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

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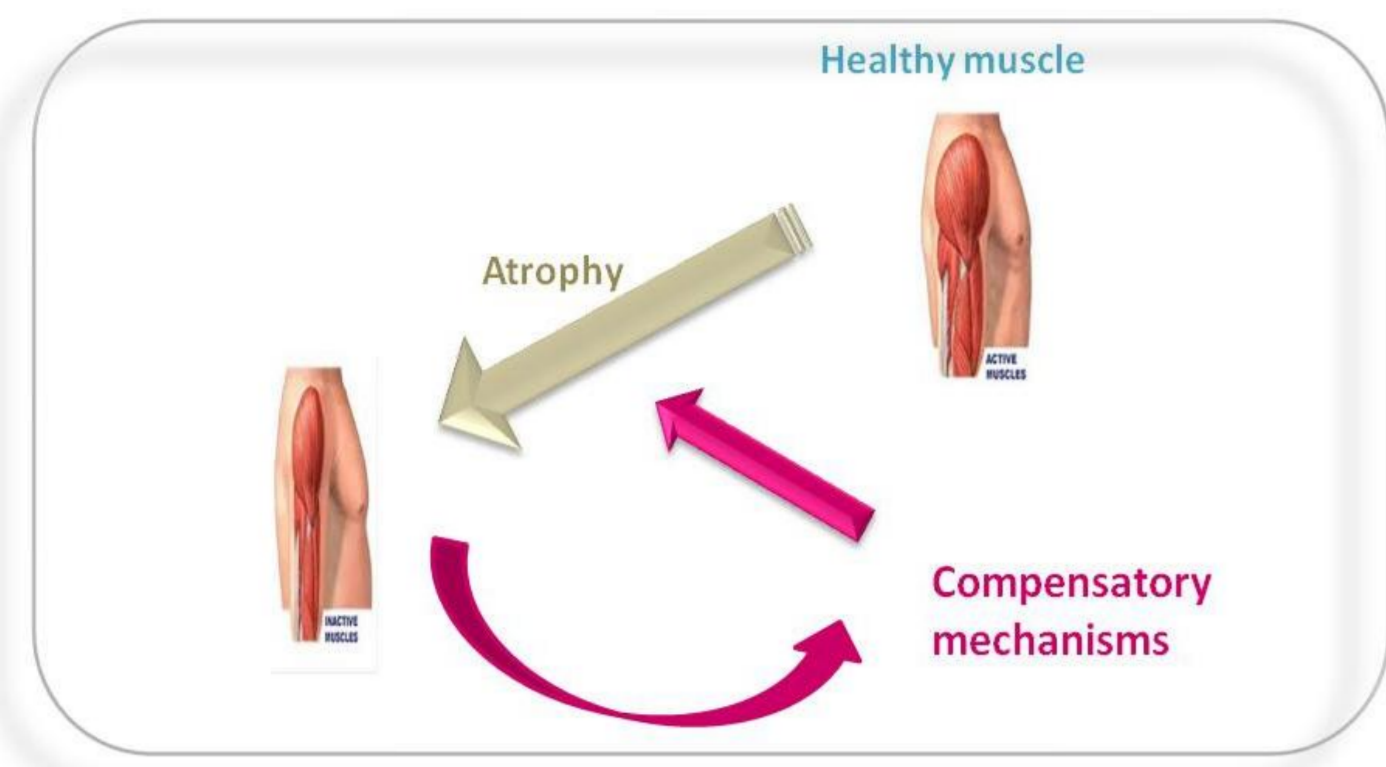
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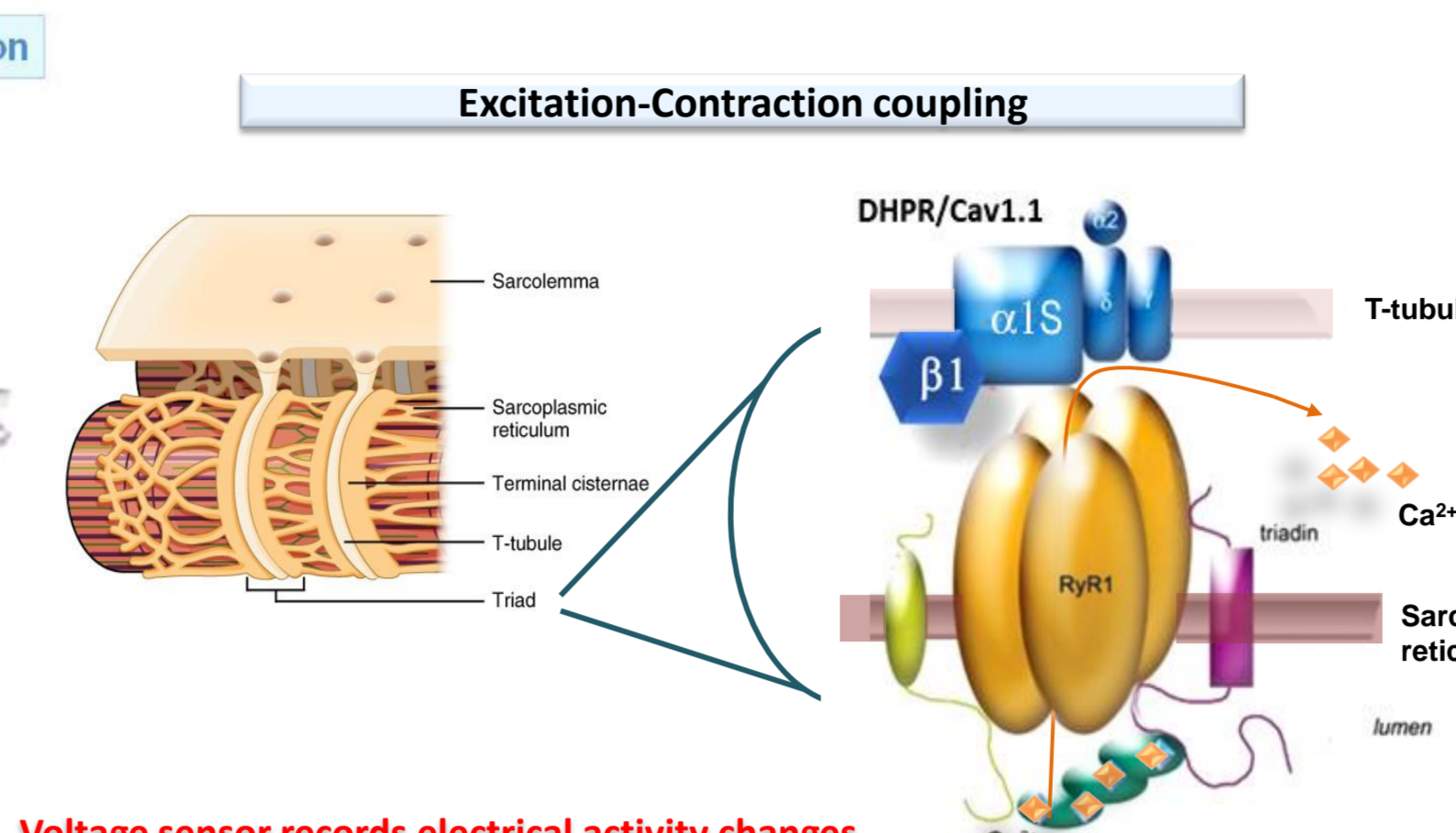
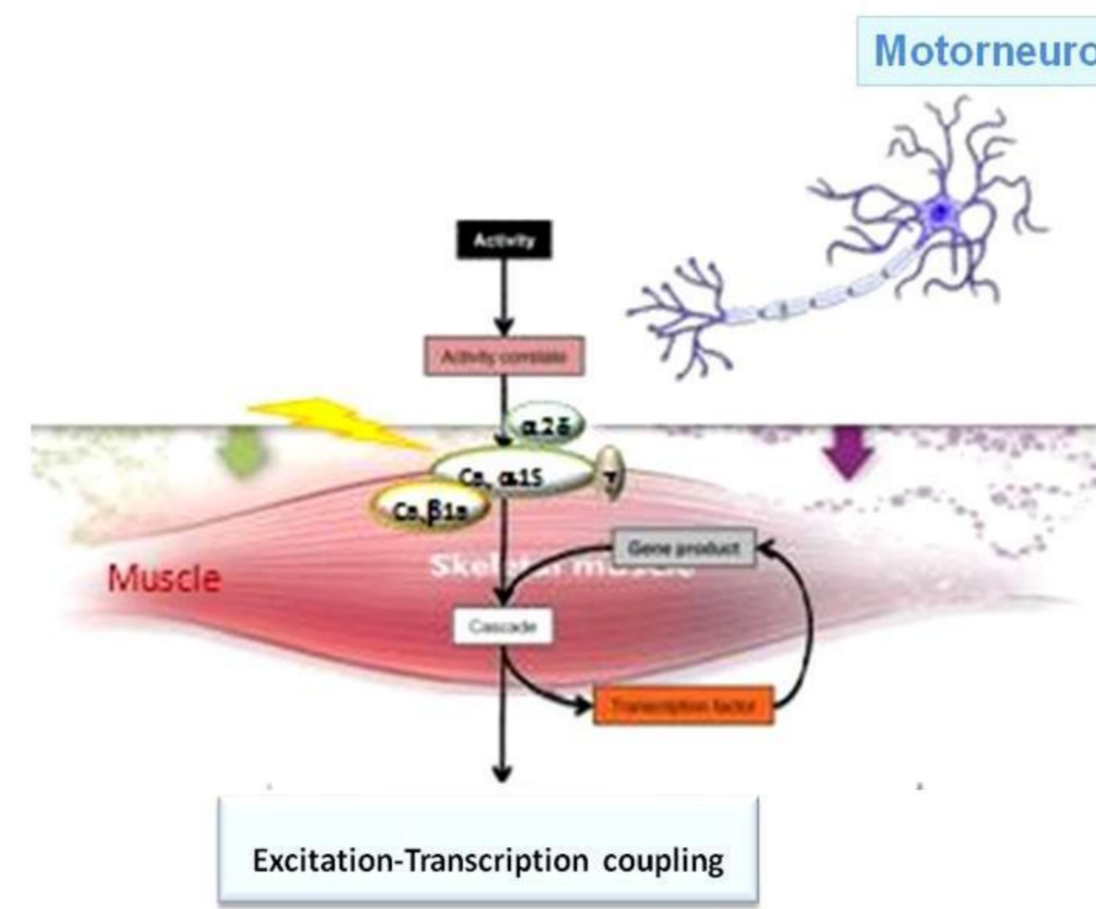
INTRODUCTION

