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► To cite this version:

M Traoré, C Benedetto, P de la Grange, J.Y. Hogrel, France Piétri-rouxel, et al.. CaVb1: The missing link from voltage sensing to muscle mass homeostasis. Molecular mechanisms of muscle wasting during aging and disease, Sep 2018, Ascona (CH), Switzerland. hal-04002366

HAL Id: hal-04002366

<https://hal.science/hal-04002366v1>

Submitted on 2 Mar 2023

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CaVβ1: The missing link from voltage sensing to muscle mass homeostasis

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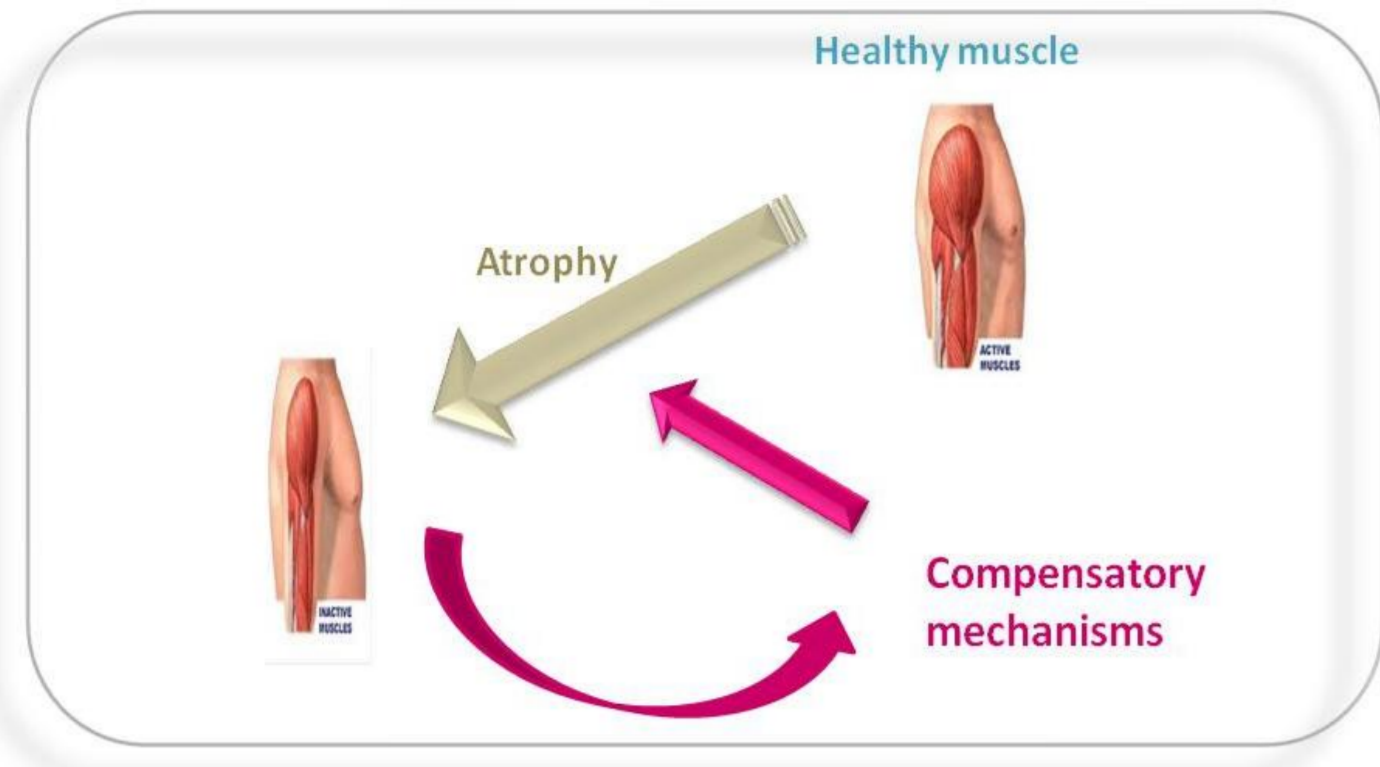
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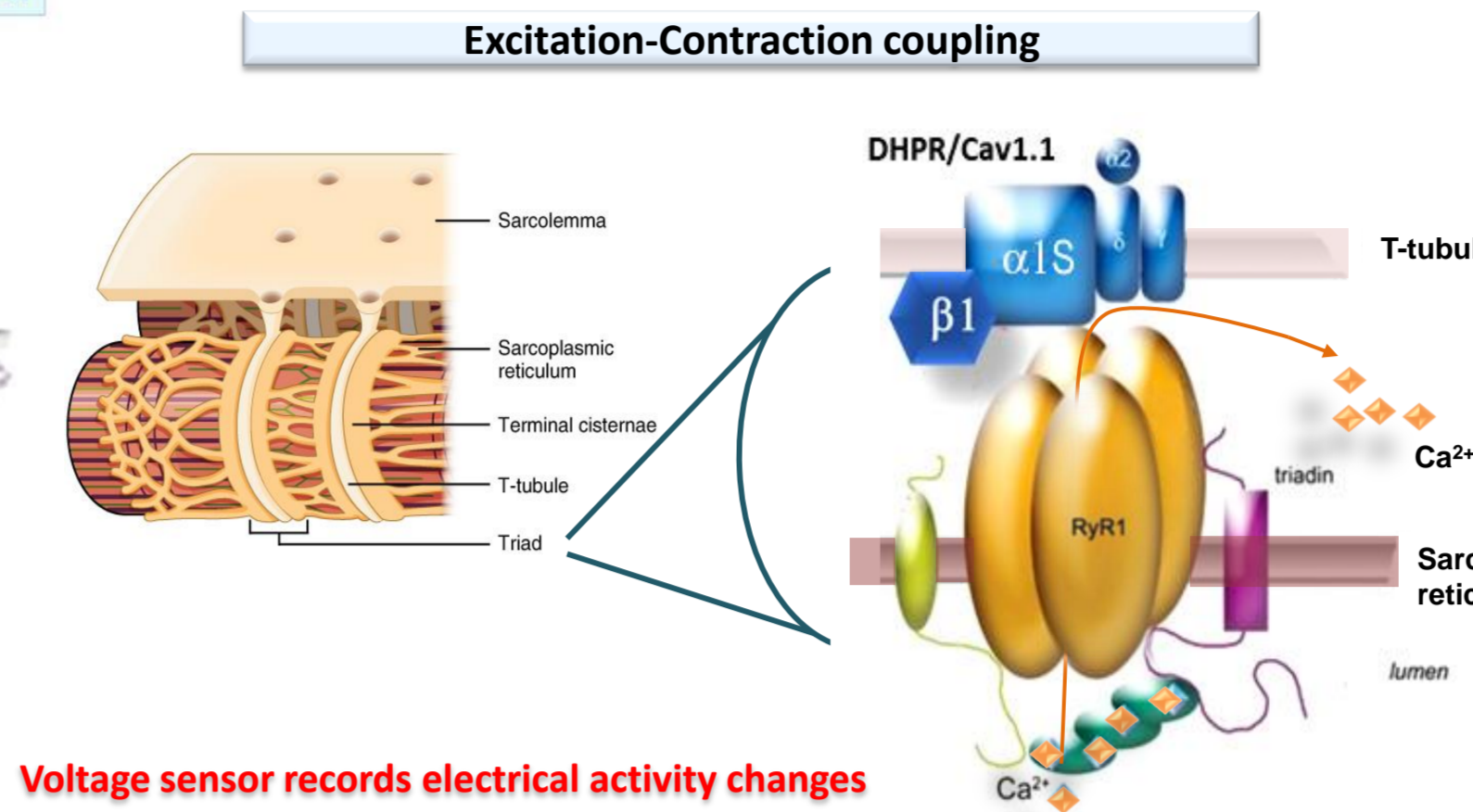
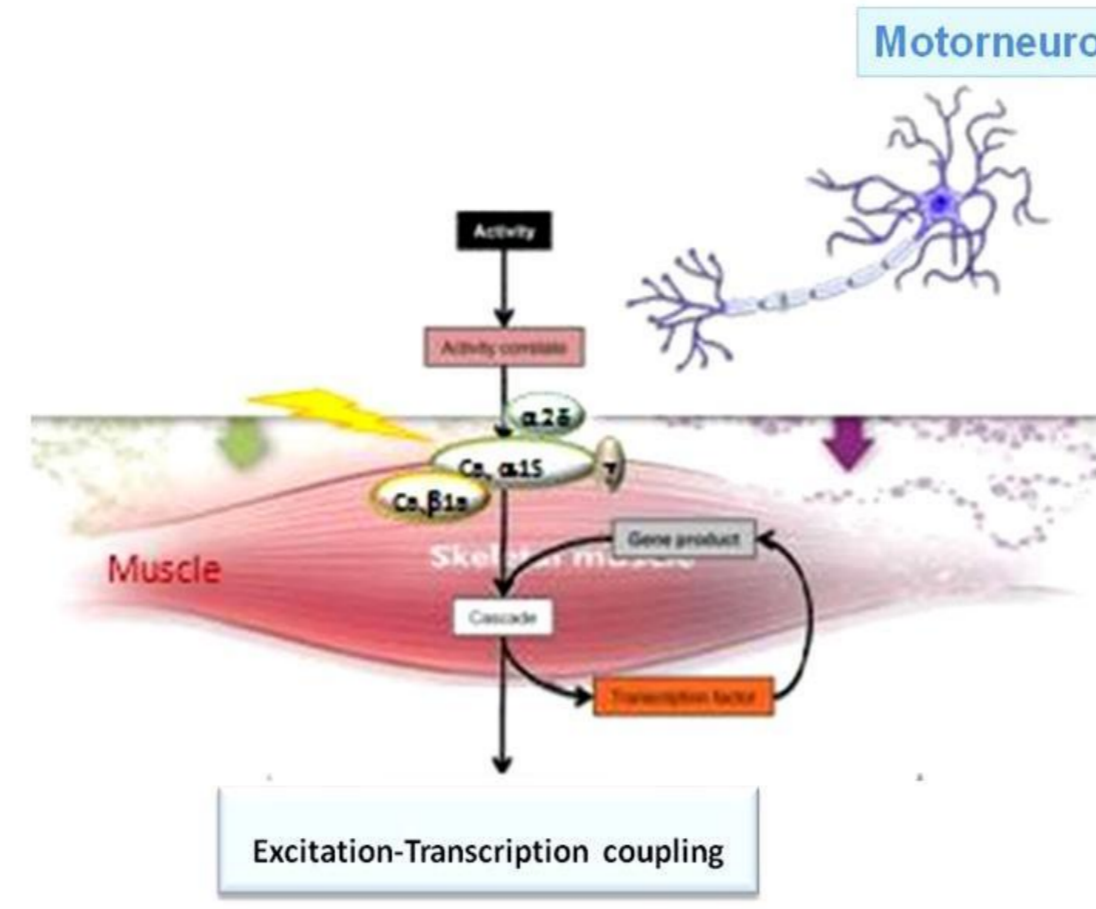
INTRODUCTION

