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Musashi Proteins in Neural Stem/Progenitor Cells

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1. Introduction

Many RNA-binding proteins are encoded in the genomes of various organisms and play a critical role in several life systems. The human genome contains thousands of RNA-binding proteins (Glisovic *et al.*, 2008). The most important biological role for these proteins involves the post-transcriptional events in gene expression, *e.g.*, splicing, export, stabilization, localization, and translation. Recent studies have shown that these post-transcriptional events are of similar importance to transcriptional and post-translational events and are highly orchestrated (Keene *et al.*, 2007).

Musashi is an RNA-binding protein that contains typical RNA-recognition motifs (RRMs). The gene encoding the Musashi protein was originally identified in *Drosophila* and is responsible for the asymmetrical division of sensory organ precursor cells (Nakamura *et al.*, 1994). Later studies determined that Musashi proteins are RNA-binding proteins that bind to a sequence in the 3' untranslated region (UTR) of *tramtrack69* (*ttk69*) mRNA (Lai & Li, 1999). The binding of these proteins prevents the translation of *ttk69* mRNA, resulting in asymmetric cell division (Hirota *et al.*, 1999; Okabe *et al.*, 2001).

Subsequently, two highly conserved mammalian homolog proteins, Musashi1 (Msi1) and Musashi2 (Msi2), were discovered in mice (Sakakibara *et al.*, 1996, 2001). Over 90 Musashi and Musashi-like proteins have been discovered in various multicellular animals; however, these proteins have not been found in prokaryotes, plants, or monocellular organisms. The expression pattern and structure of these proteins are highly similar among various organisms (Good *et al.*, 1998; Yoda *et al.*, 2000; Kawashima *et al.*, 2000; Cuadrado *et al.*, 2002; Lowe *et al.*, 2003; Asai *et al.*, 2005; Higuchi *et al.*, 2008).

Musashi proteins are highly expressed in the vertebrate nervous system. (Kaneko *et al.*, 2000). In the mammalian central nervous system, Msi1 appears specifically in undifferentiated neural stem/precursor cells during both the embryonic and adult stages (Sakakibara *et al.*, 1996; Kaneko *et al.*, 2000; Sakakibara & Okano, 1997). Interestingly, Msi1 expression was also observed in many kinds of somatic stem cells in adult tissues, such as the eye (Raji *et al.*, 2007), intestine (Potten *et al.*, 2003), stomach (Akasaka *et al.*, 2005), mammary gland (Clarke *et al.*, 2005), and hair follicles (Sugiyama-Nakagiri *et al.*, 2006).

Later studies revealed that Msi1 maintains the stemness of the neural stem/precursor cells through the translational suppression of m-Numb, a regulator protein of the Notch signal

pathway (Imai *et al.*, 2001; Kawahara *et al.*, 2008). Although other target mRNAs of Msi1 have been recently reported, the full function of Msi1 in maintaining stem/precursor cells remains to be elucidated (Battelli *et al.*, 2006; de Sousa Abreu *et al.*, 2009; Horisawa *et al.*, 2009).

Furthermore, the relationship between Musashi proteins and several disease states have recently been reported. Msi1 is reported to play a role in a variety of cancers (Toda *et al.*, 2001; Shu *et al.*, 2002; Sakatni *et al.*, 2005) and neural disorders (Lovell & Markesbery, 2005; Ziabreva *et al.*, 2006; O'Sullivan *et al.*, 2011; Oki *et al.*, 2010; Nakayama *et al.*, 2010; Crespel *et al.*, 2005).

In this chapter, we present an overview of Musashi proteins, especially mammalian Msi1, and consider possible directions for further research.

2. The discovery of Musashi proteins and their function

Musashi was originally identified in a *Drosophila* mutant with abnormal external sensory organs (Fig.1A&B). In the early '90s, Nakamura and co-workers showed that the *musashi* gene is responsible for the asymmetrical division of sensory organ precursor (SOP) cells in *Drosophila*, which are precursors for the ectodermal system common to both neural and non-neural cell lineages in loss-of-function experiments (Nakamura *et al.*, 1994). In wild-type animals, the SOP cell divides into a non-neural precursor cell (green in Fig.1C) and a neural precursor cell (white in Fig.1C), whereas in *musashi* mutants, two non-neural precursor cells (white in Fig.1D) are produced instead. The symmetrically divided non-neural precursor cells differentiate to hair-forming cells (Sf and So in Fig.1A&B), leading to a double-bristle phenotype instead of the single-hair wild-type phenotype (Fig.1 A&B). Based on this double-hair shape, the gene was named "Musashi" after a famous Japanese swordsman who fought with two swords, Musashi Miyamoto (A.D. 1584-1645).

