although Msi1 and Msi2 have differing patterns of expression and roles within the cell (Aubert et al., 2003; Chan et al., 2006; Siddall et al., 2006; Sugiyama-Nakagiri et al., 2006; Sgubin et al., 2007; Kharas et al., 2010), both Msi1 and Msi2 are required for brain stem cell self-renewal (Sakakibara et al., 2002). In mammalian cells, Msi1 denotes multipotent stem cells in the brain (Sakakibara et al., 1996; Keyoung et al., 2001; McGuckin et al., 2004; Uchida et al., 2004), intestine (Kayahara et al., 2003; Nishimura et al., 2003; Sakatani et al., 2005) , breast (Clarke, 2005; Wang et al., 2008), and hair follicles (Sugiyama-Nakagiri et al., 2006).

2.4 Function of Musashi1 in normal and cancer stem cells

In breast cancer cells, Musashi1 maintains the expression of the embryonic stem cell (ESC) markers c-Myc, Nanog, Sox2, Bmi1 and Oct4 (Wang et al., 2010). These markers when collectively expressed in differentiated cells were able to reprogram cells, conferring them stem-like characteristics (Yu et al., 2007; Gonzalez et al., 2009; Yu et al., 2009; Stadtfeld et al., 2010). An embryonic stem cell signature in breast cancer is associated with a lower five-year survival rate (Wang et al., 2010). The expression of embryonic stem cell markers are usually found in other malignant tumors such as cervical cancer, retinoblastoma, poorly differentiated lung cancer, medulloblastoma, glioblastoma, bladder cancer, and basal-type breast cancer, and predicts lower overall survival (Ben-Porath et al., 2008; Hassan et al., 2009; Hemmati et al., 2003; Seigel et al., 2007; Stevenson et al., 2009; Ye et al., 2008).

Msi1 expression is particularly important for the proper development of the brain as suggested by a genetically engineered *msi1*$^{-/-}$ in a C57BL6 background which results in a mouse with obstructive hydrocephalus and ependymal abnormalities (Sakakibara et al., 2002). Additionally, Msi1 is known as a neural stem cell marker useful for studying the

migration and biology of neural stem/progenitor cells during development (Kaneko et al., 2000; Chan et al., 2006). In a recent study, Msi1 was shown to be required for neuronal migration of precerebellar neurons via its target gene, Robo3 (Kuwako et al., 2010). Robo3 is a receptor found on astrocytes and is required to receive signals from migrating neurons through the secretion of the Slit1 diffusable protein. Slit1 signals the change of astrocyte morphology to create astrocytic tunnels, allowing migrating neurons to navigate through the dense meshwork of the adult brain (Kaneko et al., 2010).

Consistent with its role in self-renewal, Msi1 expression is positively correlated with a label-retaining and side population human breast epithelial cells enriched in ERα, $p21^{Cip1}$, CK19 and double-positive CK14/CK18 progenitor cells (Smalley and Clarke, 2005; Clarke et al., 2005). When Msi1 is overexpressed in murine mammary epithelial cells, $CD24^{hi}$/Sca-1^{+}, $CD24^{hi}$/$CD29^{+}$, $CK14^{+}$/$CK18^{+}$ and $CK6^{+}$ and $CK19^{+}$ expression is enhanced in mammary stem and progenitor cells (Glazer et al., 2008; Wang et al., 2008). Msi1 acts in a unique autocrine pathway which consists of increased secretion of the growth factor Proliferin, loss of the Wnt inhibitor DKK3, activation of Wnt and Notch signaling (Glazer et al., 2008; Wang et al., 2008). This results in a gene expression profile indicative of the cell cycle, growth factor signaling, invasion, adhesion, survival and embryonic stem cells. In addition, $CD24^{+}$/$CD29^{hi}$ mouse mammary cells contain multipotent self-renewing mammary stem cells which can reconstitute a complete mammary gland from a single mammary stem cell and represent a cancer stem cell population in tumors from MMTV-Wnt1 and p53-null in murine breast cancer models (Shackleton et al., 2006; Zhang et al., 2008). CD24 expression is controlled through the IGF2 receptor which binds to Proliferin and coexpressed in Msi1-positive cells (Glazer et al., 2008; Wang et al., 2008). In colon cancer, high expression of Msi1 is observed as a result of increased IGF2 expression in intestinal crypt cells due to loss of imprinting, thus predisposing the crypt cells to become malignant (Sakatani et al., 2005; Cui et al., 2006). Loss of imprinting of *IGF2* is observed in other cancers such as medulloblastoma (Corcoran et al., 2008). In studies done in our lab using the cross-linked and immunoprecipitation, or CLIP analysis in U251 glioblastoma cells, IGF2 was identified as a potential target of Musashi1 (Penalva lab, unpublished results), suggesting a potential mechanism by which Msi1 may control tumor progression.

