Maturitas 92 (2016) 15–23

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review article

Menopause: Genome stability as new paradigm

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ARTICLE INFO

Article history:
Received 30 June 2016
Accepted 7 July 2016

Keywords:
Menopause
GWAS
Genetics
DNA repair and maintenance
Health risks
New paradigm

ABSTRACT

Menopause is defined as the age-dependent permanent cessation of menstruation and ovulation due to ovarian failure. Menopause occurs on average around the age of 51 years. Recent genome-wide association studies (GWAS) have identified over 44 genetic variants that are associated with age of onset of natural menopause. Genes linked with menopause can be classified into three major groups: genes implicated in genome stability (DNA repair), immune function and mitochondrial biogenesis. Biological and epidemiological data indicate that reproductive performance, age at menopause and longevity are interlinked through common genetic factors, which play a pivotal role in DNA repair and genome maintenance, which has been linked before with the process of ageing. Consequently, ageing of the soma as a result of inefficient DNA repair appears also to be responsible for failure to reproduce and the subsequent occurrence of menopause. In this way reproductive performance may be strongly linked to the physical condition of the soma and may be a very good predictor of general health in later life.

Contents

1. Introduction

Menopause is defined as the natural, permanent cessation of menstruation and ovulation due to ovarian failure. “Spontaneous” or natural menopause occurs after 12 months of amenorrhea as ovarian hormone secretion diminishes, on average around the age of 51 years in Caucasian women. The large variation in normal

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http://dx.doi.org/10.1016/j.maturitas.2016.07.006
0378-5122/

menopausal age, ranging from as early as 40 years to as late as 62 years, is thought to represent the variability in ovarian ageing [1]. Multiple factors, including hormonal and environmental exposures, socio-economic status, nutrition, medical care, and stress throughout the life course are hypothesized to influence growth rate, including body size, weight and height, development in general as well as the ageing process and hence life expectancy in humans. In women this applies to menarche and menopause as well. The complexity of these factors and the pathways related to their effects on each sentinel event complicate evaluation of the relationship between menarche and menopause [2]. Establishing a trend in the age at which menopause occurs is challenging due to small sample sizes, a selective or non-representative population source, and inconsistent definitions for menopause across studies that range from self-definition to use of biomarkers plus reported absence of menses for 12 consecutive months. Hence, secular changes in menopausal age are more controversial with individual studies reporting conflicting findings [2]. Approximately 85% of women report symptoms of varying type and severity during their menopausal transition. Symptoms experienced may include vasomotor symptoms, sleep disturbances, psychological symptoms, cognitive and urogenital problems as well as sexual dysfunction [3]. Moreover, the end of a woman's reproductive lifespan is associated with multiple adverse outcomes, including breast cancer, cardiovascular disease and infertility. The biological processes that govern the timing of the beginning and end of reproductive life span are not well understood. Genetic variants are known to contribute to about 50% of the variation in both age at menarche and menopause [4]. This paper reviews the results of large-scale genetic association studies and discusses the impact of these findings on our current understanding of menopause. Finally, it will present a novel paradigm for ovarian ageing.

2. Early genetic studies on age of menopause

Despite the strong genetic component, very few genes associated with age at natural menopause (ANM) have been identified. In days prior to the development of GWAS, genetic studies had to rely on genome-wide linkage analysis and the so-called "candidate gene association" approach. The former method requires family data and can detect rare genetic variants with relatively large effects on the trait studied. This approach, however, is not suitable for the identification of variants with smaller effects. This is mainly due to differences in associations studied (i.e. linkage/co-segregation vs. true linkage) and the resolution of the genomic mapping (large blocks in genuine linkage studies vs SNP's in LD blocks in GWAS). Moreover, candidate gene approaches are based on educated guesses as to which genes or pathways are most likely to be associated with a certain phenotype. This strategy is limited however, by our incomplete knowledge of the function of the human genome, and thus may miss important novel genes or pathways [5].

Two genome-wide linkage analyses of ANM have been published to date. The first study was conducted in Dutch sister pairs using a selective sampling scheme restricting the sample to female sibling pairs with menopausal ages in the extremes of the menopausal age distribution. That study identified a significant locus at the X chromosome as well as a suggestive locus at the short arm of chromosome 9. The linkage peak on the X chromosome was located in a region previously associated with premature ovarian insufficiency (POI), and subgroup analysis demonstrated that the peak was due to women undergoing early menopause [6]. A second genome-wide linkage study for ANM was conducted in women participating in the community-based Framingham Heart Study. No significant loci were identified but three suggestive loci were reported on chromosomes 8, 11 and 16. The two previously reported loci at the chromosomes 9 and X could not be confirmed [7]. A recurrent problem in all these studies is that successful replications are generally missing. Moreover, it seems very likely that a lot of genetic variants with small effects are determining age at menopause and consequently larger well-defined cohorts are needed to detect this genetic variation.

