

**Spermatogenesis and Maturation Arrest**  
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Infertility is defined as the inability of couples in reproductive age to achieve a pregnancy after one year of unprotected intercourse. Infertility is a major clinical problem affecting people medically and psychosocially. Worldwide, approximately 10-15% of couples are considered infertile. According to the World Health Organization (WHO), infertility causes are classified into male factors, female factors, combined factors from both male and female, and unexplained infertility.

The most common causes of male infertility are sperm production problems such as chromosomal or genetic causes, twisting of the testis in scrotum, blockage of sperm transport such as absence of vas deferens, vasectomy or prostate-related problems, sexual problems such as retrograde and premature ejaculation, failure of ejaculation, erectile dysfunction, spinal cord injury, prostate surgery or some medicines, or hormonal problems such as pituitary tumors or congenital lack of LH and/or FSH. Male factors are diagnosed in almost 50% of infertility cases, either solely (20%) or in combination with female factors (30-40%).

With reference to WHO standards, if the semen sample count is less than 15 million per ml (oligozoospermia), motility is less than 40% (asthenozoospermia), normal morphology is less than 4% (teratozoospermia), or combination between two or all three of these abnormalities the sample is usually considered as abnormal and the cause of infertility is attributed to male factor. However, the most difficult male problem is azoospermia. Azoospermia is defined as the absence of spermatozoa in the ejaculate. Azoospermia is identified in 15% of infertile men and classified into obstructive azoospermia (OA) or non-obstructive azoospermia (NOA).

Obstructive azoospermia is the consequence of physical blockage to the male excurrent ductal system and may occur in any region between the rete testis and the ejaculatory ducts. It comprises 40% of azoospermia cases and is typically accompanied by preservation of normal exocrine and endocrine function and normal spermatogenesis in the testis.

On the other hand, approximately 60% of azoospermia cases are non-obstructive (NOA) which is often caused by impaired spermatogenesis in testes. NOA results from primary testicular failure (elevated LH, FSH, small testes), secondary testicular failure (congenital hypogonadotropic hypogonadism with decreased LH and FSH, small testes), or incomplete testicular failure (either increased FSH and normal volume testes, normal FSH and small testes, or normal FSH and

normal testis volume). Recently, extensive efforts are being paid to understand the molecular bases underlying NOA male infertility, knowing that more than 50% of the causes in NOA are still unknown.

It is well established that when spermatogonia enter the first meiotic phase they go through programmed double strand breaks (DSB's). DSB's are formed throughout the genome during meiosis to facilitate the crossing over process, during which the exchange of genes between homologous chromosomes happen, resulting in a mixture of parental characteristics in offspring which contributes to genetic variability.

For spermatogonia to continue its division to form sperms, a tight homologous recombination for the DSB's should take place. This task is usually performed by the recruitment of double strand repair (DSR) proteins. DSR proteins are encoded by members of repair genes families and are responsible for DNA repair, keeping gene structure intact in addition to keeping DNA working optimally.

Many repair genes have been identified including MDC1, MSH5, MLH1, RAD51, CHFR, and the regulating protein BRCA1. However the trigger to begin DSB's repair starts when a complex (MRN) composed of three proteins MRE11/RAD50/NBS1 recruits a kinase called Ataxia-Telangiectasia Mutated (ATM) to phosphorylate the histone H2AX, the phosphorylated form of this histone is called  $\gamma$ H2AX.

The phosphorylation of H2AX is usually not enough to initiate the repair, for that to happen a feed- forward loop is needed to amplify the signal. Mediator of DNA-Damage Checkpoint 1 (MDC1) protein senses  $\gamma$ H2AX and cooperates with NBS1 to recruit more ATM to the DSB area. MDC1 also binds directly to the auto-modified ATM, to insure the sustained  $\gamma$ H2AX formation. Many studies indicated that mutations in ATM lead to male infertility particularly NOA; yet no studies have yet shed light on the relationship between other double strand repair proteins including MDC1,ATR and BRCA1 and non- obstructive azoospermia male infertility.

The talk will discuss the effect of genetic variation and/or mutations in the genes encoding ATM, ATR, MDC1 and BRCA1 proteins on their ability to sense the location of the DSB's on chromosomes leading to improper homologues recombination, rendering the cell arrested at the first meiotic division causing non-obstructive azoospermia.