3. Musashi1 as a critical regulator in brain tumors

Musashi1 expression has been seen to be elevated in brain tumors such as glioma and medulloblastoma. In gliomas, high Msi1 expression was identified as a poor prognostic factor (Kanemura et al., 2001). In *in vivo* xenograft models, silencing of Musashi1 by small interfering RNAs caused a reduction in tumor growth of both glioblastoma and medulloblastoma cells (Penalva lab, unpublished results). We summarized below the connections between Msi1 and brain tumor-related pathways.

3.1 Notch pathway

Musashi1 and Notch 1 expression correlate in areas of tumor proliferation and infiltration (Kanemura et al., 2001). Furthermore, suppression subtractive hybridization experiments established an association between Msi1 and Notch pathway activation in medulloblastoma cells (Yokota et al., 2004). Notch is a well-conserved signaling pathway that regulates cell fate, cell proliferation, and cell death during development (Artavanis-Tsakonas et al., 1999). Upon binding, cleavage of the Notch receptor occurs in two separate events. The first event

is catalyzed by the ADAM-family of metalloproteinases. The second event is catalyzed by the γ-secretase protein complex; this complex consists of four proteins, presenilin, nicastrin, PEN2, and APH2 (Fortini, 2002). Cleavage by the γ-secretase protein complex releases the Notch intracellular domain, or NICD, which then localizes in the nucleus and transactivates transcription (Schweisguth, 2004). Musashi1 interacts with the Notch pathway via post-transcriptional regulation of the negative Notch regulator, Numb. Upon binding to the 3′ untranslated region of Numb, Musashi1 causes translational repression, thus effectively releasing Notch inhibition (Imai et al., 2001).

3.2 Wnt pathway

Wnt is an essential signaling pathway required for developmental processes such as body axis specification and morphogenic signaling (Cadigan and Nusse, 1997). Wnt is a family of secreted cysteine-rich glycoproteins that act in a paracrine-like fashion over short distances to activate signaling pathways. Msi1 influences Wnt pathway activation by repressing the translation of p21, a cyclin-dependent kinase inhibitor, required for the transition between the G_1 and S phase of the cell cycle (Battelli et al., 2006). Additionally, p21 negatively regulates Wnt4 transcription, thus connecting cell cycle regulation with the Wnt signaling pathway (Devgan et al., 2005).

3.3 Hedgehog pathway

The Hedgehog pathway initiates with the secretion of Hedgehog ligand from different tissues during development (Ingham and McMahon, 2001). Upon binding, the Hedgehog ligand inactivates the Patched-1 Hedgehog receptor, leading to the release of the catalytic inhibition on the Smoothened G-protein-coupled receptor signal transduction molecule (Villavicencio et al., 2000; Chen et al., 2002). This event activates the Hedgehog signal transduction cascade with the subsequent activation of transcription by the glioma-associated oncogene zinc finger transcription factor GLI2 and GLI3 of Hedgehog target genes (Dahmane et al., 2001). Msi1 interacts with the Hedgehog pathway by interfering with the expression of several key Hedgehog components such as SMO and GLI1. Morover, inhibition of Msi1 causes increased sensitivity to cyclopamine, a Hedgehog pathway inhibitor, resulting in a decrease in cell proliferation (Sanchez-Diaz et al., 2008).

