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CYTOSKELETON

Formins induce nuclear actin assembly

> formins drive actin assembly in the nucleus

Formins promote the assembly of actin filaments in the cytoplasm. This leads to the release of MAL (megakaryocytic acute leukaemia; also known as MRTF) from monomeric G-actin and the accumulation of this cofactor, which stimulates serum response factor (SRF)-dependent expression of cytoskeletal target genes, in the nucleus. Although diaphanous-related formins (mDia) have been detected in the nucleus, it was unclear whether they have a nuclear function. Now, Grosse and colleagues show that activated nuclear mDia promotes the assembly of a nuclear actin network that results in MAL–SRF-dependent gene expression.

First, the authors showed that a constitutively active version of mammalian mDia1 (Dia1ct, which is predominantly nuclear) induced SRF-dependent gene expression to a similar level as its cytoplasmic counterpart (Dia1ct fused to a nuclear export signal (NES-Dia1ct)) or constitutively active MAL. Moreover, they found that nuclear actin polymerization was required for Dia1ct-driven SRF activity, as Dia1ct did not induce SRF activity when an actin mutant that cannot polymerize was overexpressed in the nucleus. Interestingly, only nuclear Dia1ct but not cytoplasmic NES-Dia1ct could prevent the sequestration of MAL by nuclear G-actin, which suggests that nuclear actin polymerization releases MAL from G-actin. Moreover, cells expressing a dominant-negative mDia mutant that localizes exclusively to the nucleus exhibited decreased serum-induced SRF activity compared with control cells, suggesting that nuclear mDia is required for the serum response.

Next, the authors assessed nuclear actin assembly dynamics in cultured mammalian cells. Using an F-actin-specific probe fused to a nuclear localization sequence (NLS) as well as phalloidin staining to label actin, they confirmed that serum rapidly induces nuclear actin polymerization and showed that knockdown of mammalian mDia1 and mDia2 decreased the assembly rates. This supports the notion that formins drive actin assembly in the nucleus in response to serum.

So, can MAL–SRF activity be induced upon nuclear mDia activation? To activate endogenous formins in the nucleus, the authors used an optogenetic tool, whereby mDia autoinhibition is released by the photoactivation of a diaphanous autoregulatory domain. Indeed, repeated illumination of cells, and thus mDia activation, resulted in the reversible assembly of nuclear actin filaments, MAL nuclear accumulation and SRF activity.

Together, these results show that the assembly of dynamic nuclear actin networks in response to serum is dependent on nuclear mDia activation.

Andrea Du Toit

ORIGINAL RESEARCH PAPER Baarlink, C., Wang, H. & Grosse, R. Nuclear actin network assembly by formins regulates the SRF coactivator MAL. *Science* 4 Apr 2013 (doi:10.1126/science.1235038)

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