Supplementary Information

HnRNP C, YB-1 and hnRNP L coordinately enhance skipping of human *MUSK* exon 10 to generate a Wnt-insensitive MuSK isoform

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Supplementary information includes:

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Supplementary Figures S1-S7

Supplementary Table 1. *MUSK* transcript isoforms in human skeletal muscle tissue and cells

	***MUSK* transcript isoform (%)**		
	Isoforms A and B	**Isoform C**	**Isoform D**
Human skeletal muscle tissue (HSKM)	88 ± 5.68	0.07 ± 0.08	12 ± 5.60
Human primary myoblast (SkMC)			
Undifferentiated	66 ± 1.07	19 ± 0.93	15 ± 0.28
Differentiated	81 ± 1.27	13 ± 0.77	6 ± 0.51
Immortalized human myogenic cells (KD3)			
Undifferentiated	59 ± 1.30	20 ± 0.88	21 ± 0.74
Differentiated	78 ± 0.20	17 ± 0.68	6 ± 0.59

Values represent mean ± standard deviation (SD) of three independent experiments. Transcript isoforms are shown in Fig. S2(c) according to the annotation of ENSEMBL 76.

Supplementary Table 2. Primer sequences for making constructs

Primers	5' – 3' sequences
pcDNA-human-MUSK	
hMusk-ex8/F	CACCATGGTTTCTTCTGGGTCC
hMusk-ex11/R	CTAGATGTGGCAGTCTGGCACAG
hMusk-int8/F	TCCTAGCAGAAGCGGAGAACT
hMusk-int8/R	TCCGCTTCTGCTAGGAGGAAGGAGGGAGGAATGA
hMusk-int9/F	CCCAAAGCTTTCCACATCTATC
hMusk-int9/R	TGGAAAGCTTTGGGAAACATACTCCACCGCACT
hMusk-int10/F	CAGAATTTAGGCTCTGCCAC
hMusk-int10/R	GCAGAGCCTAAATTCTGCCTCAAGTGATCCACCCACT
pSPL3-human-MUSK	
X10NotF	AGTTAGCGGCCGCTTCCCAAAGCTTTCCACATC
X10PacR	ATGTATTAATTAACCTCAAGTGATCCACCCACT
pSPL3-mouse-Musk	
musX10NotF	AGTTAGCGGCCGCCGTGCAAGAGCTATGTAAGCTGACTG
musX10PacR	ATGTATTAATTAACTTTCTGACTGAGCCAGACTCTAA
Deletion constructs of pSPL3-human-MUSK	
ui-200F	AGTTAGCGGCCGCAGCCCTGTGGAGTAGC
ui-150F	AGTTAGCGGCCGCAATATTCAAATGGAGCGTGTC
ui-100F	AGTTAGCGGCCGCTTTCTGAGACACAGATGTG
X10-150R	ATGTATTAATTAAGAGCCACTGCACCCAGGCA
X10-92R	ATGTATTAATTAAACTGTTGCATATTAC
X10-60R	ATGTATTAATTAACTCCTTCTGTTGTGCAG
Chimeric minigene constructs of pSPL3-human-MUSK	
UichF	GAATTCTGGAGCTCGAGCGGCCGCGACAGTCTCTA
UichR	GTAGCCTTTGTTATCTTTCTGTGGTTTACTGAAAGAAGTG
Ech-F	GTTGTTCATTTCTTCTTTCAGTAAGTCACAGAAAG
Ech-R	CTTTGACTTATTTTTGAGATTTTACCTGCAAATGG
Dich/F	CTACTCCTATTCCCATTTGCAGGTAAAACTTTG
Dich/R	CAGGTACGGGATCATTAATTAACAAACTCTTGGC
181/F (second half chimera)	CTGAGGAGGCCCAAGAGCTACTGATCCACACTGCGTGGAATGAGC
180/R (first half chimera)	TTCATTCCAGGCCGTGTGGACCAGGCAGCTCCTGGGCGTCCTC
Block-scanning mutagenesis of pSPL3-human-MUSK	
MBS1F	GAAATGTTGTTCATTTCTTCTTTCAGTAATCAGTATGACTCTCAGTATGGCTACTGCGCCCAG
MBS1R	CTGGGCGCAGTAGCCATACTGAGAGTCATACTGATTACTGAAAGAAGAAATGAACAACATTTC
MBS2F	CAGAAAGATAACAATCAGTATGACTCTCAGTATGGAGGGGAGGTG
MBS2R	CACCTCCCCTCCATACTGAGAGTCATACTGATTGTTATCTTTCTG
MBS6F	CTCAACACCTCCTTCAGTATGACTCTCAGTATGCAAGAGCTACTG
MBS6R	CAGTAGCTCTTGCATACTGAGAGTCATACTGAAGGAGGTGTTGAG
MBS8F	ACTGGTCCACACTCAGTATGACTCTCAGTATGTAGTGAGCCCAGT
MBS8R	ACTGGGCTCACTACATACTGAGAGTCATACTGAGTGTGGACCAGT
MBS3F	CTGCGCCCAGTACATCAGTATGACTCTCAGTATGGTCCTGGCAAAAG
MBS3R	CTTTTGCCAGGACCATACTGAGAGTCATACTGATGTACTGGGCGCAG
MBS4F	AGGTGTGTAATGCATCAGTATGACTCTCAGTATGTGTTTTTCTCAACAC
MBS4R	GTGTTGAGAAAAACACATACTGAGAGTCATACTGATGCATTACACACCT
MBS5F	GCAAAAGATGCTCTTCAGTATGACTCTCAGTATGATGCGGACCCTGAG
MBS5R	CTCAGGGTCCGCATCATACTGAGAGTCATACTGAAGAGCATCTTTTGC
MBS7F	GACCCTGAGGAGGCCTCAGTATGACTCTCAGTATGGGCCTGGAATGAAC
MBS7R	GTTCATTCCAGGCCCATACTGAGAGTCATACTGAGGCCTCCTCAGGGTC
MBS9F	GGAATGAACTGAAAGTCAGTATGACTCTCAGTATGCCAGCTGCTGAG
MBS9R	CTCAGCAGCTGGCATACTGAGAGTCATACTGACTTTCAGTTCATTCC
MBS10F	GAGCCCAGTCTGCCGGTCAGTATGACTCTCAGTATGGTGTAACCACATC
MBS10R	GATGTGGTTACACCATACTGAGAGTCATACTGACCGGCAGACTGGGCTC
MBS11F	GCTGAGGCTTTGTTTCAGTATGACTCTCAGTATGAGTGCAGTCCTGGA
MBS11R	TCCAGGACTGCACTCATACTGAGAGTCATACTGAAACAAAGCCTCAGC
MBS12F	ACCACATCTTCCAGGTCAGTATGACTCTCAGTATGCCTACTCCTATTC
MBS12R	GAATAGGAGTAGGCATACTGAGAGTCATACTGACCTGGAAGATGTGGT
MBS13F	GTCCTGGAGTAGTGTCAGTATGACTCTCAGTATGCAGGTAAAATCTC
MBS13R	GAGATTTTACCTGCATACTGAGAGTCATACTGACACTACTCCAGGAC