Early candidate gene studies focused on genes involved in sex-steroid biosynthesis and metabolic pathways or in vascular homeostasis, yielding inconsistent associations with SNP's in oestrogen receptors and the onset of natural menopause (for a comprehensive review see He and Murabito) [5]. Multiple CYP family members have been examined in association with ANM. A common polymorphism in the *CYP1B1* gene was found to be associated with an older ANM. Different polymorphisms in the *CYP19A1* gene were associated with ANM. Similarly, genes involved in the vascular pathway such as *F5*, *APOE* and *NOS3* so far have yielded conflicting results that need to be confirmed to determine their associations with ANM. Association studies of candidate genes involved in other biological pathways implicated in intra-ovarian regulators of folliculogenesis are sparse and the results are inconclusive at this stage as they have not been replicated in other studies with a similar design [5]. Another study examined the relationship between Anti-Müllerian Hormone (AMH) and its receptors and age of natural menopause. A common polymorphism in the *AMH* gene was not associated with age at menopause. However, a polymorphism in the AMH type 2 receptor (*AMHR2*) was significantly associated with age at menopause. Moreover, this SNP also showed significant interaction with the number of offspring. Nulliparous women homozygous for the G-allele entered menopause about 2–3 years earlier compared with nulliparous women homozygous for the A-allele. The latter finding was replicated in another cohort in the same study [8]. These findings suggest a role for AMH signalling in the regulation of the primordial follicle recruitment in women and therefore a role in the onset of menopause [9]. A more comprehensive candidate gene study examined 278 pre-specified candidate genes in nine groups of biologically plausible pathways and related phenotypes [10]. Of the candidate genes studied sixteen were found to be significantly associated with ANM. Of note, one SNP in the *FSHB* gene was found to be associated with an older age at menarche as well as an older ANM. The study also confirmed previously identified polymorphisms in the *FSHB* and *ESR2* genes. It established the relationship between the sex steroid-hormone metabolism and biosynthesis pathway and ANM. Moreover, genes involved in POI were associated with age at menopause. This finding supports the hypothesis that genes leading to the extremes of phenotypes also influence normal phenotypic variation in the general population [5,10].

2.1. Results of genome-wide association studies (GWAS) in menopause

GWAS can overcome the aforementioned difficulties: they can be carried out at a very large scale and represent an unbiased, hypothesis-free approach to discover novel susceptibility loci for all kind of diseases as well as traits like age at menopause.

The first GWAS conducted was a joint analysis of two traits i.e. menarche and menopause, in about 17,000 women. For ANM, the authors identified 13 SNPs clustered at chromosomes 5, 6, 19 and 20 [11]. In a similar second study from the Netherlands the loci on chromosomes 19 and 20 were replicated and another locus at chromosome 13 was identified to be associated with ANM [12]. Subsequently, the four common genetic variants (i.e. rs 480666 on chromosome 9; rs 16991615 on chromosome 20,: rs 9379896 on chromosome 6 and rs 244715 on chromosome

5) identified by genome-wide association studies had a significant impact on the odds of having early menopause in an independent cohort from the Breakthrough Generations Study, suggesting that common genetic variants influencing natural menopause constitute also risk factors for early onset of menopause [13].

A recent meta-analysis of ANM was performed in nearly 40,000 women of European ancestry from 22 studies with replication in an additional 14,000 women. Four of the previously reported loci were confirmed, and thirteen novel loci were identified highlighting pathways important to somatic as well as reproductive ageing. The genes involved can be classified into three major groups: genes implicated in DNA repair and genome maintenance, mitochondrial biogenesis, as well as in immune function. None of the identified genes appeared to have an evident connection with folliculogenesis [14]. However, most of the syndromes caused by DNA repair gene defects are associated with infertility in mice as well as with POI in humans [15]. A further age at menopause GWAS signal in or near *FSHB* is associated with circulating FSH levels. Previously, the menopausal rise in hypothalamic and pituitary hormone secretion was thought to be a passive consequence of loss of sex steroid feedback inhibition. Although it is possible that the implicated proteins also have peripheral actions directly on the ovary, increasing evidence suggests that central neural control is involved in reproductive ageing [16].

