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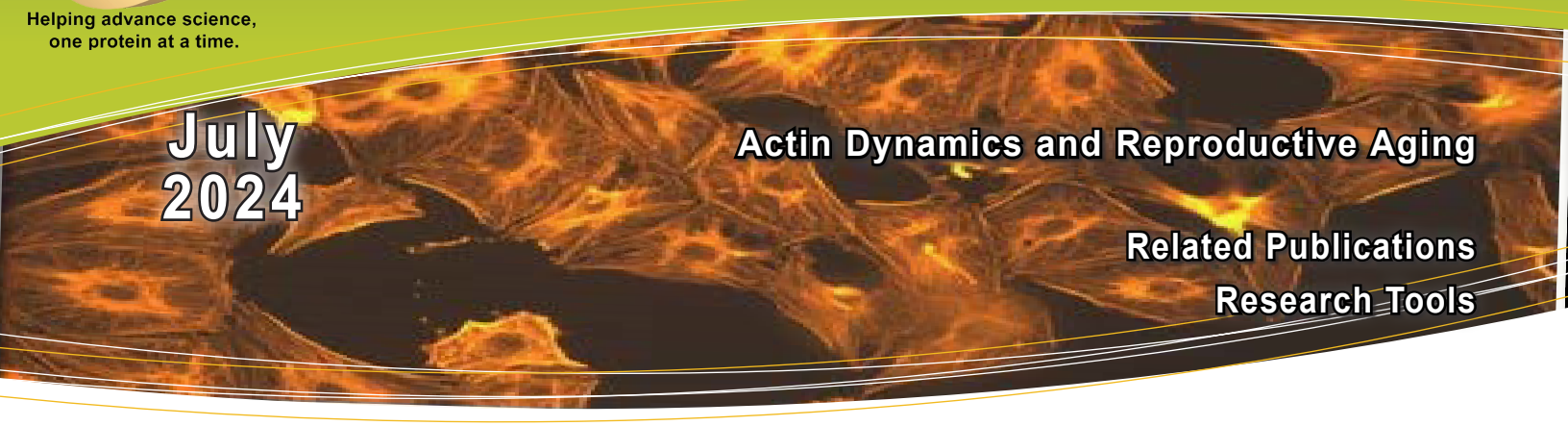

Actin Dynamics and Reproductive Aging

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Actin Dynamics and Reproductive Aging

Introduction

The actin cytoskeleton is crucial in various cellular processes, such as cellular migration, phagocytosis, and intracellular trafficking. Aging results in changes in actin expression and dynamics, which can contribute to multiple age-associated diseases and conditions, including cancer, vascular diseases, and neurodegenerative diseases[1]. Studies in yeast have revealed that the actin cytoskeleton is critical for nutrient metabolism and even lifespan determination[2].

Humans have three types of actins: α-, β- and γ-actin[3]. There are three α-actin isoforms found in contractile structures in muscle cells (cardiac, skeletal, and smooth muscle). β- and γ-actin are found in both muscle and non-muscle cells. Actin monomers (G-actin) can polymerize into long, helical filaments (F-actin). The helical structure of actin and the orientation of actin subunits create a directionality, which is important for the function of actin-binding motor proteins.

With age, the quantity and quality of oocytes diminish, and fertility significantly decreases from 35 years of age until menopause. Energy metabolism is one mechanism underlying the diminished quality of oocytes, and it has garnered much attention[4]. Recent evidence indicates that actin is essential for mammalian reproduction, and changes in actin dynamics with age impact age-related fertility and reproductive outcomes, which we highlight in this newsletter.

The Roles of Actin in Meiosis

Haploid mammalian eggs develop from diploid oocytes through meiosis I. Following fertilization, the egg undergoes meiosis II, separating sister chromatids. The segregation of chromosomes and subsequent sister chromatids relies on the function of the meiotic spindle[5]. The meiotic spindle is made of microtubules composed of tubulin subunits. Spindle microtubules are responsible for chromosome alignment to facilitate division. Recent evidence demonstrates that, in addition to tubulin, spindle actin is essential for proper spindle function[5]. Spindle actin helps bundle microtubules into functional k-fibers, and loss of spindle actin results in reduced k-fiber stability and errors in chromosome segregation[5,6]. In addition to spindle function, actin dynamics are essential for cytokinesis as actin forms a contractile ring that separates newly formed daughter cells. Following meiosis and fertilization, the newly formed embryo undergoes mitotic division. The mitotic spindle, which is required for mitotic cell division, differs from the meiotic spindle in that microtubules are nucleated from centrosomes. Here too, actin has been shown to be involved in the mitotic spindle and mitotic cytokinesis, underscoring the importance of actin in embryo development beyond meiosis[7].