Supplementary Table 2. Continued

Primers	5' – 3' sequences
pH-mB5 minigene	
SDM/5F	CTGGCAAAAGATGCTCTTGTCTTCTTCAACACCTCCTATGCGGAC
SDM/5R	GTCCGCATAGGAGGTGTTGAAGAAGACAAGAGCATCTTTTGCCAG
pH-mB12 minigene	
SDM/BS12F	CTTCCAGGAGTGCAGCCCTGGAGTGGTGCCTACTCCTATTCC
SDM/BS12R	GGAATAGGAGTAGGCACCACTCCAGGGCTGCACTCCTGGAAG
pSPL3-human-MUSK-*MS2-PP7*	
MG-MS2/F	CAAAAGATGCTCTTGACATGAGGATCACCCATGTCAACACCTCCTATGC
MG-MS2/R	GCATAGGAGGTGTTGACATGGGTGATCCTCATGTCAAGAGCATCTTTTG
MG/pp7/F	GATCACCCATGTGGCACGAAGATATGGCTTCGTGCCCTATGCGGACCCTG
MG/pp7/R	CAGGGTCCGCATAGGGCACGAAGCCATATCTTCGTGCCACATGGGTGATC
MS2- or PP7-fused effector constructs	
pcC/F	CACCATGGCCAGCAACGTTAC
pcC/R	AGAGTCATCCTCGCCATTG
pp7-insYB1-F	GCTGAGGCGGCCGCGATGTCCAAAACCATCGTTCTTTCGGTCG
pp7-insYB1-R	TGGATCTGCGGCCGCACGGCCCAGCGGCACAAG
Xho1-pp7/F	AGTTACTCGAGTATGTCCAAAACCATCGTTCTTTCGGTCG
Xba1-pp7/R	ATGTATCTAGACTACGGCCCAGCGGCACAAGGTTG
pc-pp7/F	CACCATGTCCAAAACCATCGTTC
pc-pp7/R	ACGGCCCAGCGGCAC

