BDR SEMINAR in Kobe

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16:00-17:00, 7F Seminar Room, DB Building A

Selective mRNA Translation Regulates Muscle Stem Cell Activity

Summary

Regeneration of adult tissues depends on somatic stem cells that remain quiescent, yet are primed to enter a differentiation program. Growing evidence indicates that these properties are regulated in part by maintaining low levels of protein synthesis in quiescent adult stem cells, but it remains unclear whether 'selective' mRNA translation defines stem cell properties. We show that a general repression of translation, mediated by the phosphorylation of translation initiation factor eIF2α at serine 51 (P-eIF2α), is required for muscle stem cell (MuSC) quiescence and self-renewal. Skeletal muscle stem cells unable to phosphorylate eIF2α exit quiescence, activate the myogenic program and differentiate, but do not self-renew. Pharmacological inhibition of eIF2α dephosphorylation permits ex vivo expansion of MuSCs that retain regenerative capacity after engraftment into the mdx mouse model of Duchenne muscular dystrophy. While eIF2α phosphorylation leads to a general repression of protein synthesis, specific mRNAs are selectively translated in a P-eIF2α dependent manner. In MuSCs, we show that the mRNA for centrosome/spindle apparatus associated protein Tacc3 is selectively translated in a P-eIF2α dependent manner. MuSCs deficient for Tacc3 activate the myogenic program, but are defective in both proliferation and self-renewal, leading to defects in both regeneration of muscle and restoration of the MuSC pool. We propose a model whereby P-eIF2α ensures in part the robust translational silencing of accumulating mRNAs that is needed to prevent the activation and subsequent differentiation of MuSCs while, on the other hand, allows selective translation of specific mRNAs needed for MuSC expansion and self-renewal.

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