Muscle plasticity and compensatory response

Electrical activity and Excitation-Transcription coupling



- Causes:**
- ✓ Myopathies-neuromuscular diseases
 - ✓ Nerve damage
 - ✓ Disuse-immobilization



The candidate: Ca_vβ1



- Adult (healthy) muscle**
- Anchors Ca_vα1S at the T-tubule membrane
 - Mediates Ca_vα1S-RyR interaction in E-C coupling
- Developing muscle**
- (Independent of E-C coupling)
 - Transcription factor function in MPCs
 - Required for neuromuscular synaptic patterning in embryo (before innervation)

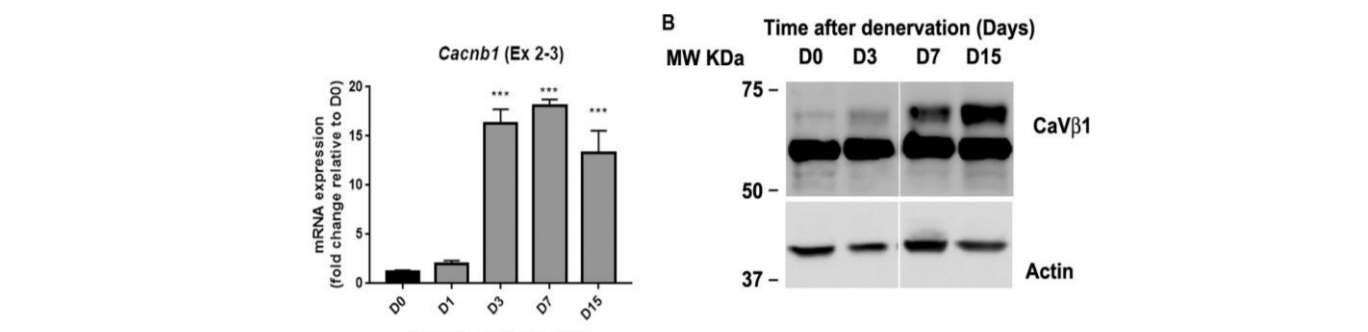
Deciphering the mechanisms governing skeletal muscle plasticity is essential for understanding pathophysiological processes, including age-related sarcopenia. Muscle activity reverses atrophy, but the connection between these processes is unknown. The voltage sensor Cav1.1 has a central role in excitation-contraction coupling, raising the possibility that it may also initiate the adaptive response to changes in muscle activity. Here, we reveal the existence of a transcription switch for the beta subunit of Cav1.1 (CaVβ1) that depends on the innervation state of the muscle. We show that denervation triggers the expression of a novel embryonic isoform, CaVβ1E. CaVβ1E boosts downstream GDF5 signaling to counteract muscle loss after denervation. We further report that aged muscle expresses significantly reduced levels of CaVβ1E and that CaVβ1E overexpression in aging muscle reduces sarcopenia by rescuing GDF5 expression. Crucially, we also identify human hCaVβ1E and show a tight negative correlation between hCaVβ1E expression and age-related sarcopenia in people, suggesting that the mechanisms underlying muscle mass homeostasis are conserved across species