Supplementary Table 3: Primer sequences for RT-PCR

Primers	5' – 3' sequences
Splicing of endogenous human MUSK	
hMuSK-ex8/F	GCTGCAGCCACCATCAGCAT
hMuSK-ex11/R	TGCTGCATTCTGGCACGGACA
Splicing of endogenous mouse Musk	
mMuSKex8/F	AAGTTCAGTACCGCAAAGGC
mMuSKex11/R	AGAAGAGCTCCTTTACCGCC
*Splicing of pcDNA-human-*MUSK	
pcDNA-F	TCCAGTACCCTTCACCATG
BGH-R	TAGAAGGCACAGTCGAGG
Splicing analysis of pSPL3 human/mouse minigenes	
pSPL3-F	TCTGAGTCACCTGGACAACC
pSPL3-R	ATCTCAGTGGTATTTGTGAGC
Expression of endogenous human MUSK *variants (Real-time RT-PCR)*	
H-MuSK-8/F	GCTGCAGCCACCATCAGCAT
H-MuSK-10R	GCACTCCTGGAAGATGTGGT
H-MuSK-8-11/F	ACCATCAGCATAGCAGAG
H-MuSK-8-9-11/F	AGCATAGCAGAATGGAGAG
H-MuSK-11/R	TGCTGCATTCTGGCACGGACA
Endogenous human protein expression	
RT-hnRNP C/F	ATGTGGAGGCAATCTTTTCG
RT-hnRNP C/R	TTTCCTCGGTTCACTTTTGG
RT-hnRNP L/F	TTCTGCTTATATGGCAATGTGG
RT-hnRNP L/R	GACTGACCAGGCATGATGG
RT-YB1/F	GTCATCGCAACGAAGGTTTT
RT-YB1/R	AACTGGAACACCACCAGGAC
GAPDH-human-F	ATGGCACCGTCAAGGCTGAGA
GAPDH-human-R	GGCATGGACTGTGGTCATGAG
MYOG-human1-F	GGTGCCCAGCGAATGC
MYOG-human1-R	TGATGCTGTCCACGATGGA
Endogenous mouse protein expression	
GAPDH-mouse-F	ACCACAGTCCATGCCATCAC
GAPDH-mouse-R	TCCACCACCCTGTTGCTGTA
Myogenin-mouse-F	TCCAGTACATTGAGCGCCTAC
Myogenin-mouse-F	ACATATCCTCCACCGTGATGC
Additional target genes regulated by hnRNP C or/and YB-1	
srsf11/F	CAGACTCAGCAGTTGTGGCAC
srsf11/R	CAAGCCCCCAAAATGAGAGTTC
faim/F	TTGGTACTCGCGCCTGCAGAG
faim/R	CTCGTTTGCCTGATGTAGTCCC
SUB1/F	CAAGTTGCTCCAGAAAAACC
SUB1/R	CAGGATCCATCCAATATTCTC
CKLF/F	ACGCGATGGATAACGTGCAG
CKLF/R	GATTGAACAGAAGCTTCCGGT
RBM14/F	GGCTGCGGCGACAAAATGAAGATATTC
RBM14/R	ACGAAAGCTGCGACTCTGAT
cdc73/F	CGTGCACCTTTCTCATCCTG
cdc73/R	GAGTAGATCGCTGAAGACCT
lrrc42/F	CTTCACTGTGTCCCACCCTTC
lrrc42/R	CAAAGCTCCACAGAAAAGCC
IL7R/F	CTGAGGCTCCTTTTGACCTG
IL7R/R	GGAGACTGGGCCATACGATA
NBPF3/F	CTGTTTAGACCCAGGCGAAG
NBPF3/R	TGACGTTTGTGGCAGAAGAG

Supplementary Table 4. Overlap extension PCR primers to synthesize RNA probes

Primers	5' – 3' sequences
T7-F	TAATACGACTCACTATAGGG
H-B5-R	AGGAGGTGTTGAGAAAAACACCCTATAG
m-B5-R	AGGAGGTGTTGAAGAAGACACCCTATAG
H-B5D5-R	GGAGGTGTTGAACAACCCTATAG
H-B12-R	ACTACTCCAGGACTGCACTCCCCTATAG
m-B12-R	ACCACTCCAGGGCTGCACTCCCCTATAG
H-B12D12-R	ACTCCAGTGCACTCCCCTATAG
H-mut1-R	GGAGGTGTTGAGAAAAAGAACCCTATAG
H-mut2-R	GGAGGTGTTGAGAAAAGCAACCCTATAG
H-mut3-R	GGAGGTGTTGAGAAAGACAACCCTATAG
H-mut4-R	GGAGGTGTTGAGAAGAACAACCCTATAG
H-mut5-R	GGAGGTGTTGAGAGAAACAACCCTATAG
H-mut6-R	GGAGGTGTTGAGGAAAACAACCCTATAG
H-mut7-R	GGAGGTGTTGACAAAAACAACCCTATAG
H-mut8-R	GGAGGTGTTGCGAAAAACAACCCTATAG
H-mut9-R	GGAGGTGTTCAGAAAAACAACCCTATAG
H-mut10-R	GGAGGTGTAGAGAAAAACAACCCTATAG
H-mut11-R	GGAGGTGATGAGAAAAACAACCCTATAG
H-mut12-R	GGAGGTCTTGAGAAAAACAACCCTATAG
H-mut13-R	GGAGGCGTTGAGAAAAACAACCCTATAG
H-mut14-R	GGAGCTGTTGAGAAAAACAACCCTATAG
H-mut15-R	GGACGTGTTGAGAAAAACAACCCTATAG
H-mut16-R	GGCGGTGTTGAGAAAAACAACCCTATAG

FIGURE LEGENDS

Figure S1. Sequence alignment of MuSK Fz-CRD, as well as FZD1 across different species. Conserved cysteine residues are shown by red letters and boxed by blue lines. In human, *MUSK* exon 10 encoding 6 cysteines and exon 11 encoding 4 cysteines constitute Fz-CRD.

