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Review Article

A Hypothetical Molecular Mechanism Linking Loss of BRCA1 Function to Infertility

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Abstract

The BRCA1 gene has been well studied for its role as a tumor suppressor by repairing double-stranded DNA via homologous recombination during cell replication. Thus, an aberrant BRCA1 gene has extensively been shown to increase the risk for breast cancer and certain ovarian cancers through years of research. However, BRCA1's unique relationship to female fertility is not as well researched. Studies have shown that a lower ovarian primary follicle pool has been associated with BRCA1 mutations and increased infertility rates, but the molecular link has yet to be fully elucidated. Our previous research proposed a novel Ubc9-Caveolin-1-VEGF-SIRT1-ER-⍰ axis facilitated by functional BRCA1 with a novel downstream target being the tumor-promoting enzyme, Ubc9. It was shown that a mutated BRCA1 led to an accumulation of Ubc9, which resulted in reduced expression of Caveolin-1 and increased VEGF promoting tumor growth and metastasis. Furthermore, functional BRCA1 bound to Ubc9 activates the expression of SIRT1. Evidence suggests that SIRT activation is related to higher Anti-Mullerian Hormone (AMH) levels and increased fertility. This study proposes a hypothetical molecular mechanism for BRCA1 mutation and infertility. Continued research into our proposed BRCA1-Ubc9-SIRT1-AMH axis could yield potential new targets for chemotherapy against breast and ovarian cancer and could yield new methods for fertility treatments and preservation

Keywords: BRCA1; BRCA1a; Ubc9; TNBC; HGSOC; Cav-1; VEGF; SIRT1; AMH; Infertility; Biomarkers

Introduction

Infertility: Prevalence and Implications

Infertility is a pervasive issue that impacts the lives of millions of families worldwide. According to the World Health Organization, 12-13 in 100 hopeful parents are affected by infertility each year. Recent studies in the United States have indicated that up to 12% of persons with uteri at reproductive age (15-44) have struggled with infertility in their lifetime. Reproductive endocrinology and infertility continue to be a rapidly growing field as increasing numbers of couples seek counseling and medical support in bearing children [1]. Many prospective parents feel societal and cultural pressure to bear children making infertility a source of significant distress from feelings of inadequacy that can lead to depression [2]. Infertility also has apparent racial disparities, with African Americans two-fold more likely to suffer in silence or experience it for a more extended period than their Caucasian counterparts [3,4]. When African American patients seek help with assisted reproductive technology, their live birth success rate is significantly lower than that of Caucasian and Hispanic patients [5]. Theories have been proposed to explain this disparity, but more research is needed. Infertility is a far-reaching, complex disorder that poses many challenges to providers and patients, making it an essential field of study.

Infertility: Definition and Potential Causes

Clinically, infertility is defined as a disorder of the reproductive system where there is an inability to conceive after twelve months or more of regular unprotected intercourse. This definition can be stratified into primary and secondary infertility. Primary infertility is the inability to conceive or carry a pregnancy to live birth. Secondary infertility is the inability to do so after successfully bearing at least one child previously [6]. The causes of infertility encompass structural, hormonal, environmental, and genetic factors. Much research has been conducted regarding the

structural and hormonal causes of infertility with the emergence of more effective, targeted therapy. However, there is a dearth of information about potential genetic causes. This paper will focus on the emerging evidence that defects in the BRCA1 gene (one of many DNA repair genes) are associated with challenges in fertility [7].

