Seminarios internos del IBFG

APC^{FZR-1} is required for the formation of stem cell niche in *Caenorhabditis elegans*

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APC/C is a ubiquitin E3 ligase highly conserved across species. This regulator was assumed to be specialized in cell cycle regulation, but an increasing number of reports describe that APC/C works in processes other than the cell cycle. In particular, upon the interaction with Cdh1/*fzr-1*, one of its co-activators, this complex plays roles further than the cell cycle, including developmental decisions.

Cdh1/*fzr-1* is not essential in fungi like *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, or *Ustilago maydis*, although it is required for alternative programs such as mating, sporulation or virulence. In metazoan, the picture is slightly more complicated. Genetic ablation of *fzr-1* in mice resulted in embryonic lethality, but for instance, loss-of-function mutants in Drosophila Fzr1 are fully viable. In the case of *Caenorhabditis elegans*, the reported results are not precise. Microinjection of antisense RNA into the gonads of the worm resulted in a high percentage of embryonic lethality. However, the two characterized mutant alleles (*ok380 and Ku298*) showed a proliferation similar to wild-type worms, suggesting that most likely, they are hypomorphic alleles.

We deleted the entire *fzr-1* gene through CRISPR, creating a loss-of-function allele *fzr-1(sal19)*. Interestingly, this deletion leads to sterility and additional defects.

C. elegans is a hermaphrodite nematode, whose reproductive system is composed of two symmetrical U-shaped gonads. Each gonad is a line of germ cells enwrapped by a tubular tissue, a monolayer of cells called the somatic gonad. One of these cells is the distal tip cell (DTC), a stem cell niche that maintains germ cell identity and leads the development of gonads. In most cases, *fzr-1(sal19)* mutants do not form gonads

because DTC is absent. The fate acquisition of the cellular types of the somatic gonad depends on binary cell fate choice decisions controlled by the Wnt pathway. A more in-depth study reveals that stem cell niches in *fzr-1* could be acquiring its fate, but losing later because of problems regarding cell fate maintenance. Our working hypothesis indicates that within somatic gonad, $APC^{FZR\text{-}1}$ seems to act downstream of the wnt pathway, specifically in the DTC lineage, most likely promoting the degradation of some elements opposing to stem cell niche fate maintenance. We believe that these negative elements could be related to chromatin regulators. For that, we are performing an educated RNAi screening of chromatin regulators with putative KEN or D Box motifs looking for the rescue of DTC loss. Our preliminary results showed that depletion of MET-2, an H3K9 histone methyltransferase, partially rescued DTC loss. MET-2 marks genes to repress their transcription, and therefore it could be an element to be avoided during the progression to some particular cell fate.