Sperm Epigenetics and its Relation with Male Infertility

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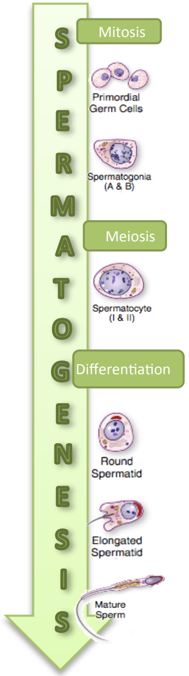
INTRODUCTION

Epigenetic comprises all those mechanisms that modify the genetic expression without altering the DNA sequence. The most important and known mechanisms are DNA methylation and histones modifications, but are not the only ones. All these mechanisms regulate gene expression through the activation or the inhibition of genes.

Spermatogenesis is the process by which a male primordial germ cell becomes a mature sperm that has the capacity to fecundate an oocyte. During this process sperm genome undergo several epigenetic modifications like DNA methylation, histone modifications, protamination or imprinting.

Mistakes during these process of maturation and differentiation of the male germ cells, may lead into unviable sperms for fecundation, and consequently in infertile men.



AIMS

- Define epigenetics and the different mechanisms involved in it.
- Study all the epigenetics mechanisms of the male germ cells. As well as, determine the epigenetics mechanisms that appear during the male germ cell differentiation and maturation.
- Find the relation between sperm epigenetics and male infertility.

Figure 1. Spermatogenesis is a well defined process whereby haploid spermatozoa, that are capable of fertilization, are produced from diploid germ cells precursors. Sperm development starts after fertilization in the fetus, where primordial germ cells differentiate from the epiblast into spermatogonies. Spermatogonies enter into mitotic arrest until puberty. The spermatogenesis is resumed when FSH appears, and stimulates differentiation from spermatogonies unto Spermatocytes. After this, starts the differentiation into a mature sperm.

MATERIAL AND METHODS

This review has been done with papers found in PubMed. Key word for search were: epigenetic, sperm, sperm epigenetics, male infertility and epigenetic and male infertility.
With these items I found 42 interesting papers, but finally, the review has been based in just 30 papers.

SPEM EPIGENETICS

DNA Methylation

DNA methylation occurs at the 5-carbon position of cytokines found in CpGs that are near promoters. The role of DNA methylation is to regulate gene expression:

- Hypermethylation→ Gene inhibition
- Hypomethylation→ Gene expression

DNMTs are the enzymes that methylate DNA. In human we have: DNMT1, DNTM3a, DNTM3b and DNMT3L

The sperm has a unique pattern of DNA Methylation that displays eight fold the number of hypomethylated spots, compared with the average of the somatic tissue.

DNA methylation changes dynamically during Spermatogenesis. This fact allow gene expression regulation in each stage of the process

Histone Variants

Post-translational modification in the N-terminal region of histones can also control gene expression. Some of the modifications are: methylation, acetylation, phosphorylation, ubiquitinylation…

In addition to this modifications, during Spermatogenesis some histones are replaced for other histones variants. Some of this variants are specific for the sperm.

ORIGINAL HISTONE	SPERM HISTONE VARIANT
H3	H3.3A – H3.3B
H2B	TH2B
H2A	TH2A.X
H1	H1t – H1t2 – HILS1

Table 1. In the male germ cells, normal histones are replaced for other histones variants.

Imprinting

In the embryonic development several genes are expressed in a mono-allelic way, depending if they are inherited by the mother or by the father.

More than 100 imprinted genes have been identified in mouse (most of them also in human). At least half are expressed from the paternal allele.

It's regulation is basically through DNA methylation of the gene region.

Protamination

Protamination it is an specific epigenetic mechanisms, only found in male germ cells. Is the process by which histones are replaced for protamines. Its function is:

- Protect DNA damage
- Compact the nucleus of the cell

Histones are replaced by transition proteins, and transition proteins by protamines.

In the human male there are two protamines, P1 and P2. The ratio P1/P2 is close to 1.0

Histones→ Transition Proteins→ Protamines

5-10% of the histones remains in the sperm DNA. These retained histones will have and important role in the early embryo.

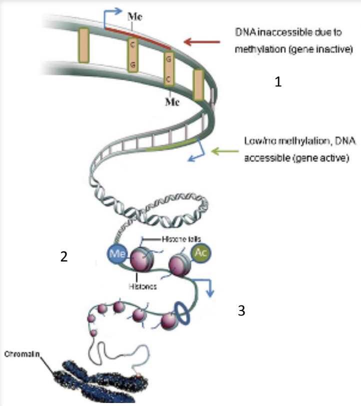


Figure 2. This are the main epigenetic mechanisms that affect gene activity:

1. DNA Methylation
2. Groups attached to histone.
3. Chromatin remodelling

(Figure modifyed form: Rajender S, Avery K, Agarwal A. Epigenetics, spermatogenesis and male infertility. Mutation research. Elsevier B.V.; 2011;727(3):62–71.)

MALE INFERTILITY

Epigenetic mistakes during Spermatogenesis can lead into **Male Infertility**

Protamines 1/Protamines 2 have to be in a ratio that lies close to 1.0. Perturbation of this ratio in either direction causes: poor semen quality, increase DNA damage and decrease fertility.

Disruption of some of the DNMTs results in aberrant **DNA methylation**.

Imprinting is essential for a normal embryo development. It's disruption can cause development defects or infertile sperm.

After protamination some **histones** are **retained** in the sperm.
This histones retention is essential for the early embryo. Protamine incorporation to this sites may affect transcription genes in the early embryo

CONCLUSIONS

Male germ cells undergoes thought several epigenetic modifications during spermatogenesis. These modifications include: DNA methylation, histones modifications and histones variants, protamination, imprinting and others. Some of this epigenetics mechanisms are well known, but there are others that we still need to understand their role and function in the regulation of gene expression in the sperm.

The epigenetics mechanisms in the male germ cell are important for achieving good maturation and sperms ready for fecundation. Whereas, epigenetics mistakes during spermatogenesis can lead into infertil sperms.

Up to now, very few studies have related epigenetic problems with male infertility. But the discover of this relation, may give rise into the answer of idiopathic causes of male infertility, which origin is still unknown. It remains a lot to do and discover in the field of sperm epigenetics and male infertility