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)

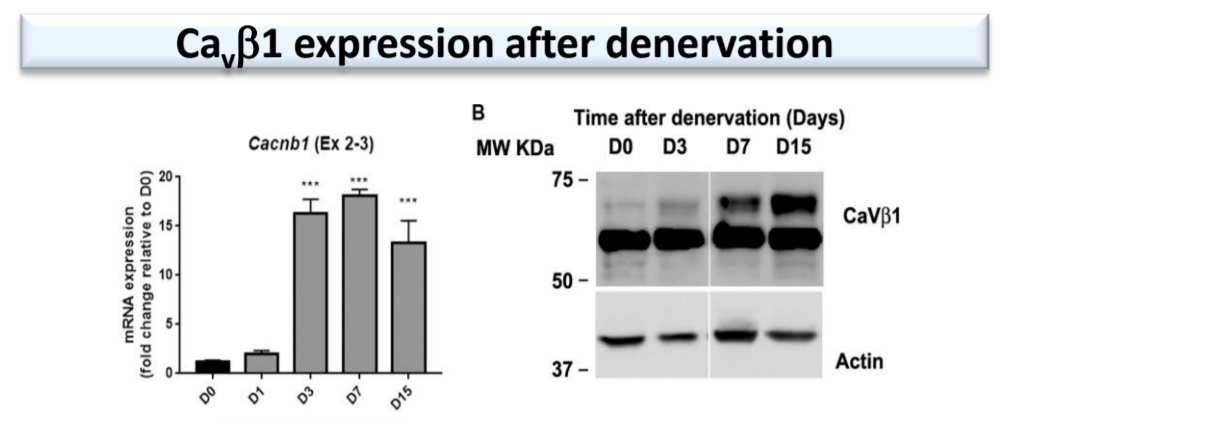
- Transcription factor function in MPCs
- Required for neuromuscular synaptic patterning in embryo (before innervation)