Figure S2. Genomic structure of human *MUSK* and splicing isoforms. (a) Genomic and CDS structures of human *MUSK*. Green and red boxes show constitutive and alternative exons, respectively. Black boxes indicate UTRs. (b) Partial genomic sequence of human *MUSK* gene spanning exon 8 to exon 11. Genomic coordinates of each exon according to GRCh37/hg19 are shown in blue. Green and red uppercase nucleotides indicate constitutive and alternative exons, respectively. Introns are shown by black lowercase letters. (c) Schematics of human *MUSK* transcripts annotated in ENSEMBL 76. Black and blue connecting lines indicate constitutive and alternative splicing, respectively. Constitutively and alternatively spliced exons are indicated in green and red, respectively. Shaded exons represent 5' and 3' UTRs. (d) RT-PCR of endogenous *MUSK* transcripts spanning exons 8 to 11 using total RNA isolated from human skeletal muscle (HSKM), undifferentiated immortalized human myogenic cells (KD3), and undifferentiated primary human myoblasts (SkMC). Closed arrowhead points to an exon 10-included product, which is comprised of isoforms A and B in panel (c). Open arrowhead points to exon 10-skipped products, which are comprised of overlapping fragments of isoforms C and D in panel (c). Inclusion and skipping of the 7-nt exon 9 could not be differentiated on a gel. (e) RT-PCR of endogenous *Musk* transcripts spanning exons 8 to 11 of total RNA isolated from the indicated mouse skeletal muscles and the differentiated C2C12 mouse myotubes. Note that exon 10-skipped product is not detected in any of the mouse samples. (f) Alternative human *MUSK* transcripts harboring different combinations of exons 9 and 10 that we identified by cloning and sequencing the RT-PCR products in (d). The ENSEMBL transcripts for isoforms A-D are shown in (c).

Figure S3. Additional information for Figs. 2, 3, and 4. (a) Schematic of pSPL3-human-*MUSK* constructs with sequential deletions of upstream or downstream introns to identify minimal sequences to drive skipping of exon 10. RT-PCR of the respective minigenes in

HeLa cells are shown at the bottom. (b) ESS12 RNA probes carrying human (H-B12), mouse (m-B12), and partially deleted (H-B12Δ6) sequences. (c) ^{32}P-labeled H-B12 and m-B12 RNA probes are incubated with or without HeLa nuclear extract and resolved on a native polyacrylamide gel. (d) Coomassie blue staining of RNA affinity-purified products of HeLa nuclear extract using the indicated biotinylated RNA probes. (e) RT-PCR of pSPL3-human-*MUSK* (pH-wt) minigene in HeLa cells treated with the second set of siRNAs. mRNA targets of the second set of siRNAs are different from those of the first set shown in Fig. 4b.

Figure S4. Additional information for Fig. 5. (a) Immunoblotting of mock-, hnRNP C-, and non-depleted HeLa nuclear extracts showing efficient removal of hnRNP C. (b) Mock-depleted (ΔMock) and hnRNP C-depleted (ΔhnRNP C) HeLa nuclear extracts are affinity-purified with the indicated RNA probes and resolved by immunoblotting (IB). NuEx, native HeLa nuclear extract used as an input. (c) Tethering of only MS2 and PP7 to pSPL3-human-*MUSK*-MS2-PP7 has no effect on splicing regulation of *MUSK* exon 10. (d) Schematic of pSPL3-human-*MUSK*-non-MS2-PP7 that lacks MS2- and PP7-binding sites, as well as ESS5. RT-PCR of pSPL3-human-*MUSK*-non-MS2-PP7 in HeLa cells co-transfected with the indicated effectors. (e) Expressions of cDNA constructs in HeLa cells are detected by immunoblotting (IB). Expressions of cDNAs for YB-1 and hnRNPs L in HeLa cells are also shown in Fig. 4c. Native and recombinant proteins are indicated by ‘endo’ and ‘exo’, respectively.

Figure S5. Molecular interactions among the splicing repressors of *MUSK*. HeLa nuclear extract is immunoprecipitated with the indicated IP-antibody in the presence or absence of RNase, and the precipitated products are immunoblotted with the indicated IB-antibody. Ten-times diluted native HeLa nuclear extract are indicated by ‘Input (10%)’.

Figure S6. Effects of hnRNP C and YB-1 on splicing of alternative exons other than *MUSK* exon 10. RT-PCR of alternatively spliced exons that are coordinately regulated by both hnRNP C and YB-1 (a), hnRNP C (b), and YB-1 (c) in HeLa cells. Closed and open arrowheads point to exon-included and exon-skipped transcripts, respectively.

Figure S7. Additional information for Fig. 6. (a) Phase-contrast images showing a temporal profile of differentiation of primary human myoblasts (SkMC). (b) RT-PCR showing alternative skipping of endogenous *MUSK* exon 10 (Isoforms C and D as shown in Fig. S2c) at different differentiation days of SkMC. (c) RT-PCR of endogenous *Musk* transcripts spanning exons 8 to 11 at different differentiation days of mouse myoblast cells (C2C12).