3.4 Mining through the cancer genome atlas

To better understand the participation of Msi1 in glioblastoma, we conducted an expression correlation study to identify genes closely associated with Msi1. Glioblastoma (GBM) data from The Cancer Genome Atlas (TCGA) consortium was collected representing microarrays performed on GBM in nearly 500 patients (The Cancer Genome Atlas Research Network, 2008). The microarray results were downloaded from 7 distinct batches of experiments and then filtered for only those tumors assayed by the Agilent 244K platform and then combined to form a single dataset comprising expression results for 17815 genes across all patients. Due to data access restrictions patients could not be stratified by age, gender, or race. The data were re-normalized using quantile normalization, and the correlation with Msi1 and all other genes was computed for each batch stratum. The mean correlation across batches was computed for each gene, and the absolute value of the correlation was used to sort the genes from most correlated to least correlated with MSI1.

The genes with significant expression correlation with Musahi1 (~250 genes) were then analyzed for ontological information pertaining to disease states (**Figure 2 and 3**), biological processes (**Figure 4**), and functional association using Ariadne Genomics Pathway Studio (**Figure 5**). Identified genes were not found to have significant change in correlation levels across the four known subtypes of glioblastoma tumors (Classical, Mesenchymal, Proneural, and Neural) as defined by the TCGA (Parsons et al., 2008). Approximately 10% of the genes were shown to have interactions with other genes within the group (**Figure 5**). Major nodes in this network include CSF3 (Granulocyte colony stimulating factor), GnRH (Gonadotropin-releasing hormone), RARA (Retinoic acid receptor alpha), and RELB. All of these genes have a strong positive correlation with MSI1 expression in the TCGA expression data.

Disease State	Gene Symbol (Positive Correlation with MSI1)	Gene Symbol (Negative Correlation with MSI1)
Neoplasms	ALOX12, CSF3, CX3CL1, CYP2S1, ERCC2, FCGR1A, FPR1, GATA5, GNRH2, HOXB9, IL1F7, INHBC, MOS, MSMB, NOTCH3, PPY, RARA, RASSF3, RELB, SFTPA1, SOCS1, TFF2, TSPO, TYROBP, WNT3A	AKT3, CNTN1, CTGF, LIG4, MAPK9, MBD1, PIK3CB, SNIP1, SPIN1, TRIM37
Death	ALOX12, CSF3, CX3CL1, ERCC2, FCGR1A, NOTCH3, RARA, RELB, SFTPA1, SLC4A1, SOCS1, TYROBP	ATE1, CTCF, GRM1, MAPK9, PIK3CB
Inflammation	ALOX15, CCL24, CSF3, CX3CL1, DEFB4A, FCGR1A, FPR1, GNRH1, IL12RB1, RELB, RETNLB, SFTPA1, SOCS1, TFF2, TYROBP, VSIG4	MAPK9
Breast Neoplasms	CSF3, DPF3, ERCC2, GNRH1, GNRH2, HOXB9, NOTCH3, NOTCH4, OPRL1, RARA, RELB, TFF2, TSPO, WNT3A	AKT3, MAPK9, SLC39A6
Infection	CSF3, CST5, CX3CL1, DEFB4A, FCGR1A, FPR1, GNRH1, IL12RB1, PGLYRP4, PRSS22, RETNLB, SFTPA1, SOCS1, TYROBP, VSIG4	MAPK9
Wounds and Injuries	ALOX12, ALOX15, CCL24, CSF3, CX3CL1, DEFB4A, FCGR1A, FPR1, NOTCH3, RELB, RETNLB, SFTPA1, SOCS1, TFF2, TSPO	GRM1, MAPK9
Diabetes Mellitus	ALOX12, ALOX15, CSF3, CX3CL1, GNRH1, NEUROG3, NOTCH3, PPY, RETNLB, SOCS1	LIG4, MAPK9
Adenocarcinoma	ALOX12, CSF3, CX3CL1, GNRH1, HOXB9, MSMB, NOTCH3, SFTPA1, SLC4A1	
Prostatic Neoplasms	ALOX12, ALOX15, CSF3, GNRH1, MRGPRE, MSMB, RELB, WNT3A	AKT3, PIK3CB
Pancreatic Neoplasms	ALOX15, CX3CL1, GNRH1, LRG1, NOTCH3, PPY, TFF2	MBD1
Neutrophil Infiltration	ALOX15, CCL24, CSF3, DEFB4A, FCGR1A, FPR1	
Bone Resorption	CSF3, CX3CL1, NOTCH3, RELB, SOCS1, WNT3A	
Myeloid Leukemia	CSF3, RARA, SLC4A1, SOCS1	
B-Cell Lymphoma	FCGR1A, SLC4A1, SPIB	CTCF