Ca_vβ1 in adult skeletal muscle after electrical activity alteration

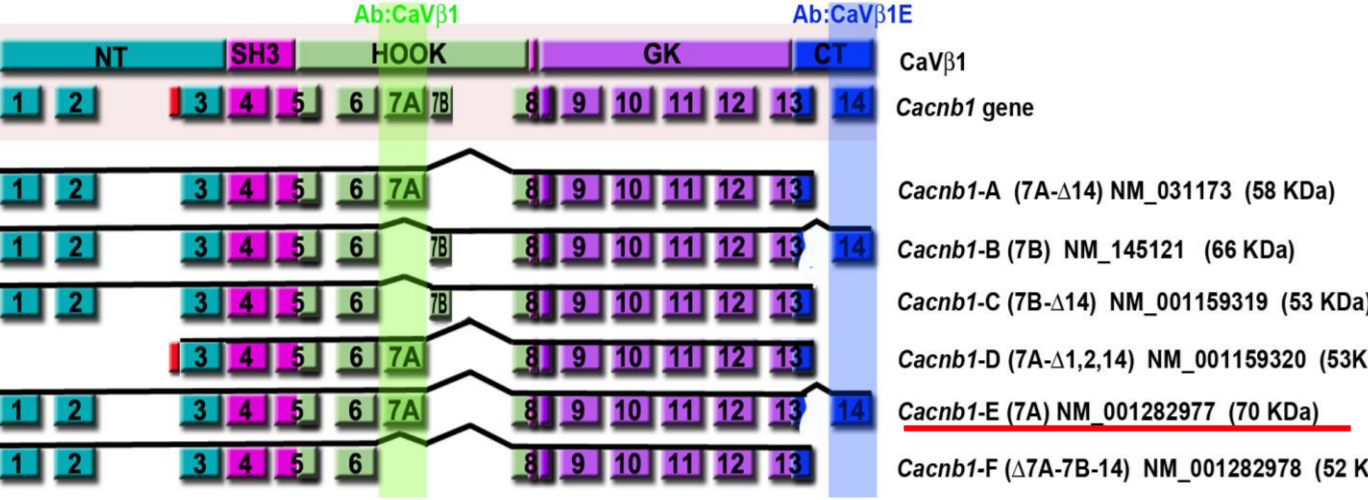
Exon level analysis: Distribution of alternative events

Alternative first exon of *Cacnb1* transcript in muscle after denervation

Ca_vβ1 expression after denervation



Denervation induces a strong increase of mRNA levels of Ca_vβ1 related to the appearance of an upper extra band: splicing isoform expression?



- Ca_vβ1-A has been considered (until now) the specific muscle isoform
- Upper band size would be consistent with Ca_vβ1-E expression

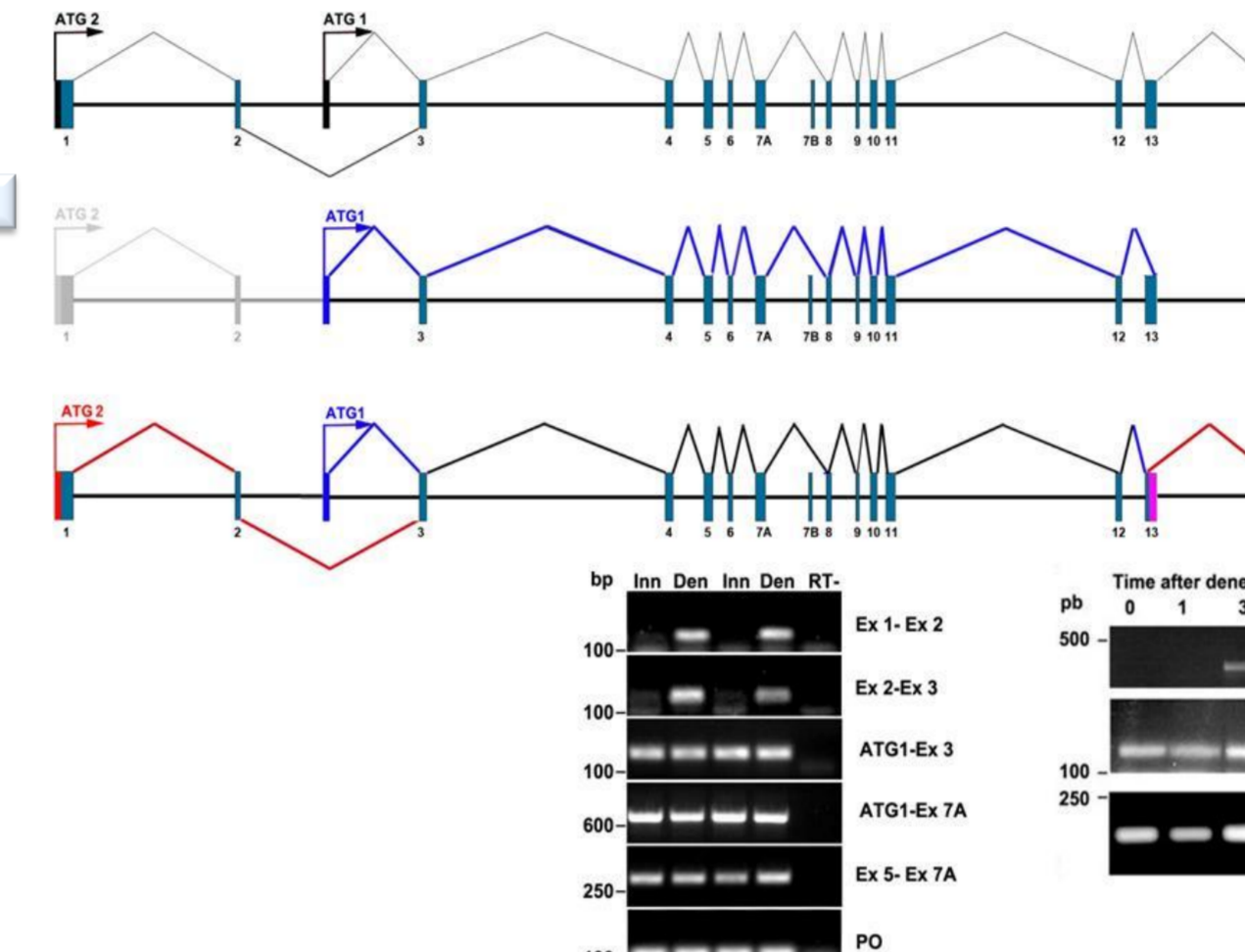
RNAseq: Illumina sequencing, NextSeq500, Paired-end Exon level analysis: Summary

