



HAL
open science

CaVb1: The missing link from voltage sensing to muscle mass homeostasis

M Traoré, C Benedetto, P de la Grange, J.Y. Hogrel, France Piétri-rouxel,
Sestina Falcone

► 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-04002366>

Submitted on 2 Mar 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Traoré M.^{1*}, Gentil, C.^{2*}, Benedetto C.², De la Grange P.³, Hogrel J.Y.⁴, Ferry, A.² Piétri-Rouxel, F.^{2*} and Falcone, S.^{2*},

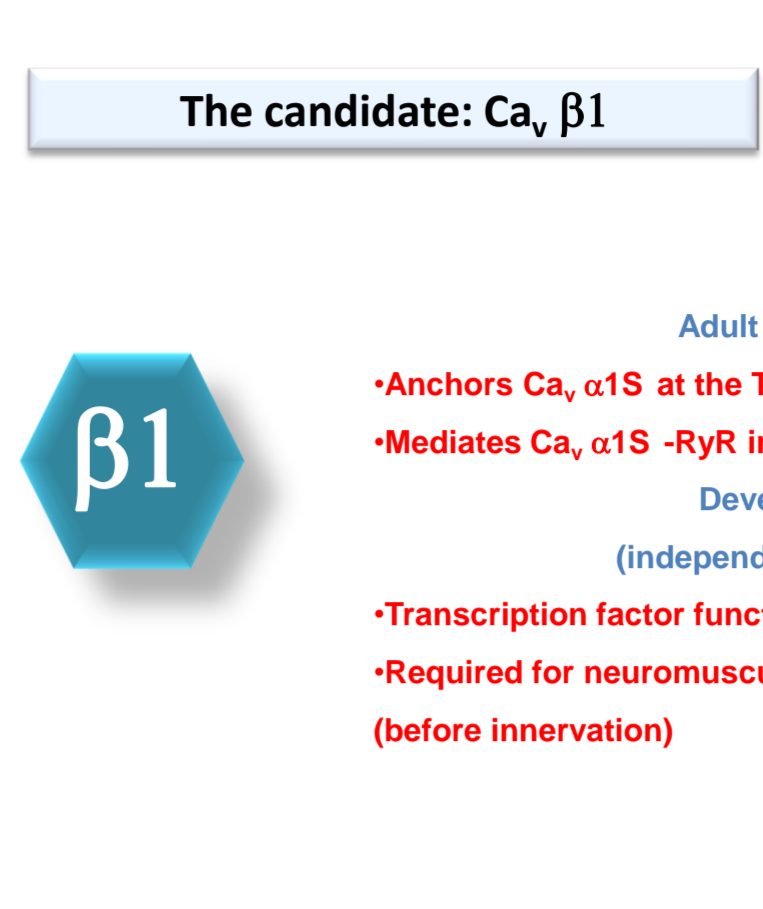
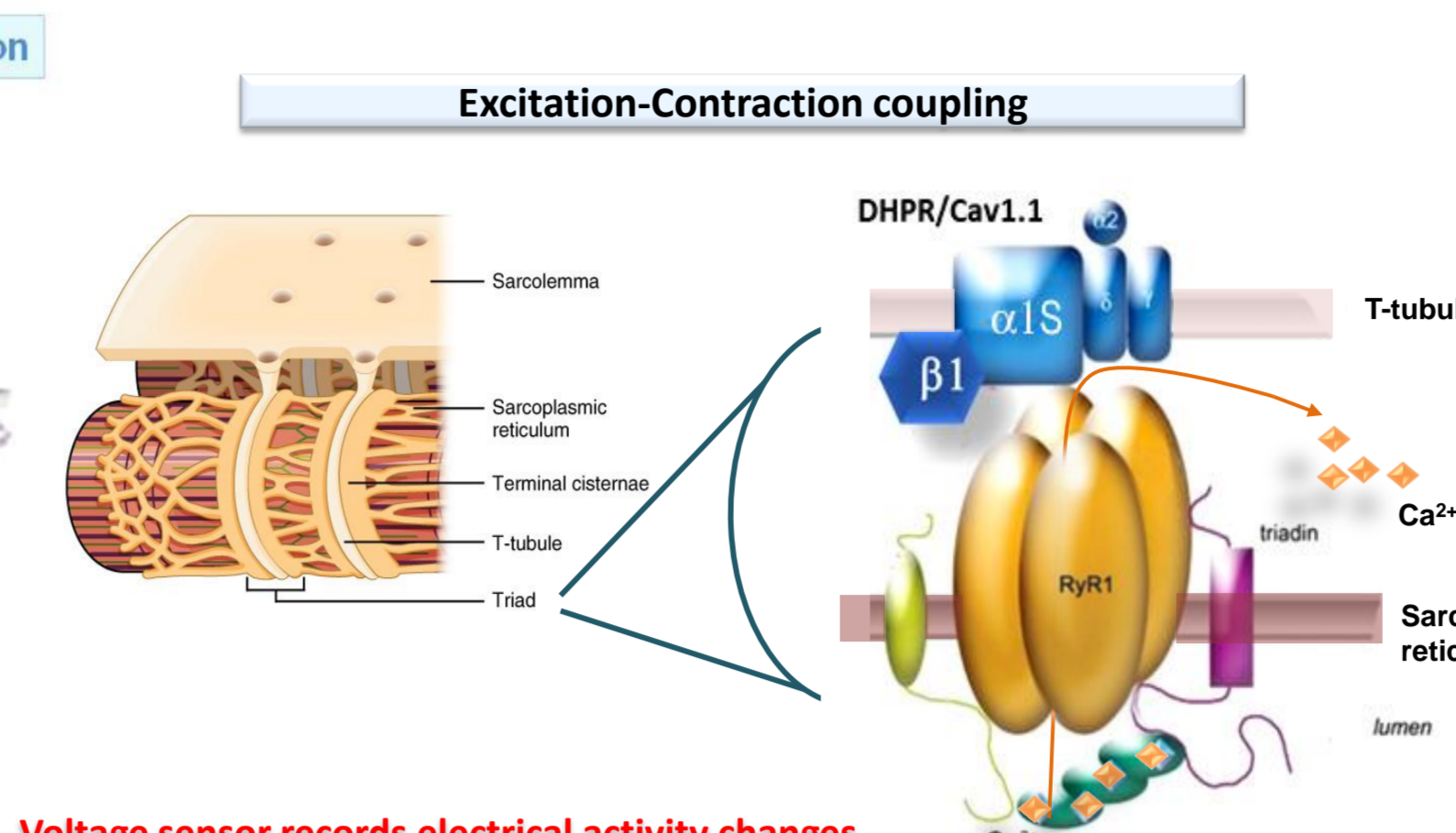
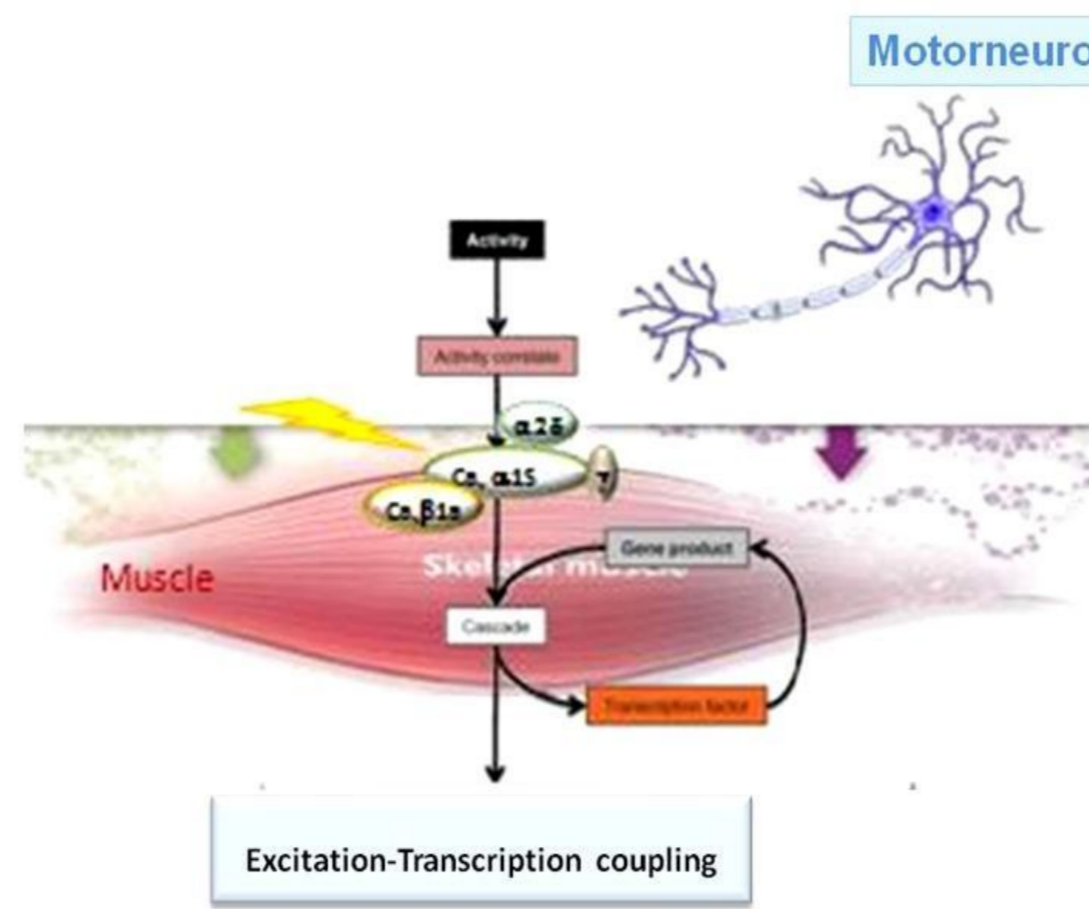
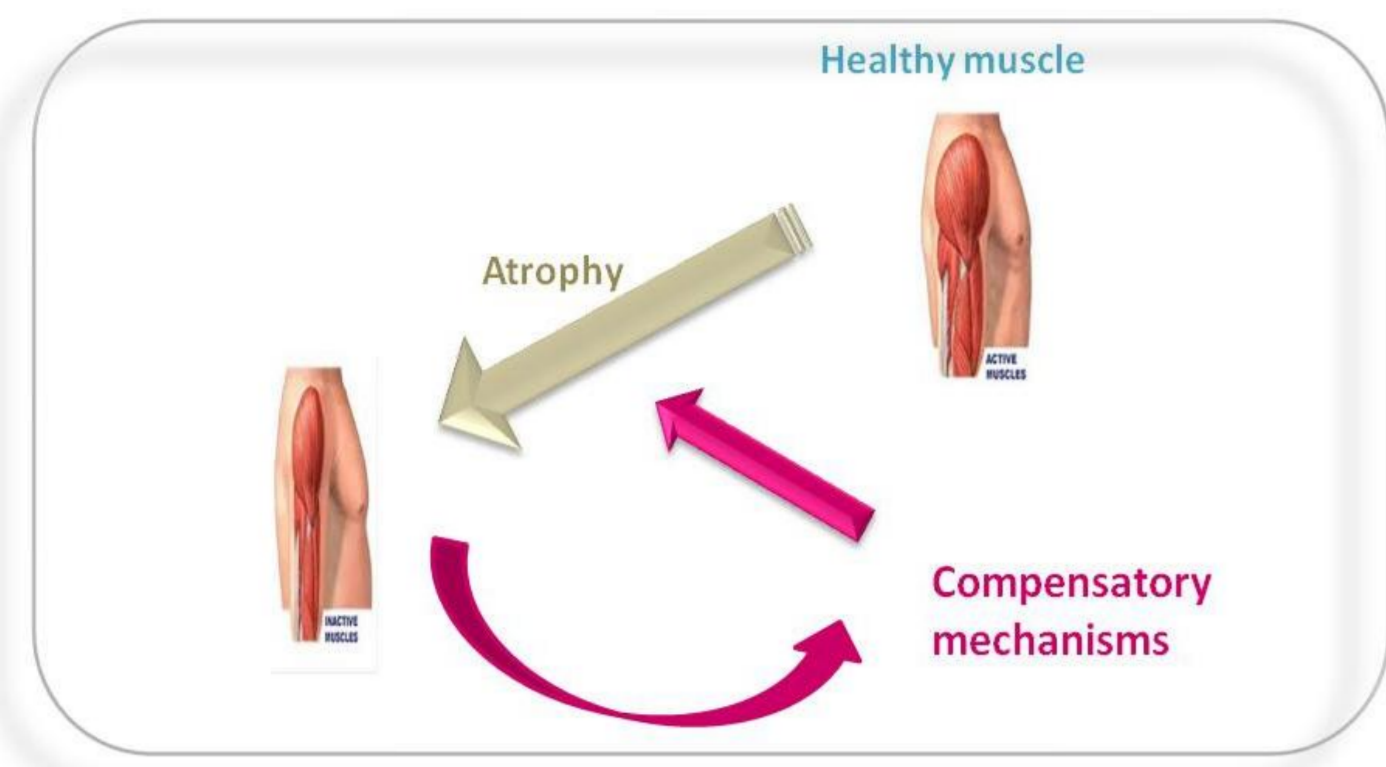
²Sorbonne Université, UPMC Univ Paris 06, Myology Research Center, INSERM U974 Institut de Myologie, Paris, France; ¹Inovarian; Paris, France; ³Genosplice, Paris, France

