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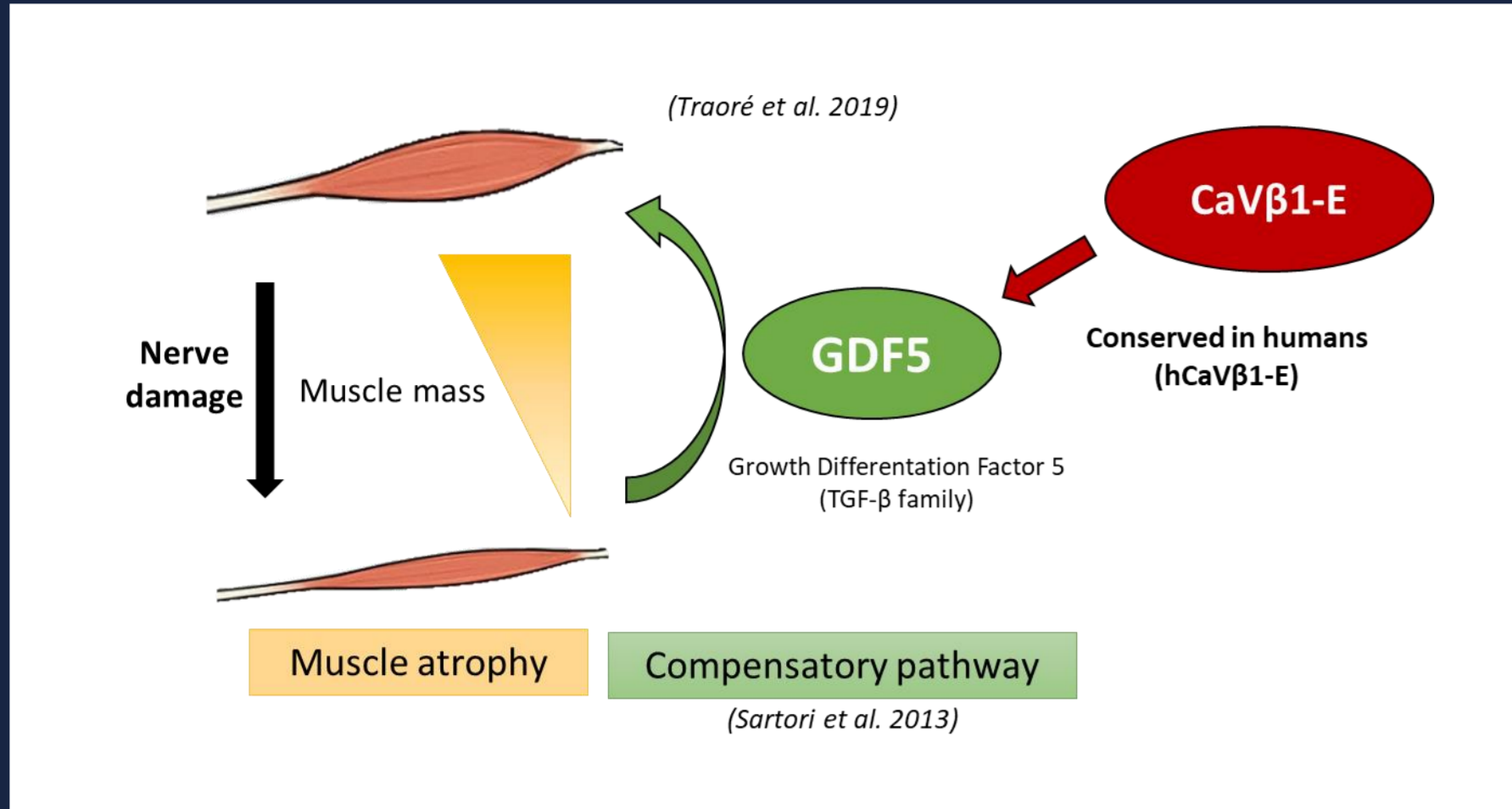
CaVβ1A and CaVβ1E embryonic isoforms in adult skeletal muscle, a Mbn1 related-expression

