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Musashi1: an RBP with versatile functions in normal and cancer stem cells

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1. ABSTRACT

Musashi1 (Msi1) is a highly conserved RNA binding protein that was initially identified in *Drosophila* by its ability to regulate sensory organ development and asymmetric cell division. Studies in mammalian cells reveal multiple functions for Musashi1 in normal and abnormal processes by mediating different post-transcriptional processes. According to our recent studies, Musashi1 very likely controls hundreds of targets, forming networks that regulate apoptosis, differentiation, proliferation and cell cycle. Musashi1 is a characteristic stem cell marker that regulates the balance between self-renewal and differentiation. Over-expression of Musashi1 has been associated with numerous tumor types and its function is required for tumor growth in breast, colon, medulloblastoma and glioblastoma. Musashi1 has also been implicated in neurogenesis and neurodegenerative diseases, and is emerging as a potential therapeutic target in both regenerative medicine and cancer.

2. INTRODUCTION

Musashi (Msi) is an evolutionarily conserved RNA-binding protein (RBP) that modulates translation by binding to $(G/A)U_{1-3}(AGU)$ motifs in the 3'-UTR of its target mRNAs (1). Msi1 blocks expression of Numb (2), a negative regulator of Notch, $p21^{Cip1}$, an inhibitor of cyclin-dependent kinases (3), and doublecortin (Dcx), a microtubule-binding protein involved in neural stem cell migration (4), but increases expression of Roundabout3 (Robo3), a receptor involved in axonal guidance (5). Additional targets for Msi1 have been identified in tumor cells by RIP-chip analysis, which pertain to the cell cycle, apoptosis, proliferation and differentiation. The ability of Msi1 to either increase or decrease protein expression suggests the duality of its function in translation (6, 7). As a repressor, Msi1 functions by interacting with poly(A)-binding protein (PABP) and blocking its interaction with other components of the translation complex (8).

Msi1 was first identified in *Drosophila* as a determinant of sensory organ development and asymmetric cell division (9). The mutated Msi phenotype in the fly resulted in a double sensory shaft phenotype that was reminiscent of the two sword technique made famous by the 17th century samurai, Miyamoto Musashi. In mammalian cells, Msi1 denotes multipotent stem cells in the brain (10-13), intestine (14-16), breast (17, 18), hair follicles (19) and hematopoietic system (20). Msi is expressed in neural stem and progenitor cells as two paralogs, Msi1 and Msi2, which have similar RNA-binding properties (10, 21, 22). Although, their distribution is tissue-specific and have distinct roles in some instances (19, 20, 23-26), both Msi1 and Msi2 are required for brain stem cell self-renewal (22).

3. MUSASHI EXPRESSION IN STEM CELLS AND CANCER

3.1. Stem cells

The multipotential nature of Msi1-expressing cells is supported by the ability of Msi1-expressing breast cancer cells to maintain expression of the embryonic stem cell (ESC) markers c-Myc, Nanog, Sox2, Bmi1 and Oct4 (27), which collectively can reprogram pluripotent embryonic stem cells (28-31) . An embryonic stem cell-like signature is commonly associated with several cancers, including cervical cancer (32), retinoblastoma (33), poorly differentiated lung cancer (34-36), medulloblastoma (37), glioblastoma (34, 37), bladder cancer (34) and basal type breast cancer (34), and predicts lower overall survival. These findings are consistent with the lower five year survival of patients with Msi1-positive breast cancer that may be predictive of a more basal-like, undifferentiated and aggressive form of this disease (27).

The presence of Msi1 is required for proper development of the brain as a genetically engineered *msi1*$^{-/-}$ in a C57BL6 background results in a mouse with obstructive hydrocephalus and ependymal abnormalities (22). Additionally, Msi1 is an effective marker for studying the migration and biology of neural stem/progenitor cells during development (24, 38). A recent study demonstrates that Musashi1 is required for neuronal migration of precerebellar neurons through its interaction with and Robo3 (5). Robo3 is a receptor found on astrocytes and is required to receive signals from migrating neurons through the secretion of the Slit1 diffusable protein. Upon signaling from neuron-secreted Slit1, astrocyte morphology changes to create astrocytic tunnels, allowing migrating neurons to navigate through the dense meshwork of the adult brain (39).