Fig. 2. Msi1-correlated genes are involved in disease processes. The table above shows the incidence of genes from the TCGA data set shown to be correlated with MSI1 in various diseases. Genes in red were positively correlated with MSI1 expression while genes in green were negatively correlated with MSI1 expression.

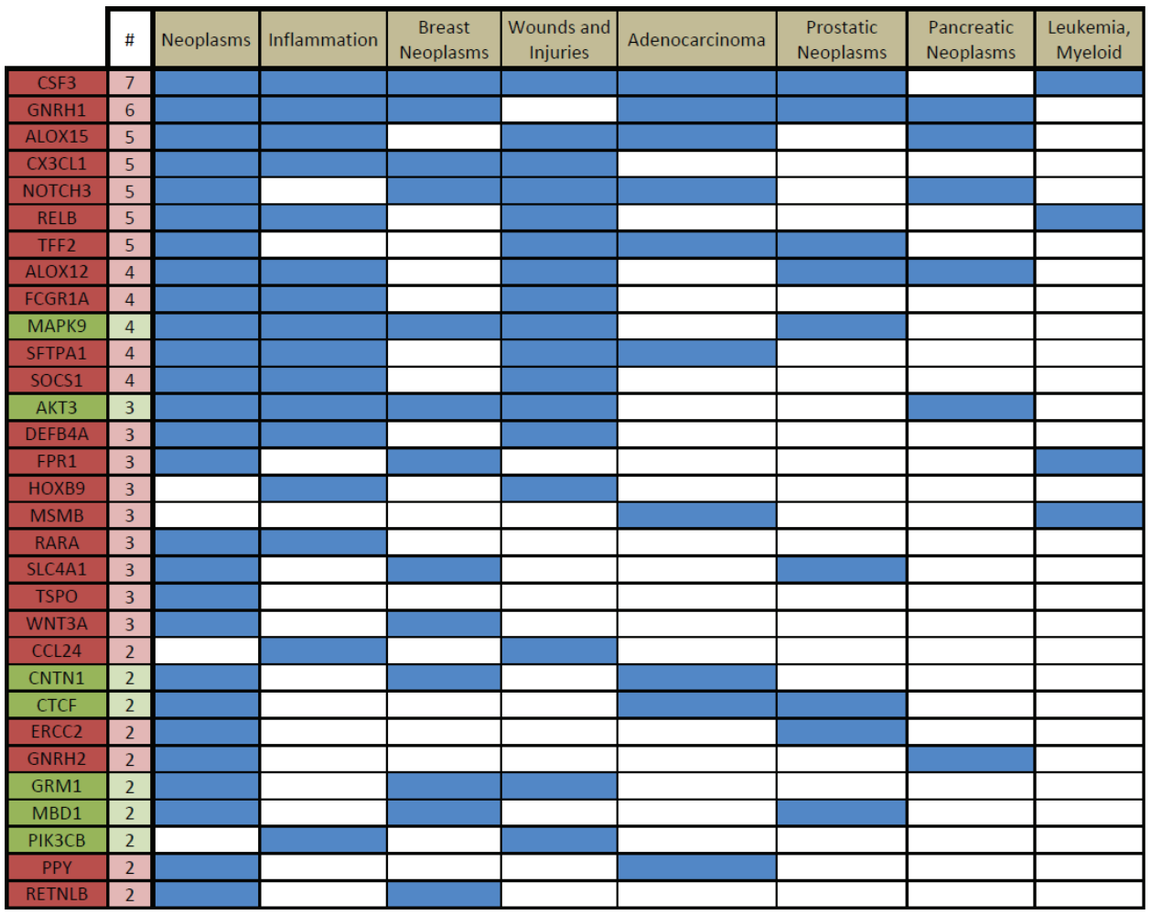

Fig. 3. Msi1-correlated genes have implication in important disease states. Genes and Disease were sorted by incidence count which is also given adjacent to or bellow each group respectively. Genes in red were positively correlated with MSI1 expression while genes in green were negatively correlated with MSI1 expression.