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

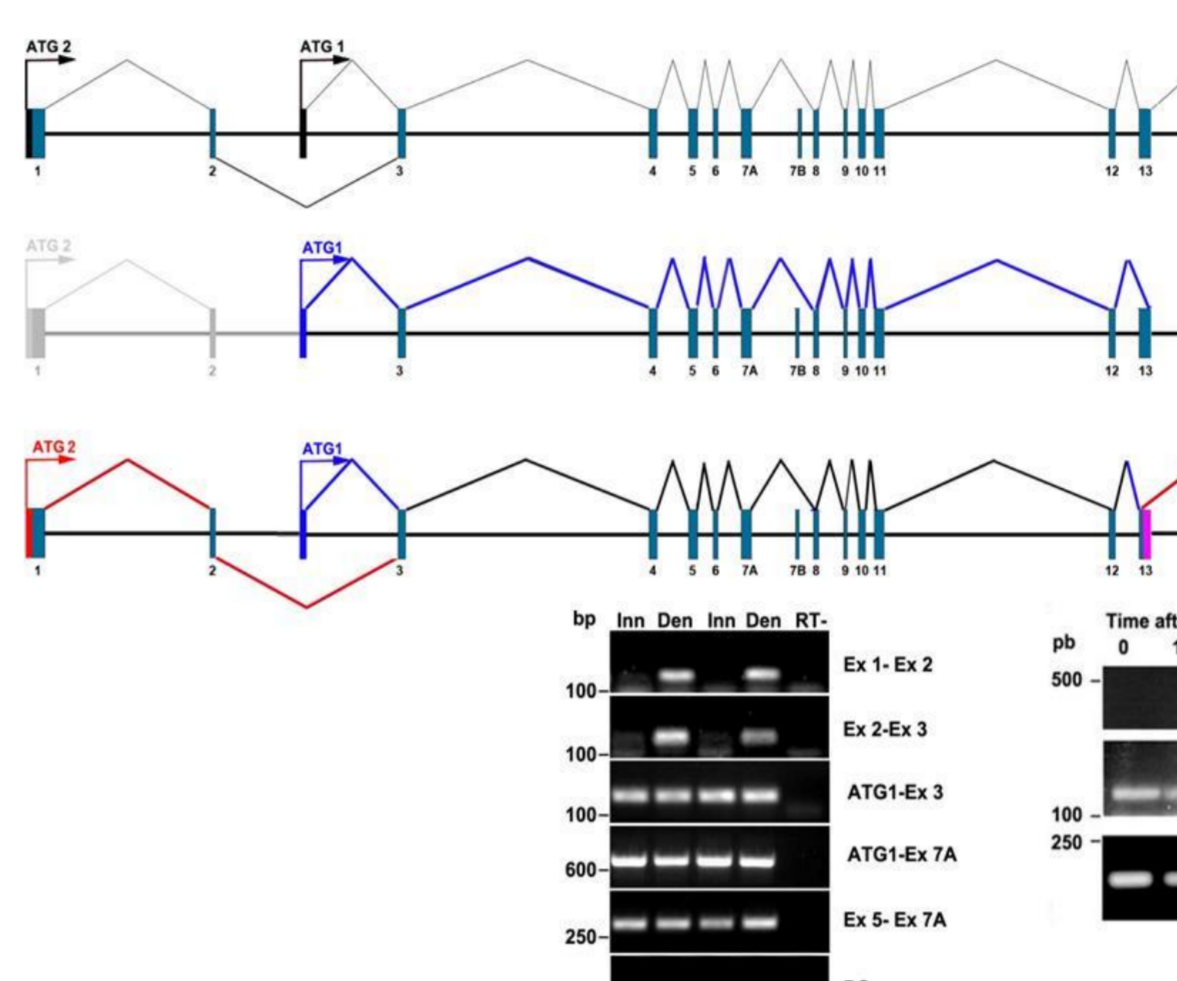
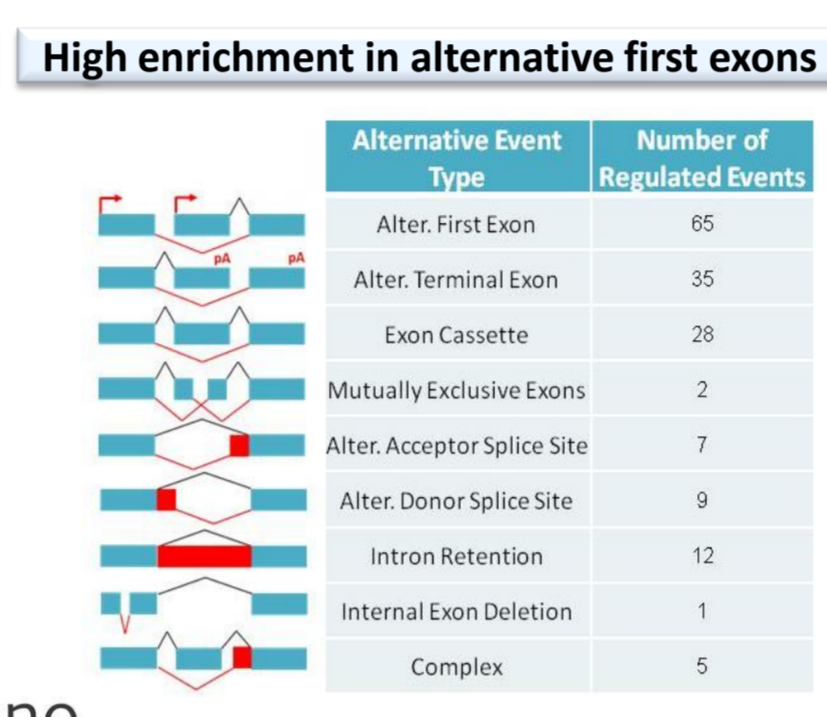
Exon level analysis: Distribution of alternative events

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



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.