Msi1 is associated with label-retaining and side population (40) human breast epithelial cells enriched in ERα, $p21^{Cip1}$, CK19 and double-positive CK14/CK18 progenitor cells (41). Over-expression of Msi1 in mouse mammary epithelial cells results in expansion of $CD24^{hi}$/Sca-1^{+}, $CD24^{hi}$/$CD29^{+}$, $CK14^{+}$/$CK18^{+}$ and $CK6^{+}$ and $CK19^{+}$ stem and progenitor cells (18, 42). This occurs through a unique autocrine pathway associated with increased secretion of the growth factor Proliferin, loss of the Wnt inhibitor DKK3, activation of Wnt and Notch signaling (18, 42), and a gene expression profile indicative of the cell cycle, growth factor signaling, invasion, adhesion, survival and embryonic stem cells. Importantly, $CD24^{+}$/$CD29^{hi}$ mouse mammary cells contain multipotent self-renewing mammary stem cells capable of reconstituting the gland from a single cell (43), and represent a tumor initiating cell population in tumors from MMTV-Wnt1 (43) and p53-null (44) mice. Interestingly, CD24 is linked to signaling through the G-protein-coupled IGF2 receptor, the receptor activated in Msi1-expressing cells (18, 42) and for which Proliferin serves as a ligand (45) (Figure 1). These findings are consistent with the high expression of Msi1 resulting from increased IGF2 expression in intestinal crypt cells due to loss of imprinting, and their predisposition to tumorigenesis (16). Loss of imprinting of *IGF2* is associated with Wilm's tumor, lung, ovarian, liver and colon cancer (46), and may be associated with progression of medulloblastoma, since loss of function of IGF2 suppresses tumor formation in heterozygous Patched1 mice (47). Importantly, CLIP analysis of U251 glioblastoma cells has identified an Msi1 consensus binding site in the IGF2 3' UTR (Penalva Lab, unpublished results), suggesting a potential mechanism by which Msi1 may control tumor progression in various malignancies. In contrast to most tissues, bone marrow stem cells contain Msi2, which regulates asymmetric cell division, and genes expressed under the control of Ras, ERK, cyclin D1, Raf1 and Myc, as well as bone marrow engraftment (20). Msi2 was required for BCR-ABL-induced leukemogenesis and was associated with a worse clinical outcome (20).

3.2. Brain tumors

Increased Msi1 expression was first noted in glioblastoma and medulloblastoma (37, 48, 49), and was associated with Notch1 expression and areas of tumor proliferation and infiltration (50). Msi1 and Notch pathway activation was demonstrated in medulloblastoma cells by suppression subtractive hybridization (51). Downregulation of Msi1 in Daoy medulloblastoma cells by RNA interference inhibited proliferation and sensitized cells to the Hedgehog pathway SMO inhibitor, cyclopamine (6), suggesting that Msi1 is important in maintaining the viability of medulloblastomas of this subtype (52). siRNA-mediated KD impaired xenograft grow of both medulloblastoma and glioblastoma cells (Penalva Lab, unpublished results). Interestingly, the Msi1 promoter has been used to drive herpes simplex virus type 1 replication in human glioblastoma multiforme xenografts, producing a two-log increase in viral replication and higher therapeutic activity (53, 54).

3.3. Breast cancer

The Notch pathway plays an important role in stem cell self-renewal and cell fate determination (55, 56). In human breast stem cells (57), Notch promotes either stem cell self-renewal or differentiation in a tissue context-dependent manner (58). Notch is activated by sequential proteolytic cleavage of its membrane-associated form to a constitutively active intracellular form (NIC) that serves as a transcription coactivator (59). Maintenance of NIC is influenced by the negative regulator Numb (60, 61), which

