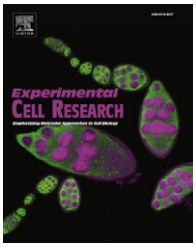
EXPERIMENTAL CELL RESEARCH 318 (2012) 1394–1399

Available online at www.sciencedirect.com

SciVerse ScienceDirect

www.elsevier.com/locate/yexcr



Review Article

Chromosomal, metabolic, environmental, and hormonal origins of aneuploidy in mammalian oocytes

*Keith T. Jones**, *Simon I.R. Lane*

Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, NSW 2308, Australia

ARTICLE INFORMATION

Article Chronology:
Received 30 November 2011
Revised version received
15 February 2012
Accepted 15 February 2012
Available online 24 February 2012

Keywords:
Aneuploidy
Spindle assembly checkpoint
Meiosis
Oocyte
Aging
Cell cycle

ABSTRACT

Aneuploidy is a leading cause of early embryo loss, miscarriage and birth defects in humans. It is predominantly brought about by the mis-segregation of homologous chromosomes (bivalents) in the first meiotic division (MI) of the oocyte, with advanced maternal age being a risk factor. Although its etiology is likely to be multifactorial the predominating factors remain amenable for study in models such as mice. Homologous chromosome separation in MI is achieved by the mono-orientation of functionally paired sister kinetochores but despite this unique division the Spindle Assembly Checkpoint (SAC), which prevents sister chromatid mis-segregation in mitosis, is functional in mouse oocytes. However, it remains to be fully established what types of error the SAC respond to, for example the presence of univalents, and how sensitive it is to attachment or tension defects in bivalent alignment. Such errors may increase with advanced maternal age as chromosomes lose their cohesive ties and the oocyte has less capacity to service the metabolic needs associated with meiotic division. Environmental insults and hormonal changes could also affect the fidelity of this process. Here we review how all these factors converge on the meiotic spindle during MI to cause mis-segregation errors.

Contents

* *Corresponding author.*
E-mail address: Keith.jones@newcastle.edu.au (K.T. Jones).

0014-4827/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.yexcr.2012.02.012

Introduction

The meiotic divisions in mammalian oocytes

All oocytes are created from primordial germ cells during fetal life. Before birth, their chromosomes undergo pre-meiotic S-phase, homologous chromosomes pair, recombine and begin to resolve as the synaptonemal complex, that has acted as a scaffold for these events, is dissolved. By birth, oocytes are arrested at the dictyate stage of meiosis I (MI), and remain so, enclosed in primordial follicles until the follicle is recruited to begin growth. A luteinising hormone (LH) surge triggers ovulation of the oocyte from the follicle as well as initiating resumption of MI in the oocyte. Thus by the time of ovulation, the oocyte has completed MI and has re-arrested at metaphase of meiosis II (MII). The sperm breaks this arrest at fertilization, and the oocyte completes its second meiotic division. All these events are covered in detail in other reviews [1,2].

Meiotic segregation: Homologous chromosomes in MI, sister chromatids in MII

Pairs of homologous chromosomes (i.e. paternal and maternal chromosome 1 etc.) are zippered together by the synaptonemal complex during fetal recombination. The process of double strand breakage and repair, which happens during recombination, physically ties the homologous chromosomes together (they 'crossover') such that typically 1–2 chiasmata, which are the morphological manifestations of crossover, are observed on each pair. These are not distributed randomly but tend to occur preferentially at certain foci. However, the numbers of recombination sites between homologous chromosomes are found to be highly variable, with some chromosome arms having no sites and others having many.

In the hours just preceding ovulation triggered by LH, it is the homologous chromosomes, also known as 'bivalents', which are segregated (Fig. 1A). The sister kinetochores of each chromatid pair acts as a functional unit in MI, and this ensures their mono-orientation to just one spindle pole and thus commitment to co-segregate. The MI oocyte divides asymmetrically resulting in the extrusion of a polar body, containing half of the newly segregated bivalents, it then quickly rearrests at metaphase of MII, a division in which sister chromatids are segregated (Fig. 1B). MII therefore resembles the mitotic division.