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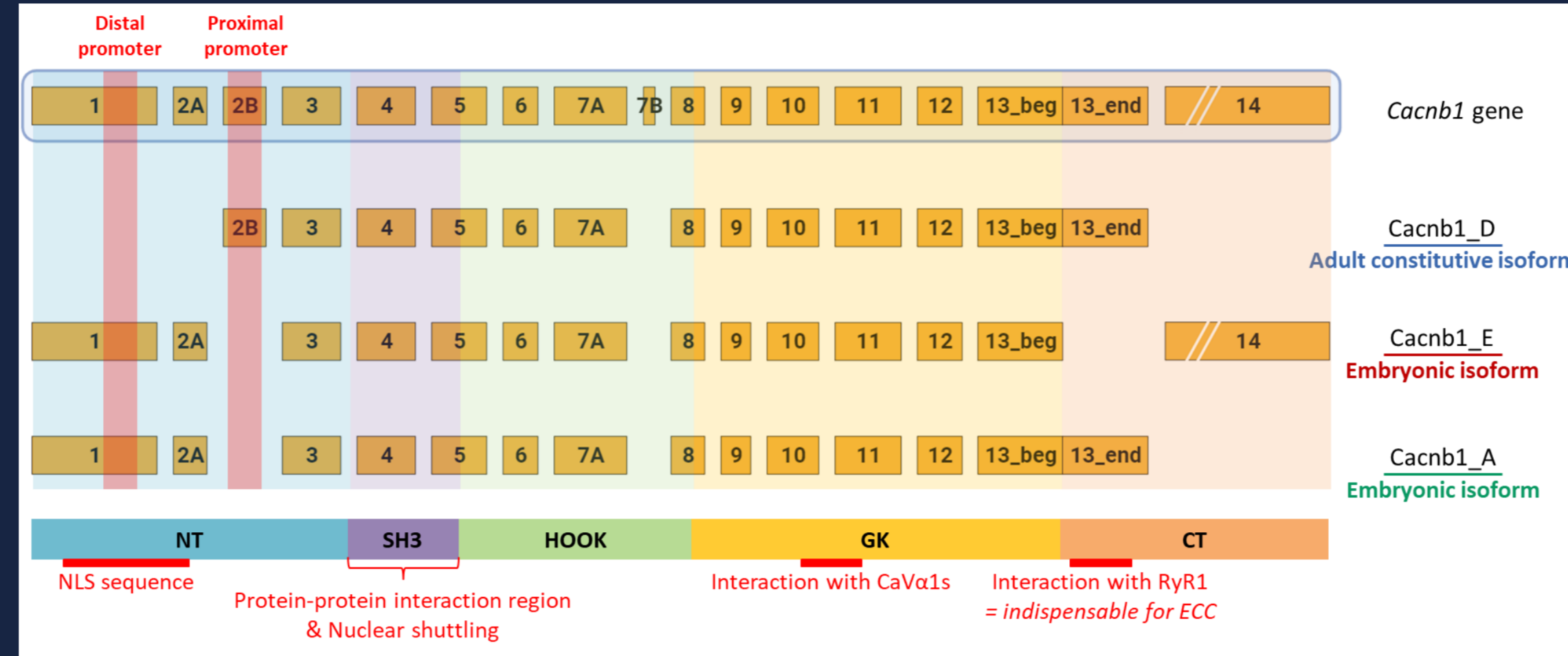
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INTRODUCTION