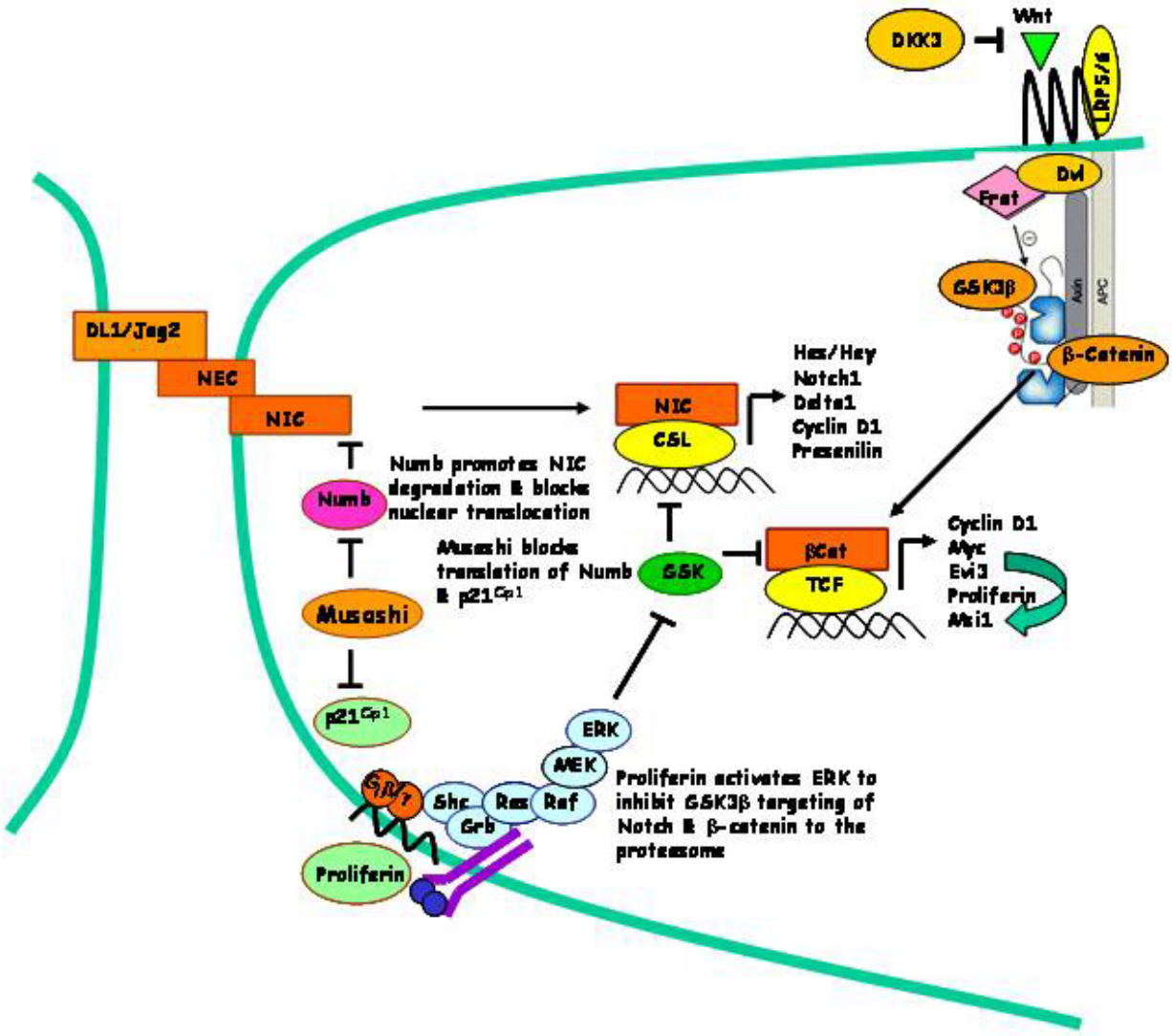

Figure 1. Musashi1 signaling pathways in mammary progenitor cell proliferation. Msi1 blocks translation of Numb and $p21^{Cip1}$ in mammalian cells. Mammary epithelial cells over-expressing Msi1 exhibit reduced Dickkopf 3 (DKK3) mRNA and protein expression, but it is unknown if this occurs indirectly or by interference with RNA processing or translation. Extracellular Notch (NEC) binds its ligand Delta1 (DL1) or Jagged2 (Jag2), which initiates proteolytic processing of Notch to intracellular Notch (NIC). Inhibition of translation of the ubiquitin ligase Numb by Msi1 increases NIC, which serves as a co-activator of CSL to drive Notch-dependent transcription of DL1, Jag2, Notch1, Hes1, cyclin D1 and presenilin, the latter of which forms part of the proteolytic γ-secretase complex. Inhibition of $p21^{Cip1}$ relieves its inhibitory effect on cyclin D-dependent protein kinases to increase G1/S transit through the cell cycle. Loss of DKK3 expression activates the Wnt pathway and the nuclear localization of β-catenin and transcription of β-catenin/TCF-dependent target genes, including cyclin D1 and D2 and Proliferin (PLF1), and possibly Msi1 itself. PLF1 activates ERK through the G-protein-coupled IGF-2 receptor, which results in inhibition of GSK3β and further increases activation of the Notch and Wnt pathways through an autoregulatory loop. The net result of these processes is the stimulation of stem and progenitor cell proliferation.

ubiquitinates NIC and targets it for proteasomal destruction, and whose expression is inhibited by Msi1 (60) (Figure 1). Tissues that strongly express Msi1 show little or no expression of Numb (51). NIC and the Notch ligands Jagged and Delta are highly expressed in breast cancer (62-64), whereas, 50% of high grade human breast cancers exhibit loss of Numb, which correlates inversely with tumor grade (65). Msi1 is abundant in most breast cancer cell lines, but low in breast epithelial cells (18, 27, 66). Msi1 is highly expressed in ~40% of primary breast tumors and in 100% of lymph node-positive cells, and is prognostic for poor survival (27). In breast cancer cell lines, Msi1 expression correlates with ErbB2 and Notch activity (27), and ErbB2-induced cell proliferation and cyclin D1 expression is dependent on Notch activation and suppression of Numb (66). Thus, these findings suggest an