BRCA1 genes: Tumor Suppression and Cancer Association

The BRCA genes are well studied in cancer research, specifically breast cancer and certain ovarian cancers. BRCA1 and BRCA2 function as tumor suppressor genes that repair double-stranded DNA breaks through homologous recombination during cell replication [8]. Mutations and aberrations in both BRCA 1 and BRCA 2 have proven to be associated with a 65-80% increased risk of breast cancer, and 20-45% increased risk in ovarian cancer, compared to 2.9% and 1.9% lifetime risk in the general population, respectively [9]. Furthermore, BRCA1 has been associated with more aggressive forms of breast cancer, triple-negative breast cancer, and high-grade serous ovarian cancer (HGSOC). Triple-negative breast cancer (TNBC) is so named due to its lack of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2), making it particularly resistant to existing chemotherapies. As a result, many patients with either mutation have increasingly been recommended for prophylactic procedures such as bilateral mastectomy and bilateral salpingo-oophorectomy (BSO) at an early age [10]. These prophylactic procedures and the combined effects of chemotherapy and radiation already pose a significant challenge to fertility preservation in BRCA mutation carriers, especially those who develop breast cancer or HGSOC. This paper will discuss the additional effects of BRCA genes, specifically on the ovarian follicular pool, leading to decreased fertility in the absence of these factors. African American women have been shown to have increased rates of both TNBC and BRCA1 mutation compared to other ethnicities making research into the molecular basis of BRCA1 as a means for therapy an essential topic for decreasing health disparities in breast cancer and infertility.

Correlating loss of BRCA1 Gene function to Infertility

Though the diagnosis of infertility is clinical, fertility is largely determined by the size of an individual's ovarian follicular pool. This number can be highly variable. Females are born with all the primordial follicles, or oocytes, they will ever have. The natural atresia of these primordial follicles begins before birth. The peak number of follicles is around 7 million occurring during the 2nd trimester of gestation [11]. By birth, female infants are left with around 2 million follicles that decrease to 300,000 – 400,000 by the start of puberty [11]. Following puberty and the initiation of regular menstruation, typically, one oocyte is shed monthly. This is considered an ovulatory cycle that marks a female as fertile. Natural atresia occurs throughout life until the primordial follicle pool is virtually depleted, after which ovarian failure occurs, or menopause, at the average age of 51 in the US [12]. Overall, 99.9% of all oocytes undergo atresia or apoptosis [7]. The number of follicles women are born with is variable, as well as how quickly they deplete their supply.

The BRCA genes have been of increasing interest for their potential role in aging and infertility. The National Institute of Health published a multi-institutional collaboration proposing an explanation to age-related fertility decline based on cellular repair mechanisms. It specifically proposes the BRCA1 gene can be actively researched as a cause of decreased ovarian follicle reserve due to accelerated "aging" of the ovaries. They propose that certain repair molecules, including BRCA1, ATM, RAD51, and MRE11, decrease in ovarian supply over the years. This decrease in repair mechanism molecules leads to increased cellular suicide and follicular atresia [7].

Two clinical studies have shown links between BRCA1 mutation carriers and decreased fertility. Daum et al. observed a decrease in primordial follicle reserve in BRCA1 mutation carriers who underwent ovarian cryopreservation and IVF prior to chemotherapy. The control group and BRCA1 mutation carrier group had similar baseline characteristics, but the latter group required higher doses of hormone for ovulation stimulation, resulting in lower yield per cycle and had fewer oocytes per ovarian fragment [13]. A prospective cohort study by Phillips et al. measured relative levels of anti-Mullerian hormone (AMH) in BRCA1 and BRCA 2 mutation carriers. AMH is released by ovarian primordial follicles and is commonly used as a reliable proxy for fertility in the clinical setting [14]. Decreased levels of AMH increases the activation rate and thus depletion rate of the primordial follicle pool leading to low fertility/infertility and possibly early menopause. AMH is low at birth, peaks during puberty, and then declines with age to an undetectable level at menopause. AMH is thus a useful marker for ovarian function [15,16]. Phillips found that BRCA1 carriers had a 25% decrease in AMH in the third and fourth decade, whereas the BRCA2 mutation carriers had comparable levels to non-carriers. The study focused on patients who did not undergo prophylactic procedures or cancer treatment due to their BRCA mutation carrier status [17]. Both studies indicate a link between clinically decreased fertility and BRCA1 mutation carrier status.