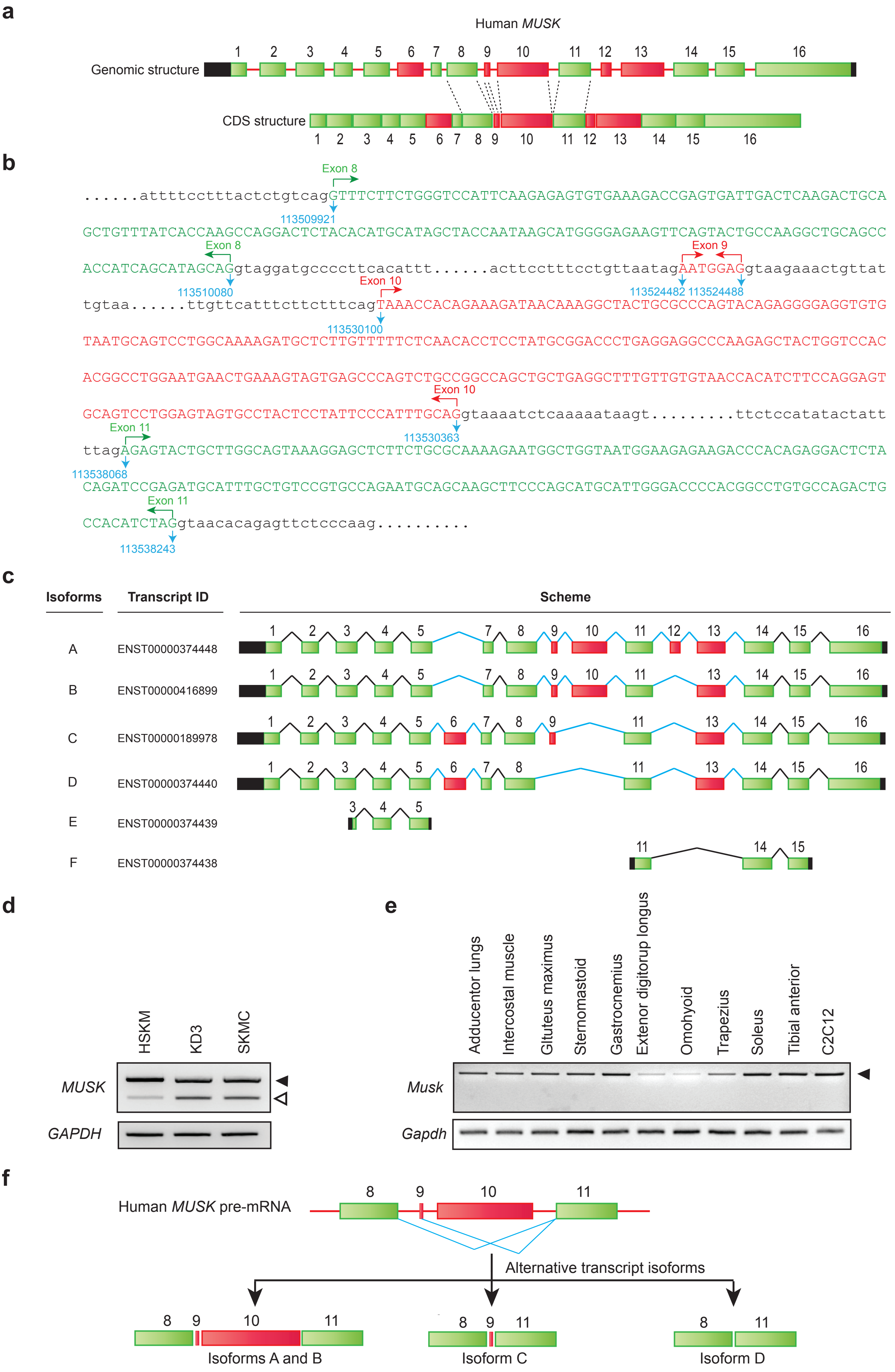
MuSK Fz-CRD

	Exon 10	Exon 11
Human	DNKGY C AQYRGEV C NAVLAKDALVFLNTSYA-DPEEAQELLVHTAWNELKVVSPV C RPAAEALL C NHIFQE C SP-GVVPTPIPI C	REY C LAVKELF C AKEWLVMEEKTHRGLYRSEMHLLSVPE C SKLPSMHWDPTA C ARL
Chimpange	DNKGY C AQYRGEV C NAVLAKDALVFLNTSYA-DPEEAQELLVHTAWNELKVVSPV C RPAAEALL C NHIFQE C SP-GVVPTPIPI C	REY C LAVKELF C AKEWLAMEEKTHRGLYRSEMHLLSVPE C SKLPSMHWDPTA C ARL
Mouse	DSQGY C AQYRGEV C DAVLAKDALVFFNTSYR-DPEDAQELLIHTAWNELKAVSPL C RPAAEALL C NHLFQE C SP-GVVPTPMPI C	REY C LAVKELF C AKEWLAMEGKTHRGLYRSGMHFLPVPE C SKLPSMHQDPTA C TRL
Rat	ESKGY C AQYRGEV C DAVLVKDSLVFFNTSYP-DPEEAQELLIHTAWNELKAVSPL C RPAAEALL C NHLFQE C SP-GVLPTPMPI C	REY C LAVKELF C AKEWQAMEGKAHRGLYRSGMHLLPVPE C SKLPSMHRDPTA C TRL
Opossums	EDPGY C STYRGEV C GAVLAKDALVFYNSSYQ-DSGDAQELLVQTIWSDLKALSPL C QPAMESLL C NHIFQG C NPARFMPTPKPL C	REH C LAVKDLF C AKEWLALEEKAHKGLYKSGLHLFTLPE C TKLPSMHREPMA C TKV
Chicken	GDAGY C STYRGEV C SAILSRNALVFFNSSYA-DPEETQELLVHTAWTELKTVSSF C QPAAESLL C NYIFQE C KPSGVGPAPKPI C	REN C LAVKDLY C FKEWLSMEENSQRGIYKPGLMLLALPE C NRLPSLHQDPSA C THI
Zebrafish	GHAGY C STYRGDV C RNVLRRDALVFFNYSLP-NPEDAQEYLAQSAWPELDGVSSF C RPAARSLL C HSTFQD C NPSGLGPAPKPV C	REH C LTVKELY C YKEWRSAEERSQRGFQ-----HITLPE C TSLPSQQADPSS C TAV

