

Susceptibility of mammalian oocytes to chromosome segregation errors with maternal aging

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List of publications included as part of the thesis

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Yun Y, Lane SI, Holt JE, Jones KT. Ndc80 N-terminal modification imposes a robust SAC signalling in mouse oocytes. **(In submit)**

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Statement of Contribution of Others

Three publications (chapter 2, 3 and 4) are included for consideration in this thesis. The research higher degree candidate Yan Yun carried out all experiments except that Dr Simon Lane constructed the Venus-Ndc80 vector in chapter 4. The manuscripts in chapter 3 and 4 were initially written by Yan Yun with correction from all other co-authors. The manuscript in chapter 2 was drafted by Prof. Keith Jones. Dr Simon Lane wrote the software developed for live chromosome tracking and kinetochore analysis and prepared Figure 3E-H and Figure 5 in chapter 2. All other data analysis and figure preparation were performed by Yan Yun.

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List of additional publications

Lane SI, Yun Y, Jones KT (2012) Timing of anaphase-promoting complex activation in mouse oocytes is predicted by microtubule-kinetochore attachment but not by bivalent alignment or tension. *Development* **139**: 1947-1955

Yun Y, Lane SI, Holt JE, Jones KT. Premature Separation of Dyads is the origin for maternal age related aneuploidy in mammalian eggs found from chromosome tracking. The Society for Reproductive Biology (SRB), Gold Coast, Australia (2012), **Oral presentation**

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Yun Y, Holt JE, Lane SI, McLaughlin MA, Merriman JA and Jones KT. Reduced spindle assembly checkpoint in oocytes from aged mice. The Society for Reproductive Biology (SRB), Melbourne, Australia (2014), **Oral presentation** (Oozoa award finalists)

Yun Y, Lane SI, Holt JE, Jones KT. N-terminal modification of Ndc80 can induce a spindle assembly checkpoint arrest in mouse oocytes. American Society for Cell Biology (ASCB), Philadelphia, United States (2014), **Poster presentation**

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Abstract

Advancing maternal age is a well-established risk factor associated with chromosome segregation errors in oocytes. In this thesis, I employed real-time high resolution imaging to examine the onset of aneuploidy and mechanisms regulating chromosome segregation in mouse oocytes. Specifically I determined 1) that although considerable cohesion loss occurs during MI, bivalent dynamics are not grossly affected, instead premature separation of dyads in MII was found to be the major segregation defect; 2) aged oocytes have decreased levels of SAC proteins on the kinetochores and possess both a lowered ability to maintain SAC arrest and re-establish bivalent biorientation following spindle disruption; 3) a genetic basis to aneuploidy susceptibility is likely to exist as suggested by the distinct aneuploidy phenotypes of two different mouse strains and 4) demonstrated that Ndc80 N-terminal modification was able to impose a robust SAC signalling, in doing so prevent chromosome mis-segregation in young mouse oocytes. Altogether this thesis directly examined the precise timing of chromosome segregation errors, and re-emphasized the role of a weakened SAC in maternal age-related aneuploidy.

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List of commonly used abbreviations

APC/C; Anaphase-Promoting Complex or Cyclosome

CPC; Chromosomal Passenger Complex

GVBD; Germinal Vesicle Breakdown

KT-MT; Kinetochore-Microtubule

MCC; Mitotic Checkpoint Complex

MetII; Metaphase II

MI; Meiosis I

MII; Meiosis II

NDJ; Non-disjunction

PBE; first Polar Body Extrusion

PSSC; Premature Separation of Sister Chromatids

SAC; Spindle Assembly Checkpoint