- ▶ 1,022 events/exons were found significantly regulated:
 - 164 alternative events from "Pattern" analysis;
 - 858 from "Exon" analysis only (i.e., without a priori on alternative event information).
- ▶ 706 distinct genes are involved.

High enrichment in alternative first exons

Alternative Event Type	Number of Regulated Events
Alter. First Exon	85
Alter. Terminal Exon	35
Exon Cassette	28
Mutually Exclusive Exons	2
Alter. Acceptor Splice Site	7
Alter. Donor Splice Site	9
Intron Retention	12
Internal Exon Deletion	1
Complex	5

Many regulated alternative events

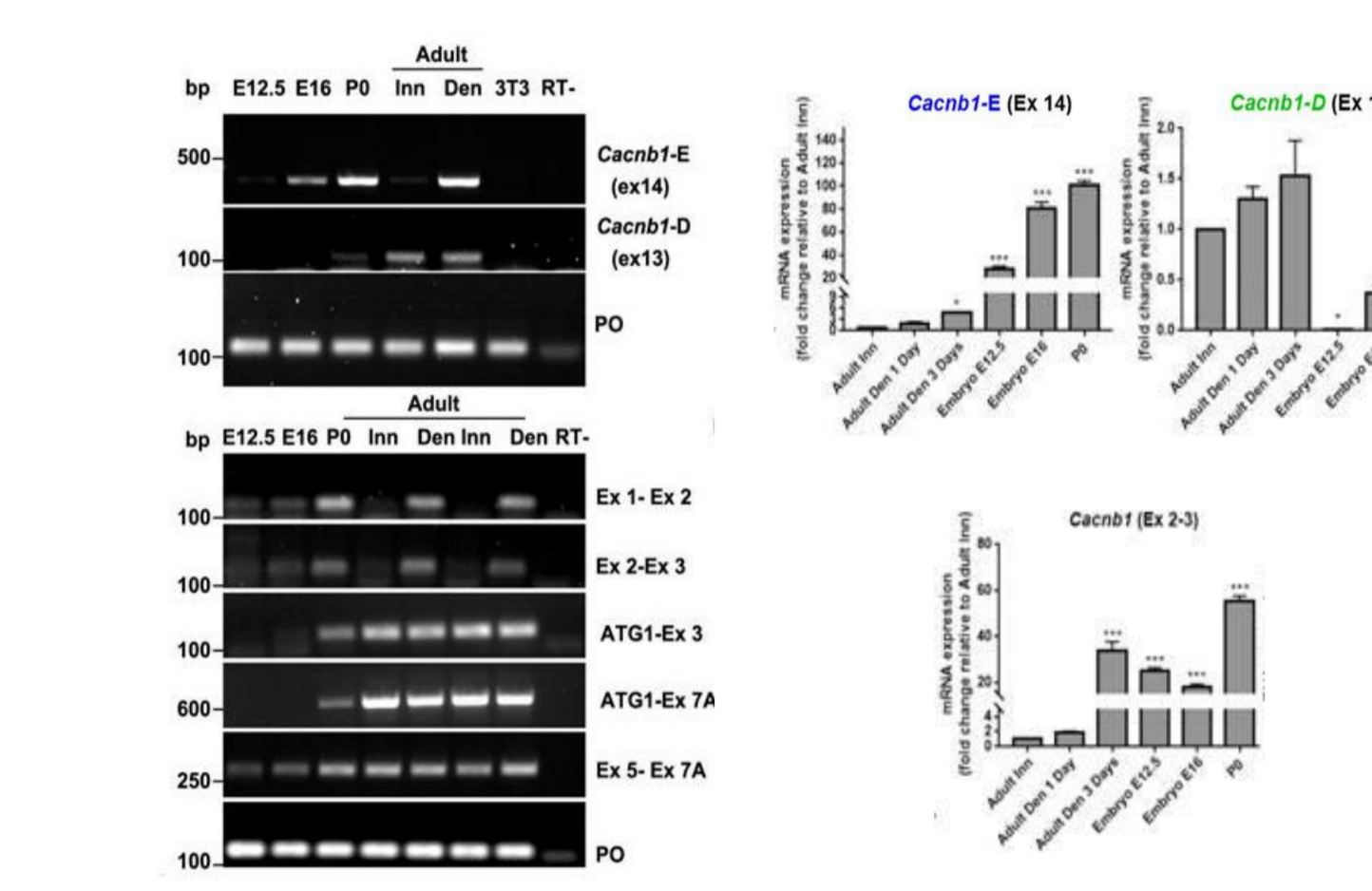


• Two different promoters *Cacnb1* gene → innervation state of muscle

• Innervation → Activation of the ATG1 → Ca_vβ1D and NOT Ca_vβ1A

• Denervation → Activation of the ATG2 → Ca_vβ1D + Ca_vβ1E

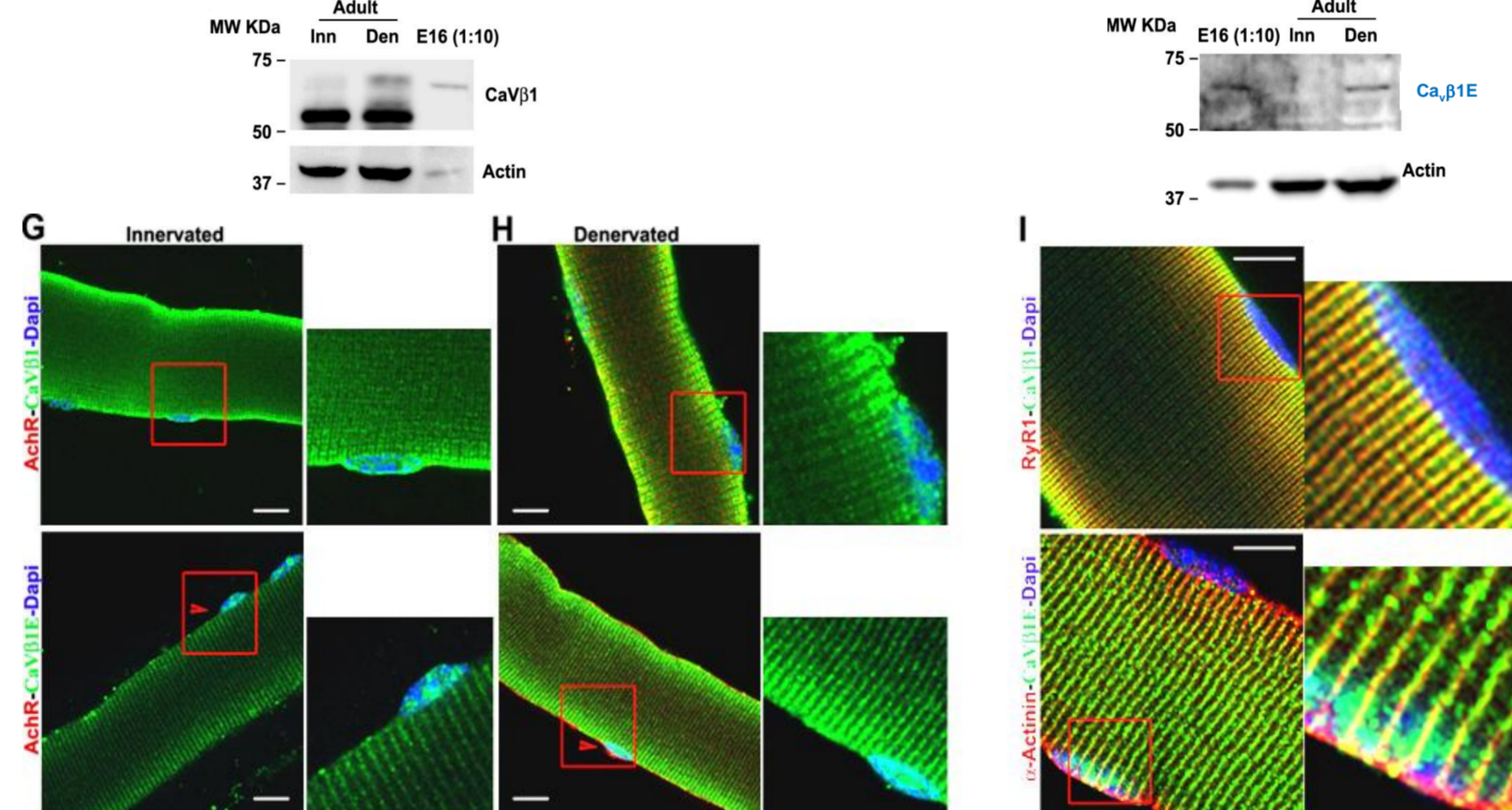
A new Ca_vβ1 isoform: embryonic?



Ca_vβ1E → embryonic Ca_vβ1 variant expressed by activation of the promoter upstream ex1