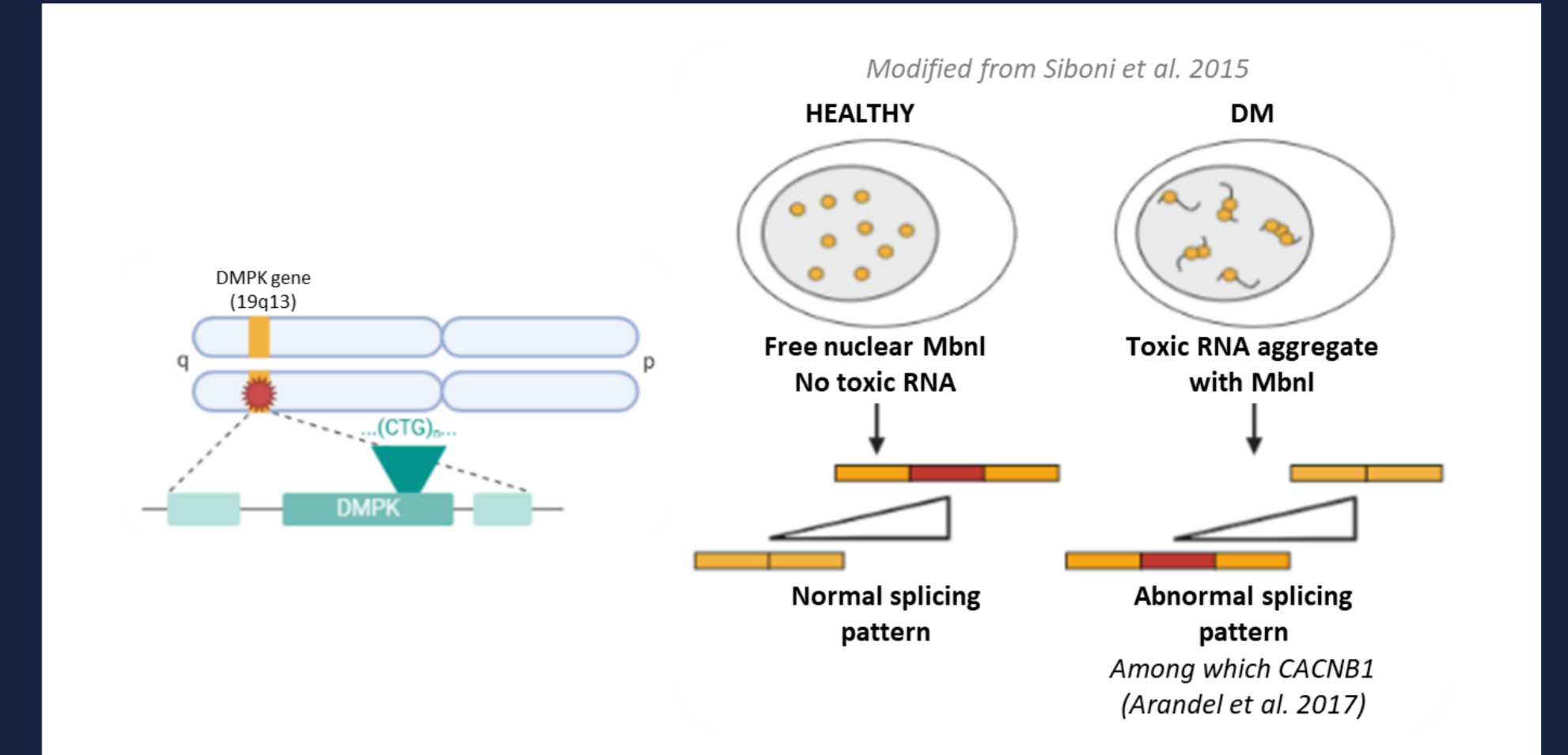
CaVβ1-E/GDF5 axis in muscle mass homeostasis