3.5 Genes that correlate with Msi1 expression are important players in glioblastoma

Among the genes identified in the TCGA analysis, a few should be highlighted based on its importance and role in gliomagenesis. We will summarize the functions of granulocyte colony stimulating factor 3 (CSF3), gonadotropin-releasing hormone (GnRH), retinoic acid receptor alpha (RARA), Notch3/4, DNA ligase IV (LIG4), excision repair cross-complementing rodent repair deficiency, complementation group 2 (ERCC2), and (C-X3-C motif) ligand 1 (CX3CL1).

3.5.1 Granulocyte colony stimulating factor 3

Granulocyte colony stimulating factor (CSF3) is a cytokine that controls the production, differentiation, and function of granulocytes. In the central nervous system, CSF3 plays an important role by inducing neurogenesis, maintain neuroplasticity, halting tissue degradation through inhibition of apoptosis and promoting cell survival through the MAPK, PI3K, and Akt pathways (Schneider et al., 2005).

Pathway	Gene Symbol (Positive Correlation with MSI1)	Gene Symbol (Negative Correlation with MSI1)
Cell Cycle Regulation	ADRA1D, ALOX12, ALOX15, BEST4, CCL24, CHRNE, CLCN1, CSF3, CX3CL1, DEFB4A, ERCC2, FCGR1A, FPR1, GALK1, GNRH1, GNRH2, HOXB9, IL12RB1, IL17RE, IL1F7, INHBC, KCNK7, KRT6B, MOS, MRGPRX3, MSI1, MSMB, NEUROG3, NFKBID, NOTCH3, NOTCH4, OPRL1, OR10J5, PPY, RARA, RASSF3, RASSF5, RELB, RETNLB, SCN4A, SFTPA1, SLC4A1, SOCS1, SPIB, TFF2, TSHB, TSPO, TYROBP, VSIG4, WNT3A	AKT3, ATE1, CDC40, CHRM5, CNTN1, CP110, CTCF, DPEP1, GRM1, KCNAB1, KPNA6, LIG4, MAPK9, PIK3CB, RSBN1, SLC39A6, SNIP1, SNX19, SPNS1, STXBP5, TRIM23, TRIM37, UBR5
Cell Proliferation	ADRA1D, ALOX12, ALOX15, BAALC, CCL24, CD320, CSF3, CX3CL1, DEFB4A, DHH, FCGR1A, FPR1, GALK1, GATA5, GNRH1, GNRH2, HOXB9, IL12RB1, KRT6B, MOS, MSMB, NEUROG3, NOTCH3, NOTCH4, OPRL1, RARA, RASSF3, RELB, RETNLB, SFTPA1, SLC4A1, SOCS1, SPATA12, TFF2, TSPO, TYROBP, VSIG4, WNT3A	AKT3, CHRM5, CNTN1, CTCF, GRM1, LIG4, MAPK9, PIK3CB, PSMD6, PUM2, SNIP1, UBR5
Apoptosis	ADRA1D, ALOX12, ALOX15, CSF3, CST5, CX3CL1, DEFB4A, ERCC2, FCGR1A, FPR1, GJB3, GNRH1, GNRH2, MAP3K9, MOS, MSMB, NEUROG3, NOTCH3, NOTCH4, OPA3, PROKR2, RARA, RASSF3, RASSF5, RELB, RETNLB, RPL13A, SFTPA1, SOCS1, TFF2, TSPO, TYROBP, WNT3A	AKT3, CTCF, GRM1, LIG4, MAPK9, MBD1, NEK1, PIK3CB, SLC39A6, SPIN1, SPNS1
Cell Differentiation	ADRA1D, ALOX15, BAALC, CD320, CSF3, CST5, CX3CL1, DHH, FCGR1A, FOXE3, FPR1, GATA5, GNRH1, HOXB9, IL12RB1, LCE3B, LRG1, MOS, MRPL12, MSMB, NEUROG3, NOTCH3, NOTCH4, RARA, RELB, RETNLB, SFTPA1, SOCS1, SPIB, TFF2, TSPO, TYROBP, VSIG4, WNT3A	AKT3, CNTN1, CTCF, MAPK9, MBD1, PUM2, UBR5
Sonic Hedgehog Pathway	ALOX15, CLCN1, CSF3, CX3CL1, DEFB4A, DHH, FCGR1A, FOXE3, FPR1, GALK1, GNRH1, GNRH2, HOXB9, MOS, NFKBID, NOTCH3, RARA, RELB, SFTPA1, TSHB, TSPO, WNT3A	AKT3, GRM1, MAPK9, RSBN1, SNIP1, STXBP5, UBR5
Notch Pathway	ALOX12, CHRNE, CSF3, CX3CL1, DEFB4A, FCGR1A, FPR1, GNRH1, GNRH2, MOS, NOTCH3, NOTCH4, RARA, RASSF3, RASSF5, RELB, SFTPA1, SLC4A1, SOCS1, TFF2, TSHB, TSPO, TYROBP, WNT3A	AP1AR, CDC40, CNTN1, MAPK9, PIK3CB
Cell Survival	ADRA1D, ALOX12, CSF3, CX3CL1, FCGR1A, GNRH1, MSMB, NOTCH3, RARA, RELB, SOCS1, SPIB, TSPO, WNT3A	AKT3, CTCF, GRM1, LIG4, MAPK9, PIK3CB
Neurogenesis	CSF3, NEUROG3, NOTCH3, RARA, WNT3A	GRM1, LIG4, MBD1