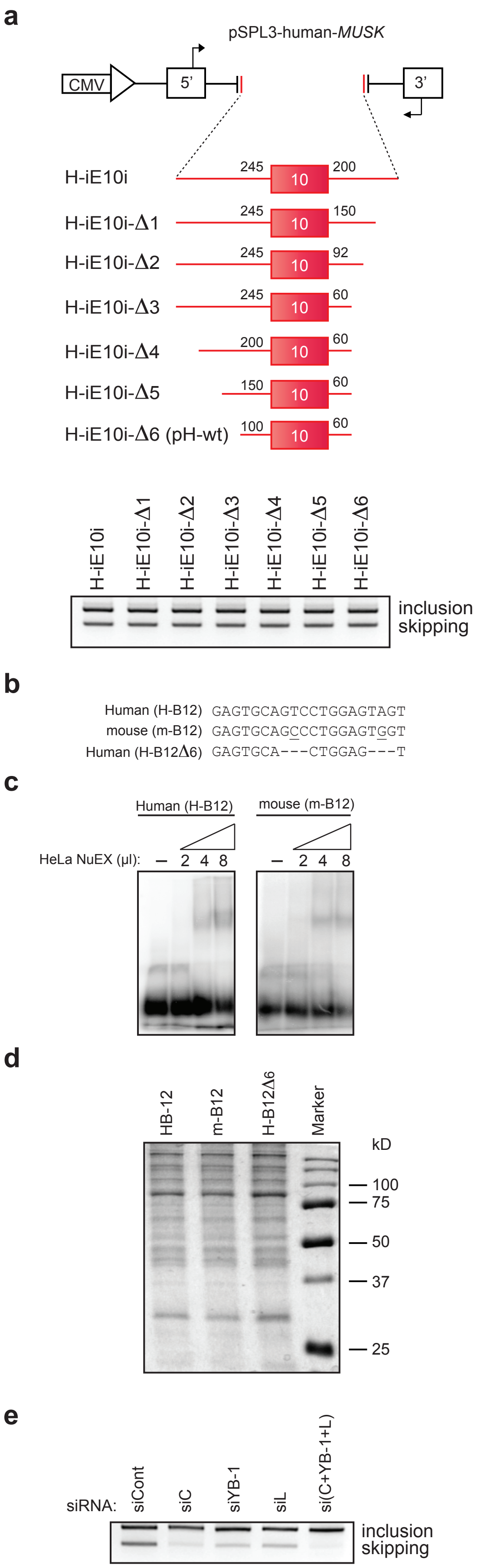
FZD1

Human	DHGY- C QPISIPL C TDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQ----- C SAELKFFL C SMYAPV C TVLEQAL---PP C	RSL C ERARQG- C EALMNKFGFQWPD-----------TLK C EKFPVHGAGE-L C VGQNT
Chimpange	DHGF- C QPISIPL C TDIAYNQTILPNLLGHTNQEDAGLEVHQFYPLVKVQ----- C SPELRFFL C SMYAPV C TVLDQAI---PP C	RSL C ERARQG- C EALMNKFGFQWPE-----------RLR C ENFPVHGAGE-I C VGQNT
Mouse	DHGY- C QPISIPL C TDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQ----- C SAELKFFL C SMYAPV C TVLEQAL---PP C	RSL C ERARQG- C EALMNKFGFQWPD-----------TLK C EKFPVHGAGE-L C VGQNT
Rat	DHGY- C QPISIPL C TDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQ----- C SAELKFFL C SMYAPV C TVLEQAL---PP C	RSL C ERA-QG- C EALMNKFGFQWPD-----------TLK C EKFPVHGAGE-L C VGQNT
Opossums	DHGY- C QPISIPL C TDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQ----- C SAELKFFL C SMYAPV C TVLEQAL---PP C	RSL C ERARQG- C EALMNKFGFQWPD-----------TLR C EKFPVHGAGE-L C VGQNT
Chicken	DHGY- C QPISIPL C TDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQ----- C SAELKFFL C SMYAPV C TVLEQAL---PP C	RSL C ERARQG- C EALMNKFGFQWPD-----------TLR C EKFPVHGAGE-L C VGQNA
Zebrafish	EHGF- C QPISIPL C TDIAYNETIMPNLLGHTNQEDAGLEVHQFYPLVKVQ----- C SPDLKFFL C SMYAPV C TVLEQAL---PP C	RSL C ERARQG- C EALMNKFGFQWPE-----------SLA C ESFPVHG-GE-L C VGQNT