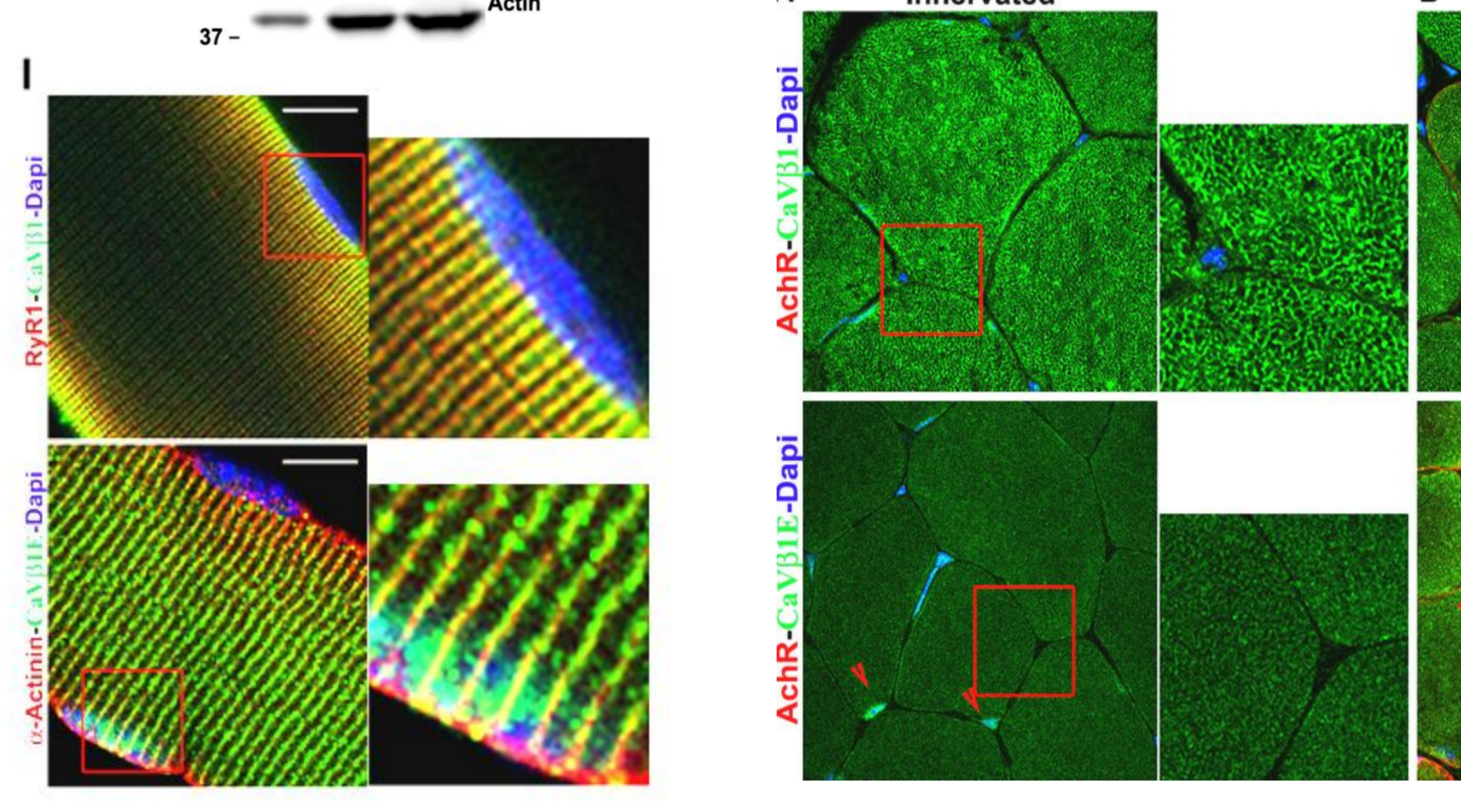
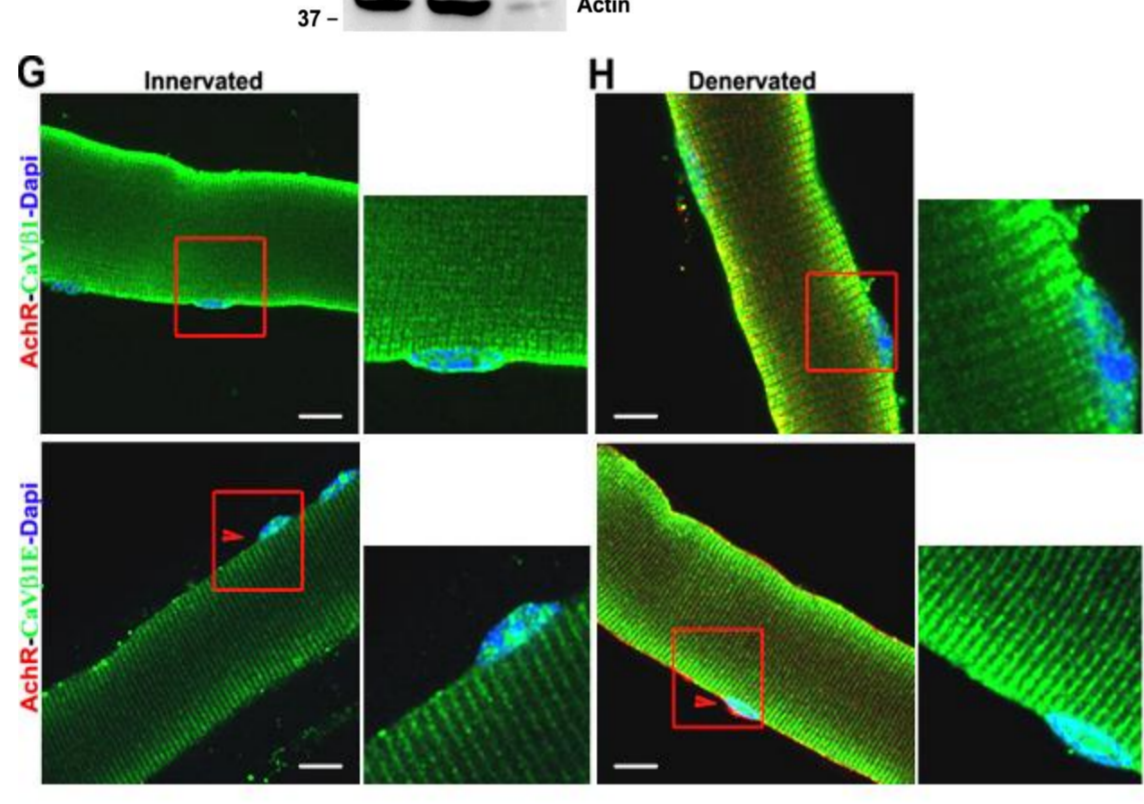
