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Exploring the regulation and molecular function of androglobin

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Androglobin (Adgb) has been recently identified as a novel globin lineage consisting of a large chimeric protein with a unique domain structure. Adgb contains an N-terminal protease domain and a central circularly permuted globin domain, split in two parts and separated by an IQ calmodulin-binding motif. In this thesis, we present the first study of the regulation of the androglobin gene locus. Endogenous Adgb expression levels are low in the large majority of cell lines analyzed to date. In HEK293T and HeLa, androglobin gene expression is likely repressed by DNA methylation and the promoter region is regulated by numerous transcription factors (TF). Additionally, an intronic regulatory region has been identified as a TF-dependent repressor of androglobin promoter activity. Lastly, we suggest a similarly regulated promoter-overlapping antisense long non-coding RNA as a putative regulator of androglobin gene expression.

This new member of the globin family is evolutionary ancient and extremely conserved, being present in mammals down to more basal animal clades and also unicellular organisms, indicating a conserved function. The hexacoordination of the Adgb heme group and its downregulation in hypoxia in mammalian cell culture and in mice, together with a decreased expression in human tumor biopsies, suggest that this globin might harbor functions independent of the O_2 transport and supply of the classical globins. On the other hand, co-immunoprecipitation studies confirmed its ability to bind calmodulin and FRET biosensor-based investigations suggest the presence of a functional protease domain, both exclusive for this new globin family. These observations suggest that Adgb might be involved in previously unknown pathways, unprecedented in vertebrate globins in a similar manner as the established prokaryotic globin-coupled sensors.

Adgb expression is mostly abundant in testis, followed by several other organs such as lung, ovary, brain, kidney or heart. In testis, it is only detected at the postmeiotic stages of spermatogenesis. An Adgb-deficient mouse model generated by our group displays male infertility, indicating a crucial role of Adgb in reproduction. To gain additional insights into the physiological role of Adgb in testis tissue, we performed immunoprecipitation followed by mass spectrometry and identified multiple interactors that play important roles in chromatoid body formation and regulatory RNA processing. One of Adgb major interactors validated by FRET analysis, Miwi, is an essential chromatoid body component involved in piRNA biogenesis and target mRNA regulation. Similarly regulated genes in Adgb-deficient and Miwi-deficient mice suggest a possible role for Adgb in gene regulation during spermatogenesis.

In conclusion, in this thesis we have investigated for the first time multiple regulation and functional aspects of this intriguing novel globin family member and extensively expanded existing knowledge on Adgb.

Jury:
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