Abstract

Cullin-dependent ubiquitin ligases are responsible for the regulation of most cellular processes. Despite their mutated forms being the cause of many human diseases, their physiological roles are not sufficiently described. In the presented results, we focused on the physiological role of ubiquitin ligase SCFFBXO38 (SKP1-CULLIN1-FBXO38), whose mutated forms are responsible for the progression of distal neuropathy. Preparation of mouse model deficient in FBXO38 revealed that homozygous pups were born in a lower than expected ratio. Animals were growth-retarded, both at the level of the whole organism and individual organs, especially the liver and testes. Males with a deletion in the Fbxo38 gene had significantly lower reproductive capacity, which was associated with lower production of mature sperm and pathological changes in the structure of seminiferous tubules. We found that the FBXO38 protein is functionally expressed in Sertoli cells responsible for regulating spermatogenesis and seminiferous tubules integrity. Detailed analysis of spermatogenic populations revealed a defect at the level of spermatocyte differentiation. The dynamics of this differentiation depend on the hematotesticular barrier functional integrity formed by the intercellular junctions of Sertoli cells. We confirmed that the retention capacity of this barrier was reduced in mutated animals, which correlated with a decrease in the expression of its major subunit claudin 11.

In summary, this work led to the discovery of a new function of the ubiquitin-proteasome system in the regulation of spermatogenesis. This result may be relevant in identifying the causes of reduced fertility in the current human population.