Cacnb1 isoforms in skeletal muscle



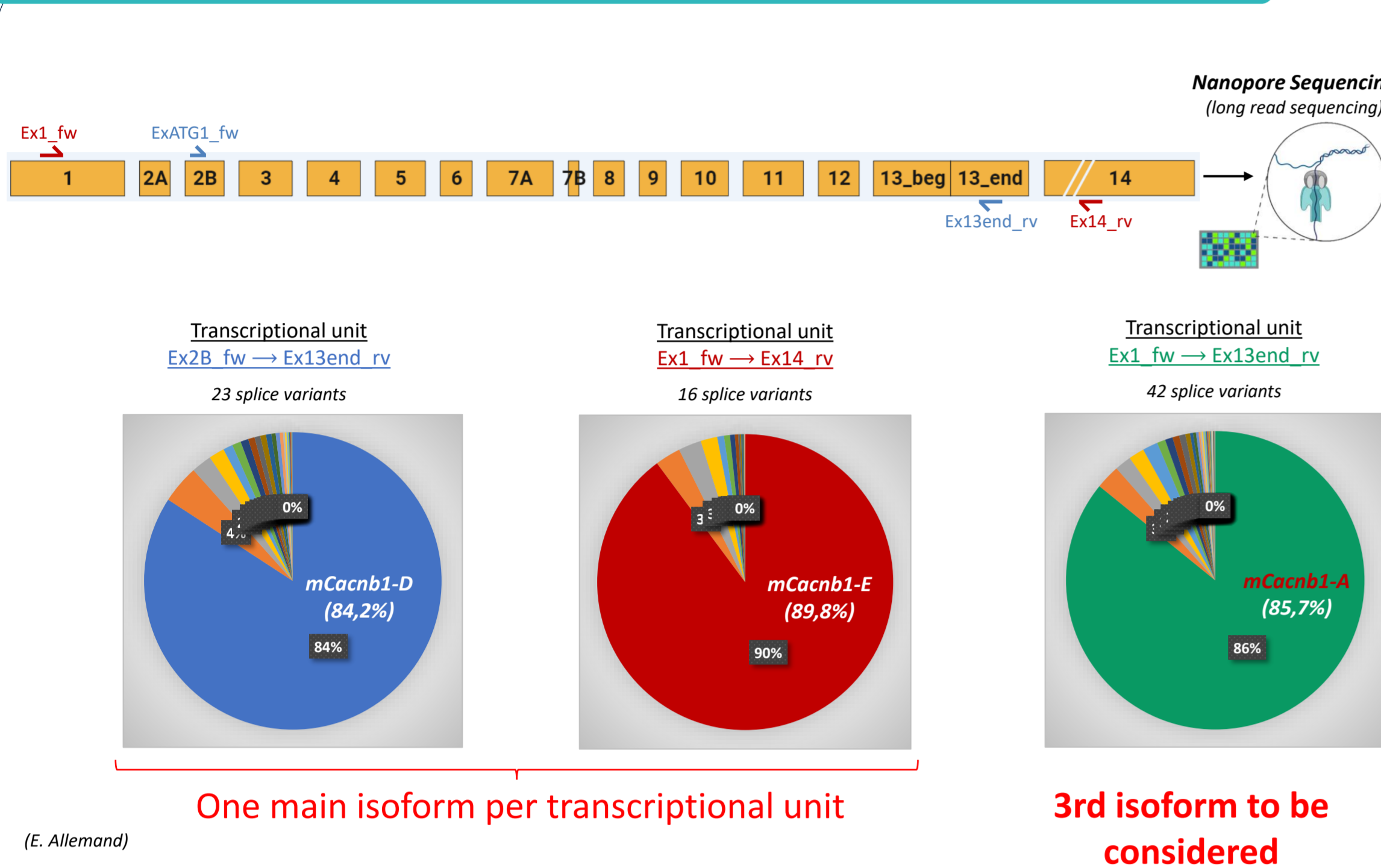
Implication of MBNLs in DM1 pathophysiology



