Long-glucocorticoid-induced leucine zipper (L-GILZ) interacts Ras pathways and is involved in spermatogenesis failure

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A correct balance between spermatogonial stem cells (SSCs) self-renewal and differentiation is essential for the maintenance of spermatogenesis throughout life (Wong et al. 2005), but the cellular pathways regulating proliferation, differentiation and survival of the undifferentiated spermatogonia are only partially known.
Glucocorticoid-Induced Leucine Zipper (GILZ), was initially described as a regulator of immune response and an important player of the anti-inflammatory and immunomodulatory effects of glucocorticoids. Glucocorticoid effects are in part due to the GILZ-mediated modulation of cell proliferation and differentiation (Ayroldi and Riccardi. 2009). In particular, we have shown that GILZ directly binds Ras, inhibits downstream Mapk/Erk Ras dependent signals thus functioning as a physiological brake on cell proliferation (Ayroldi et al. 2007).
The gilz locus gene is characterized by two main isoforms, gilz and a longer isoform long-gilz (L-gilz) that are differentially expressed in various tissues (Bruscoli et al. 2010).

L-GILZ is the only isoform expressed in testis and is highly expressed in spermatogonia and primary spermatocytes. L-GILZ is involved in the control of the spermatogenesis: GILZ deficiency in knockout (GILZ KO) mice leads to a complete loss of germ cell lineage does not proceed beyond the prophase of the first meiotic division, resulting in male sterility. Spermatogenesis failure is intrinsic to germ cells and not due to defect in endocrine or stem cell niche compartments (Bruscoli et al, 2012).
Here we show that L-GILZ regulates Ras pathway in undifferentiated spermatogonia by direct binding of Ras and phosphorylation of Erk and Akt. Lack of L-GILZ causes Ras activation and loss of the spermatogenesis cell lineage. Moreover, spermatogenesis failure in GILZ KO mice is associated with increased proliferation and aberrant differentiation of undifferentiated spermatogonia. The increased proliferation in GILZ KO spermatogonia associates with Ras signaling pathway deregulation and massive apoptotic cell death. Notably the germ cell lineage in GILZ KO cells is characterized by an accumulation of unrepaired chromosomal damage in the first cycles of spermatogenesis.
These results identify L-GILZ as a novel important factor for undifferentiated spermatogonia function and maintenance of spermatogenesis.

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