Prof. Dr. Mariusz P. Kowalewski
Institute of Veterinary Anatomy, Vetsuisse Faculty
University of Zurich
Winterthurerstrasse 260
CH-8057 Zurich
Switzerland

Hypoxia and HIF1α-mediated responses in steroidogenic cells.

Steroidogenesis involves multiple steps leading to the synthesis of steroid hormones using cholesterol as a common substrate. The translocation of cholesterol throughout mitochondrial membranes, i.e. to the inner mitochondrial membrane, where the conversion of pregnenolone from cholesterol takes place, is the key rate-limiting steps in this process. This step is facilitated by the Steroidogenic Acute Regulatory (STAR) protein. In fact, STAR is responsible for 85-90% of all cholesterol transport across mitochondrial membranes. Its synthesis is regulated through cAMP-mediated pathways involving transcriptional, translational and post-translational mechanisms. The downstream cascades involve activation of several kinases and their signaling cascades, like PKA, PKC or MAPK, and functional interactions between them. In ovarian follicles, with vasculature restricted to theca layers, steroidogenesis takes place under reduced oxygen (O2) content (hypoxia), suggesting a modulatory role of hypoxia. Indeed, recently, the modulatory role of hypoxia (reduced oxygen (O_2) tension) and hypoxia inducible factor (HIF) 1α upon STAR functionality and steroidogenesis, has been shown in ovarian granulosa cells. As a part of heterodimer complexes and master regulator in biological responses to hypoxia, HIF1α has been implicated as a direct transcriptional regulator of STAR. The most recent studies from our research group provided evidence for novel regulatory pathways in HIF1α-mediated steroidogenesis in granulosa cells, involving transcriptional factors regulating STAR: (P)CREB, (P)cJUN and CBP. The expression and activity of HIF1α are regulated by O_2-independent and O_2-dependent mechanisms. The latter involve factor inhibiting HIF (FIH), prolyl hydroxylases (PHD1, 2, 3) and von Hippel Lindau (VHL) suppressor protein. Their involvement in steroidogenic cells and ovarian expression, were investigated recently. Thus, besides confirming the expression of all these factors in murine ovaries, their expression was localized predominantly in growing secondary and tertiary follicles, indicating the existence of HIF1α-controlling mechanisms within growing ovarian follicles, physiologically characterized by reduced O_2 concentration. The observed expression patterns led us also to the conclusion that their hydroxylation of HIF1α in granulosa cells must depend predominantly on O_2 availability, and not on modulation of their availability. From our *in vitro* studies, PHDs, predominantly PHD2, was proposed as the major O2-sensing player stabilizing HIF1α in granulosa cells, possibly involved in a self-regulatory loop protecting granulosa cells from detrimentally high levels of HIF1α. Our studies substantiate the biphasic effects of HIF-complexes on STAR and steroidogenesis. Thus, whereas HIF1a is required for basal and cAMP-stimulated STAR expression in granulosa cells, it exhibits a STAR expression/function suppressing mode of action in its excessive presence. Finally, hypothesizing that HIF1α mediates the expression of cumulus-derived markers of oocyte maturation affecting the oocyte maturation rates and consequently the developmental rates of embryos, we proved the functional involvement of HIF1α in controlling the outcome of *in vitro* production (IVP) in cattle. Despite the recent achievements, further research is needed to deepen our knowledge about hypoxia/HIF1α-mediated effects on steroidogenic cell function, in particular on STAR-dependent provision of steroids.