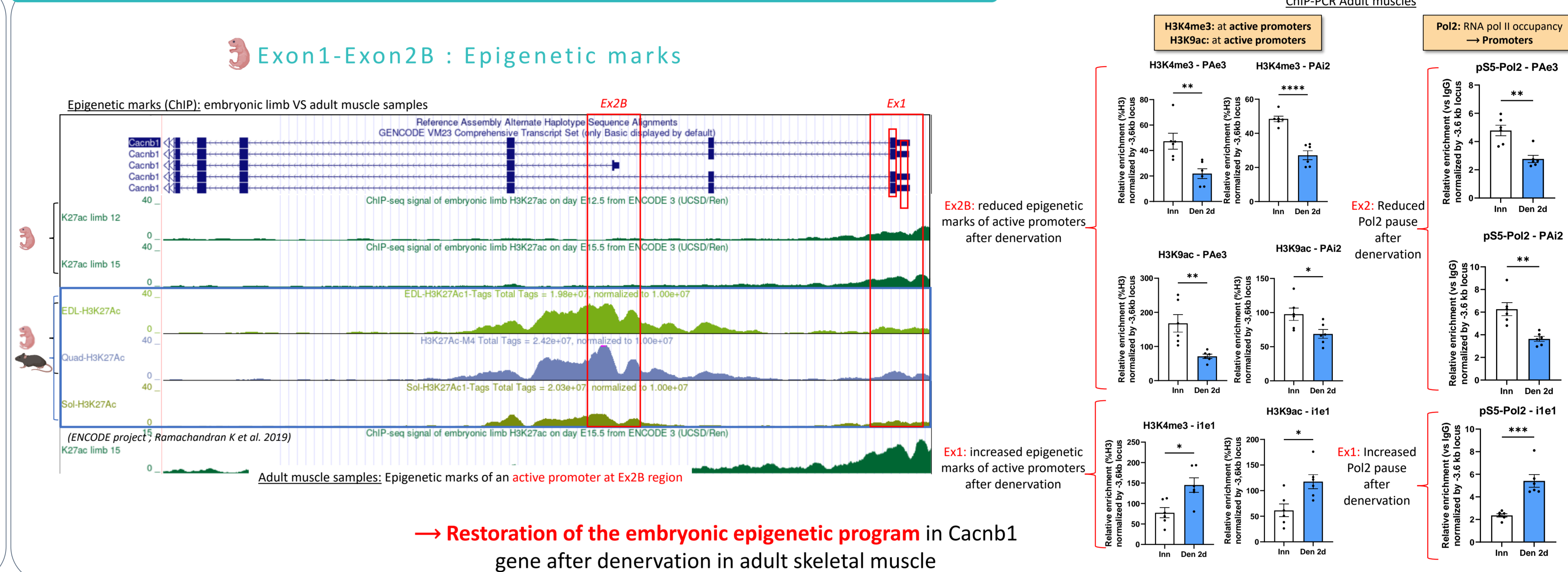
Voltage-gated calcium channels (CaVs or VGCCs) are major regulators of calcium-related cellular functions. In skeletal muscle, though the essential component of the pore channel is the CaVα1 subunit, the CaVβ1 subunit is an essential subunit guaranteeing CaV fine-tuning activity. CaVβ1, encoded by Cacnb1 gene, exists as several variants in skeletal muscle. Our recent work demonstrates CaVβ1D as the constitutive adult isoform, localized with CaVα1 at the triad. On the other hand, our previous and present works show that CaVβ1E and CaVβ1A are expressed at late embryogenesis and peri-natal stages and that these embryonic isoforms are re-expressed after sciatic nerve resection in adult skeletal muscle, both at mRNA and protein level enabling the expression of GDF5 (Growth Differentiation Factor 5) to counteract excessive muscle wasting (Traoré et al. 2019). However, the mechanisms leading to the increase these embryonic isoform expressions are unknown to date.

Our RNAseq data analysis in innervated versus denervated muscles revealed MuscleBlind-Like (MBNL) proteins as potential candidates regulating CaVβ1 expression in skeletal muscle. Interestingly, in a human model of Dystrophy Myotonic 1 (DM1), the sequestration of MBNLs in toxic nuclear aggregates is related to an impaired splicing of CaVβ1 transcript (CACNB1) (Arandel et al. 2017). Here, we evaluate the effect of a modulation of MBNLs protein levels on the expression of CaVβ1 isoforms in both *in vitro* and *in vivo* systems as well as in pathological mouse models of DM1.

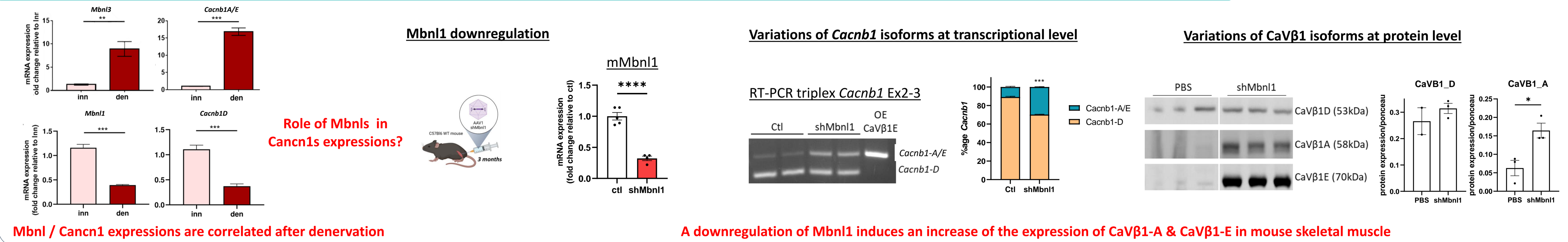
Diversity of CaVβ1 isoforms in skeletal muscle