Characterization of Ca_vβ1E in adult skeletal muscle

Ca_vβ1 isoforms localization in adult skeletal muscle

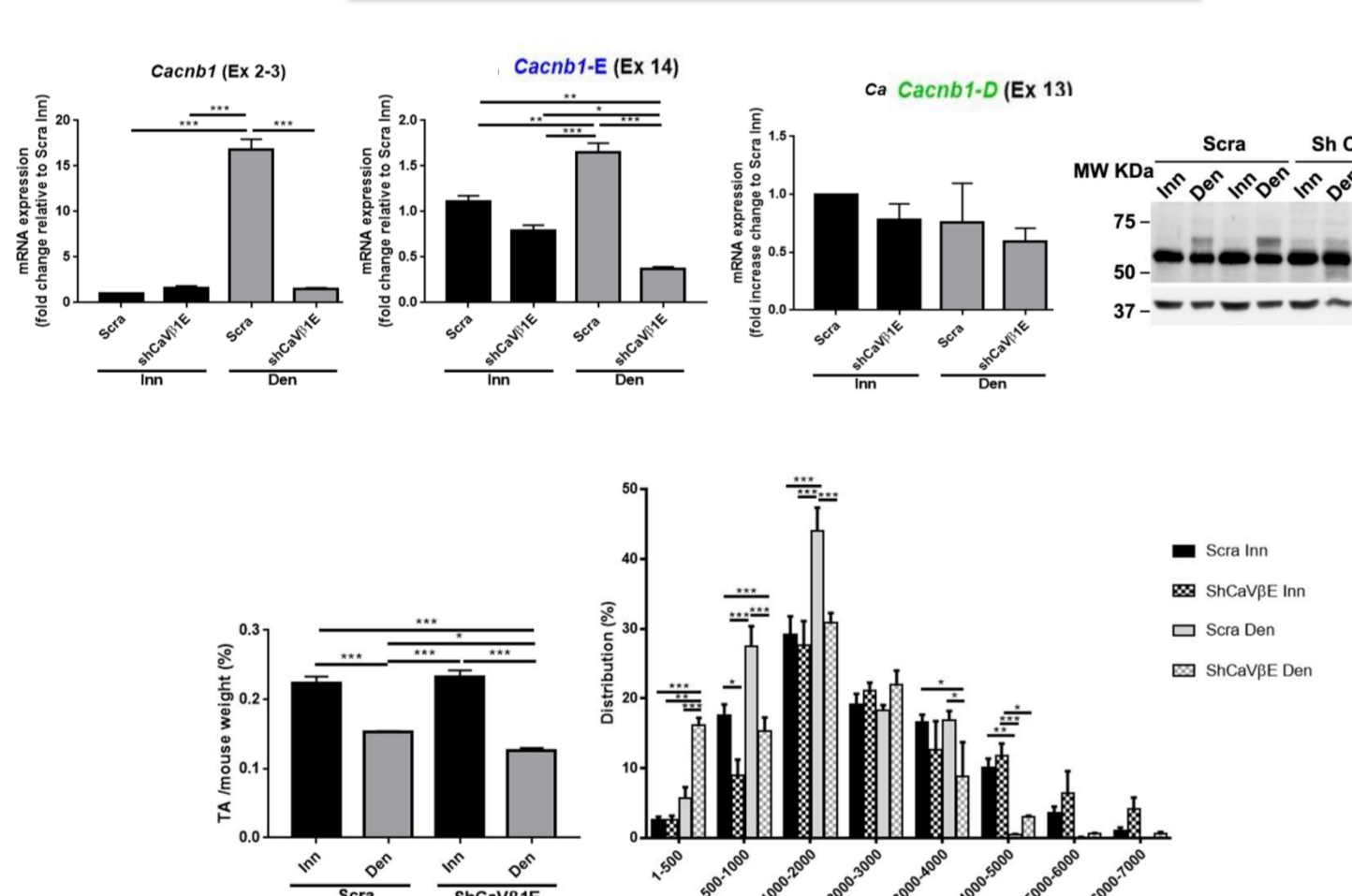


Ca_vβ1E and Ca_vβ1D have different localization in adult skeletal muscle

- Ca_vβ1E → embryonic Ca_vβ1 variant → transcription at ATG1 exclusively
- Intracellular localization of Ca_vβ1E looks different from Ca_vβ1D in adult
- Ca_vβ1E → Nuclear enrichment

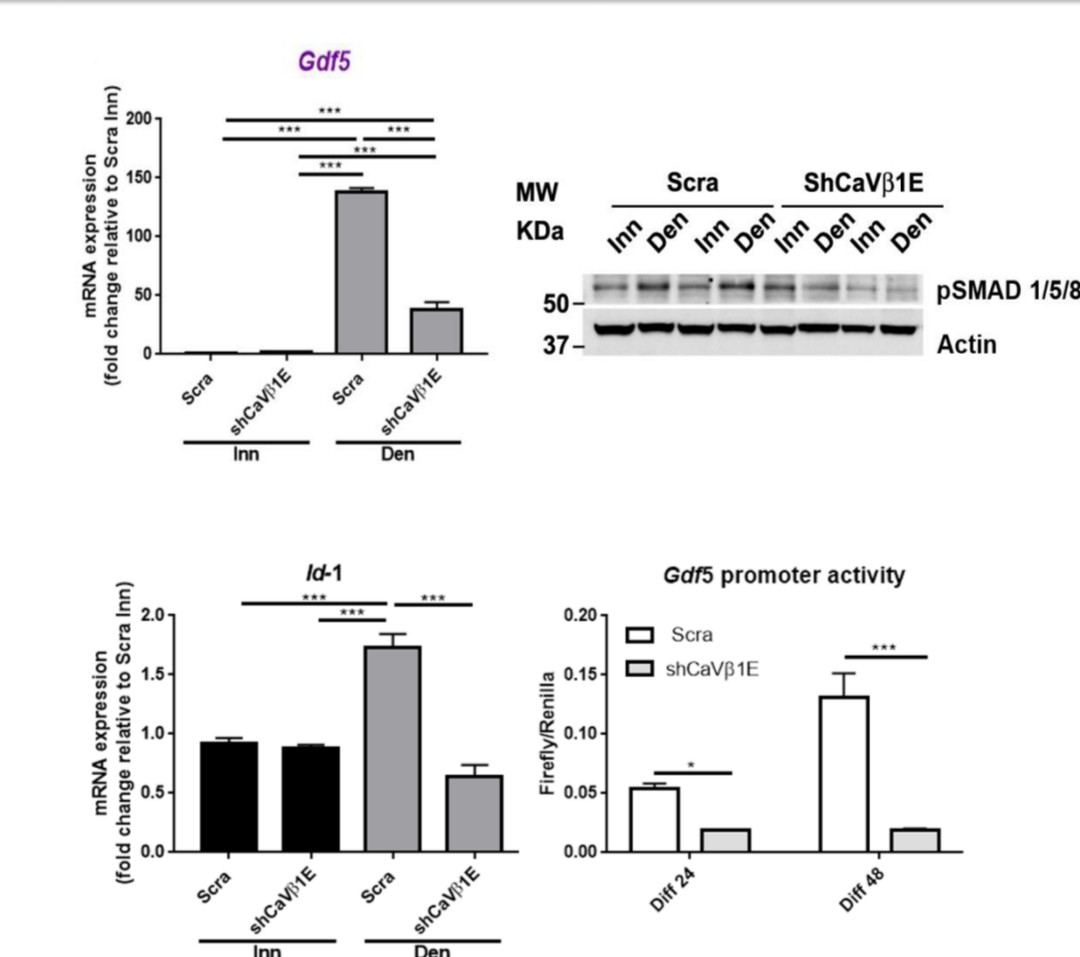
Function of Ca_vβ1E in adult and aging skeletal muscle