important role for Msi1 in mediating progression in ErbB2-positive breast cancer.

3.4. Colon cancer

Msi1 is localized to the crypt cells in the small intestine, which is consistent with its high expression in stem and progenitor cells (16, 67). Msi1 is markedly increased as much as 100-fold in intestinal adenomas arising in APC^{Min} mice expressing a mutation in the APC gene and exhibiting constitutive activation of the Wnt pathway (68). Crossing APC^{Min} mice with mice exhibiting a loss of maternal imprinting of IGF2 doubled the number of adenomas with a less differentiated phenotype and increased Msi1 expression (16). Importantly, patients with loss of IGF2 imprinting have increased Msi1 expression in colon crypt cells, suggesting an association between epigenetics, Msi1, stem cells and a predisposition to colon cancer (46). Colon tumors arising in APC^{Min} mice expressing constitutively active $K\text{-}Ras^{G12D}$ express increased Msi1 (69). Msi1 is also associated with CD133-positive colorectal tumor cells grown as spheroid cultures (70), which are highly resistant to oxaliplatin and 5-fluorouracil (71). These data are consistent with the persistence of Msi1-positive cell in the crypts after exposure to a toxic dose of 5-fluorouracil (72), and suggest that Msi1-positive cells are generally drug-resistant. Importantly, 'knockdown' of Msi1 by RNA interference inhibited colon tumor cell growth (73), suggesting a potential approach for resensitizing tumor cells to drug treatment. It was recently shown that Msi1 can confer tumorigenic properties to progenitor cells. Intestinal epithelium progenitor cells over expressing Msi1 showed an increase in proliferation via the activation of Wnt and Notch pathways, and acquired tumorigenic properties as xenografts (74).

Overall, these studies suggest that Msi1 is highly expressed in malignancies with a less differentiated, more aggressive and drug-resistant phenotype, and in fact, highly aggressive malignancies, including melanoma, head and neck cancer and non-small cell lung cancer, express the highest levels of Msi1 (Wang and Glazer, unpublished results).