Actin Dynamics in Age-Related Aneuploidies

Prior to segregation, homologous chromosomes are held together by cohesin. At the same time, sister chromatids remain bound at their centromeres by cohesin. During meiosis I, the cohesin between homologous chromosomes is cleaved, but the cohesin between sister chromatids is protected. Premature separation of sister chromatids results in errors in chromosome segregation, resulting in eggs with the incorrect number of chromosomes, or aneuploidy[8].

In humans, the most common aneuploidies are trisomies[8], such as Trisomy 21, which causes Down Syndrome, and Klinefelter syndrome (47,XXY), where phenotypic males have two X chromosomes. The prevalence of aneuploidies is dramatically higher in pregnancies that occur at advanced maternal age[9]. One cause of this phenomenon is, in part, the depletion of cohesin in aged oocytes[9]. However, Dunkley and Mogessie argued that cohesin depletion alone could not account for the rapid increase in aneuploidies and demonstrated in a 2023 Science Advances publication that actin limits age-related egg aneuploidies[10]. Specifically, they demonstrated that F-actin was responsible for maintaining the association of sister chromatids after cohesin depletion in aged eggs. They also demonstrated that disruption of F-actin in young eggs resulted in premature chromatid separation similar to aged eggs. Confirming this role, they showed that stabilization of F-actin decreased premature chromatin separation in aged eggs. Importantly, these findings were dependent on microtubule dynamics. The authors hypothesized that F-actin may be counteracting the pulling force of spindle microtubules.

The Aged Epigenome and Actin Dynamics

Epigenetic changes are modifications that result in changes in gene expression without modifying the genes themselves. These alterations include methylation, acetylation,

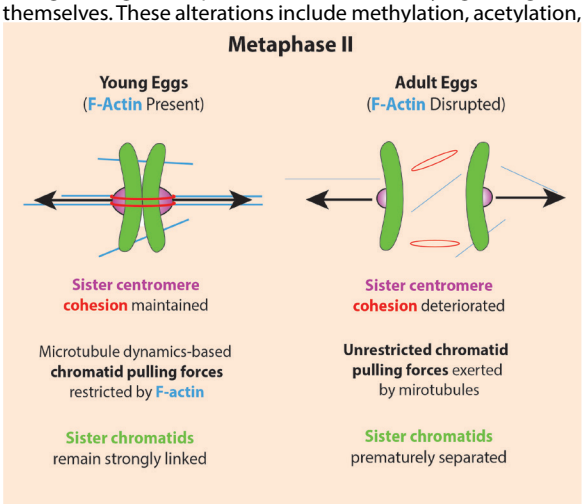

Figure 1. F-actin disruption accelerates aging-like premature chromatid separation in young eggs. Adapted from Dunkley et al. 2023[10]

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Sponsored Conferences

Small GTPases: Membrane Traffic and Cytoskeleton - FASEB Loews Ventana Canyon Resort, Tuscon AZ July 21st-July 25th, 2024

Neurobiology of Brain Discorders - GRS Rey Don Jaime Grand Hotel, Castelldefels, B, Spain. August 3rd-4th, 2024

Cytoskeleton Products

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phosphorylation, ubiquitylation, and sumoylation, which can be found on DNA, RNA, and histones[11]. DNA methylation is a biomarker of aging that can reliably determine the age of tissues across the lifespan[12].
For years, we have heard, sometimes contradictory, discussions of the benefits of resveratrol—a polyphenol found in the skin of grapes and red wine—as an anti-aging agent and a supplement with benefits against a wide range of ailments[13]. Based on pre-clinical animal studies, reproductive aging is among the list of resveratrol beneficiaries[14,15], though some studies underscore remaining unknowns for human fertility[16]. The mechanisms for the role of resveratrol in reproductive aging remain poorly understood.