Sirtuins, and Ovarian Aging

Going further, research has suggested certain molecular mechanisms can explain the complex concept of ovarian aging. A study by Zhou et al. explored Sirtuins possible role in ovarian aging. Ovarian aging is a steady decrease in follicle number and quality of eggs. Caloric restriction without malnutrition is a commonly used method to delay aging and promote longevity in experimental animal models. Zhou et al. postulated that caloric restriction may cause a cascade that activates Sirtuins (SIRT1, SIRT3, and SIRT6) to elicit anti-aging effects [18]. They expounded this concept to ovarian aging and found that the mice on a calorie-restricted diet had a significantly greater number of primordial follicles than the control mice. They also found that these mice under caloric restriction had increased levels of SIRT1, SIRT3, and SIRT6 in the ovaries, which

was positively correlated with the size of the primordial follicle pool. A similar study done by Zhou et al. set out to elucidate the specific effects of SIRT1 and its possible relationship to ovarian lifespan and follicle reserve. They used obesity-induced mouse models to demonstrate the effects of SIRT1 as obesity has been known to negatively impact fertility. The Obese mice were given SRT1720, which is a known specific activator of SIRT1 [18]. The SRT1720 treated mice lost weight and showed similar effects as the calorie-restricted mice. SRT1720 increased the follicle reserve and down-regulated mammalian target of rapamycin (mTOR). mTOR has been suggested to be involved in the activation of primordial follicles in mammals and is inhibited by SIRT1 [18]. Thus, this suggests SIRT1 has a similar action to AMH by inhibiting activation and preserving the ovarian follicle pool.

BRCA1, Ubc9, Sirtuins and a Potential Axis for Novel Therapy

In our previous work, we first proposed a novel Ubc9 -Caveolin-1-VEGF- SIRT1-ER-a axis that is facilitated by functional BRCA1 [19]. When BRCA1 is mutated, this axis is disturbed, and it results in TNBC with epithelial to mesenchymal transition that allows for metastasis to the lungs [20]. This mechanism identifies a novel downstream target for BRCA1: SUMO conjugating enzyme Ubc9. Ubc9 is a tumor-promoting enzyme that has been shown to be a key player in not only the migration of BRCA1 mutant TNBC cells but also HGSOC cells. BRCA1 binding to Ubc9, displays tumor suppressor function. BRCA1 tethers Ubc9 to prevent Ubc9 tumor-promoting effects. Furthermore, when Ubc9 is bound to BRCA1, SIRT1 expression is activated [20]. Mutant BRCA1 cannot bind Ubc9 leading to accumulation of the enzyme causing reduced expression of Caveolin-1 and increased levels of vascular endothelial growth factor (VEGF), which promotes tumor growth and metastasis. Extrapolating further, the objective of this study is to investigate the association and effects of varying levels of Ubc9, SIRT1, and AMH in BRCA1 mutation carriers, as it relates to fertility. We have previously shown that BRCA1 binds Ubc9, and this leads to the activation of SIRT1 expression. The evidence that is shown in this study suggests that SIRT1 activation is related to high levels of Anti-Mullerian Hormone (AMH) and high fertility. We thus hypothesize that a mutation or dysfunction in the BRCA1 gene would lead to an increase in the concentration of Ubc9 activity, and in turn, SIRT1 and AMH levels would be suppressed. This would ultimately lead to a significant decrease in fertility, rapid rate of follicular atresia, damage to oocyte and ovarian cancer.