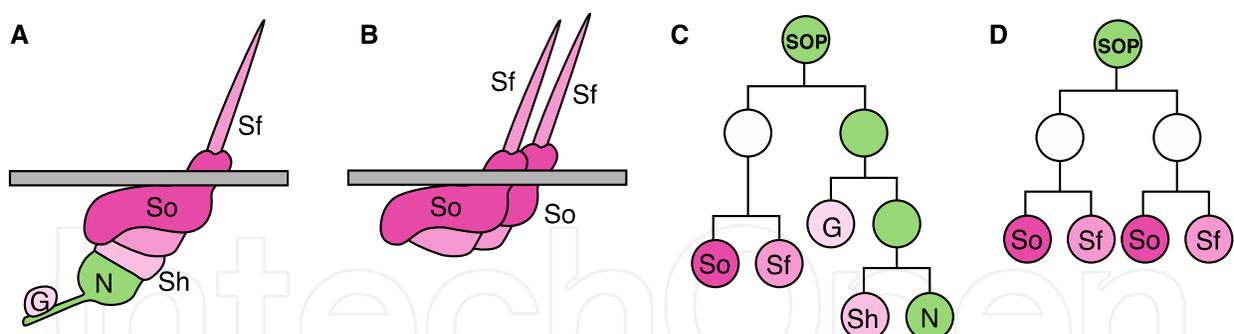
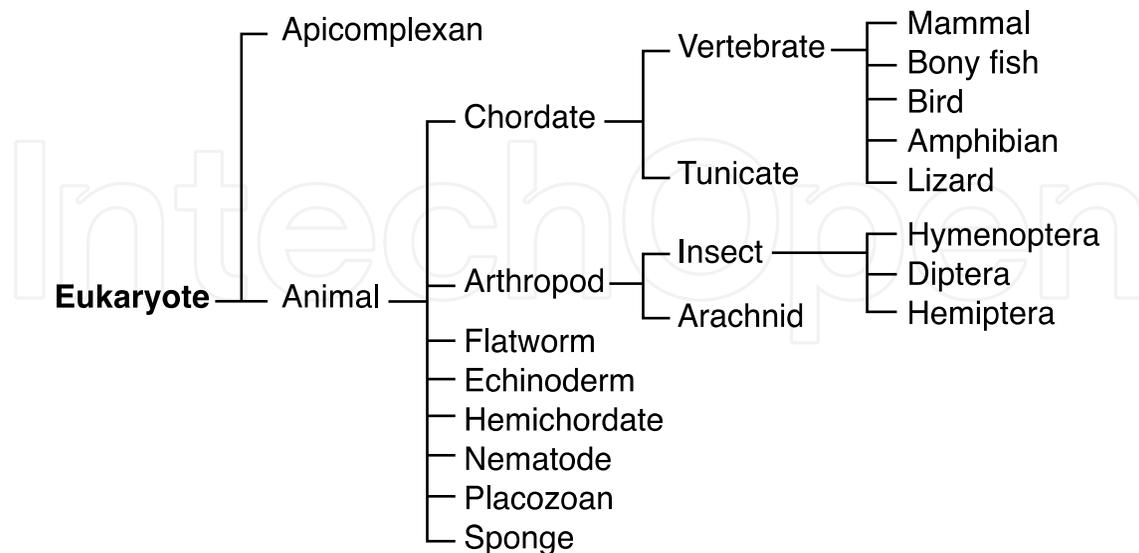


Fig. 1. Structures and cell lineages of the external sensory organs in *Drosophila* (A & B) Structures of the adult external sensory organs (mechanosensory bristles) in wild-type (A) and musashi mutant (B) animals. The cell lineages contain neuron (N; green) and non-neuronal support cells (magenta), a shaft cell (Sf), a socket cell (So), a sheath cell (Sh) and glia (G); (C & D) Cell lineages of the mechanosensory bristle in wild-type (C) and *musashi* mutant (D) animals. Cells with neuronal potential are green, and non-neuronal cells are magenta and white.

Subsequent studies revealed that the Musashi protein, which has RNA-binding activity, introduces neural differentiation potential for one daughter cell of the SOP cell via selective translational repression of the mRNA of a neural differentiation inhibitory factor (a transcription repressor possessing a BTB domain and zinc-finger domain) called *ttk69*

(Okabe *et al.*, 2001). The *ttk69* protein is located downstream in the Notch signaling pathway and acts as a determinant of non-neural identity.



All listed organisms are multi-cellular eukaryotes.

Fig. 2. A dendrogram of the organisms bearing the *musashi* or *musashi*-related genes.

The Systematic Evolution of Ligands by EXponential enrichment (SELEX) assay (Tuerk & Gold, 1990), an *in vitro* selection method for RNA, was employed to identify the specific target RNA motifs of Musashi proteins from a synthesized random-sequence RNA library. Uridine-rich sequences containing two or three (GUU...UAG) or (GUU...UG) repeats were identified as Musashi binding targets (Okabe *et al.*, 2001). Indeed, *ttk69* mRNA contains 15 of these motif sequences in the 3'UTR, and it has been demonstrated that the Musashi protein binds to the 3'UTR of *ttk69* mRNA and inhibits the translation of a reporter gene linked to the 3'UTR *in vitro* (Okabe *et al.*, 2001).