⁴Institut de Myologie, GH Pitié-Salpêtrière, Paris France

INTRODUCTION

Muscle plasticity and compensatory response

Electrical activity and Excitation-Transcription coupling



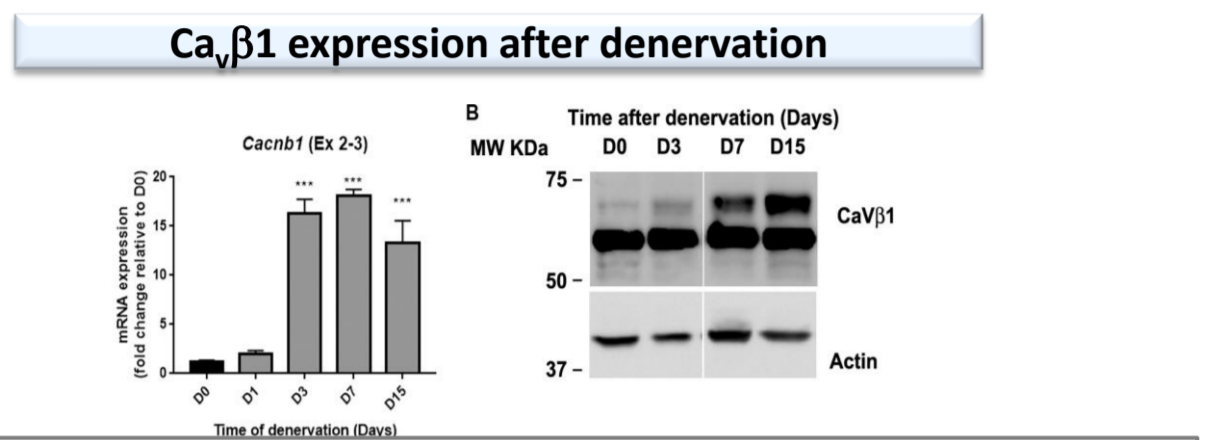
- Causes:**
- ✓ Myopathies-neuromuscular diseases
 - ✓ Nerve damage
 - ✓ Disuse-immobilization