Whether the identified European menopause loci are also relevant for other ethnicities has also been studied. A recent GWAS meta-analysis in 6500 women with African ancestry derived from 11 studies across the USA revealed identical loci being associated with age at menopause [17]. Similarly, the 17 by GWAS identified European SNPs, plus 3 additional SNPs that were not in linkage disequilibrium (LD) in an Asian ancestry population, have been evaluated among 3500 Chinese women with a natural menopause. All 22 SNPs showed the same direction of association as in the European ancestry populations. Furthermore, 8 SNPs showed significant associations with ANM in Chinese women [18]. Moreover, a recent meta-analysis looking at whole-blood gene expression in nearly 15,000 individuals of European ancestry identified about 1500 genes that are differentially expressed with chronological age. This study identified a compendium of genes and pathways associated with human chronological age. By leveraging transcriptional information across large, multi-ethnic cohorts, different tissue types and genomic repositories, they captured an unprecedented overview of the complex and temporally dynamic biological pathways orchestrating the ageing process. Their results of an age-expression and pathway enrichment analysis were consistent with known ageing mechanisms including dysregulation of transcription and translation, metabolic function, DNA damage accumulation, immune senescence, ribosome biogenesis and mitochondrial decline [19]. These studies provided evidence that genetic variants influencing reproductive traits identified in women of European ancestry are also important in women of African and Asian ancestry, suggesting that menopause is largely regulated in a similar fashion amongst different ethnic populations and points to a strong evolutionary conservation of the underlying mechanism(s).

Finally, a very recent, more extensive genetic analysis in nearly 70,000 women, incorporating common as well as low-frequency coding variants, identified 44 regions with common variants, including two regions harbouring additional rare missense alleles of large effect. This study confirmed all loci previously reported and further strengthened the connection with DNA repair and genome maintenance pathways [20]. Of the 44 GWAS-highlighted regions 29 contained one or more DNA damage response (DDR) genes within 500 kb and for 18 of these the DDR candidate gene was the nearest gene or the signal was associated with the expression of a DDR gene at the locus. Moreover, seven of the ten significantly associated ANM pathways were also involved in DDR. The notion that the loci linked to ANM are preserved over long ethnic distances, implying strong conservation of the underlying molecular mechanism is in consistent with the fact that the genome maintenance machinery is exceptionally strongly conserved in essence even from yeast to mammals [21].

2.2. From GWAS to candidate genes

Few previous candidate genes have exceeded the conventional genome-wide significance threshold in the published GWAS of age at menarche and ANM. This lack of overlap is likely due to the very stringent significance threshold used in GWAS to restrict the number of false-positives at the cost of an increase of false-negatives. Indeed, when a less stringent significance threshold was used in GWAS, SNPs in or near five of the pre-GWAS candidate genes were found significantly associated with ANM [14]. Another possible explanation of this inconsistency is suboptimal genomic coverage for some candidate genes in these GWAS, as important genetic variants may not have been included and tested. Lastly, the lack of control for population stratification and the small sample size in some candidate gene association studies may account for some of the discrepancies [5].

To date GWAS have identified over 44 common susceptibility loci for ANM [20]. Together these account only for 2.5–4.1% of the observed variation in ANM [22]. Recently, investigators have used genome-wide association in a bivariate meta-analysis of both menarche and menopause to identify genes involved in determining a woman's reproductive lifespan. They observed a significant genetic correlation between the two traits using genome-wide complex trait analysis. However, they were unable to detect robust statistical evidence for individual variants with an effect on both traits. Genetic studies have identified dozens of highly penetrant rare mutations associated with reproductive disorders, and also numerous common genetic variants associated with the timing of puberty or menopause. These findings, alongside other functional studies, have highlighted a diverse range of mechanisms involved in reproductive ageing, implicating core biological processes such as cell cycle regulation and energy homeostasis [16]. Moreover, a novel association with age at menopause was detected for a variant in the DNA mismatch repair gene *MSH6* that showed altered mRNA expression levels in multiple tissues [4]. Recessive mutations in two gene members of the mini chromosome maintenance family i.e. *MCM8* and *MCM9* segregate with the premature ovarian insufficiency (POI) phenotype in family studies [23,24]. Indeed, a GWAS locus at *MCM8* has a fairly large effect on normal menopausal timing, with each minor allele increasing menopausal age by 1 year [14]. Compared with fibroblasts from unaffected daughters, DNA break repair was deficient in fibroblasts from the affected individuals, likely due to inhibited recruitment of *MCM8* to sites of DNA damage [23]. Both *MCM8* and *MCM9* mutations inhibit the formation of foci at the site of doublestrand breaks (DSBs). *MCM8* and *MCM9* form a complex with each other at sites of DSBs and recruit *RAD51* to promote repair via the error-free homologous recombination repair pathway [25]. Mouse knockout models of these two genes show gonadal failure and chromosomal instability, which demonstrates the key role of DSB repair in oocyte formation as well as oocyte survival [25,26]. A notable inclusion in the most recent list of DDR annotated genes is BRCA1, which is implicated in hereditary forms of breast and ovarian cancer and is strongly involved in DSB repair by homologous recombination. In addition, seven direct binding partners of *BRCA1*: *BRE, MSH6, POLR2H, FAM175A, UIMC1, RAD51* and *CHEK2* were among the ANM-associated genes, further emphasizing the