Ca_vβ1-E and muscle mass homeostasis



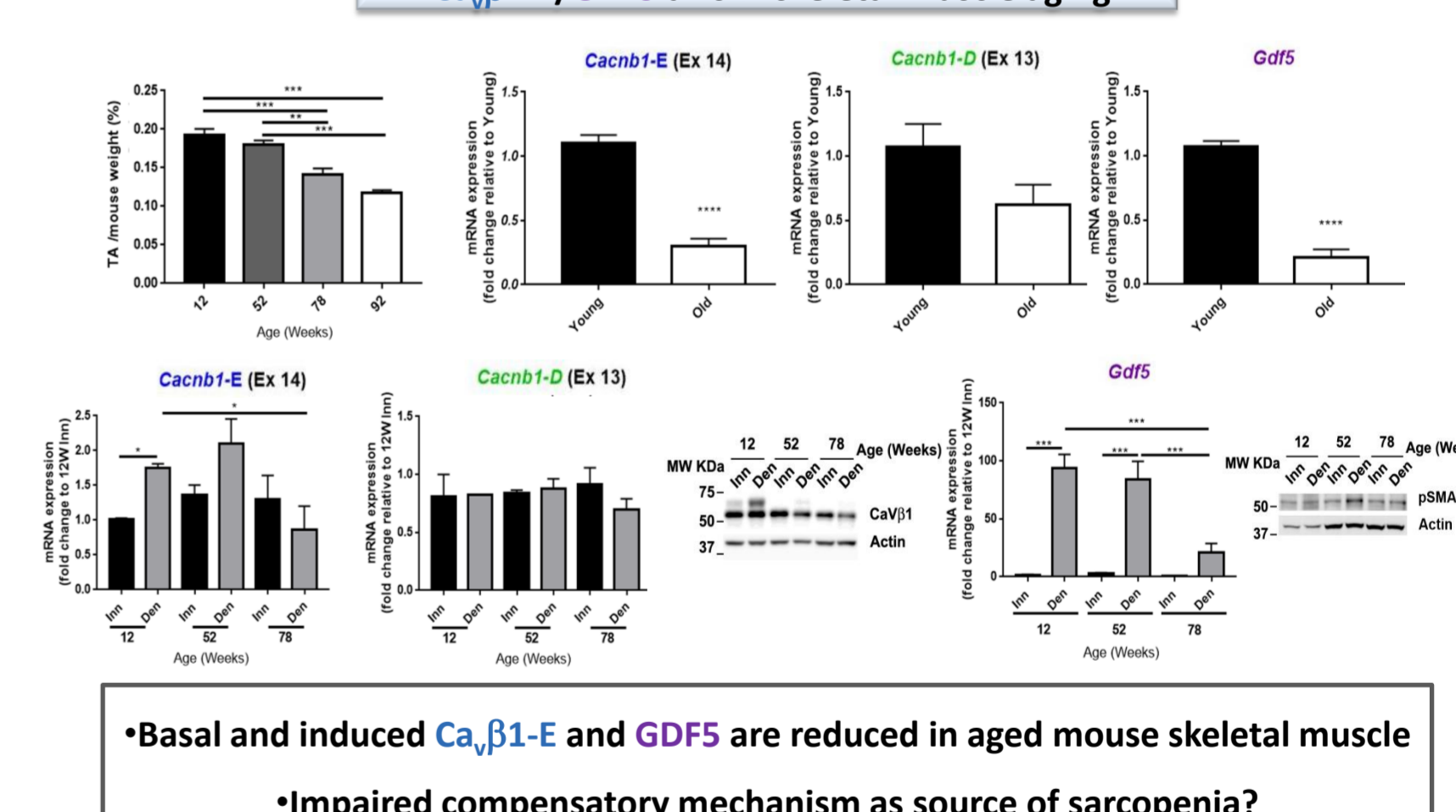
Ca_vβ1-E ablation increases atrophy after denervation: loss of compensatory response?

Gdf5 expression and signaling in Ca_vβ1-E Knock-Down (KD) muscle



Ca_vβ1E induction after denervation is needed for Gdf5 transcription and compensatory response activation

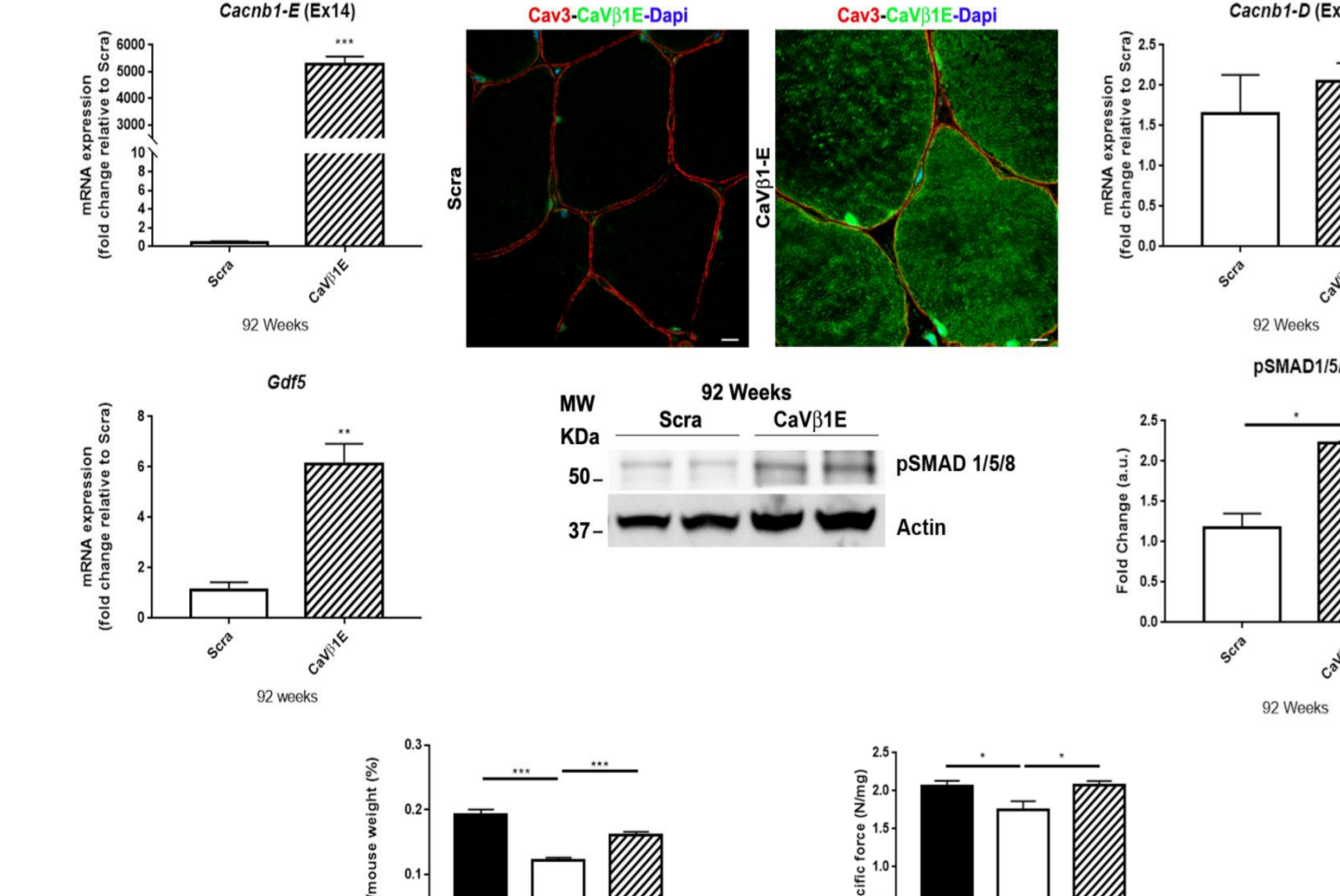
Ca_vβ1-E/GDF5 axis in skeletal muscle aging