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

Caβ1 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

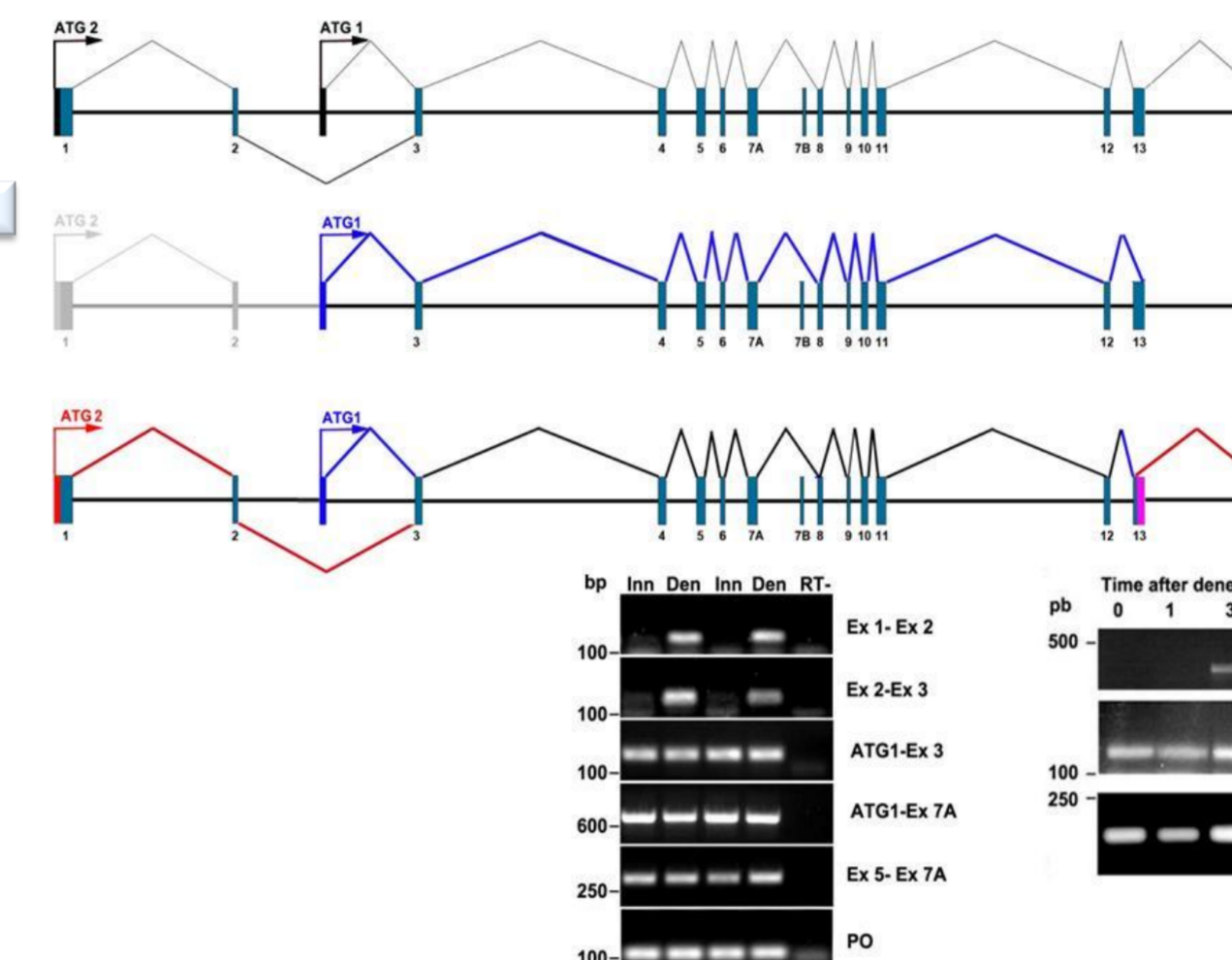


RNAseq: Illumina sequencing, NextSeq500, Paired-end
Exon level analysis: Summary

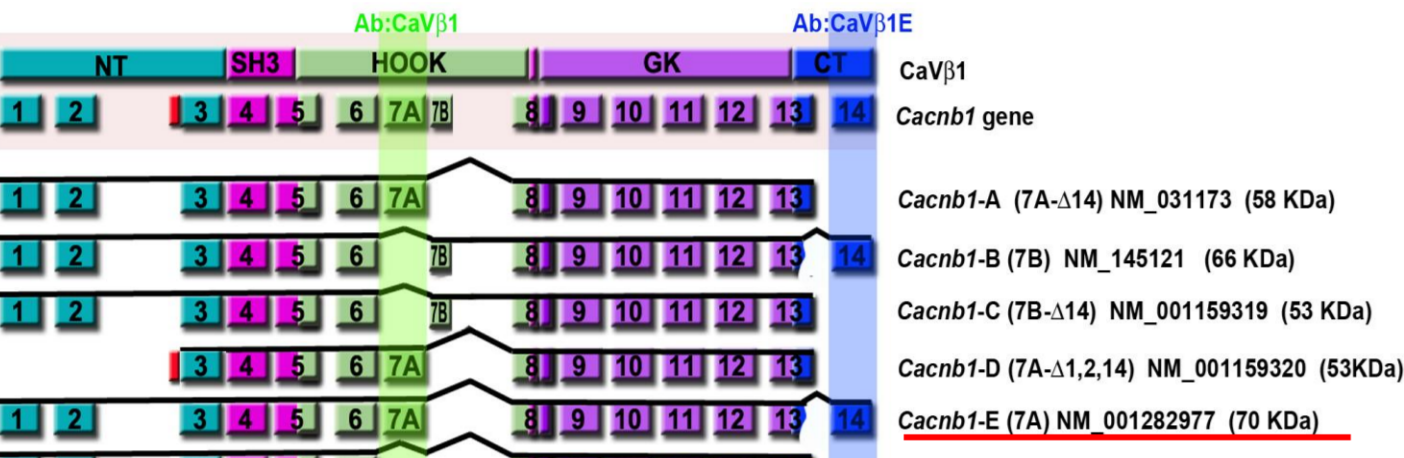
- 1,022 events/exons were found significantly regulated:
 - 164 alternative events from "Pattern" analysis;
 - 858 from "Exon" analysis only (i.e., without a priori on alternative event information).
- 706 distinct genes are involved.

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



Denervation induces a strong increase of mRNA levels of Caβ1 related to the appearance of an upper extra band: splicing isoform expression?