Musashi and Musashi-like proteins have since been discovered in several multicellular organisms, but these genes have not been found in prokaryotes, plants, or monocellular organisms (Fig.2). This implies that the Musashi protein is specifically required for the development and evolution of multicellular animals.

3. The homologs of Musashi protein in mammals

Further studies in *Drosophila* have revealed that the Musashi protein is also expressed in the compound eye primordium (Hirota *et al.*, 1999), CNS (Nakamura *et al.*, 1994), and neural stem/precursor cells in the larval brain (Nakamura *et al.*, 1994), which have many characteristics in common with mammalian neural stem cells (NSCs) (Ito & Hotta, 1992). Thus, to elucidate the functions of the Musashi gene family in mammals, a homolog search and immunohistochemical studies were performed in mice.

Two highly conserved homolog genes, *musashi1* (*msi1*) (Sakakibara *et al.*, 1996) and *musashi2* (*msi2*) (Sakakibara *et al.*, 2001), were discovered in mice. While the length of these proteins are considerably shorter than that of *Drosophila* Musashi, the RNA-recognition motifs (RRMs) were highly conserved (~95% identical) between mammalian and insect systems (Fig.3).

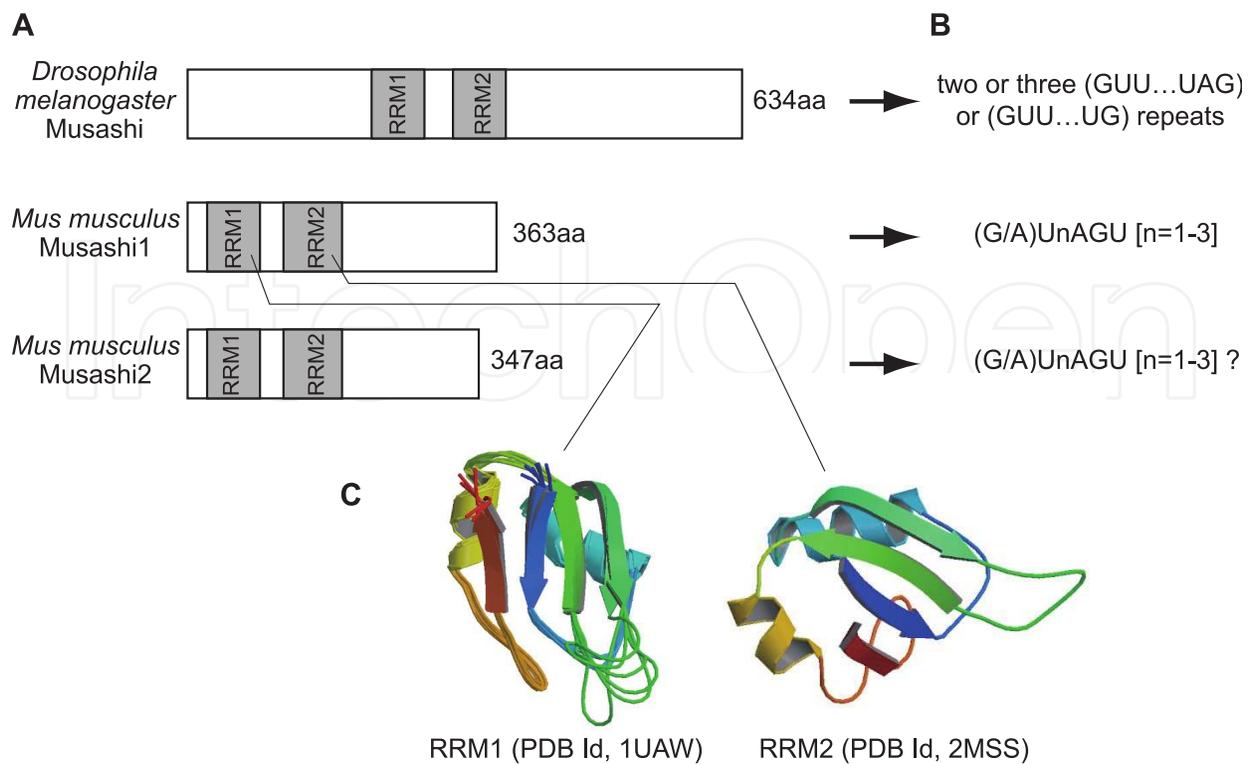


Fig. 3. The structures of Musashi proteins and their target RNA sequences (A) Primary structures of Musashi proteins in *Drosophila melanogaster* and *Mus musculus*. (B) Musashi binding motifs in target mRNAs. (C) Partial 3D structures of RRM1 and RRM2 of Msi1 protein.