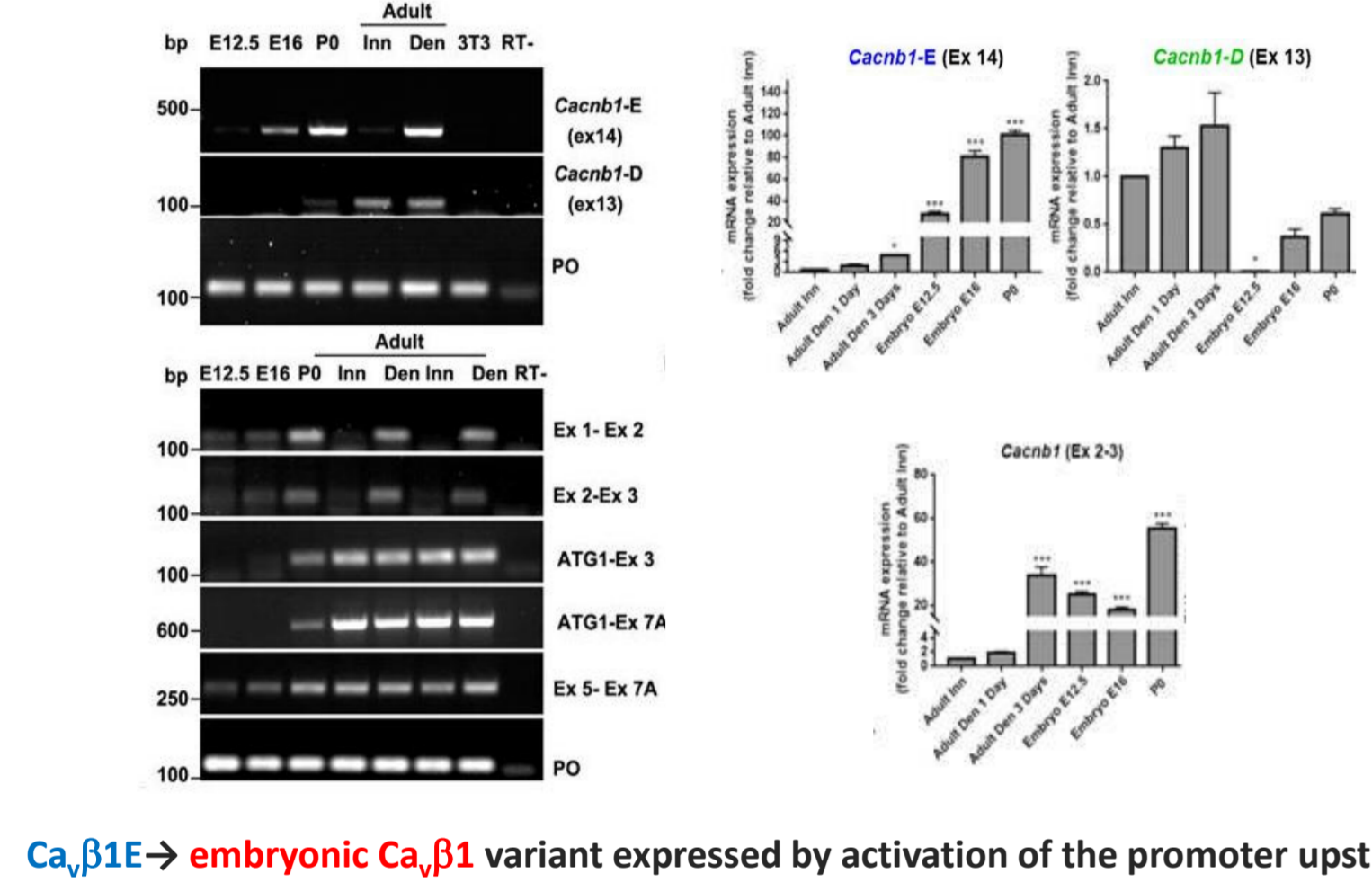
Two different promoters *Cacnb1* gene → innervation state of muscle