- Caβ1-A has been considered (until now) the specific muscle isoform
- Upper band size would be consistent with Caβ1-E expression

Many regulated alternative events

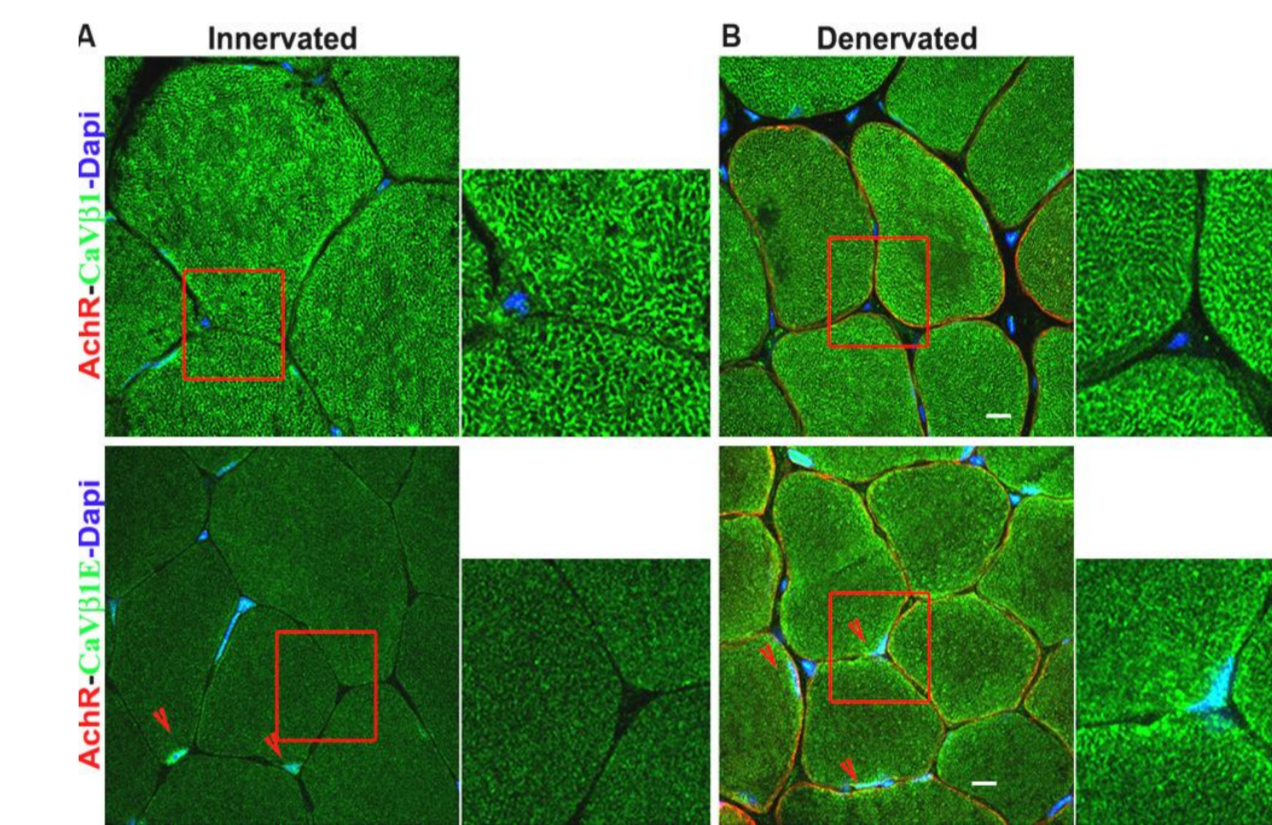
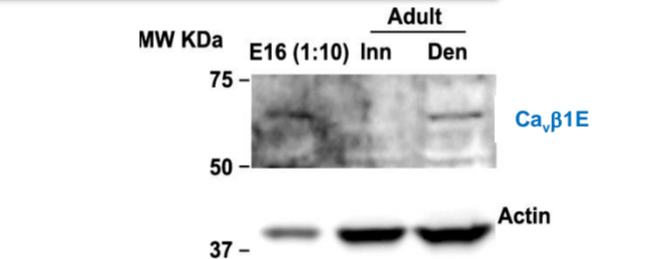
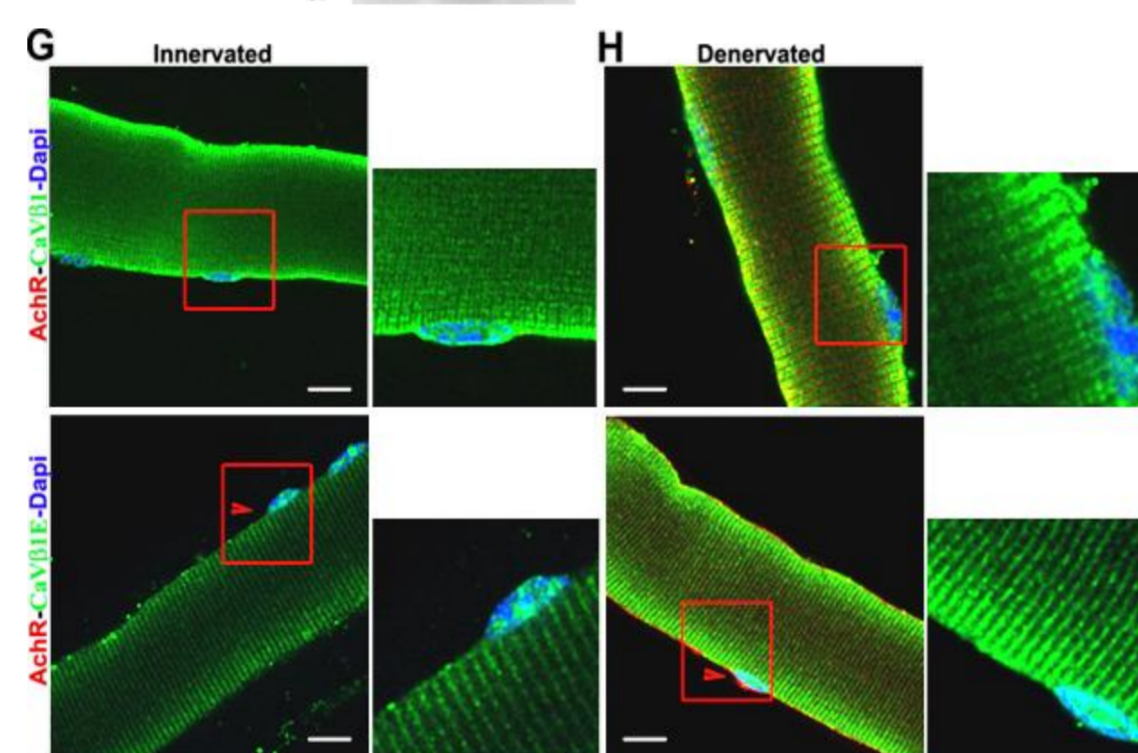
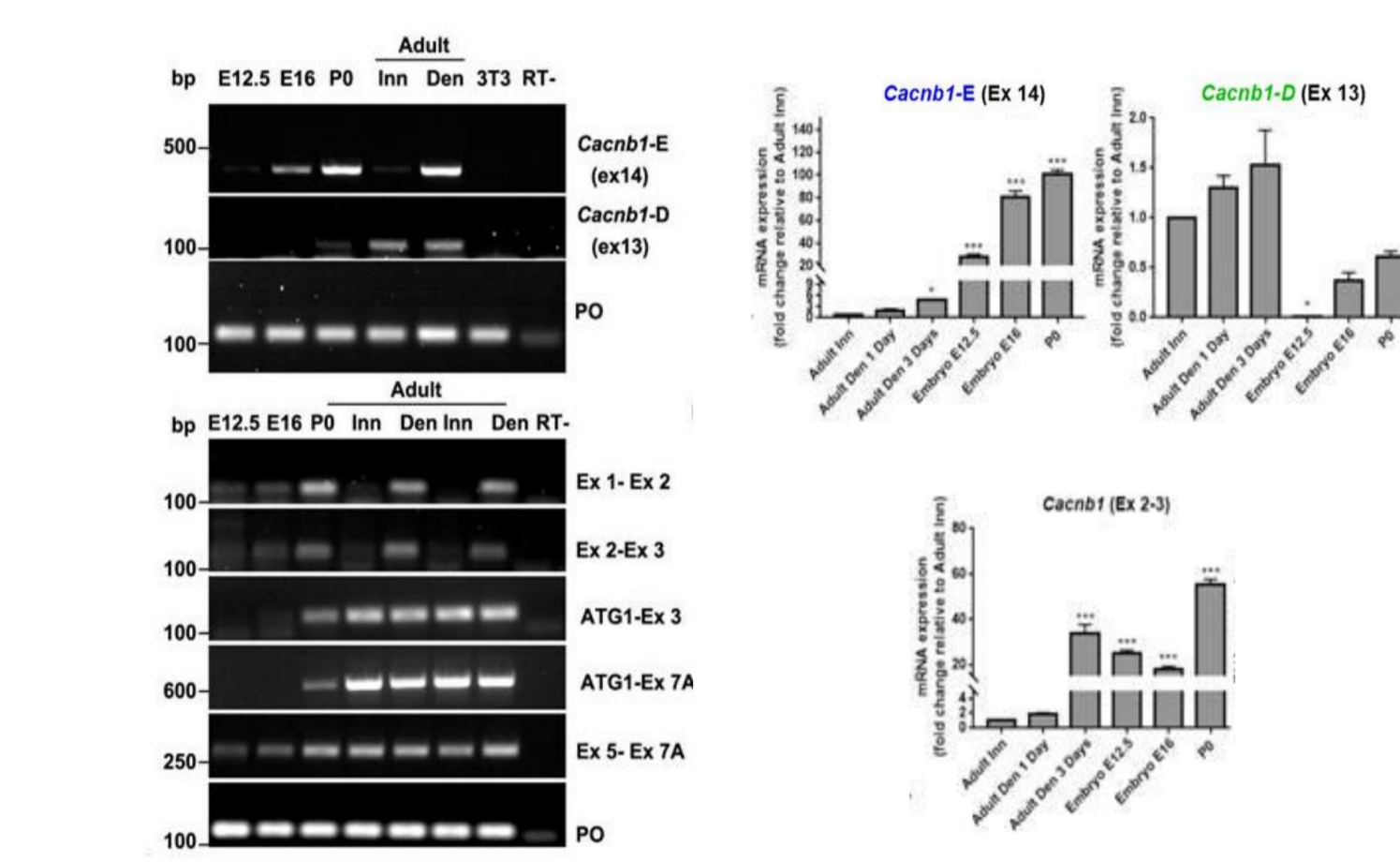