Conclusions

The presence of patients with BRCA1 mutation or dysfunction has profound impacts on women's lives across the globe. The role that BRCA1 plays in tumor suppression and the mutation's impacts on cancer development is a strong area of research. However, there is increasing evidence that BRCA1 dysfunction independently correlates with decreased fertility. Studies have correlated the mutation with decreased numbers of primordial follicles, increased difficulty with ART, and decreased levels of AMH [7-17]. Furthermore, studies have shown similar molecular messengers and regulators in ovarian aging as in tumorigenesis such as Sirtuins [18]. Given our previous work outlining the molecular model for BRCA1/1a mutation and dysfunction and its impacts on ovarian cancer through Ubc9 and SIRT1, we can extend our model to ovarian aging and fertility. Knowing that wild-type BRCA1/1a binds Ubc9 to prevent its aggregation allowing the activation of SIRT1 allows us to propose a molecular mechanism that connects BRCA1/1a dysfunction to decreased SIRT1 activation, which then leads to loss of ovarian follicular preserves (Figure1).

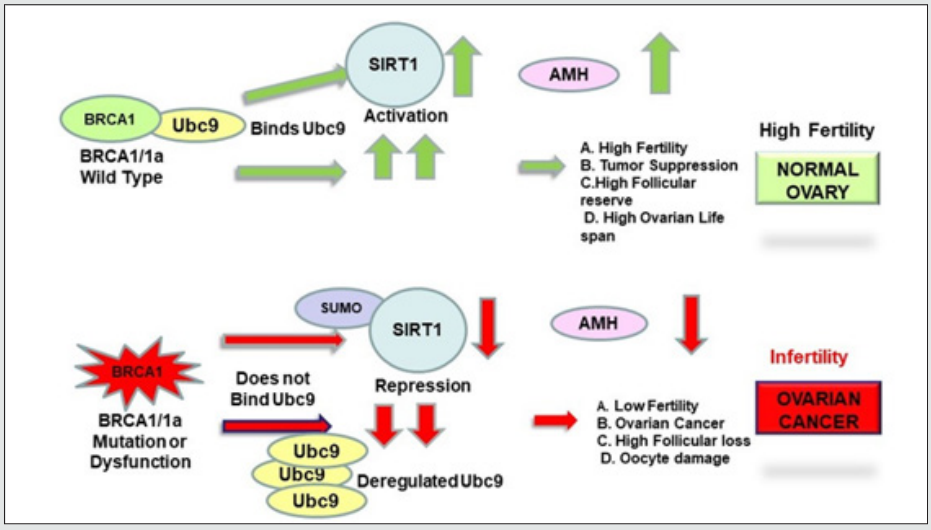

Figure 1: Novel Molecular Mechanism for the development of Infertility in women with BRCA1 mutations or dysfunction. Model for normal ovarian function where wild type BRCA1/1a functions as a tumor suppressor and promotes higher follicular reserve. Abnormal ovarian function is demonstrated with a mutated/dysfunctional BRCA1/1a that fails to bind Ubc9, leading to increased rates of cancer and lower follicular reserve.

The potential impact of this mechanism is far-reaching. African American women are two-fold more likely to experience infertility than their Caucasian counterparts even after adjusting for marital status, socioeconomic situations, and other common risk factors for infertility [3]. African American women are more likely to suffer in silence with infertility and experience it for a longer period than Caucasian women [3,4]. Also, when African American women do seek out help with assisted reproductive technology, their live birth success rate is significantly lower than that of Caucasian and Hispanic women [5]. Combining this information with the apparent increased prevalence of the BRCA1/1a mutation among African American women with breast cancer, the health disparity in this population is two-fold [21]. Reproductive justice supports the right of mothers to bear or not bear children and raise families in a healthy and safe environment. Patients with BRCA1/1a mutation and dysfunction must navigate a complicated and emotionally fraught series of decisions regarding their health in addition to the burden of decreased fertility. Without more knowledge of the causes of this potentially devastating problem, we cannot help these patients receive the support they need to conceive and bear children. With the increasing focus on aging and fertility, it is imperative that more research is conducted to shed light on molecular mechanisms for potential therapy and recommendations.

