DNA methylation landscape of male fertility: influences of ageing and infertility

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Spermatogenesis is a highly orchestrated process involving the entry of the most undifferentiated male germ cell type, spermatogonia, into differentiation, followed by meiosis, and ultimately spermiogenesis, resulting in a haploid sperm that is able of fertilisation. In mammals, fertilisation and development are dependent on correct establishment of epigenetic marks in the gametes, namely DNA methylation patterns in sperm. During pre-natal life, both male and female germlines undergo two waves of genome-wide, the second of which dramatically separates the germline from somatic cell lineages from a genome regulation point of view. For a long time, it was considered that the patterns of DNA methylation in the male germline were established prenatally and maintained throughout life. This idea was challenged by studies evaluating the sperm methylome during ageing and the methylome status of spermatogenic cells at different points of spermatogenesis. We found that the sperm of older men (>65 years) displayed over 200 differentially methylated regions compared to sperm obtained from younger men (<25 years). In a follow-up study, we not only found changes in similar regions between different men of the same age but also detected methylation changes in the same individual within a period of less than 6 years. Epigenetic changes, such as DNA methylation, are per definition inheritable through mitosis and meiosis. The finding of alterations with age indicates that the maintenance of such patterns is not faithful or is actively occurring in the germline. In order to evaluate whether DNA methylation is reprogrammed during spermatogenesis, we performed whole methylome sequencing on sorted undifferentiated and differentiating spermatogonia, primary spermatocytes, and spermatids obtained from testicular biopsies of men with full spermatogenesis. We found that DNA methylation decreases significantly around meiosis and increases again in spermatids. Interestingly, some regions remain demethylated after meiosis and are associated with genes that are expressed specifically in spermatids. When evaluating germ cells obtained from men with cryptozoospermia, we found methylation changes that were mostly affecting transposable elements (“jumping genes”), indicating a potentially new aetiology for this type of male infertility. In summary, DNA methylation in the male germline is constantly being remodelled throughout life and both ageing and infertility are associated with changes in the DNA methylation patterns of human sperm.