- Two different promoters Cacnb1 gene → innervation state of muscle
- Innervation → Activation of the ATG1 → Caβ1D and NOT Caβ1A
- Denervation → Activation of the ATG2 → Caβ1D + Caβ1E

A new Caβ1 isoform: embryonic?

Characterization of Caβ1E in adult skeletal muscle

Caβ1 isoforms localization in adult skeletal muscle



- Caβ1E → embryonic Caβ1 variant → transcription at ATG1 exclusively
- Intracellular localization of Caβ1E looks different from Caβ1D in adult
- Caβ1E → Nuclear enrichment

Caβ1E → embryonic Caβ1 variant expressed by activation of the promoter upstream ex1

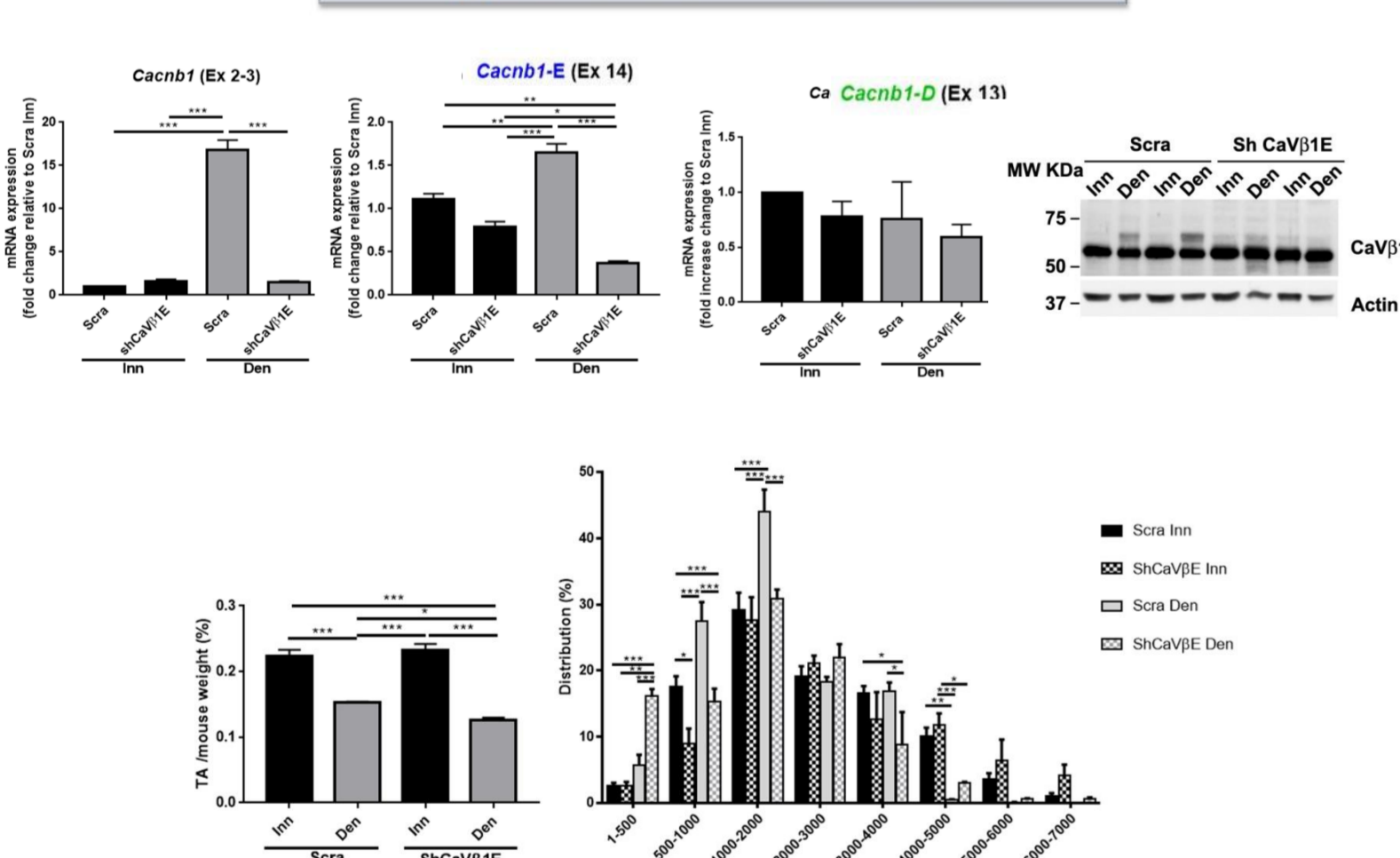
Caβ1E and Caβ1D have different localization in adult skeletal muscle