- **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?

Characterization of Ca_vβ1E in adult skeletal muscle

Ca_vβ1 isoforms 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

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

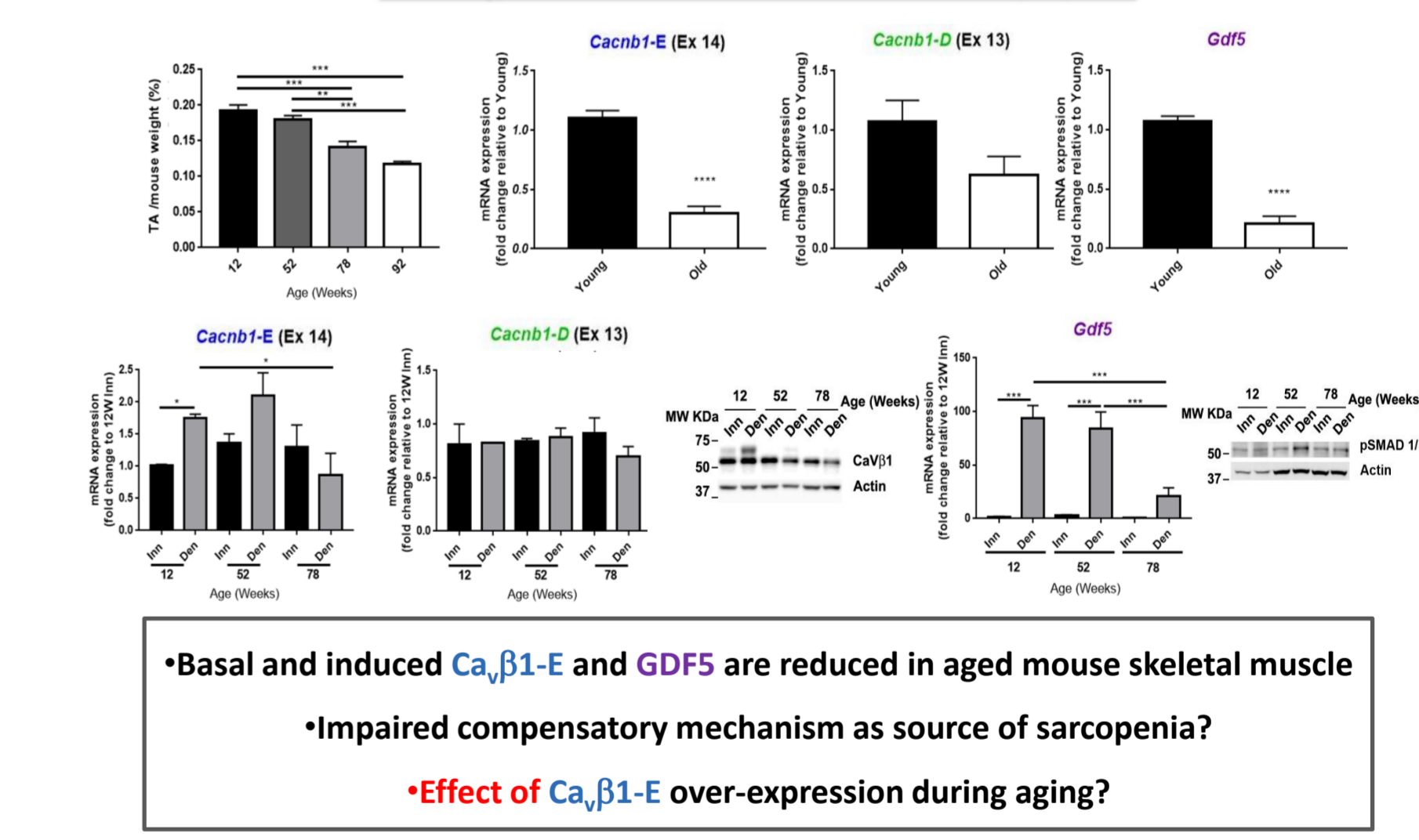
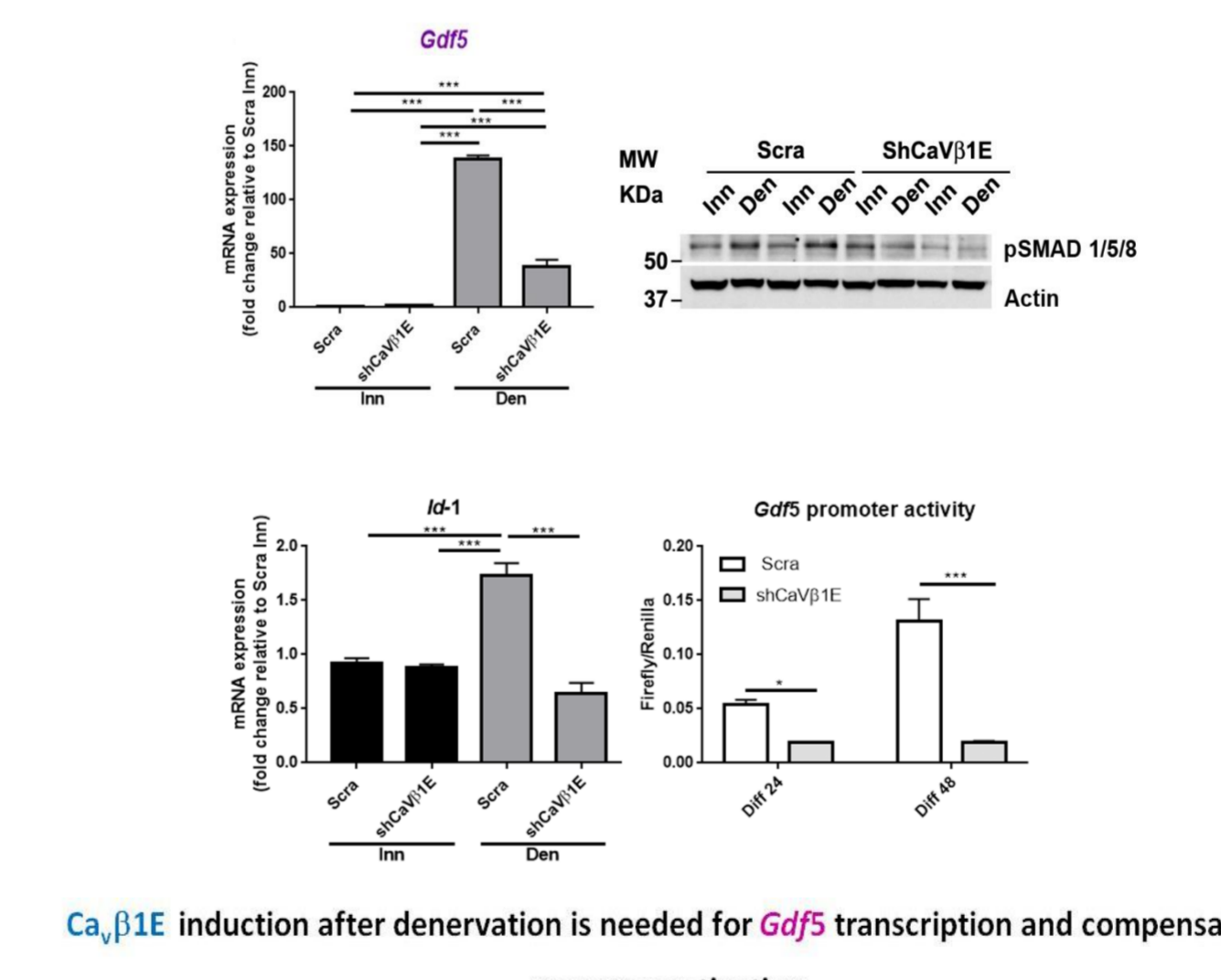
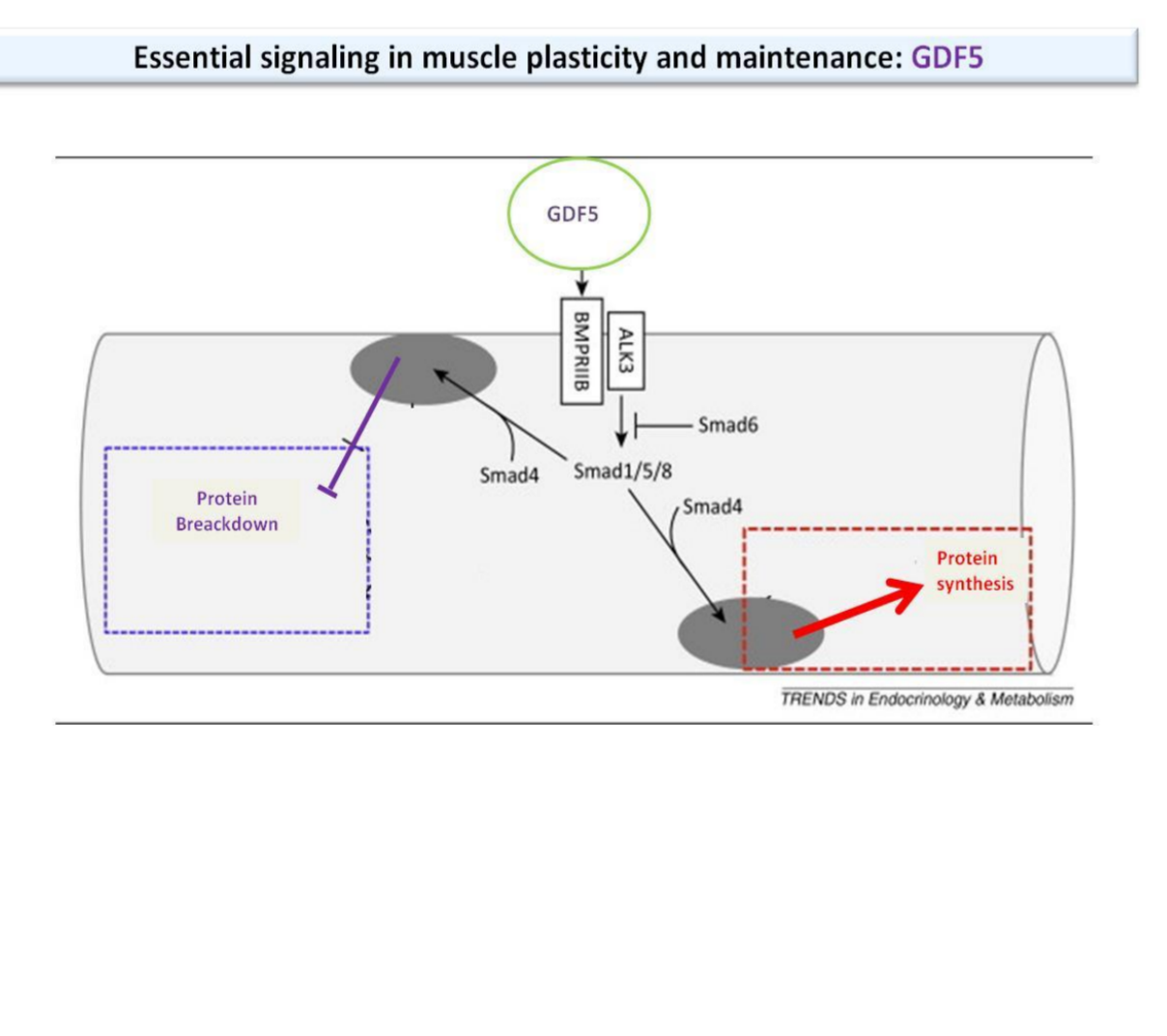
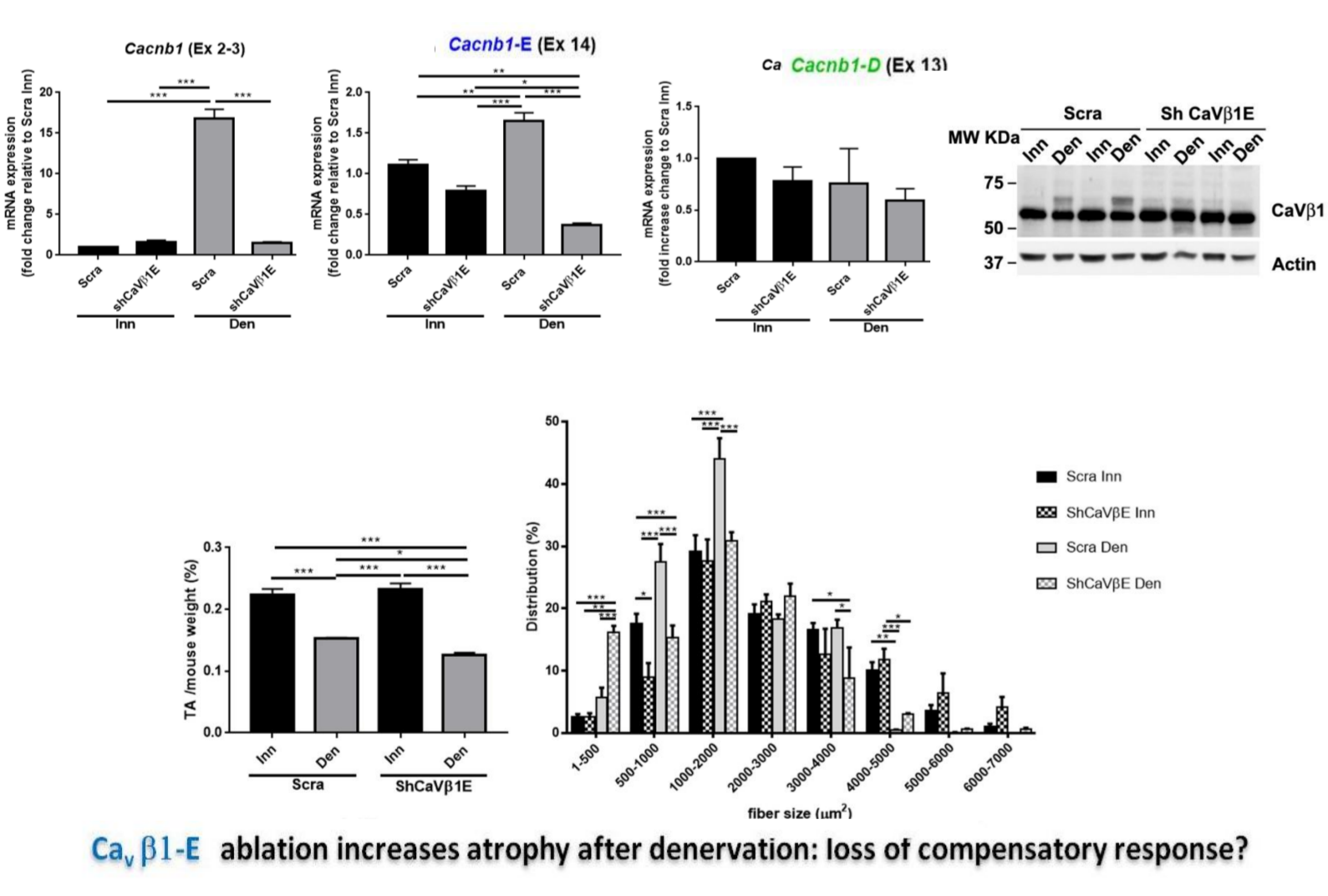
Ca_vβ1E and Ca_vβ1D have different localization in adult skeletal muscle