A high level of expression of Msi1 in NSCs of the periventricular area and undifferentiated neural precursor cells (Sakakibara *et al.*, 1996; Kaneko *et al.*, 2000; Sakakibara & Okano, 1997) was observed. Therefore, Msi1 is now widely used as a marker of NSCs and progenitor cells in the CNS of a variety of vertebrates. These cells, which can form neurospheres, were identified in the adult human brain using this approach (Pincus *et al.*, 1998). Precise immunohistochemical analyses revealed that Msi1 is strongly expressed in the ventricular zone of the neural tube in embryos and in neurogenic sites within the postnatal brain, including the subventricular zone (SVZ), olfactory bulb, and rostral migratory stream (RMS) (Sakakibara & Okano, 1997). The Msi1 protein is expressed in neural stem/progenitor cells within these tissues and is rapidly down-regulated in post-mitotic neurons (Sakakibara *et al.*, 1996).

The Msi2 protein in mice is a paralog of Msi1, displaying more than 90% homology with the Msi1 protein in the RRM1 and RRM2 domains (Sakakibara *et al.*, 2001) (Fig.3). Although the expression pattern in the CNS is very similar between the members of this family, Msi2 is also continuously expressed in a subset of neuronal lineage cells, such as parvalbumin-containing GABA neurons in the neocortex and neurons in several nuclei of the basal ganglia (Sakakibara *et al.*, 2001). Other reports have also shown a differential expression pattern of these genes in uroepithelial cells (Nikpour *et al.*, 2010). Although the functional properties (*e.g.*, RNA-binding specificity) of the two proteins are similar, these differences in expression might explain the functional assignment of these proteins.

Although the partial 3D structures of RRM of Msi1 protein have been solved by NMR, the full-length 3D structures of Msi1 and Msi2 remain to be elucidated (Nagata *et al.*, 1999; Miyanoiri *et al.*, 2003).

The human genome also contains both *msi1* and *msi2* genes (Good *et al.*, 1998; Sakakibara *et al.*, 2001). The structure and expression pattern of these proteins in the CNS highly resemble those in mice. As described below, Musashi proteins are related to several diseases. Functional studies in mice will thus contribute to therapeutic developments for Musashi-related conditions.

Additionally, a small Msi2-like gene, LOC100504473, has been found near the Msi2 locus on the mouse genome, but its expression and function are yet to be defined.

4. Molecular and physiological functions of Musashi proteins in stem/progenitor cells

To identify the target RNAs of Msi1 in mammals, a SELEX analysis from a random-sequence RNA library was performed, similar to those done in *Drosophila*. The selected consensus sequence revealed that the mouse Msi1 protein binds specifically to RNAs that possess a (G/A)UnAGU [n=1-3] sequence (Imai *et al.*, 2001) (Fig.3).

A survey for the motif was performed in mRNAs expressed in the embryonic CNS. The 3'UTR region of *m-numb* mRNA (Zhong *et al.*, 1996) was highlighted as a candidate target. Subsequent experiments found that *m-munb* mRNA is a specific binding target of the Msi1 protein *in vitro* and *in vivo*. Its translation is repressed by the Msi1 protein (Imai *et al.*, 2001; Kawahara *et al.*, 2008).

The m-Numb protein binds to the intracellular domain of the Notch protein, which has nuclear translocation and transactivation activities, and inhibits the Notch signaling pathway (Berdnik *et al.*, 2002), which positively regulates neural stem cell self-renewal (Nakamura *et al.*, 2000; Hitoshi *et al.*, 2002; Tokunaga *et al.*, 2004) (Fig.4). In agreement with this hypothesis, oscillation in the expression of the *hes1* gene, a downstream target of Notch, controls the differentiation of embryonic stem cells to neural cells (Kobayashi *et al.*, 2009). Indeed, the Msi1 protein induces the expression of the *hes1* gene (Imai *et al.*, 2001; Yokota *et al.*, 2004).

Musashi proteins in both mammalian species and *Drosophila* contribute to maintaining the stem/progenitor cell status via translational repression of target mRNA. However, the target mRNAs are, interestingly, not orthologous. This result implies a highly conserved function of Musashi proteins in maintaining the stemness of progenitor/stem cells and the probable presence of other unknown target RNAs of the Musashi proteins.

Recently, mammalian Msi1 protein expression was identified not only in CNS, but also in other tissues and organs in embryonic or adult stages, including the eye (*e.g.*, corneal epithelium, corneal endothelium, stromal keratocyte, progenitor cell of the limbus, equatorial lens stem cell, differentiated lens fiber, and retinal pigment epithelium cells) (Raji *et al.*, 2007; Susaki *et al.*, 2009), intestine (small intestinal crypt, colon crypt, columnar cell, and epithelial cell) (Kayahara *et al.*, 2003; Nishimura *et al.*, 2003; Potten *et al.*, 2003; Asai *et al.*,

