BIOMEDICAL CENTER

The Laboratory of Reproductive Medicine presents

Dr. Petr ŠOLC

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and his lecture entitled

DNA DAMAGE RESPONSE IN MAMMALIAN OOCYTES AND EARLY EMBRYOS

Because low levels of DNA double strand breaks (DSBs) appear not to activate the ATM-mediated prophase I checkpoint in full-grown oocytes, there may exist mechanisms to protect chromosome integrity during meiotic maturation. Using live imaging we demonstrate that low levels of DSBs induced by the radiomimetic drug Neocarzinostatin (NCS) increase the incidence of chromosome fragments and lagging chromosomes but do not lead to APC/C activation and anaphase onset delay. The number of DSBs, represented by γH2AX foci, significantly decreases between prophase I and metaphase II in both control and NCS-treated oocytes. Transient treatment with NCS increases >2-fold the number of DSBs in prophase I oocytes, but less than 30% of these oocytes enter anaphase with segregation errors. MRE11, but not ATM, is essential to detect DSBs in prophase I and is involved in H2AX phosphorylation during metaphase I. Inhibiting MRE11 by mirin during meiotic maturation results in anaphase bridges and also increases the number of γH2AX foci in metaphase II. Compromised DNA integrity in mirin-treated oocytes indicates a role for MRE11 in chromosome integrity during meiotic maturation.

In somatic cells, DNA damage checkpoints are activated after increased level of double-strand DNA breaks (DSBs) and they delay the cell cycle progression to provide time for DNA repair. Inefficient checkpoint signalling compromises the genome integrity and it may leads to uncontrolled cell divisions. Two pronuclei in 1-cell stage embryo (zygote), unobvious lengths of cell cycle stages and only maternally expressed genes during the first two cell divisions make cell cycle of the early mammalian embryos significantly different from somatic cells. It was shown that G1/S checkpoint is not active in zygotes and zygotes arrest only in G2-phase after increased DSBs. Using confocal imaging of live or fixed embryos we demonstrate that low level of DSBs, induced in the first G1-phase by short treatment with NCS, increases the incidence of chromosome fragments but do not activate any checkpoints in zygotes. Although many NCS-treated embryos form micronuclei in 2-cell stage the onset and progress of the second S-phase is not affected suggesting the absence of the G1/S and intra S-phase checkpoints also in 2-cell stage embryos. Finally, NCS treated embryos arrest in G2-phase of the 2-cell stage.

In summary, our data suggest that although oocytes do not have DSBs DNA damage checkpoints that prevent meiotic maturation in the presence of high level of DSBs they possess DNA protecting activities trying to protect DNA against erosion. Moreover, the G2-checkpoint in 2-cell stage embryos is the first active and robust DNA damage checkpoint during early mammalian development.

Tuesday 30th October, 2 p.m.

seminar room of Biomedical Center

The lecture will be about 45 min., accompanied by small refreshment.

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