Aneuploidy in MI is common and increases with maternal age

Whole chromosome aneuploidies in dividing somatic cells result from the misegregation of sister chromatids, such that daughter cells have more or less chromosomes than their mother. Such aneuploidies are common in oocytes and are usually incompatible with development to term. Trisomy 21, Down Syndrome, is one of the few viable aneuploidies, although here again most trisomies are lost during gestation. MI, in which bivalents segregate, is believed to be the primary division in which errors arise. Interestingly maternal age plays a strong factor in the prevalence of aneuploidy, so for example a large recent study observed that the rate of mis-segregation for the most clinically relevant aneuplodies (chromosomes 13, 16, 18, 21, 22) increased from 20% to 60% in women between the ages of 35 and +43 years [3].

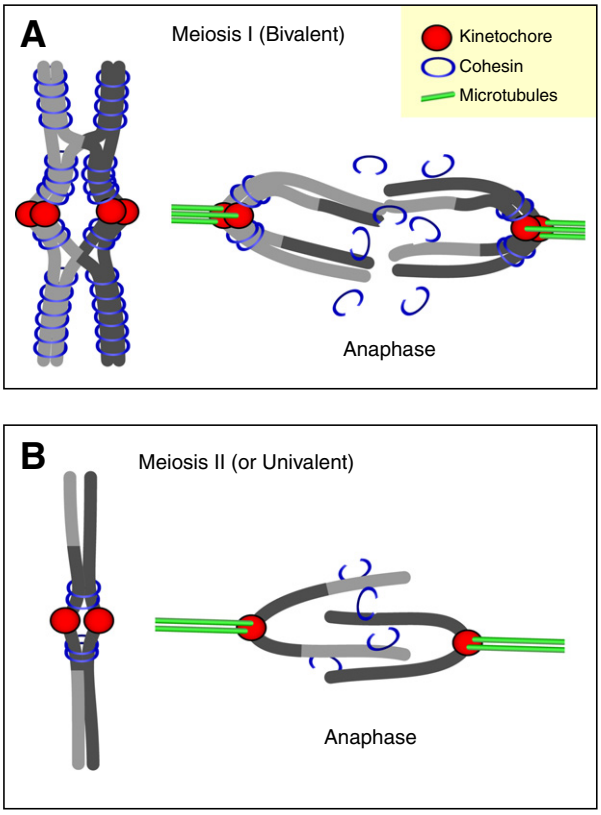


Fig. 1 – Chromosome segregation in meiosis. Schematic of the structure of homologous chromosomes (bivalents) in meiosis I (A) and sister chromatids in meiosis II (B). Right, illustration of how paired kinetochores in meiosis I act as a functional unit and so become mono-orientated (A) but in meiosis II kinetochores are unfused and are bioriented. Any univalents present in meiosis I could have their sister kinetochores unfused and so achieve biorientation.

The spindle assembly checkpoint is present and functional in MI

The spindle assembly checkpoint (SAC) is a surveillance mechanism employed in mitotic cells to prevent sister chromatid mis-segregation [4,5]. It does this by generating a signal that stops Cdc20 from activating the anaphase promoting complex/cyclosome (APC) before congression and alignment (biorientation) of all chromosomes on the metaphase plate. Segregation of sister chromatids is therefore only allowed at anaphase-onset, triggered by APC^{Cdc20} mediated by cyclin B1 and securin degradation, which results in a fall in CDK1 activity and rise in separase activity respectively. The SAC consists of several proteins from the Mad (mitotic arrest deficient) and Bub (budding uninhibited by benzimidazoles) families as well as Mps1, and in somatic cells it is widely reported that their loss is associated with aneuploidy.

It is tempting to infer that the high incidence of aneuploidy in oocytes is due simply to a loss of the SAC pathway. In women, a significant reduction in transcript levels for Mad2 and Bub1 has been associated with increased maternal age [6] but studies in aging mice, which also develop high rates of aneuploidy have