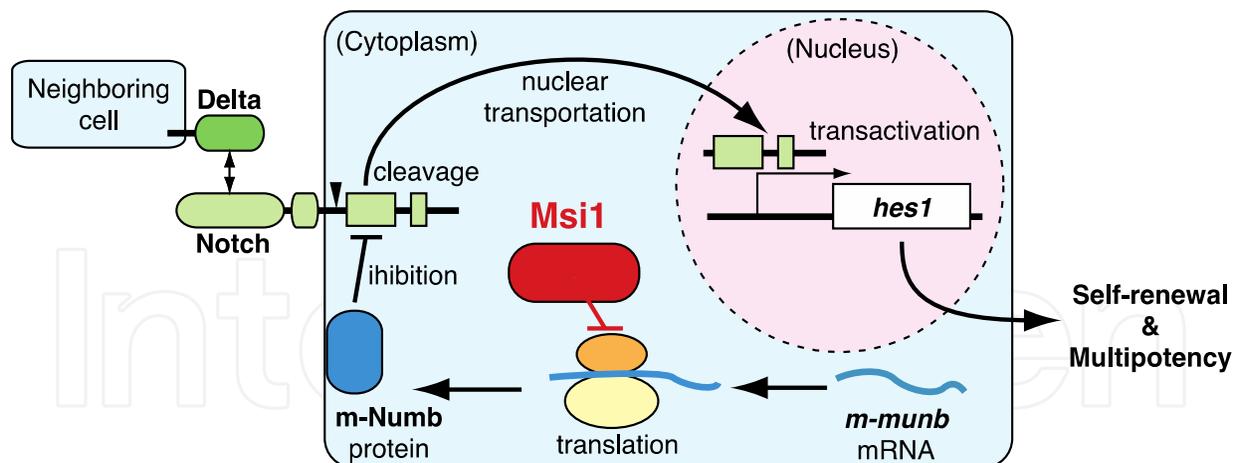


Fig. 4. A model for Msi1 function in the regulation of Notch signaling. Msi1 translationally regulates *m-numb* gene expression. Because m-Numb blocks the activation of the Notch signal induced by Delta on neighboring cells, translational repression of m-Numb by Msi1 stimulates Notch signaling and HES1 pathways.

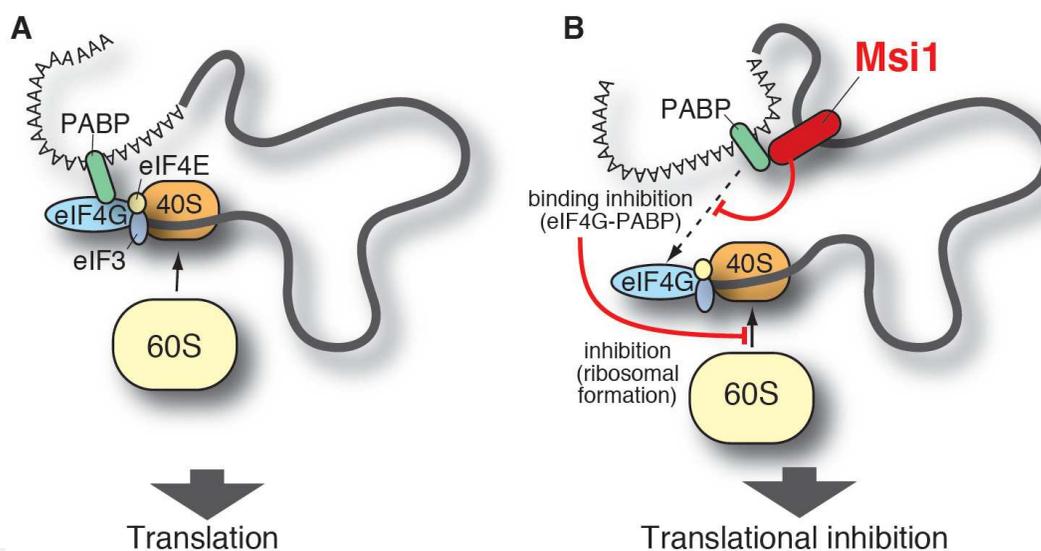


Fig. 5. Schematic representation of the molecular function of Msi1. (A) Translation of a non-target mRNA of Msi1; (B) Translational inhibition of a target mRNA of Msi1. The Msi1 protein interacts with the 3'UTR of its target mRNA and PABP and subsequently inhibits translation initiation by competing with eIF4G for PABP. These sequential events inhibit the formation of the 80S ribosome complex.

2005; Samuel *et al.*, 2008; Murata *et al.*, 2008), stomach (luminal compartment of the mucosa, isthmus/neck region, and fetal pyloric gland) (Nagata *et al.*, 2006; Akasaka *et al.*, 2005; Asai *et al.*, 2005; Murata *et al.*, 2008), breast (mammary gland epithelial cell) (Clarke *et al.*, 2005), and hair follicles (keratinocyte) (Sugiyama-Nakagiri *et al.*, 2006). These studies suggest that the Msi1 protein may be an effective marker for stem/progenitor cells in various tissues and acts as a regulator of the stem cell status of cells.

On the other hand, the function of the Msi2 protein in neural stem/progenitor cells is still unclear, though it is known that Msi1 and Msi2 have similar RNA-binding specificity

(Sakakibara *et al.*, 2001). The results of an Msi1 and Msi2 double knockout experiment suggested that these proteins have mutually complementary functions (Sakakibara *et al.*, 2002).