Fig. 4. Msi1-correlated genes are involved in many cancer-related processes. The table above shows the incidence of genes correlated with MSI1 in various pathways. Genes in red were positively correlated with MSI1 expression while genes in green were negatively correlated with MSI1 expression.

3.5.2 Gonadotropin-releasing hormone

Gonadotropin-releasing hormone (GnRH) is a tropic peptide hormone that facilitates the release of follicle-stimulating hormone and luteinizing hormone from the anterior pituitary. GnRH-mediated signaling may be important for the growth and maintenance of gliomas. The use of the GnRH agonist Zoladex results in inhibition of cell proliferation in two glioblastoma cell lines (U87MG and U373) thus presenting GnRH signaling as a potential therapeutic target (Marelli et al., 2009).

3.5.3 Retinoic acid receptor alpha

Retinoic acid receptor alpha (RARA) is a ligand-dependent nuclear receptor that upon binding to retinoic acid, can affect processes such as development, differentiation, apoptosis, and transcription of clock genes. Glioblastoma is extremely sensitive to retinoic acid, which flattens cell morphology, forming intercellular cross-bridges, and reduces anchorage-independent growth (Mukherjee and Das, 1995). Treatment of glioblastoma cells *in vitro* results in growth arrest and induces differentiation through the Notch pathway (Ying et al., 2011).

