**Role of Jab1 in skeletal muscle development and muscular dystrophy.**

Jab1 is a nuclear/cytoplasmic molecule that, at transcriptional and post-transcriptional level, is involved in the control of cell cycle, differentiation growth and migration.

We recently reported that Jab1 acts downstream the laminin211 pathway and its inactivation in Schwann cells causes a dysmyelinating neuropathy, which is the phenocopy of what observed in mouse mutants for laminin211. Loss of Jab1 results in p27 accumulation in Schwann cell nuclei, which arrested in differentiation and proliferation, thus causing the neuropathy. Reduction of p27 levels in Jab1 null Schwann cells was sufficient to rescue the neuropathy (Porrello 2014).

Mutation in laminin211 also causes a severe muscular dystrophy, known as Merosin-deficient Congenital Muscular Dystrophy (CMD1A). We have preliminary data showing that Jab1 is expressed in skeletal muscle, and it is regulated during muscle development. Mice with muscle-conditional ablation of Jab1 develop muscular dystrophy and that p27 is inversely regulated. Interestingly, CMD1A mouse mutants show also in skeletal muscle reduced levels of Jab1 (and increased levels of p27), suggesting that Jab1 might play a role in the pathogenesis of laminin211-derived muscular dystrophy. We propose to investigate whether by reducing levels of p27 in skeletal muscle we may rescue muscular dystrophy in MDC1A mutants. MDC1A mutants, floxed p27 and MyoDi-cre mice (for selective inactivation of p27 in skeletal muscle) are available in the lab. Moreover, we will investigate whether selective inactivation of Jab1 in skeletal muscle (by MyoDi-cre transgene) would result in muscular dystrophy. We will investigate the molecular mechanism with the aim to widen our knowledge on the pathogenesis of MDC1A and potential therapeutic targets.


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