Recently, the molecular mechanism of translational repression by Msi1 has been uncovered. Kawahara *et al.* identified the poly(A)-binding protein (PABP) as an Msi1-binding protein and found that Msi1 competes with eIF4G for PABP binding on its target mRNAs (Fig.5) (Kawahara *et al.*, 2008).

However, the molecular machinery of other functions of Musashi protein (described below) remains to be elucidated. A survey for the co-factors of Musashi proteins is an important future task in order to fully understand the functions of these proteins.

5. Musashi-related diseases - Cancers and neural disorders

Msi1 has been shown to play a role in a variety of cancers and neural disorders.

Several studies have reported high Msi1 protein expression in many types of tumors, including glioma (Toda *et al.*, 2001), hepatoma (Shu *et al.*, 2002), colorectal adenoma (Sakatani *et al.*, 2005; Schulenburg *et al.*, 2007), teratoid/rhabdoid tumors in eye (Fujita *et al.*, 2005), non-small cell lung cancer (Kanai *et al.*, 2006), retinoblastoma (Seigel *et al.*, 2007), medulloblastoma (Nakano *et al.*, 2007; Sanchez-Diaz *et al.*, 2008), ependymoma (Nakano *et al.*, 2007), endometrial carcinoma (Götte *et al.*, 2008), neurocytoma (Yano *et al.*, 2009), glioblastoma (Liu *et al.*, 2006), and cervical carcinoma (Ye *et al.*, 2008). This might be because that many carcinoma cells are of epithelial stem cell lineage (Miller *et al.*, 2005) which express the Msi1 protein.

Although the exact function of Msi1 in these cancer cells remains unclear, the knockdown of Msi1 via siRNA resulted in arrested tumor growth in colon adenocarcinoma xenografts transplanted in athymic nude mice, reduced cancer cell proliferation, and increased apoptosis (Sureban *et al.*, 2008). These results suggest an important potential role for Msi1 in tumorigenesis and tumor proliferation.

It has also been shown that some tumors express the Msi2 protein in addition to Msi1 (Seigel *et al.*, 2007). This may indicate a complementary role of the two proteins in tumors.

Msi1 is also hypothesized to be a key player in neuronal disorders. Several reports indicate that Msi1 is relevant to neurodegenerative disorders, such as Alzheimer's disease (AD). Ectopic expression of Msi1 was observed in the hippocampus of AD patients (Lovell & Markesbery, 2005), while a significant decrease in Msi1-expressing cells was observed in the SVZ (Ziabreva *et al.*, 2006). Although it is difficult to explain these phenomena at present, the function of Msi1 in maintaining the stemness of NSCs might play a role in the pathogenesis of the disease.

Msi1 may also play a role in Parkinson's disease (PD), another type of neurodegenerative disorder. A clinical experiment found that chronic treatment with an anti-PD drug increased Msi1-positive cells in the SVZ of PD patients. The authors suggested that impaired neurogenesis may contribute to the decline in this neurodegenerative disease (O'Sullivan *et al.*, 2011).

Oki *et al.* (2010) reported an up-regulation in Msi1 expression in collapsed nervous system tissue arising from a blood circulation defect. In the ischemic striatum induced by middle

cerebral artery occlusion (MCAO), an increase in Msi1-immunoreactivity was observed in reactive astrocytes beginning at 2 days after MCAO and persisting until 14 days after MCAO. The proliferation of Msi1-positive cells was observed beginning at 4 days after MCAO and reached a peak at 7 days after MCAO (Oki *et al.*, 2010)

Nakayama *et al.* (2010) also observed an induction of Msi1-positive cells at the site of ischemic lesions beginning on day 1 after stroke in humans. This result indicates the presence of a regional regenerative response in the human cerebral cortex and the importance of Msi1 in this phenomenon (Nakayama *et al.*, 2010).

Interestingly, Msi1 protein-expressing cells are increased in the hippocampus of mesial temporal lobe epilepsy (MTLE) patients (Crespel *et al.*, 2005). Large numbers of Msi1-positive cells were also observed in the SVZ in these patients (Crespel *et al.*, 2005). Increased neurogenesis has been reported in animal models of MTLE (Crespel *et al.*, 2005). The abnormal proliferation of such Msi1-expressing neural progenitors in the hippocampus might cause epilepsy.

Unlike Msi1, the relevance of Msi2 to various diseases has not yet been elucidated. However, it was recently demonstrated that Msi2 triggers the acute transformation of chronic myelogenous leukaemia (CML) through translational control of the Numb protein in humans (Ito *et al.*, 2010; Kharas *et al.*, 2010; Nishimoto & Okano, 2010). Byers *et al.* (2011) reported that Msi2 protein expression can be a clinical prognostic biomarker of human myeloid leukaemia (Byers *et al.*, 2011)

6. Novel finding for the functions of Musashi proteins

Although Musashi proteins are thought to act as translational suppressors, MacNicol and co-workers found a novel function of Musashi in *Xenopus* oocytes. In this system, it activates the translation of *mos* mRNA (Charlesworth *et al.*, 2006), a gene that is related to the meiotic cell cycle progression (Sagata *et al.*, 1988). This is an opposite result from previous findings on the translational effect of Msi1. Interestingly, in human oocytes, a parallel physiological phenomenon is controlled by factors other than the Musashi homolog proteins (Prasad *et al.*, 2008).

