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MEIOTIC RECOMBINATION IN THE MOUSE

In mammals, meiotic recombination is required to both guarantee proper meiotc chromosome pairing and segregation during meiosis (Fig.1). Central to meioic recombination initiation, is the formation of programmed double strand breaks (DSBs), by the topoisomerase-like protein SPO11. If DSBs formation do not occur, or DSBs are not properly repaired, meiosis fails, leading to sterility. Proper processing of DSBs is under the control of several recombination factors (such as Dmc1, Rad51, RPA), which while loaded on to chromatin promotes the processing of the recombination intermediates. The proficiency of recombination factors loading onto DNA is influenced by the structure of the chromatin, and its post-translational modifications (e.g phosphorylation of the histons). In our laboratory, using a mouse genetic model, knockout for the *H2Ax* gene, PhD-student *Cristina Antinozzi* is currently investigating the role of H2Ax in meiotic recombination initiation and processing of Spo11-induced DSBs. In addition, by crossing *H2Ax* mice with *Spo11* mice, we are analyzing the effect of a reduce Spo11 dosage in a $H2Ax^{-/-}$ background ($Spo11^{+/-}$ $H2Ax^{-/-}$ mice). The ongoing project also benefit of the analyses of several other meiotic recombination-defective mice models (e.g. $Spo11^{-/-}$, $Msh5^{-/-}$, $Dmc1^{-/-}$, $MDC1^{-/-}$, $NIPA^{-/-}$) made available to us trough our external collaborators.

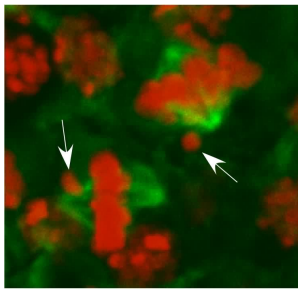

Fig.1. Lagging cromosomes (harrows) at metaphase I, in meiotic-recombination defective spermatocytes of Spo11+/-Atm-/- mice (Barchi M., Roig I. et al., 2008)

STUDY OF THE MOLECULAR MECHANISMS UNDERLYING TESTICULAR GERM CELL TUMOURS RESPONSE TO CISPLATIN-BASED CHEMOTHERAPY

Testicular Germ Cell Tumors (TGCTs), are considered to be a model for Cancer cells sensitivity to DNA-damaging agents. Indeed over 80% of patients with TGCTs can be cured using cisplatin-based chemotherapy. Unfortunately, despite the overall treatment success, 20%-50% of TC patients belonging to intermediate or poor risk groups, do not achieve a durable complete remission after initial treatment, and will eventually die from the disease. DNA repair is one of the factors influencing the cellular sensitivity/resistance towards cisplatin. In our laboratory using TGCT cell lines with different sensitivity to cisplatin, PhD student *Francesca Cavallo*, is investigating the role of DNA-damge repair mechanisms in the response to cisplatin and ionizing irradiations. The goal is the identification of the basic mechanisms at the base of cisplatin sensitivity (or acquired resistance). Such approach may leads to new insight for the identification of both new molecular markers of diagnostic value, and drug-based treatments.

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