Ectopic expression of PLCβ1 corrects differentiation of DM1 and DM2 myoblasts by normalizing cyclin D3 levels

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Myotonic dystrophies (DMs) are autosomal dominant, multisystemic diseases with a core pattern of clinical presentation including myotonia, muscular dystrophy, cardiac conduction defects, posterior iridescent cataracts, and endocrine disorders. Myotonic dystrophies (DMs) encompass at least 2 forms: myotonic dystrophy type 1 and 2. Myotonic dystrophy (DM) is a complex multisystemic disorder linked to two different genetic loci. Myotonic dystrophy type 1 (DM1) is caused by an expansion of a CTG repeat located in the 3′ untranslated region (UTR) of DMPK (myotonic dystrophy protein kinase) on chromosome 19q13.3. Myotonic dystrophy type 2 (DM2) is caused by an unstable CCTG repeat in intron 1 of ZNF9 (zinc finger protein 9) on chromosome 3q21. Therefore, both DM1 and DM2 are caused by a repeat expansion in a region transcribed into RNA but not translated into protein. The elevation of cyclin D3 in differentiated myotubes has been previously published. The lack of elevation of cyclin D3 in DM1 differentiating cells seems to be a critical event leading to impaired myoblast fusion. Cyclin D3 is a specific target for PI-PLCβ1 signaling. In particular, investigations on skeletal muscle development strengthen the contention that nuclear $PLC\beta_1$ signaling is required for the activation of the cyclin D3 promoter in C2C12 cell. Here we show that PLCβ1 expression is down-regulated during differentiation of DM1 and DM2 cells. Our evidence suggests that the overexpression of PLCβ1 in these cells is directly responsible for the overexpression of cyclin D3 and myogenin leading to an increased fusion of DM cells. Thus, normalization of cyclin D3 evoked by ectopic expression of PLCβ1 might be a therapeutic approach to correct differentiation of skeletal muscle in DM patients.

References

[1] Molecular basis for impaired muscle differentiation in myotonic dystrophy. Timchenko NA, Iakova P, Cai ZJ, Smith JR, Timchenko LT. Mol Cell Biol. 2001 Oct;21(20):6927-38.

[2] Inositide-dependent phospholipase C signaling mimics insulin in skeletal muscle differentiation by affecting specific regions of the cyclin D3 promoter. Faenza I, Ramazzotti G, Bavelloni A, Fiume R, Gaboardi GC, Follo MY, Gilmour RS, Martelli AM, Ravid K, Cocco L. Endocrinology. 2007 Mar;148(3):1108-17.

Key words
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