A similar translation-activating effect of Msi1 was also observed in mammals. Kuwako *et al.* (2010) found that the Msi1 protein up-regulates the translation of the Robo3 protein and controls midline crossing in precerebellar neurons. While previous studies reported that the Msi1-binding sites are in the 3'UTR of mRNAs, the Msi1-binding region in Robo3 mRNA is in the protein-coding region and does not bear the Msi1-binding consensus sequence (Kuwako *et al.*, 2010). This result implies that the discovery of novel Msi1 co-factors will be an important task for understanding the molecular mechanism of the Msi1 proteins in translational control.

Until recently, only a small number of Msi1-targeted mRNAs (Imai *et al.*, 2001; Battelli *et al.*, 2006) had been reported. De Sousa Abreu *et al.* (2009) performed an RNA immunoprecipitation (RIP)-Chip assay in HEK293T cells, a cell line derived from human embryonic kidney, to comprehensively identify the target mRNAs (de Sousa Abreu, 2009). They identified a group of 64 mRNAs whose genes belong to two main functional categories pertinent to tumorigenesis and protein modification. A subsequent proteomics study also revealed that

Msi1 can have not only negative but also positive effects on gene expression for some of the targets (de Sousa Abreu *et al.*, 2009). This result is consistent with other recent findings.

Our group also performed *in vitro* screening analysis to detect specific binding targets of Msi1 controlling the stem cell status of NSCs. We succeeded in identifying a novel target mRNA of Msi1, *doublecortin (dcx)*, from an mRNA library of embryonic mouse brain tissue (Horisawa *et al.*, 2009).

The *dcx* is a gene related to the migration of newborn neurons and neural development. Mutations in this gene cause an X-linked dominant disorder characterized by classic lissencephaly with severe mental retardation and epilepsy in hemizygous males and subcortical laminar heterotopia, also known as double cortex syndrome, associated with milder mental retardation and epilepsy in heterozygous females (Gleeson *et al.*, 1998; des Portes *et al.*, 1998; Sossey-Alaoui *et al.*, 1998).

The Msi1 protein specifically bound to the 3'UTR region of the mRNA *in vitro*, which contains an Msi1 binding motif, and repressed translation of a reporter gene linked to the mRNA fragment (Horisawa *et al.*, 2009).

We hypothesize that the Msi1 protein prevents inappropriate migration of NSCs through translational inhibition of the *dcx* gene. Several findings support our hypothesis. First, the Dcx protein is expressed only in neuronal precursors just differentiated from NSCs (Couillard-Despres *et al.*, 2005). Secondly, mutually exclusive protein expression of Msi1 and Dcx in human brains was observed (Crespel *et al.*, 2005). Finally, a knock-out of the Musashi family genes reduced the number of neurospheres isolated from embryonic mouse brains, while the knock-down of *dcx* prevented migration of the cells from neurospheres, leaving their structure intact (Ocbina *et al.*, 2006).

Gene symbols	Functions of the encoded proteins	Spices	Effects	References
<i>ttk69</i>	Notch signaling	<i>Drosophila melanogaster</i>	Translational suppression	Okabe <i>et al.</i> , 2001
<i>m-numb</i>	Notch signaling	<i>Mus musculus</i> (Msi1)	Translational suppression	Imai <i>et al.</i> , 2001
<i>p21^{WAF1}</i>	Cell cycle control	<i>Mus musculus</i> (Msi1)	Translational suppression	Battelli <i>et al.</i> , 2006
<i>mos</i>	Meiotic cell cycle progression	<i>Xenopus laevis</i> (Msi1)	Translational activation	Charlesworth <i>et al.</i> , 2006
<i>dcx</i>	Neural migration	<i>Mus musculus</i> (Msi1)	Translational suppression?	Horisawa <i>et al.</i> , 2009
<i>robo3</i>	Axonal guidance	<i>Mus musculus</i> (Msi1)	Translational activation	Kuwako <i>et al.</i> , 2010
<i>let-7</i>	Non coding RNA	<i>Mus musculus</i> (Msi1)	Nuclear translocation of Lin28	Kawahara <i>et al.</i> , 2010
<i>numb</i>	Notch signaling	<i>Homo sapiens</i> (Msi2)	Translational suppression	Ito <i>et al.</i> , 2010

Table 1. Known target RNAs of Musashi proteins

In addition, we also identified another candidate Msi1-binding mRNA that is related to neuronal migration and axon outgrowth (unpublished data). Thus, Msi1 might repress the maturation of neural stem/progenitor cells to neurons through direct translational inhibition of the genes that influence neuronal maturation and migration.

All of the known target RNAs of Musashi proteins, which have been validated in previous studies, are listed in Table 1.