4. MUSASHI1 AS A MARKER OF NEUROGENESIS IN NEUROLOGICAL DISEASES

Cerebrovascular disease is the third most common cause of death in the United States and is also the leading cause of neurologic dysfunction. Metabolic insults, particularly ischemia, have been shown to induce neurogenesis in the brain. As Msi1 has a distinct role early in development of the central nervous system, it suggests that Msi1 likely has a similar role in neural progenitor cells in response to hypoxia and ischemic injury. This is further implied by the presence of hypoxia-responsive element (HRE)-like sequences (ACGTG) in the promoter region of Musashi1, and its upregulation in the CA1 region of the hippocampus after ischemia (75). Increased Msi1 expression after ischemic injury has also been demonstrated in macaques after global cerebral ischemia (76, 77) as well as in the focal ischemic stroke mouse model (78), and after subarachnoid hemorrhage (26). Similar results were obtained in three studies of ischemia/infarction in *Rattus norvegicus* where increased neurogenesis, marked by Msi1, is observed in the hippocampus (79-81). Overall, these experimental models suggest that Msi1-enriched cells are recruited to the site of injury to reconstitute neural networks and possibly prevent neuronal cell death. Reactivation of proliferation and Musashi1 and nestin expression in a middle cerebral artery occlusion murine model indicates that they are differentially distributed from the epicenter of injury, suggesting differing roles for these stem and progenitor markers in cellular proliferation post-ischemia (82). In an analysis of human autoptic brains of patients with cardiogenic cerebral embolism (83), increased neurogenesis is found one day after a stroke, and is consistent with previous reports of a regenerative response in experimental models of ischemia.

Neurogenesis is also increased in animal models of mesial temporal lobe epilepsy (MTLE), but it is not known whether or not the neurogenic cells play a role in the pathogenesis of MTLE. In adult epileptic tissue, there is an increased expansion of neural progenitor cells that display high expression of Msi1 (84), and represents a potential mechanism for the restoration and replacement of neuronal tissue in the epileptic hippocampal location (85).

In multiple sclerosis, it has been suggested that spontaneous tissue regeneration occurs, an idea promising for future cell-based therapies. In an analysis of multiple sclerosis postmortem samples, cells expressing Msi1 are highly increased in cells expressing Ki67, a marker of cell proliferation, suggesting that neurogenesis is a reactive mechanism that attempts to replace cells lost by the autoimmune phenomena in MS (86).

In contrast to the involvement of Msi1 in cancer, high expression of Msi1 can be beneficial in the context of neurological disease through the recruitment of Msi1-rich neural stem cells to sites of injury. In response to neurological insult, increased neural stem/progenitor cells can be recruited to the site of injury and replace the damaged and lost cells; thus, translation of stem cell biology to practical application can be of clinical interest. However, in order to fully harness the power of stem cells, an understanding of the underlying stem cell biology must be taken in order to reduce risk in a clinical application.

5. MOLECULAR EVENTS MEDIATED BY MUSASHI1

While some of the biological roles of Msi1 have been characterized, questions remain regarding the mechanisms Msi1 employs to regulate gene expression. Structural studies of Msi1 indicate that the protein contains two RNA-binding domains, or RBDs, with the N-terminal RBD having a higher affinity for RNA than the second RBD (87). Each RBD is composed of β-sheets with the N-terminal RBD containing many positively charged residues, whose electrostatic interface mediates higher binding affinity to the negatively charged phosphodiester backbone

