Characterization of the nuclear envelope and its protein partners during human spermatogenesis

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Abstract of thesis

Infertility affects 2% of men, and may be related to quantitative anomalies and/or qualitative anomalies in the production of spermatozoa. Despite this high incidence, the genetic causes of human infertility remain largely uncharacterized.

The morphogenesis of mature spermatozoa takes place during spermiogenesis, the last phase of spermatogenesis, when the round spermatids differentiate into spermatozoa, elongated and motile cells. This differentiation involves drastic changes in the nuclear envelope associated with profound chromatin remodelling.

We have focused our work on the nuclear envelope of spermatids during human spermiogenesis. We have characterized, the nuclear lamina, a protein meshwork component of the nuclear envelope, and its protein partners potentially implicated in the linkage lamin-chromatin: LEM-domain proteins, LBR, chromatinien protein BAF and its paralogue BAF-L.

Our study of the composition and the organization of this meshwork during spermiogensis, revealed the exclusive presence of B-type lamins and the identification of the testis-specific lamin B3 isoform in human. Furthermore, we showed lamins become concentrated at the posterior pole of mature spermatozoa at the end of spermiogenisis, with the persistence of chromatin proteins BAF and BAF-L and the loss of the lamin-chromatin interface as known in somatic cells.

Our results suggest that lamin B3 could form a polymer meshwork with its functional N-terminus globular domain in spermatids, like the other B-type lamins, and we have demonstrated that its ectopic presence at the nuclear periphery in HeLa cells increases nuclear envelope plasticity. We have also discovered and characterized the lamin A2, a meiotic isoform expressed from the LMNA gene in human and mouse.

By studying abnormal globozoospermic spermatozoa, we were able to identify BAF as a potential biomarker of spermatozoa nucleus immaturity.

Moreover, we have identified the second loss-of-function mutation in the nuclear envelope protein SUN5 in three related patients, and thus demonstrated its involvement in the formation of the spermatozoa head-tail junction.

In conclusion, our characterization of the nuclear lamina and its protein partners during human spermiogenesis, provides a better understanding of its role in the differentiation of spermatids into spermatozoa, and provides a solid basis for future investigation of cases of male infertility related to nuclear anomalies.