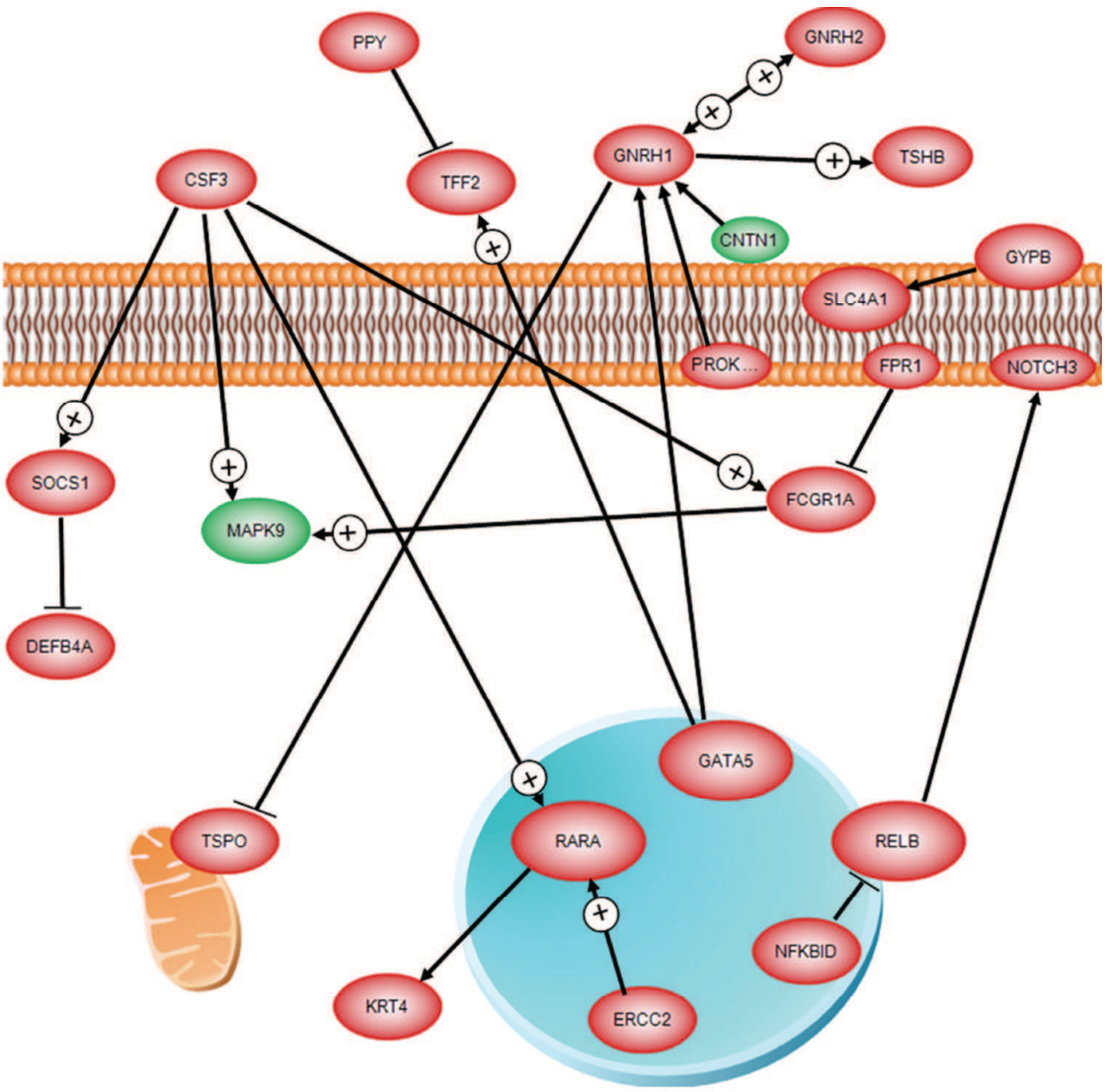

Fig. 5. Msi1-correlated genes interact in a wide network in glioblastoma. The image above shows the interactions amongst genes from the TCGA data set shown to be correlated with Msi1. Genes in red were positively correlated with Msi1 expression while genes in green were negatively correlated with Msi1 expression. The mitochondria, nucleus, and cell membrane are shown and genes are placed accordingly. Connections that involved positive changes in expression / up regulation are drawn with a "plus" symbol while those involving negative changes in expression / down regulation are shown with a bar. If no information was present or the effect was unclear only the direction of the connection was shown with an arrow.

3.5.4 Notch receptors

Notch3 and Notch4 receptors have been previously implicated in association with Msi1. Msi1 has been previously demonstrated to negatively affect Numb expression, a negative effector of the Notch pathway. Notch3 and Notch4 have previously been demonstrated to play important roles in the tumorigenesis and glioblastoma biology. Enhanced Notch3/4 expression is observed in astrocytomas and medulloblastomas in part due to the loss of the FBXW7, a Skp1-Cul1-F-box E2 ubiquitin ligase (Hagedorn et al., 2007; Xu et al., 2009). Notch3 activation has been implicated in gliomagenesis (Pierfelice et al., 2011).