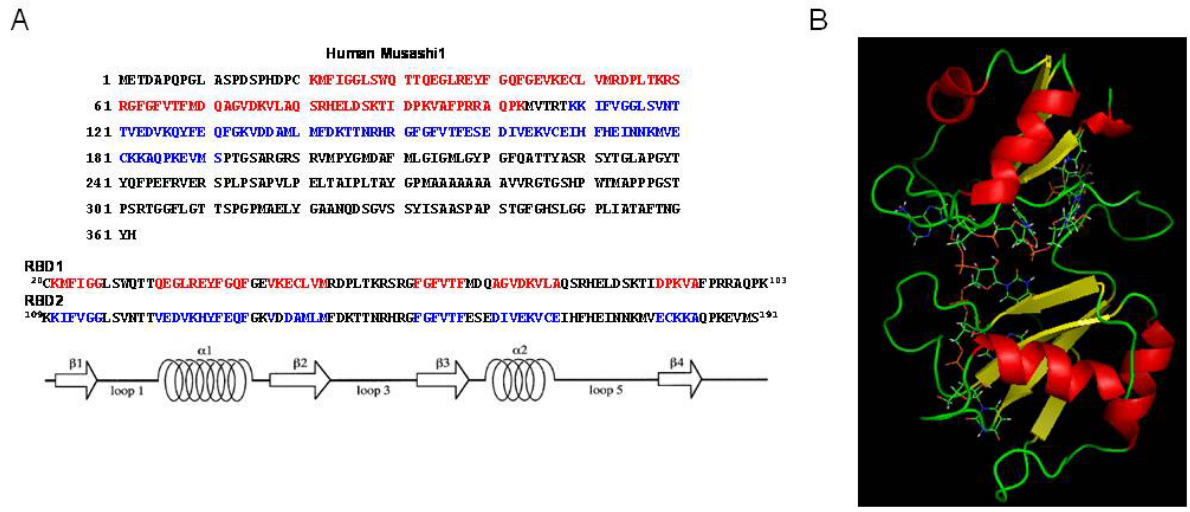

Figure 2. The protein domain structure of Musashi1. A, Msi1 contains two highly homologous RNA-binding domains (RBDs) formed by four antiparallel β-sheets packed against two α-helices. N-terminal RBD1 (*red*) directly binds to RNA and RBD2 (*blue*) enhances its affinity for its RNA recognition sequence. Interaction of RBD1 with the RNA recognition motif is dependent on its positive electrostatic surface charge and flexibility (87), and on base-stacking with conserved F63, F65 and F68 in the β3 sheet. B, The 3D structures of RBD1 (87) and RBD2 (99) have been elucidated by NMR. The mRNA-binding protein, Hrp1, in complex with RNA (100) was used as a template for modeling the structure of Msi1 (Y. Tomita and R.I. Glazer, unpublished results). The Msi1 structure has similar domain-domain contacts to other RNP-type proteins, where K93 and F96 in RBD1 are in contact with T108 and D136 in RBD2.

of RNA (Figure 2). Additionally, the N-terminal domain peptide backbone seems to be extremely flexible, possibly facilitating an induced fit mechanism of RNA:protein interaction.

Early studies identified two Msi1 mRNA targets, *NUMB* and *CDKN1A*, both of are inhibited at the level of translation. The mechanism by which Msi1 mediates translational repression was elucidated by Dr. Okano's group, which identified PABP as a Msi1-interacting protein (8). To repress translation, Msi1 competes with eIF4G for binding to PABP, and the subsequent disruption of eIF4G:PABP binding inhibits the assembly of the 80S ribosomal complex.

Msi1 may also be involved in other molecular functions, such as translation activation. This is observed for males-absent on the first (Mos) in Xenopus (88) and Roundabout3 (Robo3) in neuronal cells (5), and other genes, whose translation are potentially activated by Msi1 (8). However, the mechanism that allows Msi1 to activate translation is unknown. As with other RBPs, Msi1 can potentially mediate other functions in RNA metabolism, such as splicing. The exon 10-inclusion event of the tau mRNA is seemingly mediated by the presence of Msi1 (89). Recently, the Penalva lab found Msi1 linked to the splicosome, and proteomic studies of Msi1-bound proteins identified hnRNPAB and hnRNPDL, proteins capable of mediating alternative splicing (Penalva, unpublished results).