Function of Caβ1E in adult and aging skeletal muscle

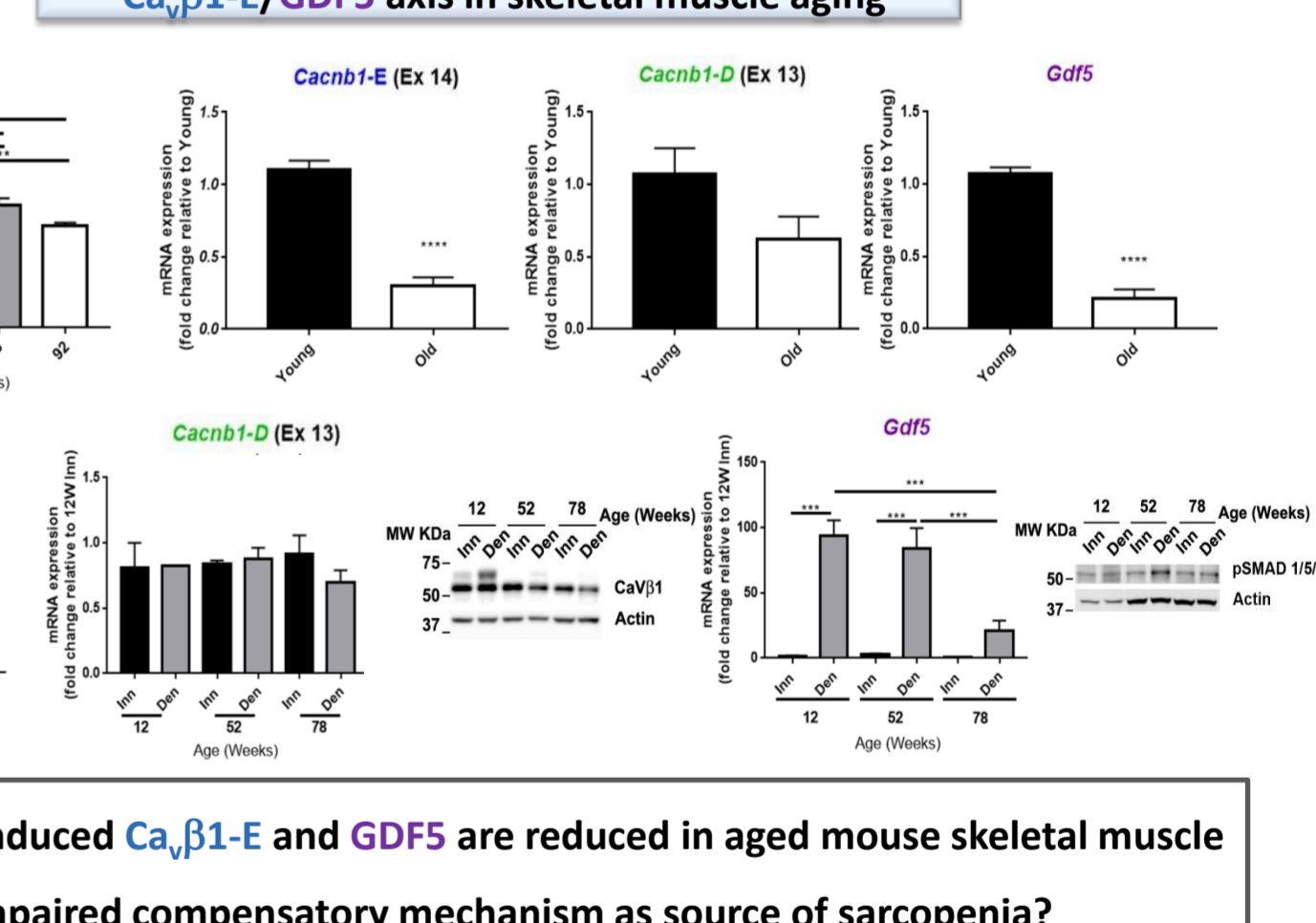
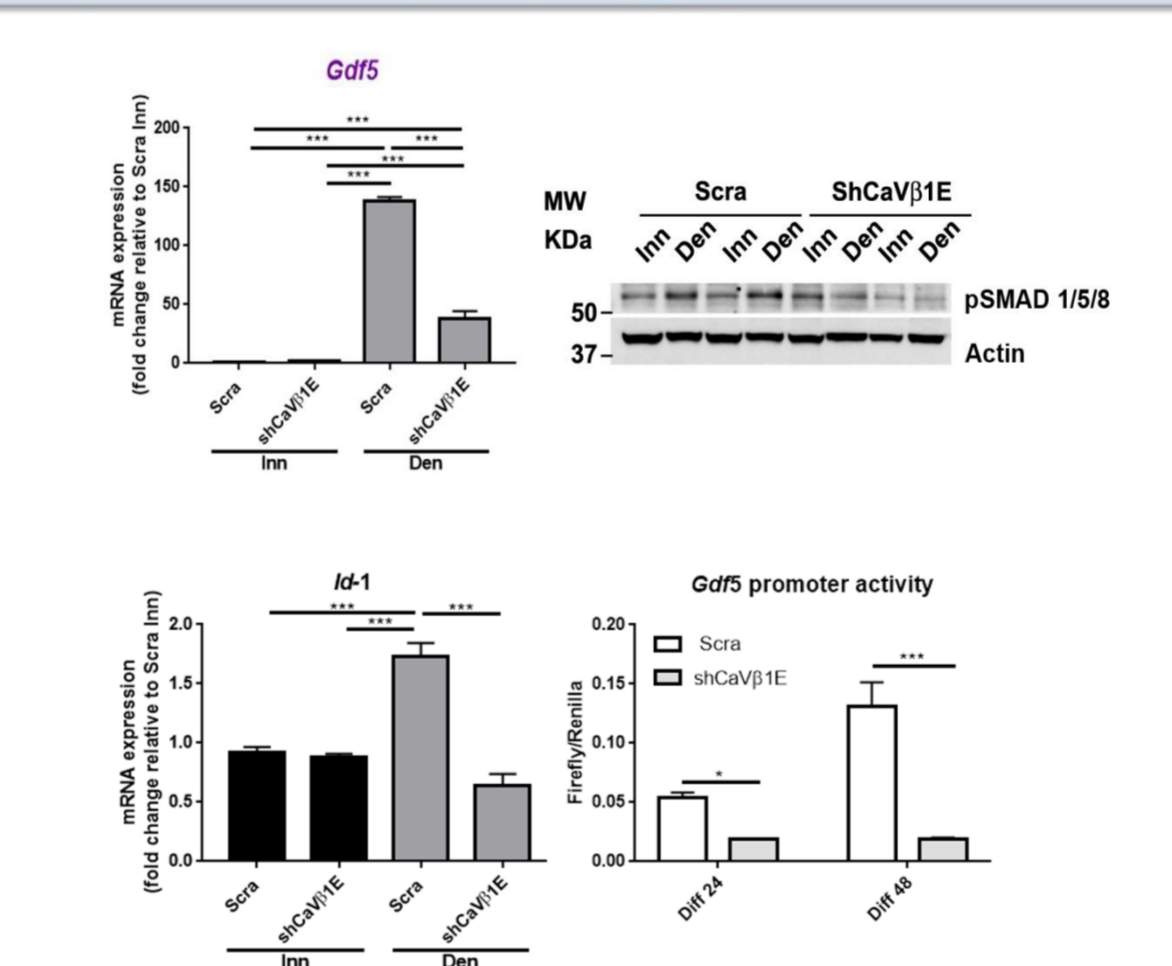
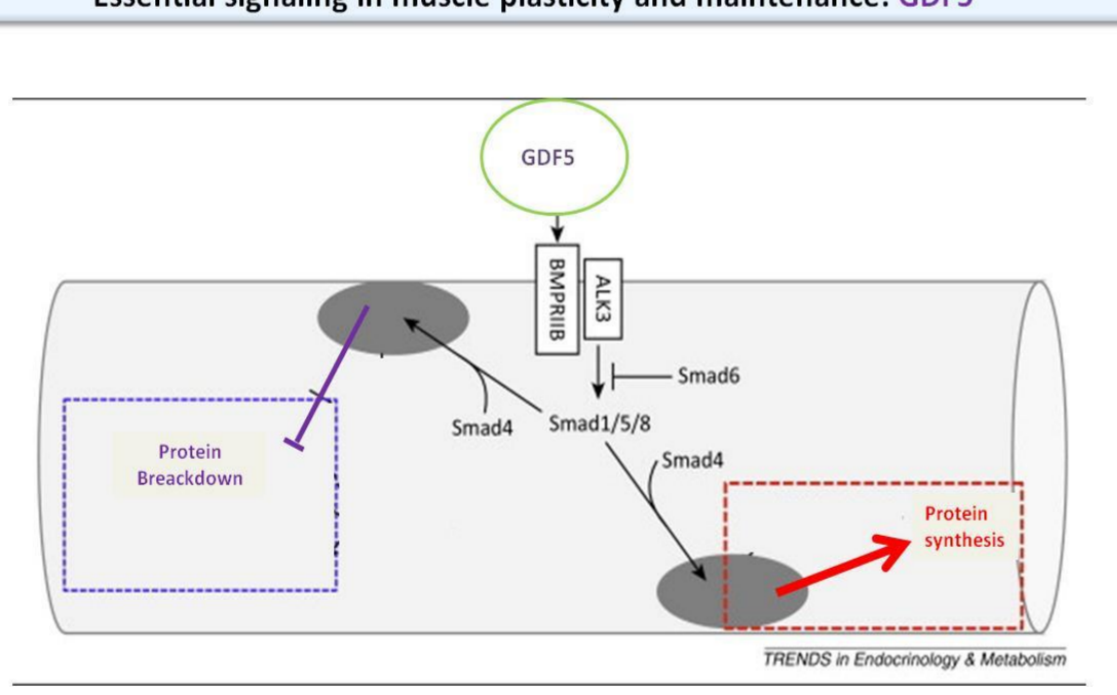
Caβ1-E and muscle mass homeostasis

