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Functional study of androglobin in spermatogenesis and renal electrolyte balance

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Globins are small metalloproteins with a globular structure which typically have functions in oxygen storage and transport. Newer globin types have been described with novel functions including NO metabolism and detoxification of reactive oxygen and nitrogen species. Androglobin (Adgb), whose expression is preferentially found in the testis tissue in mammals, was shown to be implicated in male fertility, since male Adgb KO mice are infertile. Furthermore, observations in KO mice broadened our insights on Adgb expression sites in numerous other tissues. Additionally, the lack of Adgb phenocopies primary ciliary dyskinesia, a ciliopathy affecting male fertility, and leading to hydrocephalus, cardiac hypertrophy, polycystic kidney disease (PKD) and mucus accumulation in the sinus, suggesting a possible role for Adgb in ciliogenesis. However, Adgb's mechanism in ciliogenesis remains unknown.
In addition to male infertility, Adgb KO mice display smaller testis as well as malformed sperm. Indeed, spermatids appear to show interrupted development during the elongating phase, and mature sperm display abnormalities both in terms of shape and microtubule ultrastructure and mitochondrial compartmentalization. Additionally, mass spectrometry analysis on isolated testis revealed that Adgb interacts with members of the septin (Sept) family, a group of GTP-binding proteins involved in vesicle trafficking, mitosis, and cytoskeletal remodeling. Septs have been shown to be crucial for cilia formation and the lack of certain Septs, such as Sept7 and Sept12, leads to male infertility. Co-immunoprecipitation experiments on protein extracts from testis tissue and overexpression experiments performed in parallel demonstrate that Adgb strongly interacts with Sept10, both in vivo and in vitro. Additionally, immunofluorescent staining performed on spermatozoa showed an incorrect localization of Septs in the absence of Adgb. Finally, we suggest that Adgb plays a role in the proteolytic cleavage of Sept10, in a calmodulin-dependent mechanism, that is essential for the correct localization of Sept10 in the maturing sperm. These results suggest that Adgb's absence in KO mice leads to an incorrect localization and function of Sept10 in normal spermatozoa formation.
Renal cyst formation is characterized by defective water and electrolyte handling, linked to aberrant ciliary signaling. Indeed, RNAseq data allowed the link between Adgb KO and dysregulated aldosterone-dependent sodium absorption. To understand the (patho)physiological role of Adgb, we challenged both WT and Adgb KO mice with high-potassium diet and analyzed the renal osmoregulation. Unexpectedly, Adgb-deficient mice display hyperkalemia, despite a significant increase of circulating aldosterone. Additionally, corticosterone and 11-DOC levels are significantly decreased, while progesterone is significantly increased. At the protein level, α- and β-ENaC subunits of the epithelial sodium channel were increased, however total SGK1, MR, NCC and ROMK were decreased, consistent with a potential dysregulation in aldosterone-mediated signaling. Ongoing investigations are further exploring these hypotheses.

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