A paper published last year in PNAS Nexus confirmed previous studies, demonstrating that resveratrol improved reproduction in female mice[17]. The authors further showed that resveratrol reversed gene expression changes associated with aging and reduced overall methylation in aged oocytes. When comparing oocytes from young mice with those from middle-aged and old mice, the authors revealed many differentially expressed genes, primarily the downregulation of many genes involved in actin cytoskeleton organization, actin binding, and regulation of these processes[17]. Resveratrol reversed this effect in aged oocytes, removing methylation in the promoter region of actin-related genes and restoring expression. Thus, the authors speculate that the beneficial effect of resveratrol on aged oocytes may be due, in part, to the restoration of actin organization and function. As discussed above, actin is essential for proper meiosis and mitosis during egg formation and embryo development. Additionally, there are indications that actin is directly involved in chromatin remodeling[18], which remains to be explored in the context of reproductive aging.

Summary
As maternal age continues to increase, fully understanding the mechanisms underlying age-related decreases in fertility and oocyte quality is essential. These studies clearly show that actin dynamics are involved in many aspects of reproduction and are associated with age-related reproductive decline. Many studies aimed at understanding the roles of actin dynamics, as well as other mechanisms and therapeutic strategies, in reproductive aging, have been conducted using mouse or other animal models. The translatability to human reproduction will need to be validated. Further, reproduction is not affected solely by the quantity and quality of oocytes and subsequent development of the embryo. Actin-mediated mechanisms of reproductive aging may be more broadly applicable, affecting tissues that support reproduction, like the ovaries, uterus, and testes. Indeed, evidence indicates that actin dynamics are important for the differentiation of uterine stromal fibroblasts into decidual cells, a process called decidualization that is required for a successful pregnancy[19]. Spermatogenesis has also been shown to rely on actin dynamics[20]. A more holistic understanding of the role of actin dynamics during reproductive aging is still needed.

Unlabeled Actin Proteins

Unlabeled Actins	Amount	Cat . #
Actin Protein Rabbit skeletal muscle	4 x 250 µg 2 x 1 mg 5 x 1 mg 10 x 1 mg	AKL99-A AKL99-B AKL99-C AKL99-D
Actin Protein Rabbit skeletal muscle	1 x 1 mg 5 x 1 mg	AKL95-B AKL95-C
Actin Protein Bovine cardiac muscle	1 x 1 mg 5 x 1 mg	AD99-A AD99-B
Actin Protein Smooth muscle, chicken gizzard	1 x 1 mg 5 x 1 mg	AS99-A AS99-B
Actin Protein Human platelet, non-muscle	2 x 250 µg 1 x 1 mg	APHL99-A APHL99-C
Pre-formed Actin Filaments Rabbit skeletal muscle	1 x 1 mg 5 x 1 mg	AKF99-A AKF99-B

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Actin Biochem Kits

Product	Assays	Cat. #
Actin Binding Protein Spin-Down Assay Biochem Kit Rabbit skeletal muscle actin	30-100	BK001
Actin Polymerization Biochem Kit (fluorescence format) Measure actin polymerization *in vitro*, contains rabbit skeletal muscle actin.	30-100	BK003
Actin Binding Protein Spin-Down Assay Biochem Kit Human platelet actin	30-100	BK013
G-Actin/F-actin In Vivo Assay Biochem Kit Measure the distribution of monomer and polymer actin	30-100	BK037

Pan Actin Antibody

Anti-Pan Actin Mouse Monoclonal Antibody (Clone 7A8.2.1) **RRID# AB_2884962** **Detection of actin in human, mouse, rat, and bovine**	1 x 500 µl 1 x 125 µl	AAN02 AAN02-S

Oxidized Actin and Actin Binding Protein Tools

Product	Amount	Cat #
MsrB2 Protein 6xHis	2 x 50 ug 1 x 1 mg	MB201 MB201-XL
MICAL-1 Protein 6xHis	2 x 50 ug 1 x 1 mg	MIC01 MIC01-XL
MICAL-Oxidized Actin Protein(>95% pure) Rabbit Skeletal Muscle	2 x 250 ug 1 x 1 mg	MXA95 MXA95-XL
MICAL-Oxidized (Pyrene labeled) Actin Protein (95% pure) Rabbit Skeletal Muscle	2 x 250 ug 1 x 1 mg	MPAX1 MPAX1-XL
Alpha-actinin protein: rabbit skeletal muscle	2 x 50 µg 10 x 50 µg	AT01-A AT01-C