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TRPC1: Getting physical in space

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Alteration of natural gravitational forces leads to changes in gene expression, cell growth, and cell function. External forces are sensed in cells via mechano-transduction processes that are important for initiating and mediating adaptive mechanisms. A good example is prolonged spaceflight, which leads to muscle loss and reduced skeletal muscle strength. Skeletal muscles adapt to antigravity by preferentially sacrificing slow muscle, oxidative fibers, whereas predominantly fast-twitch, anaerobic muscles are relatively spared. Specifically, exposure to microgravity exerts mechanical stress on the muscle leading to attenuated cell proliferation, disruption of cell cycle progression and alterations in gene and protein expression.[1-3] Ca^{2+} plays a central role in all 3 phases of gravitropism: perception, transduction, and response. The critical triggering factor is an increase in cytosolic [Ca^{2+}] mediated by stretch-activated channels[4] that are activated directly by mechanical stretch or via intracellular signals generated in response to stretch. It is evident that Ca^{2+} entry via such channels regulates multiple intracellular signaling mechanisms that are essential for cell growth and proliferation.

IGF-1 plays a critical role in myogenesis by stimulating calcium influx and promoting cell cycle progression. The calcium-activated phosphatase, calcineurin, and its target, nuclear factor of activated T cells (NFAT) regulate expression and function of several proteins required for myogenesis, including IGF-1[5] and the calcium channel, transient receptor potential canonical type 1 (TRPC1). TRPC1 mediates regulation of cell function by a variety of neurotransmitters and growth factors.[4] Several studies suggest that TRPC1 can also be activated in response to membrane stretch, although the exact mechanism of gating is not known. The channel is the predominant isoform expressed in proliferating C2C12 myoblasts, a widely used cell line to study the early stages of myogenesis. Furthermore, TRPC1-mediated Ca^{2+} entry stimulates cell cycle progression in muscle and other cell types.[6,7] Cell cycle phases are marked by expression and degradation of specific cyclins; e.g., cyclin B expression indicates exit from S phase, while degradation of cyclin B is a requirement for the termination of cytokinesis at the end of mitosis. There is a strong functional link between cytosolic Ca^{2+} changes and cyclin expression as well as function. Calmodulin (CaM) is involved in the transition of cells from G_1 to S phase, from G_2 to mitosis, and from anaphase to metaphase. CaM-modulated kinase II (CaMKII) activates cyclin B and subsequently also activates proteasomal degradation of cyclin B, that is required for the metaphase/anaphase transition.[3] Indeed, reduced expression of CaM results in cell cycle arrest. Thus, cell cycle is regulated by a feedforward mechanism of action, whereby mechanically gated calcium influx through TRPC1 upregulates IGF-1 expression that, in turn, causes sequestered TRPC1 channels to translocate to the muscle membrane, further augmenting calcium entry.[7]

Benavides Damm et al.[8] have now elucidated a possible mechanism that underlies the decline in muscle mass in response to prolonged microgravity exposure. They report that C2C12 mouse muscle cells exposed to simulated microgravity (SM), but not hypergravity, demonstrate retarded cell growth, delayed G_2/M phase progression, and expressed cyclin B. These investigators

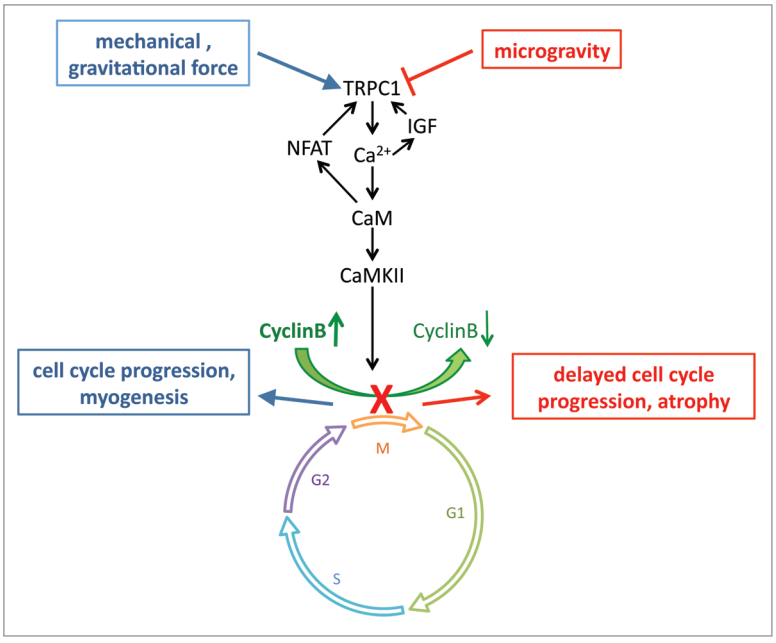

Figure 1. Functional link between TRPC1, Ca^{2+} signaling mechanisms, and cell cycle progression in skeletal muscle cells. Normal gravity or mechanical forces stimulate TRPC1 activation and promote Ca^{2+} signaling, leading to cyclin B degradation, a signal for progression of cell cycle from G_2/M to G_1 phase. This results in myogenesis. In contrast, microgravity conditions lead to loss of TRPC1 function as a result of decreased expression of the channel and, consequently, result in attenuation of cell cycle progression, possibly leading to atrophy of muscle tissue with prolonged stress. Abbreviations: TRPC1, transient receptor potential canonical 1; NFAT, nuclear factor of activated T cells; IGF, insulin like growth factor; CaM, calmodulin; CaMKII, calmodulin-dependent kinase II.

previously showed that TRPC1 expression was reduced by SM, and this coincided with accumulation of cells in the G_2/M phase.[7] Together with the findings in the recent study, these data indicate that under microgravity conditions, accumulation of the cells between G_2 and anaphase is due to downregulation of TRPC1 expression that leads to decreased Ca^{2+} entry, inhibition of CaMKII and attenuation of cyclin B degradation. Thus, TRPC1-mediated Ca^{2+} influx is able to overcome the effects of microgravity, until entry in G_2/M, when TRPC1 expression is downregulated, at which point the cells are no longer able to progress to the next phase. Interestingly, TRPC1 expression is also tightly regulated during myogenesis and is modulated by myogenic factors such sphingosine 1 phosphate and TGFβ. There is also evidence that TRPC1 has a role in muscular dystrophy in human and mouse. However, the mechanism(s) underlying channel gating as well as potential regulators, e.g., Orai1 and STIM1 proteins, and downstream cellular pathways mediating the response to mechanical stretch have not yet been clarified. Finally, the regulation of TRPC1 expression and function in skeletal myogenesis make the channel a potential molecular target in the treatment/prevention of muscle damage and enhancement of skeletal muscle regeneration.

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