6. REGULATION OF MUSASHI1

Several studies have begun to shed light on the signaling pathways that regulate Msi1 expression. The Msi1 5'-upstream sequence in the Msi1 locus contains several TCF-binding elements (1), implying that Msi1 itself may be a target gene of the Wnt pathway. Autoregulation of Msi1 expression through this pathway is suggested by the ability of the Msi1 target, $p21^{Cip1}$ (3), to negatively regulate Wnt4 and β-catenin/TCF-dependent transcription (90). This finding is consistent with increased proliferation, activation of Notch- and Wnt activity and β-catenin nuclear localization by Msi1 in mammary epithelial cells (18). Similar results in intestinal epithelial cells over-expressing Msi1 found that it was required for xenoengraftment (74).

The studies by Chepko *et al.* were the first to implicate c-Myc in mammary stem cell formation (91). Recently, we discovered that human breast epithelial cells over-expressing c-Myc resulted in a marked increase in both Msi1 protein and mRNA (Figure 3). This suggests that activation of c-Myc signaling, in addition to Wnt signaling, may be important effectors of Msi1 expression during stem cell self-renewal. This hypothesis is in agreement with the ability of Msi2 to increase asymmetric cell division in hematopoietic stem cells in concert with a gene signature indicative of Ras and Myc pathway activation (20).

Another possible regulatory mechanism that has yet to be explored in mammalian cells is whether Msi1 is a prerequisite for steroid hormone receptor signaling. Msi1 is required for progesterone-dependent meiosis in *Xenopus* oocytes (88), and this interesting finding is consistent with the association of the estrogen receptor and progesterone receptor with mouse and human mammary stem cells (41),

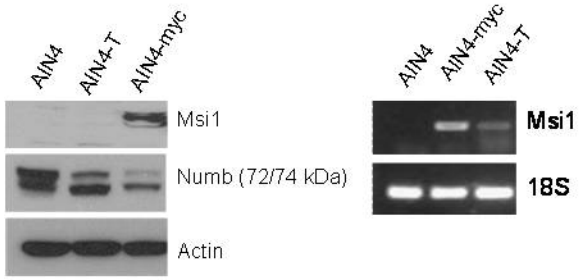

Figure 3. Expression of c-Myc in human breast epithelial cells increases Msi1 expression. Immortalized A1N4 human breast epithelial cells were transduced with either SV40 large T-antigen or c-Myc (2) and examined for Msi1 protein (left) and mRNA (right) levels. Transduction with c-Myc markedly increased Msi1 expression, whereas, SV40 T-antigen had little or no effect.

suggesting a role for Msi1 in hormone-dependent breast cancer.

Msi1 regulation also occurs at the post-transcriptional level. Msi1 expression is influenced by a family of RNA-binding proteins homologous to the *Drosophila* Elav, a protein involved in the development and maintenance of the nervous system (92, 93). The mammalian Elav family (HuR, HuB, HuC and HuD) promotes mRNA stabilization by binding to AU-rich elements in the 3'-UTR of target genes. HuD has been seen to regulate the expression of Musashi1 expression in the transition from proliferation to neural differentiation of stem/progenitor cells (94). We have recently seen that HuR, which has been implicated in a variety of tumor types (95), stabilizes Msi1 mRNAs in the context of tumor cells (Penalva, unpublished results). Additionally, Msi1 is targeted by several tumor suppressor miRNAs (Penalva, unpublished results), including miR-34a, miR-101, miR-128, miR-137 and miR-138, which are commonly down-regulated in glioblastoma and linked to disease progression (96-98), suggesting a mechanism that may contribute to its high expression in brain tumors.

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Abbreviations: APC: adenomatous polyposis coli, CDKN1A: cyclin-dependent kinase inhibitor 1A, CLIP: cross-linking and immunoprecipitation, DKK3: Dickkopf 3, ESC: embryonic stem cell, hnRNP: heterogeneous ribonucleoprotein particle, HRE: hypoxia-responsive element, IGF2: insulin-like growth factor 2, KD: knockdown, miRNA: microRNA, MMTV: mouse mammary tumor virus, Msi: Musashi1, mRNA: messenger RNA, NIC: Notch intracellular domain, PABP: poly(A) binding protein, RBD: RNA-binding domain, RIP-chip: RNA-binding protein immunoprecipitation-microarray, TCF: T-cell factor, UTR: untranslated region,

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