Susceptibility of mammalian oocytes to chromosome segregation errors with maternal aging

Yan Yun, M.S.

A thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

May 2014

School of Biomedical Sciences and Pharmacy

The University of Newcastle, Australia

Declaration

The thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository**, subject to the provisions of the Copyright Act 1968.

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Acknowledgements

I would like to say huge thanks to Prof. Keith Jones for his outstanding supervision and invaluable advice on the projects throughout my PhD duration. I also want to thank Dr Janet Holt for her diligent and critical comments on the writing of this thesis; and Prof. Eileen McLaughlin for the beneficial suggestions on the preparation of the thesis.

Many thanks to the members in the Jones' lab: Simon, Evan, Julie, Phoebe, Jess, Kyra, Suzanne, Michelle, Wai and Nikki. Without you guys around, the PhD duration would be less enjoyable. Special thanks must go to Dr Simon Lane, for his thoughtful induction of many lab techniques and helpful discussions on my projects.

Last but not least, a big thank to my family, Mum and Dad for all your understanding and support; and to my girlfriend Zhen (Jane), for her constant encouragement, which kept me always positive.

List of publications included as part of the thesis

Yun Y, Lane SI, Jones KT (2014) Premature dyad separation in meiosis II is the major segregation error with maternal age in mouse oocytes. *Development* **141:** 199-208

Yun Y, Holt JE, Lane SI, McLaughlin EA, Merriman JA, Jones KT (2014) Reduced ability to recover from spindle disruption and loss of kinetochore spindle assembly checkpoint proteins in oocytes from aged mice. *Cell Cycle* **13:** 1-10

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

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.

Dr Simon Lane

Date:

Dr Janet Holt

Date:

Dr Julie Merriman

Date:

Prof. Eileen McLaughlin

Date:

Prof. Keith Jones

Date:

Yan Yun (Candidate)

Date:

Prof. John Rostas

(Assistant Dean Research Training (ADRT))

Date:

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**

Yun Y, Lane SI, Holt JE, Jones KT. Live imaging shows pre-division during meiosis II as the leading cause of chromosome mis-segregation in oocytes from old mice. EMBO conference on Meiosis, Dresden, Germany (2013), **Poster presentation**

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 presenation**

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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.

List of figures

Chapter 1 – Introduction

Chapter 2 – Premature dyad separation in meiosis II is the major segregation error with maternal age in mouse oocytes

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