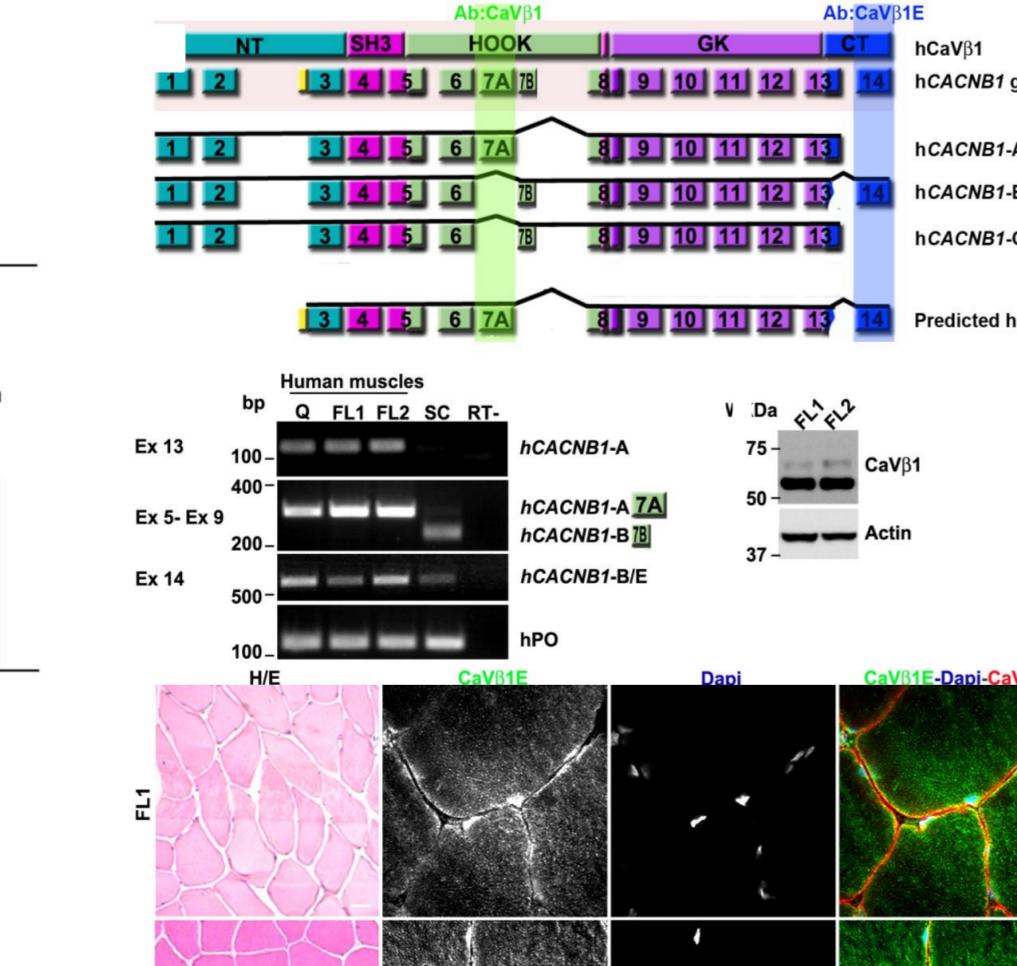
- Basal and induced Ca_vβ1-E and GDF5 are reduced in aged mouse skeletal muscle
- Impaired compensatory mechanism as source of sarcopenia?
- Effect of Ca_vβ1-E over-expression during aging?

Ca_vβ1-E/GDF5 axis: a conserved compensatory mechanism in mammals

Ca_vβ1-E Over-Expression in aging muscle



Ca_vβ1-E IN HUMANS?



• We discovered hCa_vβ1-E in HUMAN SKELETAL MUSCLE

hCa_vβ1-E expression is negatively associated to aging and muscle decline in HUMANS

Subject	Sex	Age (years)	CAVβ1E (RNA-seq)	GDF5 (RNA-seq)	Height (cm)	Weight (kg)	Lean mass (kg)	FFAT (kg)	FFAT (%)	Power (W/kg)	Specific strength (N/kg)	Score
Y1	M	28.4	0.90	1.10	187	88.7	80.2	8.6	4.5	25.5	2.5	***
Y2	M	28.0	1.00	1.10	182	84.4	77.2	7.2	3.9	24.2	2.2	**
Y3	F	24.5	0.95	0.94	163	58.2	54.4	3.8	2.3	15.1	1.5	+
Y4	F	26.1	1.00	1.00	173	75.0	71.0	4.0	2.3	18.4	1.8	+
Y5	M	28.7	1.00	0.99	185	71.9	64.6	7.3	4.0	18.5	1.7	+
Y6	M	27.1	0.95	0.96	183	73.8	70.0	3.8	2.1	17.2	1.7	+
Y7	M	32.0	1.25	1.00	180	70.0	60.0	10.0	5.5	16.0	1.6	ND
Y8	M	38.0	1.10	1.10	180	70.0	60.0	10.0	5.5	16.0	1.6	ND
Y9	M	38.0	1.10	1.10	180	70.0	60.0	10.0	5.5	16.0	1.6	ND
Y10	M	38.0	1.10	1.10	180	70.0	60.0	10.0	5.5	16.0	1.6	ND
Y11	F	74.2	1.00	0.97	161	60.3	55.0	5.3	2.9	10.0	1.0	***
Y12	F	75.0	1.00	1.14	169	60.0	56.0	4.0	2.4	10.0	1.0	***
Y13	M	78.0	0.90	0.96	186	67.1	74.0	13.1	7.1	21.0	2.1	**
Y14	M	78.0	0.90	0.95	176	61.5	52.0	9.5	5.5	18.0	1.8	**
Y15	F	77.0	0.90	0.90	160	55.0	50.0	5.0	2.5	10.0	1.0	ND
Y16	M	78.0	0.90	0.96	175	60.0	55.0	5.0	2.5	10.0	1.0	ND
Y17	M	78.0	0.70	0.70	144	48.0	45.0	3.0	1.5	10.0	1.0	ND
Y18	F	80.0	0.90	0.98	159	58.3	53.0	5.3	2.8	10.0	1.0	ND

Conclusion & Perspectives:

- GDF5: a diagnostic biomarker for sarcopenia in humans?
- GDF5 implementation: a therapeutic tool to reverse age-related (or neuromuscular disease-related) muscle waste?
- Mechanism(s) inducing Ca_vβ1 increase
- Ca_vβ1/GDF5 in reinnervation and disease models (ALS, SMA, DMD...)
- Ca_vβ1/GDF5 in myogenesis / embryogenesis