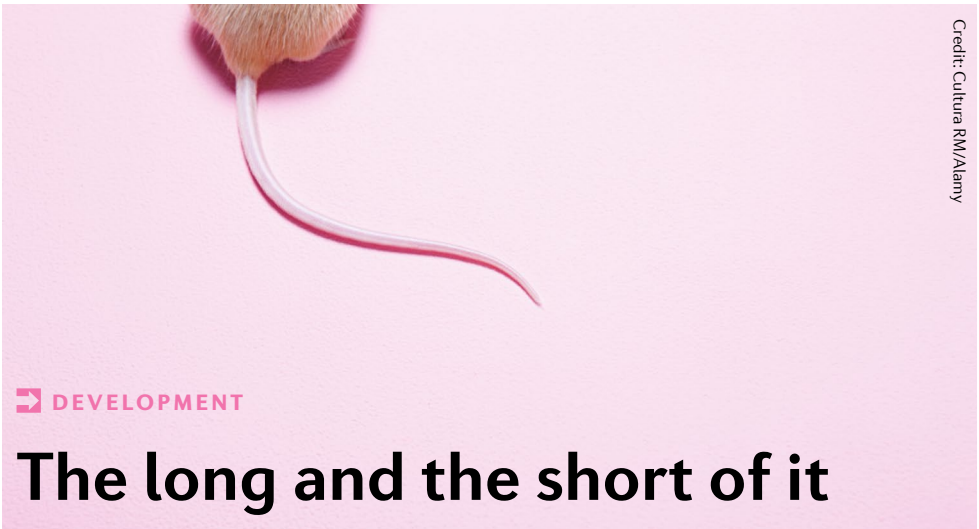

Credit: Cultura RM/Alamy

DEVELOPMENT

The long and the short of it

Two studies published in *Developmental Cell* report the generation of mice with longer and shorter than normal tails, respectively. The studies provide insight into the developmental programmes governing mouse tail development and implicate some of the key genes and gene networks involved.

Robinton et al. had observed that the overexpression of human *LIN28B* in mice during development led to a phenotype of extremely long tails. LIN28, which in vertebrates is present as two paralogues, *Lin28a* and *Lin28b*, is highly expressed in mouse embryonic stem cells and during early embryogenesis. This RNA-binding protein was previously shown to be involved in growth and metabolism and known to act as part of a highly conserved heterochronic pathway, that is, regulating the timing of development. Its suppression by the *let-7* microRNA family is necessary for cell differentiation to occur.

Robinton et al. aimed to clarify the functional role of *Lin28a* during tail development by overexpressing it in mouse embryos. To this end, the team used a *FoxD1-Cre* transgenic strain crossed with a doxycycline-inducible *Lin28a* transgenic strain, which enables temporal control of transgene expression in *FoxD1*-expressing cells. These cells include neuromesodermal progenitors in the tail bud and anterior paraxial mesoderm, the mesoderm at either side of the neural tube that gives rise to somites, blocks of cells that eventually form skeletal muscle, connective tissues and vertebrae.

Lin28a overexpression markedly increased the number of caudal vertebrae, whereas a *Lin28a* knockout exhibited reduced tail-to-body length ratio compared with controls owing to fewer caudal vertebrae; neither mouse model showed disrupted vertebral morphology.

Analyses of different *Lin28b* transgenic mouse models revealed that the predominant paralogue implicated in mouse tail development is *Lin28a*. Moreover, increasing and decreasing *let-7* levels led to fewer and more vertebrae, respectively, as expected given its role as an inhibitor of LIN28a.

Further investigations revealed that one of the mechanisms underlying the LIN28a-driven phenotypes is an increase in the proliferation of tail bud progenitors. Moreover, by downregulating *Sox2* expression, LIN28a shifts the balance of cell specification from a neural fate to a mesodermal cell fate, thereby promoting axis elongation.

A second study focused on the gene *Gdf11*, which was known to trigger tail development during embryogenesis by unknown mechanisms. Although mice deficient in GDF11 die shortly after birth, newborn knockout animals are clearly recognizable by their shortened or absent tails.

Aires et al. analysed *Gdf11*-knockout mouse embryos and found that they exhibited disrupted tail formation and structural defects, including fewer caudal vertebrae and a marked increase in the neural tube area. The team determined that this expansion was the result of an increased number of tail bud progenitors that preferentially differentiate along a neural cell fate as opposed to a mesodermal one. GDF11 signalling seemed to control the number of neuromesodermal progenitors by reorganizing the progenitor pool during the transition from trunk to tail and during extension throughout the tail.

Analysis of differential gene expression from RNA sequencing data of mutant and wild-type embryos implicated the downstream effectors of GDF11. Taken together, the findings suggest that, after the transition from trunk to tail, LIN28 and HOX13 act downstream of GDF11, with LIN28 promoting and HOX13 restricting tail bud progenitor expansion.

The implications of this work could go beyond mouse tail development; the observation that a group of multipotent cells is regulated by fundamentally different genetic networks with distinct cell competencies at subsequent developmental stages could be relevant for pathological processes such as metastasis.

Linda Koch

> “this expansion was the result of an increased number of tail bud progenitors that preferentially differentiate along a neural cell fate”

ORIGINAL ARTICLE Robinton, D. A. et al. The Lin28/*let-7* pathway regulates the mammalian caudal body axis elongation program. *Dev. Cell* https://doi.org/10.1016/j.devcel.2018.12.016 (2019) | Aires, R. et al. Tail bud progenitor activity relies on a network comprising *Gdf11*, *Lin28*, and *Hox13* genes. *Dev. Cell* https://doi.org/10.1016/j.devcel.2018.12.004 (2019)