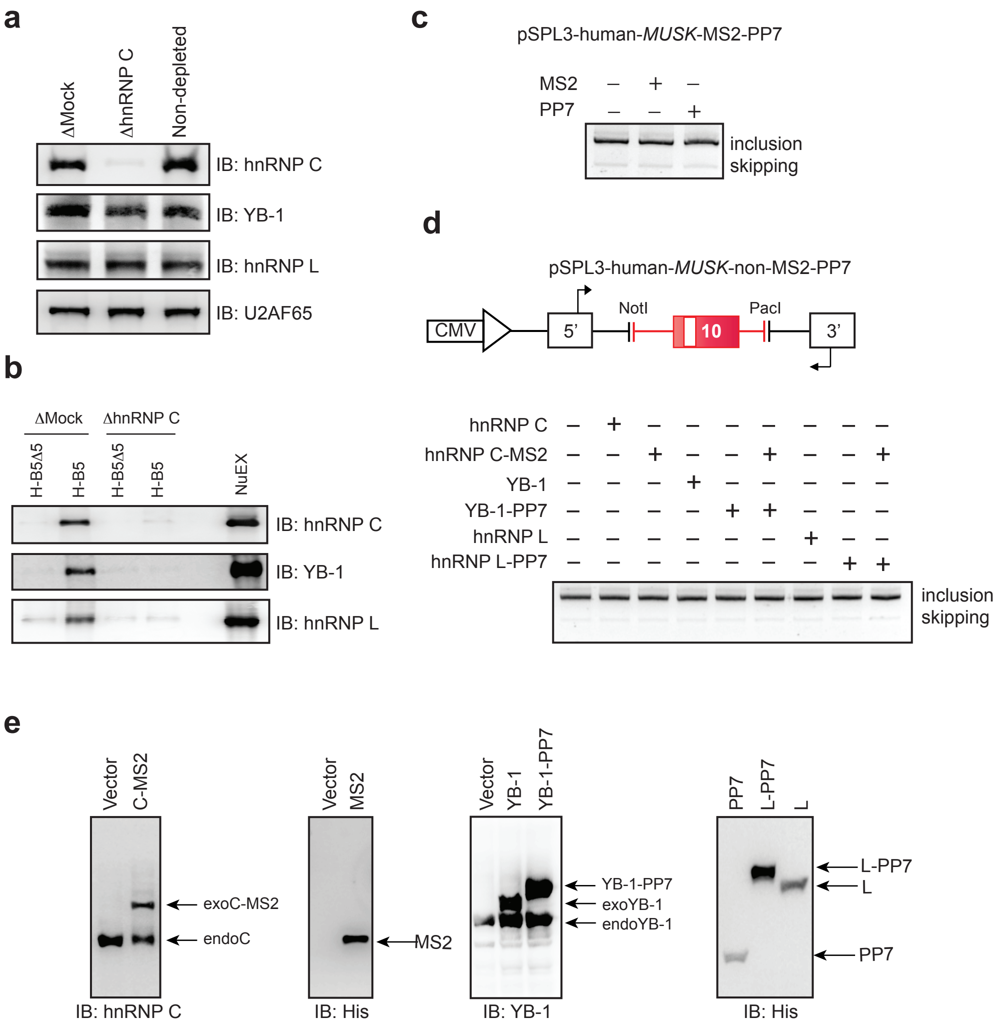
Supplementary Figure S1



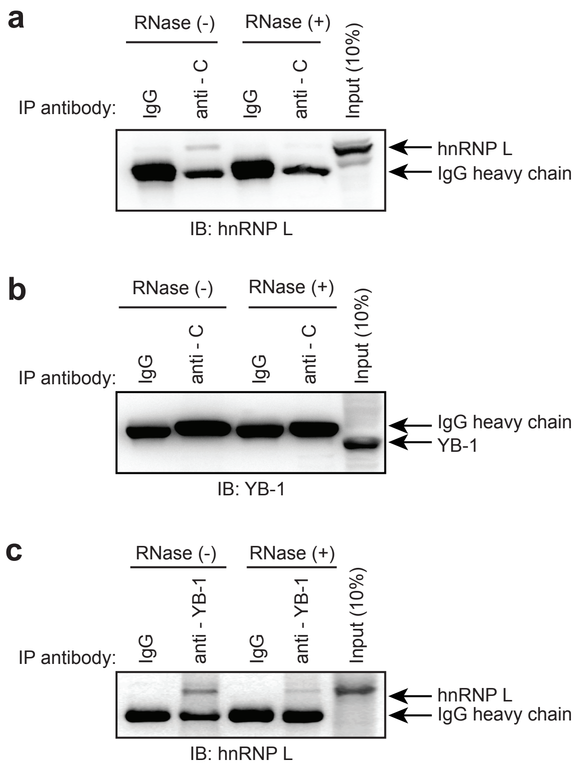
Supplementary Figure S2



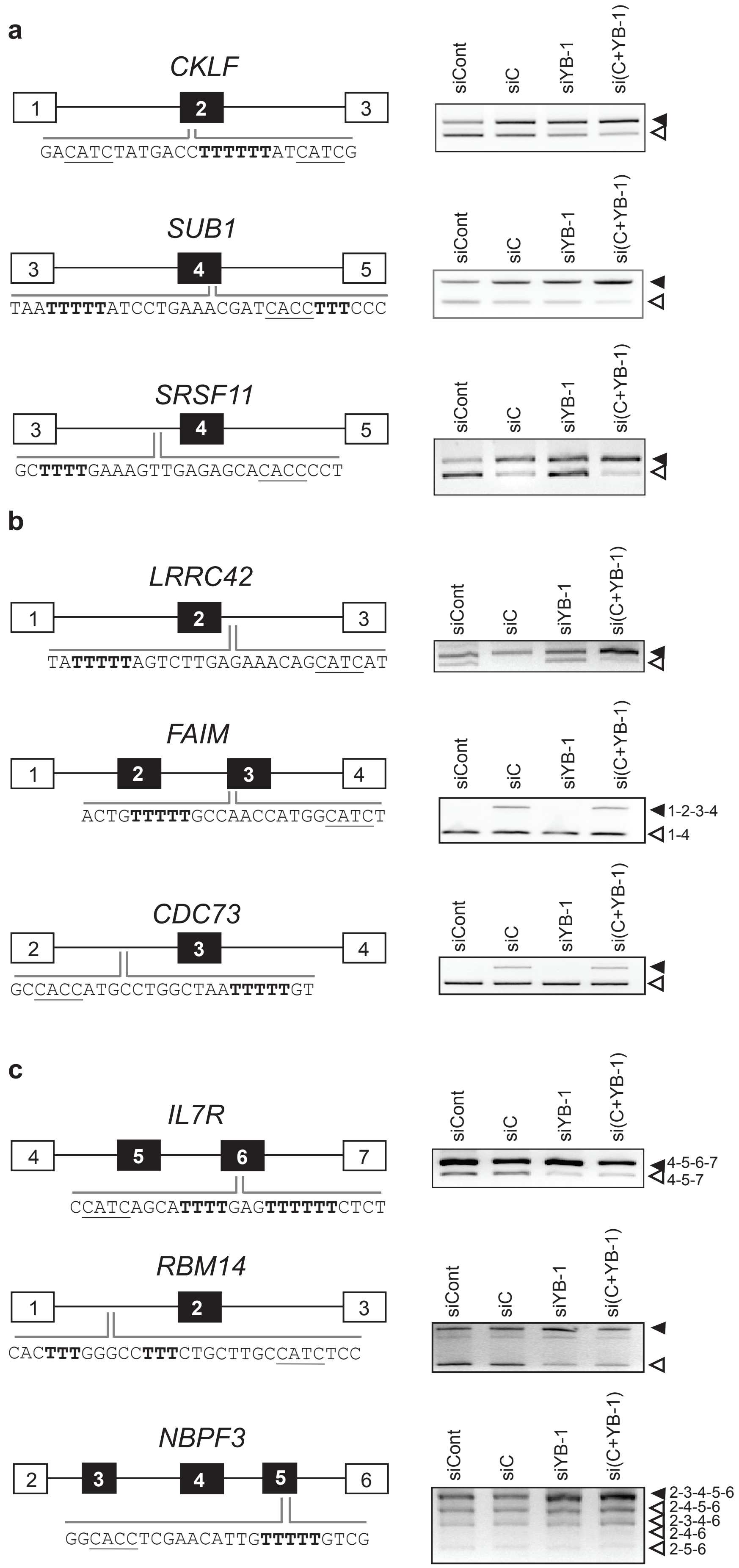