Function of Ca_vβ1E in adult and aging skeletal muscle

Ca_vβ1-E and muscle mass homeostasis

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

Ca_vβ1-E/GDF5 axis in skeletal muscle aging



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

Ca_vβ1E induction after denervation is needed for GDF5 transcription and compensatory response activation

- 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?

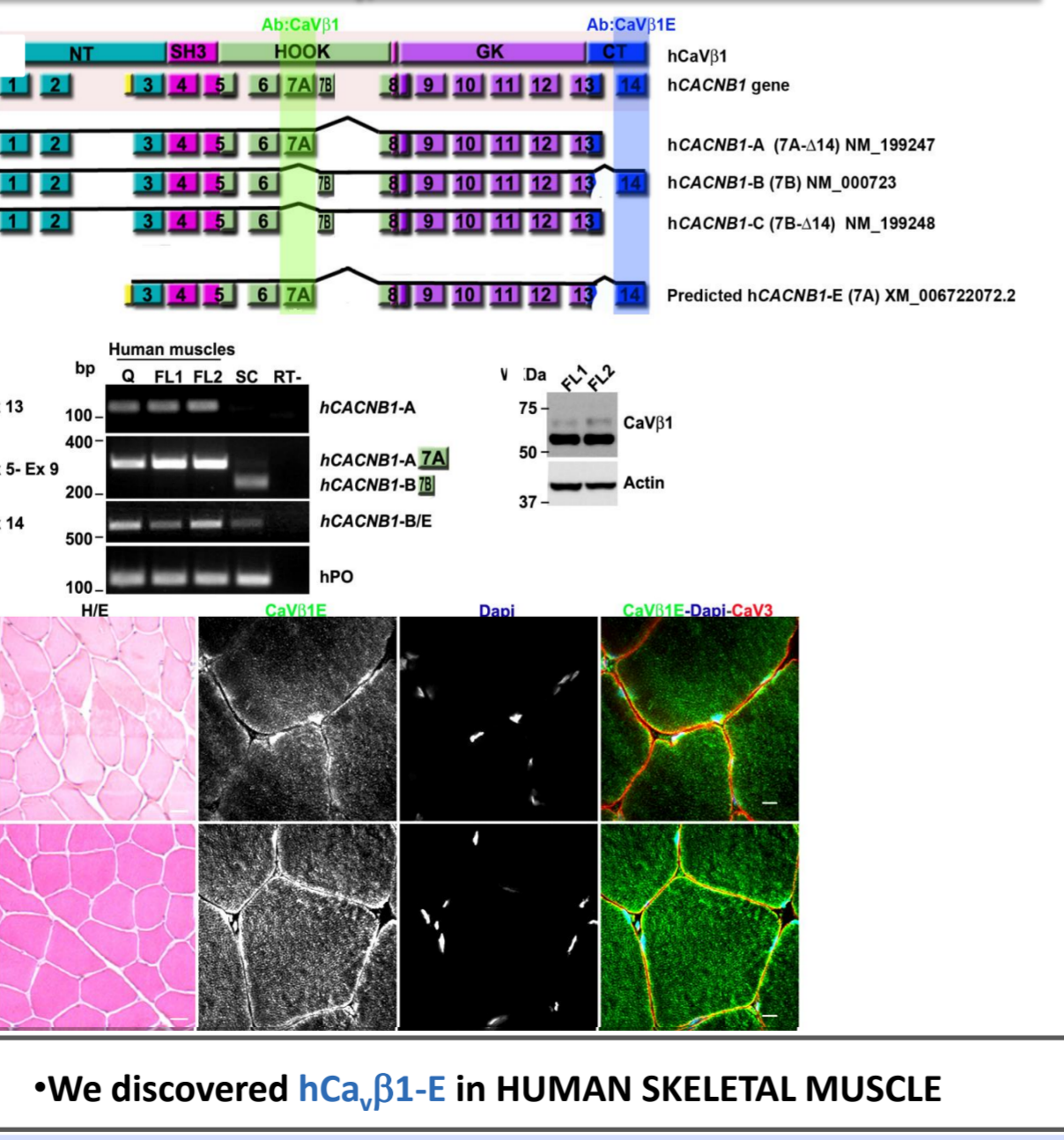
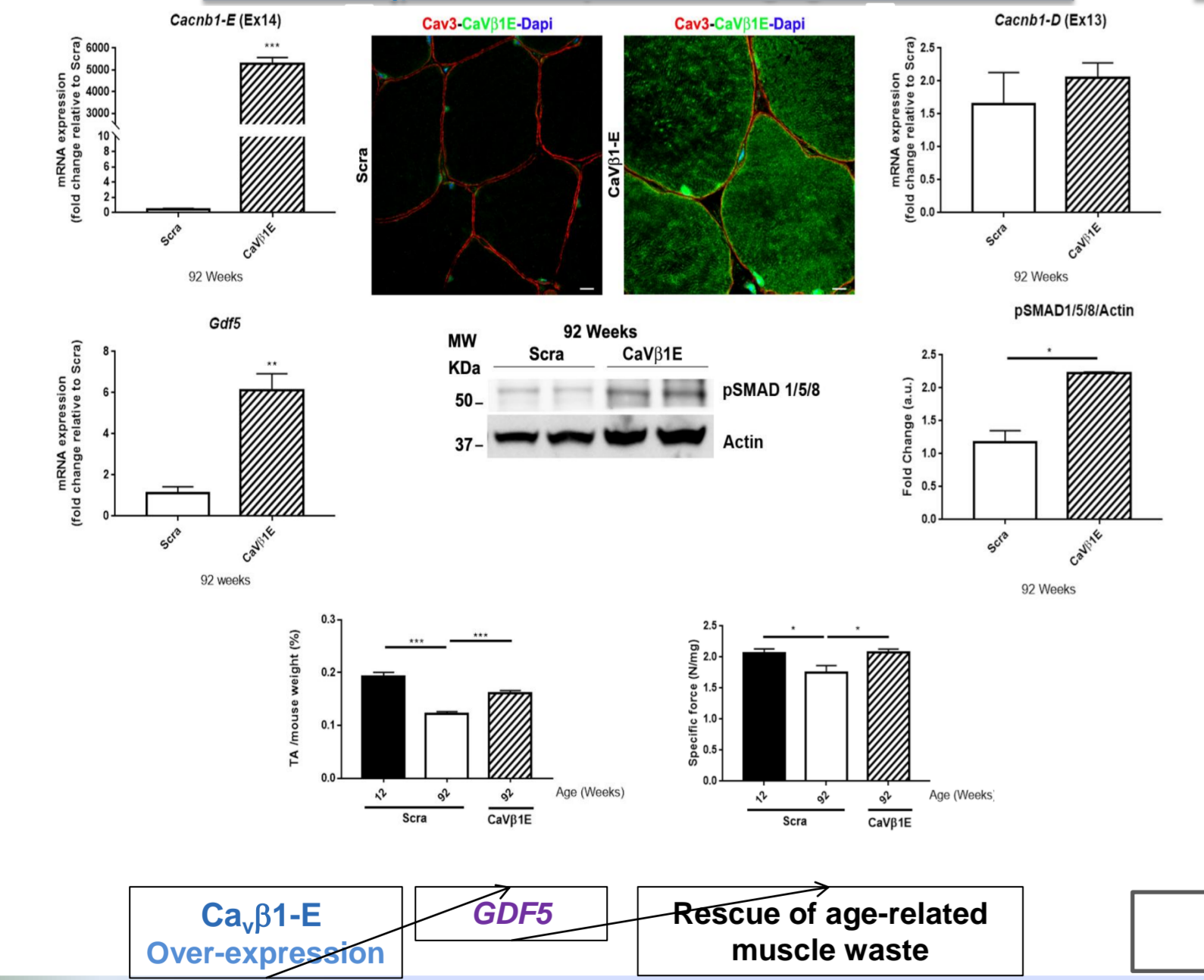
Ca_vβ1-E/GDF5 axis: a conserved compensatory mechanism in mammals

Ca_vβ1-E Over-Expression in aging muscle

Ca_vβ1-E IN HUMANS?

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

Conclusion & Perspectives:



Subject	Gender	Age (years)	CAVβ1E (hCaVβ1E)	CAVβ1E (hCaVβ1E)	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	170	88.7	89.2	8.9	4.9	48.5	2.5	***
Y2	M	28.9	1.05	1	182	94.4	92.3	10.1	5.1	51.1	2.6	***
Y3	F	24.5	0.91	0.94	163	65.2	79.4	6.8	4.1	39.4	2.4	***
Y4	F	26.1	1.02	1.08	163	75.1	79.6	6.4	3.8	42.1	2.3	***
Y5	M	28.7	1.05	0.99	185	71.9	94.6	8.7	4.5	31.2	2.7	***
Y6	M	27.1	0.95	0.96	183	73.8	79.9	6.2	4.2	31.3	2.5	***
Y7	M	32.2	1.25	1.89	180	90	90	ND	ND	ND	ND	ND
Y8	M	48.5	1.13	1.52	180	90	90	ND	ND	ND	ND	ND
Y9	M	48.5	1.13	1.52	180	90	90	ND	ND	ND	ND	ND
Y10	M	48.5	1.13	1.52	180	90	90	ND	ND	ND	ND	ND
Y11	M	48.5	1.13	1.52	180	90	90	ND	ND	ND	ND	ND
Y12	M	48.5	1.13	1.52	180	90	90	ND	ND	ND	ND	ND
Y13	M	48.5	1.13	1.52	180	90	90	ND	ND	ND	ND	ND
Y14	M	48.5	1.13	1.52	180	90	90	ND	ND	ND	ND	ND
Y15	M	48.5	1.13	1.52	180	90	90	ND	ND	ND	ND	ND
Y16	M	48.5	1.13	1.52	180	90	90	ND	ND	ND	ND	ND
Y17	M	48.5	1.13	1.52	180	90	90	ND	ND	ND	ND	ND
Y18	M	48.5	1.13	1.52	180	90	90	ND	ND	ND	ND	ND
Y19	M	48.5	1.13	1.52	180	90	90	ND	ND	ND	ND	ND
Y20	M	48.5	1.13	1.52	180	90	90	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 Ca_vβ1 increase
- Ca_vβ1/GDF5 in reinnervation and disease models (ALS, SMA, DMD...)
- Ca_vβ1/GDF5 in myogenesis /embryogenesis