The precise mechanism through which the function of Msi1 is controlled remains unclear. Although Wang *et al.* (2008) proposed that the Msi1 protein is involved in both Notch and Wnt signaling pathways as a novel autocrine process (Nagata *et al.*, 2006; Glazer *et al.*, 2008), details of the mechanism remain unclear, and direct regulators of Msi1 have not been identified.

On the other hand, Ratti *et al.* (2006) reported post-transcriptional regulation of Msi1 mRNA by embryonic lethal abnormal vision (ELAV), an RNA-binding protein of *Drosophila* (Ratti *et al.*, 2006). This is an interesting result because it may imply that some kind of cascade of post-transcriptional regulation contributes to neurogenesis, in addition to other machinery, *i.e.*, signal transduction, transcriptional regulation, and post-translational modification.

Upstream mechanisms regulating Msi1 transcription have also been studied. Kawase *et al.* (2011) found that the sixth intron of the *msi1* gene has a regulatory element for *msi1* transcription in neural stem/progenitor cells. The identification of transcription factors for the *msi1* gene will help elucidate the role of the Msi1 protein in stem cells (Kawase *et al.*, 2011).

More recently, Kawahara *et al.* (2011) discovered a novel function of the Msi1 protein. They showed that Msi1 works in concert with Lin28 to regulate post-transcriptional microRNA (miRNA) biogenesis in the cropping step, which occurs in the nucleus. This indicates that Msi1 can influence stem cell maintenance and differentiation by controlling the subcellular localization of proteins involved in miRNA synthesis, as well as by regulating the translation of its target mRNA (Kawahara *et al.*, 2011).

7. Conclusion

Somatic stem/precursor cells, including neural stem cells, are promising targets for regenerative medicine. Because these cells are derived from the patients themselves, they are not subject to the ethical questions and possible immunological rejection that are common problems in regenerative therapies using embryonic stem (ES) cell.

The Musashi family proteins are key factors for the understanding and application of somatic stem cells. Musashi proteins control the stem cell state through the translational regulation of target mRNAs, and the Musashi family is a highly conserved RNA-binding protein group expressed in undifferentiated stem/precursor cells at both embryonic and adult stages.

Although several studies have revealed that a Notch signal inhibitor, *m-numb*, and a cell cycle regulator, *p21^{WAF1}*, are direct targets of Msi1, a mouse homolog of Musashi and that the machinery involved is located in the context of both the Notch and Wnt signaling pathways (Glazer *et al.*, 2008), the full picture of Msi1 function in neural stem/precursor cells remains to be uncovered. Recently, de Sousa Abreu *et al.* employed an RNA immunoprecipitation (RIP)-chip technique to comprehensively detect Msi1 targeted mRNAs, and they identified a

group of 64 mRNAs from HEK293T cells, whose genes belong to two main functional categories pertinent to tumorigenesis: 1) cell cycle, proliferation, differentiation, and apoptosis and 2) protein modification (de Sousa Abreu *et al.*, 2009). However, a more specific survey is necessary to identify the key factors that regulate stemness. We speculate that Msi1 might have specific targets in each cell type or site, such as *dcx*, in addition to the previously discovered targets, which are related to the cell cycle, proliferation, and self-renewal.

While Musashi proteins were originally thought to act as translational suppressors, recent findings indicate that these proteins can activate the translation of specific targets (Charlesworth *et al.*, 2006; de Sousa Abreu *et al.*, 2009; Kuwako *et al.*, 2010). This result indicates that currently unknown molecular machinery may exist that differs from the translational suppression machinery (Kawahara *et al.*, 2008). Components of this machinery, *e.g.*, binding proteins of Msi1, need to be comprehensively clarified using high-throughput techniques (Rigaut *et al.*, 1999; Horisawa *et al.*, 2004, 2008).

Many researches indicate that Musashi proteins have strong associations with some diseases, such as cancers and neuronal disorders. A more complete understanding of the Musashi proteins will also contribute to the development of therapies for these diseases.

8. Acknowledgment

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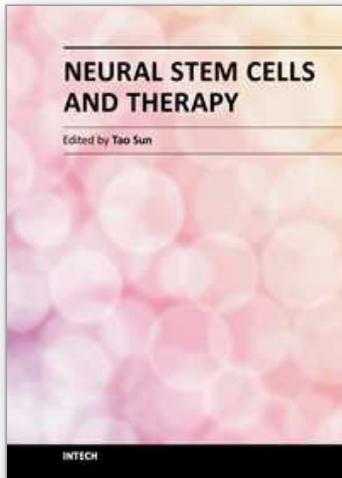
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This book is a collective work of international experts in the neural stem cell field. The book incorporates the characterization of embryonic and adult neural stem cells in both invertebrates and vertebrates. It highlights the history and the most advanced discoveries in neural stem cells, and summarizes the mechanisms of neural stem cell development. In particular, this book provides strategies and discusses the challenges of utilizing neural stem cells for therapy of neurological disorders and brain and spinal cord injuries. It is suitable for general readers, students, doctors and researchers who are interested in understanding the principles of and new discoveries in neural stem cells and therapy.

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