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References

1. American Society for Reproductive Medicine; Society for Assisted Reproductive Technology. (2017) assisted reproductive technology fertility clinic success rates report. US Department of Health and Human Services, Atlanta, GA, USA.
2. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA (2012) National, Regional, and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys. PLoS Medicine 9(12): e1001356.
3. Wellons MF, Lewis CE, Schwartz SM, Gunderson EP, Schreiner PJ (2008) Racial differences in self-reported infertility and risk factors for infertility in a cohort of black and white women: The CARDIA Women's Study. Fertility and Sterility 90(5): 1640-1648.
4. Wiltshire A, Brayboy LM, Phillips K, Matthews R, Yan F (2019) Infertility knowledge and treatment beliefs among African American women in an urban community. Contraception and Reproductive Medicine 4(1): 16.
5. Shapiro AJ, Darmon SK, Barad DH, Albertini DF, Gleicher N (2017) Effect of race and ethnicity on utilization and outcomes of assisted reproductive technology in the USA. Reproductive Biology and Endocrinology: RB&E 15(1): 44.
6. WHO | Infertility definitions and terminology (2016) WHO.
7. (2021) A molecular explanation for age-related fertility declines in women | National Institutes of Health (NIH).
8. Jackson SP, Bartek J (2016) The DNA-damage response in human biology and disease. Nature 461: 1071-1078.
9. Antoniou AC, Gayther SA, Stratton JF, Ponder BA, Easton DF (2000) Risk models for familial ovarian and breast cancer. Genet Epidemiol 18: 173-90.
10. Zhang X, Niu J, Che T, Zhu Y, Zhang H, et al. (2020) Fertility preservation in BRCA mutation carriers-efficacy and safety issues: A review. Reprod Biol Endocrinol 18(1): 11.
11. Geber S, Megale R, Vale F, Lanna AMA, Cabral ACV (2012) Variation in ovarian follicle density during human fetal development. Journal of Assisted Reproduction and Genetics 29(9): 969-972.
12. (2021) Menopause - Symptoms and causes.
13. Daum H, Peretz T, Laufer N (2018) BRCA mutations and reproduction. Fertil Steril 109(1): 33-38.
14. Grynnerup AG, Lindhard A, Sørensen S (2012) The role of anti-Müllerian hormone in female fertility and infertility - an overview. Acta Obstet Gynecol Scand91(11): 1252-1260.
15. Pankhurst MW (2017) A putative role for anti-Müllerian hormone (AMH) in optimising ovarian reserve expenditure. In Journal of Endocrinology 233 (1): R1-R13.
16. Visser JA, De Jong FH, Laven JSE, Themmen APN (2006) Anti-Müllerian hormone: A new marker for ovarian function. Reproduction 131(1): 1-9.
17. Phillips KA, Collins IM, Milne RL, McLachlan SA, Friedlander M, et al. (2016) Kathleen Cuningham Consortium for Research into Familial Breast Cancer (kConFab). Anti-Müllerian hormone serum concentrations of women with germline BRCA1 or BRCA2 mutations. Hum Reprod 31(5): 1126-1132.
18. Zhou XL, Xu JJ, Ni YH, Chen XC, Zhang HX, et al. (2014) SIRT1 activator (SRT1720) improves the follicle reserve and prolongs the ovarian lifespan of diet-induced obesity in female mice via activating SIRT1 and suppressing mTOR signaling. Journal of Ovarian Research 7(1): 97.
19. Desai A, Xu J, Aysola K, Akinbobuyi O, White M (2015) Molecular Mechanism Linking BRCA1 Dysfunction to High Grade Serous Epithelial Ovarian Cancers with Peritoneal Permeability and Ascites. J Gynecol Res 1(1): 103.
20. Xu J, Shumate C, Qin Y, Reddy V, Burnam Y (2017) A novel Ubc9 -dependent pathway regulates SIRT1- ER-α Axis and BRCA1- associated TNBC lung metastasis. Integrative Molecular Medicine 4(4).
21. Pal T, Bonner D, Cragun D, Monteiro AN, Phelan C (2015) A high frequency of BRCA mutations in young black women with breast cancer residing in Florida. Cancer 121(23): 4173-4180.

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