Supplementary Figure S3



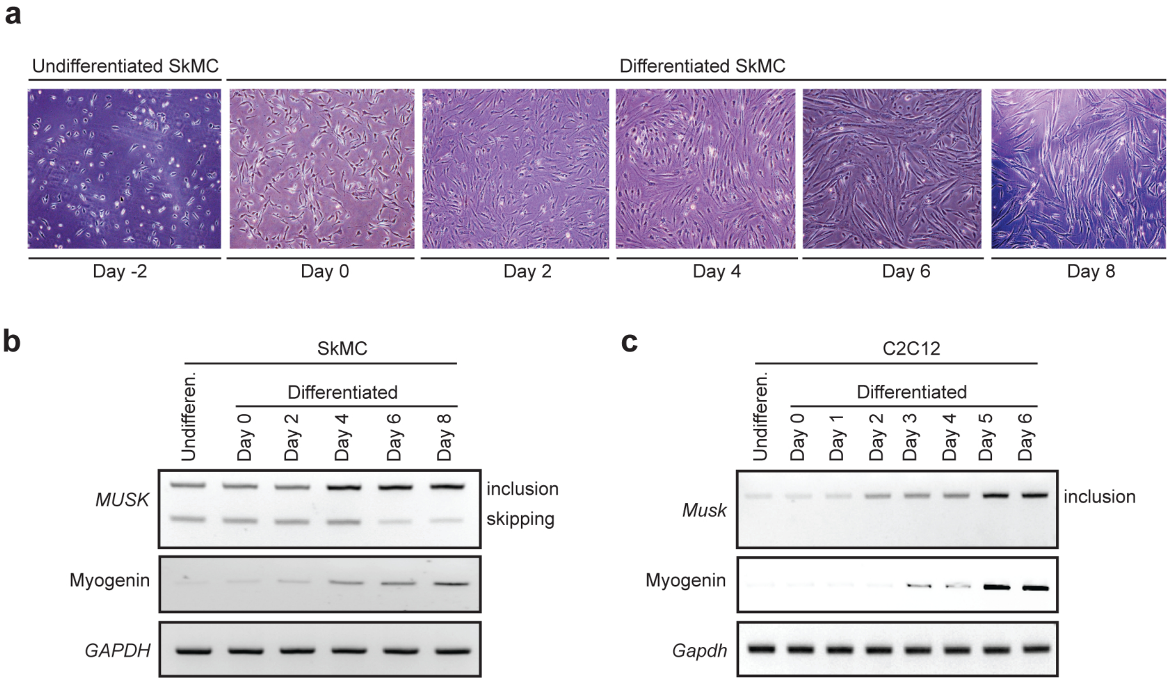
Supplementary Figure S4



Supplementary Figure S5



Supplementary Figure S6



Supplementary Figure S7