3.5.5 DNA repair enzymes

A hurdle in treatment of glioblastoma with adjuvant chemotherapy or radiation therapy is the enhanced ability for the cell to repair DNA resultant of damage induced by the chemotherapeutic or radiation. Two genes, LIG4 and ERCC2, are found to be correlated with Msi1. LIG4, or DNA ligase IV, expression causes cells to be resistant to treatment by the nitrosourea chloroethylating agent, nimustine (ACNU) through the role of DNA ligase IV in nonhomologous end joining and siRNA silencing of LIG4 results in increased cell death when induced with ACNU (Kondo et al., 2010). In human genetic studies, polymorphisms of LIG4, particularly SNP2 rs3093739:T>C, was associated with increased risk for developing gliomas, probably due to increased DNA damage and the inability for the cell to repair the damage effectively, thus leading to tumor formation (Liu et al., 2008). ERCC2, or excision repair cross-complementing rodent repair deficiency, complementation group 2, is another DNA repair gene whose expression is associated with Msi1. ERCC2 is involved in transcription-coupled nucleotide excision repair through its binding to the basal transcription factor BTF2/TFIIH complex. Allelic loss of ERCC2 is associated with a younger age of diagnosis of glioma; however, the loss of the ERCC2 gene is not associated with a difference in response to therapy or survival (Liang et al., 1995). More recently, polymorphisms in the ERCC2 gene have been revealed. Particularly, homozygosity at codon 156 for the silent AA allele results in high incidences of glioma (odds ratio 2.3), probably through an alteration in relationship with a currently unidentified gene and ERCC2 (Caggana et al., 2001). In a follow up study, it was seen that a single nucleotide polymorphism, rs13181, for ERCC2 confers a significant, protective effect (McKean-Cowdin et al., 2009).

3.5.6 Chemokine (C-X3-C motif) ligand 1

Glioblastoma also have an enhanced ability to invade adjacent normal brain tissue; one gene that has been implicated in invasion is the chemokine ligand, CX3CL1 chemokine (C-X3-C motif) ligand 1 gene mediating the cross-talk between neurons and microglia. The chemokine receptor CX3CR1 and the ligand, CX3CL1, expression is increased in human glioblastoma samples and neural cancer stem cells at the mRNA and protein level (Erreni et al., 2010; Locatelli et al., 2010). The high expression levels are inversely correlated with patient overall survival (Erreni et al., 2010). CX3CL1 is localized in the outer layer of cells of glioblastoma tumorspheres, suggesting the involvement of the chemokine system in intracellular adhesion (Erreni et al., 2010). The high levels of CX3CL1/CX3CR1 results in the recruitment of glioma-infiltrating microglia, which displays high levels of adhesion and migration *in vitro*; this suggests an important role for the chemokine system in tumor promotion (Held-Feindt et al., 2010).

4. Conclusion

Musashi1 plays a role in glioblastoma and other tumor types by affecting a complex network of genes implicated in numerous cancer-related processes and biological pathways. This is evident from the TCGA study we discussed in this chapter. Further wet-lab experimentation is required to understand the different branches of Musashi1 regulation and hopefully to provide insight for the development of novel glioblastoma therapeutics.

5. Acknowledgement

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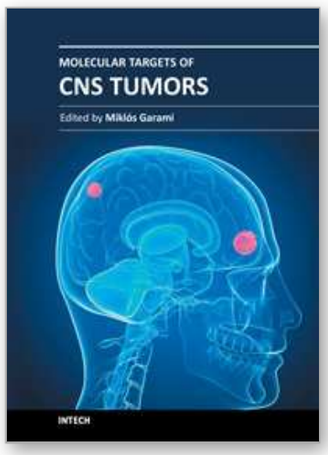

Molecular Targets of CNS Tumors

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Molecular Targets of CNS Tumors is a selected review of Central Nervous System (CNS) tumors with particular emphasis on signaling pathway of the most common CNS tumor types. To develop drugs which specifically attack the cancer cells requires an understanding of the distinct characteristics of those cells. Additional detailed information is provided on selected signal pathways in CNS tumors.

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