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EDITORS' CHOICE

Stem Cells

Proliferation or Differentiation Depends on ERK Localization

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Extracellular signal–regulated kinase (ERK) is a serine–threonine kinase that can be activated by various growth factors, including fibroblast growth factors (FGFs), and phosphorylates both cytoplasmic and nuclear targets. In skeletal muscle, ERK activity promotes two fundamentally opposing processes—the proliferation of myoblasts and the terminal differentiation of myocytes (myogenesis). Michailovici *et al*. report that the subcellular localization of ERK determined whether it promoted proliferation or differentiation during the development of skeletal muscles. FGF signaling decreased as myogenesis proceeded in both the pharyngeal mesoderm of intact chick embryos and in pharyngeal mesoderm explants, which spontaneously undergo myogenesis in culture. A pharmacological inhibitor of FGF signaling accelerated myogenesis and reduced cell proliferation in both explants and embryos, whereas overexpression of FGF8 in explants inhibited myogenesis. In both explants and in vivo, the presence of phosphorylated ERK (pERK) in the nucleus correlated with proliferation, and cytoplasmic pERK correlated with differentiation. A peptide that competes with ERK for binding to the nuclear import machinery blocked the nuclear translocation of ERK and promoted myogenesis in both explants and intact embryos. This peptide also promoted the differentiation of satellite cells (muscle precursor cells) isolated from skeletal muscle of adult mice. Double-mutant mice lacking both of the FGF inhibitors Sprouty1 and Sprouty2 had reduced myogenesis and increased pERK staining. These findings suggest that FGF-induced nuclear translocation of pERK represses the differentiation of myocytes by preventing cell cycle exit, so the myoblasts keep dividing instead of differentiating. As FGF signaling decreases, cytoplasmic pERK accumulates, promoting differentiation. Thus, a shift in the balance between nuclear and cytoplasmic pERK can switch myoblasts from a state of proliferation to a state of differentiation.

I. Michailovici, H. A. Harrington, H. H. Azogui, Y. Yahalom-Ronen, A. Plotnikov, S. Ching, M. P. H. Stumpf, O. D. Klein, R. Seger, E. Tzahor, Nuclear to cytoplasmic shuttling of ERK promotes differentiation of muscle stem/progenitor cells. *Development* **141**, 2611–2620 (2014). [PubMed]

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