Gdf5 expression and signaling in Caβ1-E Knock-Down (KD) muscle

Caβ1-E/GDF5 axis in skeletal muscle aging



Essential signaling in muscle plasticity and maintenance: GDF5



Caβ1-E ablation increases atrophy after denervation: loss of compensatory response?

Caβ1E induction after denervation is needed for Gdf5 transcription and compensatory response activation

- Basal and induced Caβ1-E and GDF5 are reduced in aged mouse skeletal muscle
- Impaired compensatory mechanism as source of sarcopenia?
- Effect of Caβ1-E over-expression during aging?

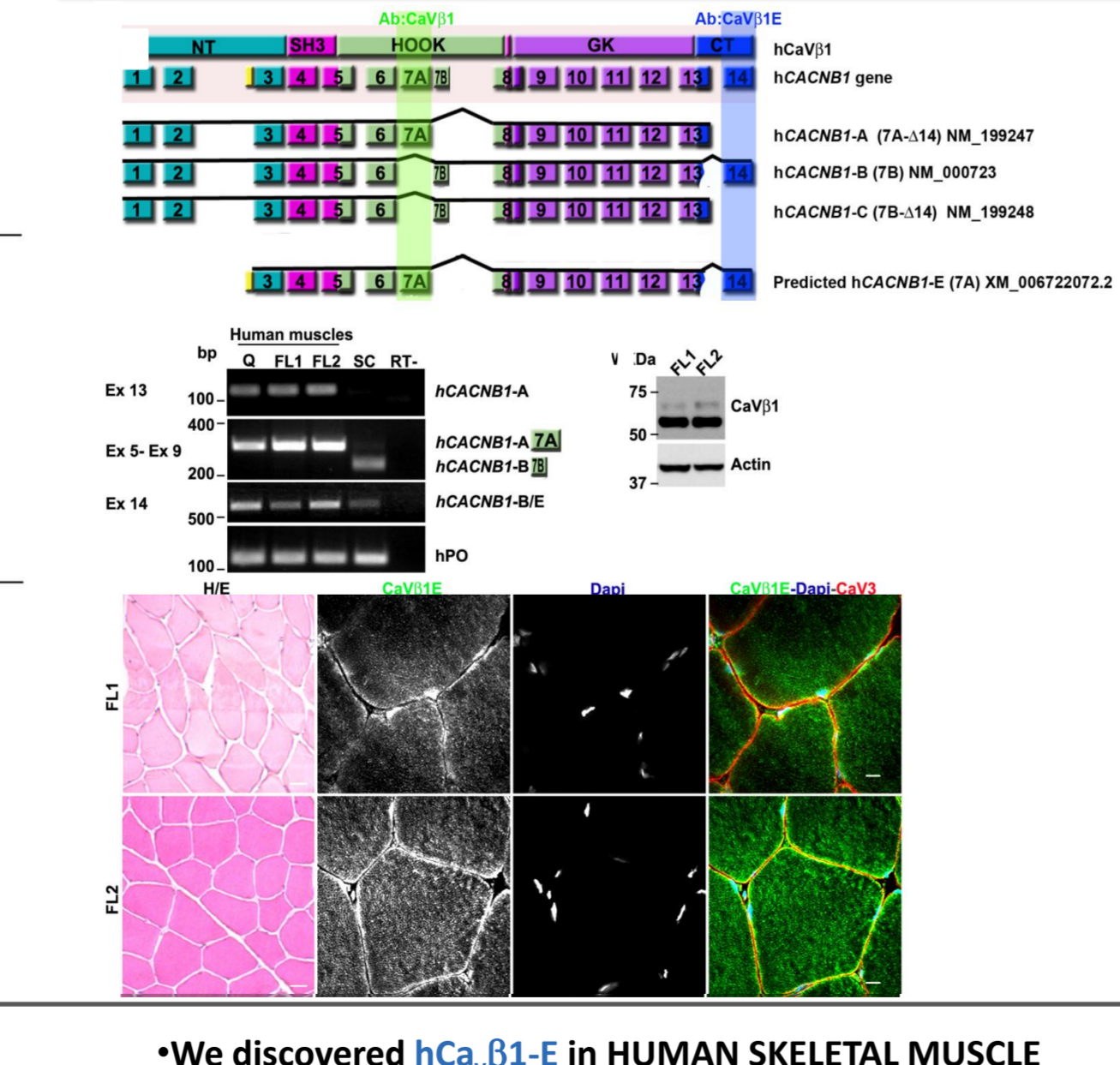
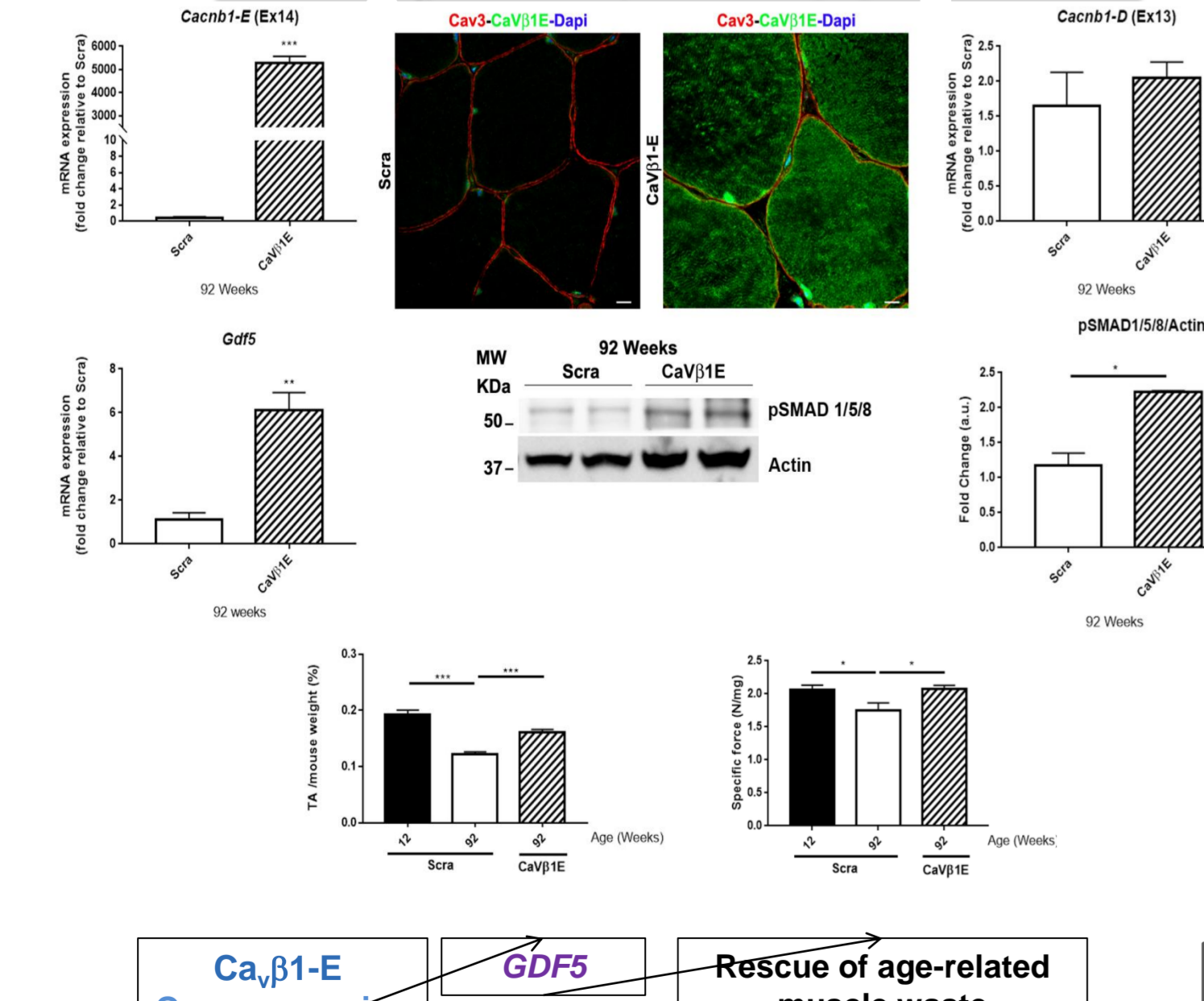
Caβ1-E/GDF5 axis: a conserved compensatory mechanism in mammals

Caβ1-E Over-Expression in aging muscle

Caβ1-E IN HUMANS?

hCaβ1-E expression is negatively associated to aging and muscle decline in HUMANS

Conclusion & Perspectives:



Subject	Gender	Age (years)	CAVβ1E (hCaβ1-E) (mRNA)	CAVβ1E (hCaβ1-E) (protein)	Height (cm)	Weight (kg)	Lean mass (kg)	FFAT (kg)	FFAT (%)	Power (W/kg)	Specific strength (W/kg)	Score
Y1	M	28.4	0.90	1.70	187	89.2	8.0	48.5	54.5	2.5	2.5	***
Y2	M	28.0	1.00	1.6	182	84.9	7.7	48.3	54.2	2.7	2.7	**
Y3	F	24.5	0.91	1.63	162	78.4	6.9	51.1	55.5	2.6	2.6	+
Y4	F	26.1	1.00	1.88	173	75.6	6.4	39.4	45.8	2.4	2.4	+
Y5	M	28.7	1.00	0.99	1.85	71.9	54.6	8.7	48.5	3.1	3.1	+
Y6	M	27.1	0.95	0.96	1.83	75.8	75.9	8.2	42.4	3.3	3.3	+
Y7	M	32.0	1.25	1.89	160	40	ND	ND	ND	ND	ND	ND
Y8	M	48.0	1.13	1.5	ND	ND	ND	ND	ND	ND	ND	ND
Y9	M	48.0	1.13	1.5	ND	ND	ND	ND	ND	ND	ND	ND
Y10	M	48.0	1.13	1.5	ND	ND	ND	ND	ND	ND	ND	ND
Y11	M	48.0	1.13	1.5	ND	ND	ND	ND	ND	ND	ND	ND
Y12	M	48.0	1.13	1.5	ND	ND	ND	ND	ND	ND	ND	ND
Y13	M	48.0	1.13	1.5	ND	ND	ND	ND	ND	ND	ND	ND
Y14	M	48.0	1.13	1.5	ND	ND	ND	ND	ND	ND	ND	ND
Y15	M	48.0	1.13	1.5	ND	ND	ND	ND	ND	ND	ND	ND
Y16	M	48.0	1.13	1.5	ND	ND	ND	ND	ND	ND	ND	ND
Y17	M	48.0	1.13	1.5	ND	ND	ND	ND	ND	ND	ND	ND
Y18	M	48.0	1.13	1.5	ND	ND	ND	ND	ND	ND	ND	ND
Y19	M	48.0	1.13	1.5	ND	ND	ND	ND	ND	ND	ND	ND
Y20	M	48.0	1.13	1.5	ND	ND	ND	ND	ND	ND	ND	ND

- 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 Caβ1 increase
- Caβ1/GDF5 in reinnervation and disease models (ALS, SMA, DMD...)
- Caβ1/GDF5 in myogenesis / embryogenesis

