Abstract

Ubiquitin ligases are responsible for the specific recognition of proteins targeted for proteasome-dependent degradation. This project focused on the molecular and functional characterization of the SCF^{FBXO38} ubiquitin ligase. As with many others, its biological function has not yet been elucidated in detail, although it is the only ubiquitin ligase whose mutations lead to the onset of a distal form of muscle atrophy. In the first part of our project, we identified new substrates for this ubiquitin ligase, the nuclear proteins ZXDA and ZXDB, with insufficiently characterized functions. Using genetic and biochemical methods, we have shown that ZXDA/B proteins act as positive regulators of centromeric chromatin integrity and that experimental inactivation of the SCF^{FBXO38} ubiquitin ligase resulted in a ZXDA/B-dependent stabilization of CENP-A and CENP-B proteins in the centromeric regions.

In the second part of the project, we focused on analyzing the mouse model deficient in the *Fbxo38* gene. We demonstrated that loss of *Fbxo38* leads to growth retardation affecting various organs, including the male reproductive system. A detailed histological examination revealed pathological alterations in the seminiferous tubules, accompanied by a lower number of spermatozoa and decreased fertility. We have shown that FBXO38 is functionally expressed in Sertoli cells, the key orchestrators of spermatogenesis. Consistent with our observations from human cancer cell lines, loss of FBXO38 resulted in stabilization of ZXDB protein and an increase in centromeric chromatin density in Sertoli cells. Finally, we discovered that FBXO38 is involved in the terminal differentiation process of Sertoli cells, and its loss resulted in their delayed maturation.

This work described a novel biochemical pathway involved in the regulation of centromeric chromatin and mouse spermatogenesis.