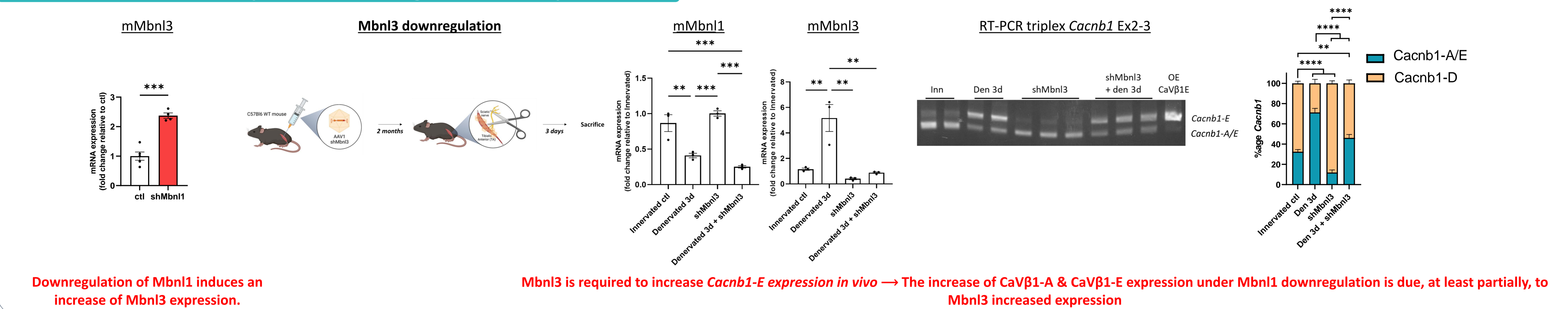
Regulation of the expression of CaVβ1 isoforms



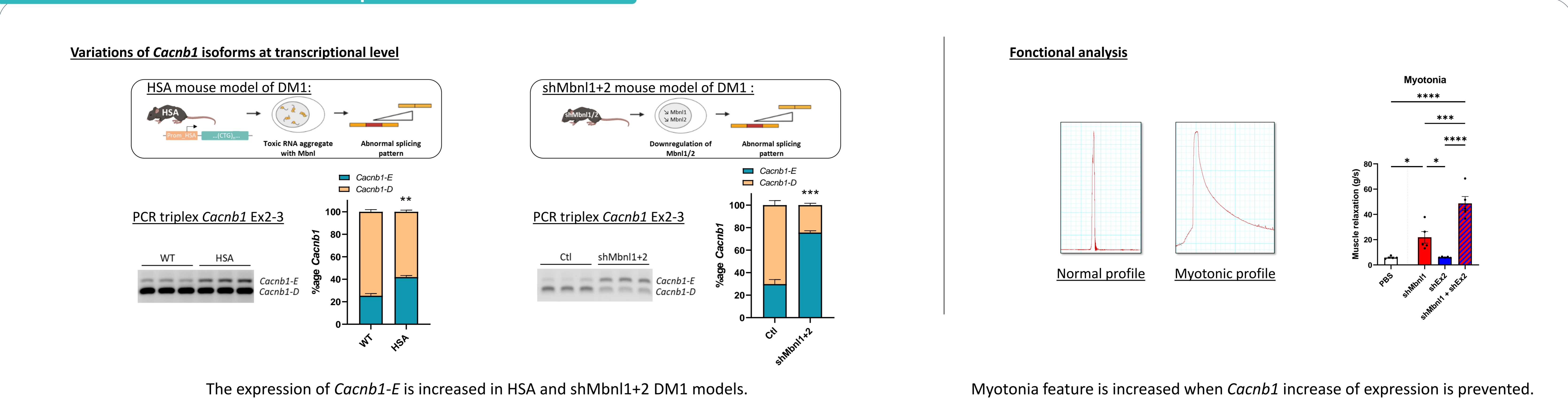
Regulation of CaVβ1 isoforms in the physiopathology of muscle disease(s): the possible role of Muscleblind-like proteins (Mbnls)



Cross-talk between Mbnl proteins in the regulation of CaVβ1 isoforms



Cacnb1 isoforms in DM1 models and potential role in the disease



CONCLUSIONS & PERSPECTIVES

- Adult Cacnb1D and embryonic Cacnb1A/E isoforms are expressed upon specific promoter activation
- A downregulation of Mbn1, and the subsequent increase of Mbn3, leads to increased CaVβ1-A and CaVβ1-E and decreased CaVβ1-D expression *in vivo*
- Mouse models of DM1 are associated with an increased Cacnb1-A and Cacnb1-E expression

- Characterization of the splicing events occurring at Cacnb1 Ex2-3 and Ex13-14
- Deciphering the role of CaVβ1-E in DM1 pathophysiology