Spindle associated membrane protein 1 (Samp1) in muscle differentiation

Skeletal muscles, the most common type of muscle in the body, are responsible for voluntary movements. Skeletal muscles are formed in a process called myogenesis (differentiation of muscles). During myogenesis a single-nucleus-myoblast (undifferentiated muscle cell) fuses with adjacent myoblasts to form multinucleated myotubes, which then further develop into myofibers (mature muscle fibers). Bundles of myofibers are collectively referred to as skeletal muscle. Defects in this process leads to reduced muscle mass and malfunctioning muscle movement. One such example is the muscle disease Emery-Dreifuss muscular dystrophy (EDMD), a condition that primarily affects skeletal and cardiac muscles. EDMD can be caused by mutations in genes encoding either Emerin or Lamin A, two proteins residing in the nuclear envelope that surrounds the genome in the cell nucleus. The disease mechanism is currently unclear, but dysfunctional myogenesis has been proposed to be involved.

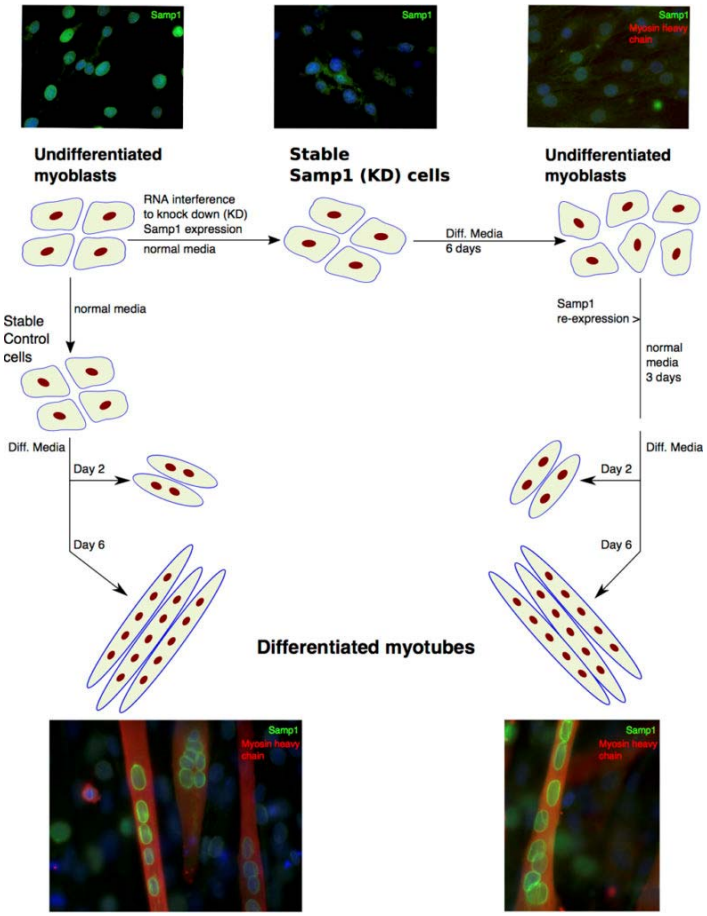

Fig. 1. Cartoon showing the experimental outlay. The insets show immunofluorescence images of undifferentiated myoblasts and differentiated myotubes as indicated. Samp1 (green), Myosin heavy chain (red) and DNA (blue).

The nuclear envelope (NE) has traditionally been considered as a mere physical barrier protecting the genome from the rest of the cell. However, more recently the NE was shown to harbor hundreds of unique proteins, some of which are involved in many regulatory and signaling functions. So far only a few of these proteins have been studied in detail, and Emerin and nuclear lamins remains the best characterized NE proteins. The recently discovered NE protein Samp1 (Spindle associated membrane protein 1) interacts with the two EDMD-linked NE proteins, Lamin A and Emerin. In our studies, we observed a dramatic increase in the expression level of Samp1 in differentiated myotubes compared to undifferentiated myoblasts. This and the variable expression of Samp1 in different tissues made us investigate a possible role for Samp1 in myogenesis. For this, we used RNA interference to generate stable c2c12 skeletal myoblasts knockdown (KD) cell lines depleted of Samp1. RNA interference is a method that makes it possible to silence or knock down (KD) the expression of specific proteins. Control cells and Samp1 (KD) myoblast cells were incubated for six days in differentiation media. As expected, the control cells differentiated into long multinucleated myotubes expressing the myogenic structural differentiation marker myosin heavy chain, whereas no myotubes were formed by the Samp1 KD cells (Fig. 1). The interrupted myogenesis was completely restored by re-expression of the Samp1 protein, showing that Samp1 is required for myogenesis of c2c12 skeletal myoblasts.

Further investigations showed that expression of the myogenic markers MyoD, Myf5, Myogenin and myf6 (MRF4) were downregulated in the Samp1 KD cells. Samp1 depleted cells also failed to exit the cell cycle, which is an important step in cell differentiation, and we found an abnormal activation of extracellular signal-related kinase (ERK), phosphoERK in Samp1depleted cells within minutes after initiating differentiation. The exact mechanism behind ERK activation in response to misregulation of certain NE protein is unknown. Loss of Samp1 did not affect the expression or distribution of its interaction partners, Emerin and Lamin A. Thus, we conclude that KD of Samp1 alone completely inhibited myogenesis and that Samp1 has an important role in myogenesis independently of Emerin or LaminA/C. The new findings presented here, together with the recent observation of mis-localization of Samp1 in cells derived from patients suffering from EDMD, may lead us closer to understanding the disease mechanism.

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