Table 1
Genome maintenance associated genes correlating with age at menopause (ANM)[a].

Gene	Pathway	Function	Risk SNP	freq	p-value	Reference
APEX1	Base-excision repair	Endonuclease	rs1713460	0.30	2E-10	Day 2015
APTX	Base-excision and single strand break repair		rs4879656	0.37	2E-8	Day 2015
BRCA1	Homologous recombination		rs1799949	0.68	8E-11	Day 2015
BRE	Homologous recombination		rs704795	0.40	2E-15	Day 2015
BRSK1	DNA damage checkpoint regulation	Kinase	rs11668344	0.36	6E-85	He et al. [11], Stolk et al. [14], Day 2015
			rs2547274	0.91	3E-13	
			rs12461110	0.35	8E-16	
CDK12	Cell cycle regulation	Kinase	rs2941505	0.32	2E-9	Day 2015
CHD7	Chromatin remodelling	Helicase	rs10957156	0.76	5E-9	Day 2015
CHEK2	DNA damage checkpoint	Kinase	rs5762534	0.84	6E-9	Day 2015
DIDO1	Apoptosis induction		rs2236553	0.24	6E-10	Day 2015
			rs13040088	0.21	2E-10	
DMC1	Homologous recombination	Recombinase	rs763121	0.36	2E-13	Day 2015
EXO1	Mismatch repair and recombination	5'–3' exonuclease	rs1635501	0.48	8E-10	Stolk et al. [14], Day 2015
			rs2236918	0.45	8E-14	
FAM175A	DNA damage cell cycle checkpoint and ds break repair		rs4693089	0.51	9E-23	Stolk et al. [14], Day 2015
FANCI	Inter-strand crosslink repair		rs2307449	0.41	4E-13	Stolk et al. [14], Day 2015
			rs1054875	0.40	2E-19	
FBXO18	Homologous recombination	DNA helicase	rs10905065	0.61	4E-8	Day 2015
HELB	Homologous recombination and translesion synthesis	DNA helicase	rs3741604	0.52	2E-5	Day 2015
			rs1183272	0.45	7E-4	
			rs7397861	0.64	7E-6	
HELQ	Homologous recombination	DNA helicase	rs4693089	0.51	9E-23	Stolk et al. [14], Day 2015
INO80	Chromatin remodelling and homologous recombination		rs9796	0.46	1E-10	Day 2015
KNTC1	Chromosome segregation		rs1727326	0.15	2E-9	Day 2015
MCM8	Homologous recombination and DNA replication		rs16991615	0.93	2E-89	He et al. [11], Stolk et al. [14], Day 2015
			rs451417	0.12	5E-9	
MLF1IP	Centromere assembly		rs6856693	0.58	1E-14	Day 2015
MSH5	Mismatch repair and meiotic recombination		rs2230365	0.84	8E-10	Day 2015
			rs707938	0.32	7E-15	
MSH6	Mismatch repair	ATPase	rs1800932	0.81	3E-11	Perry [61] Day 2015
MYCBP	Transcription regulation during cell cycle		rs4246511	0.71	5E-21	Stolk et al. [14], Day 2015
PAPD7	Sister chromatid cohesion	DNA polymerase	rs427394	0.41	4E-9	Day 2015
PARL	Regulates mitochondrial remodelling and apoptosis		rs16858210	0.75	3E-9	Day 2015
PARP2	Base-excision repair and lagging strand elongation	DNA polymerase	rs1713460	0.30	2E-10	Day 2015
POLG	Base-excision repair and mtDNA replication	Mitochondrial DNA polymerase	rs2307449	0.41	4E-13	Stolk et al. [14], Day 2015
			rs1054875	0.40	2E-19	
POLR2E	Transcription	RNA polymerase subunit	Rs349306	0.13	2E-10	Day 2015
POLR2H	Transcription	RNA polymerase subunit	rs16858210	0.75	3E-9	Day 2015
PRIM1	DNA replication initiation	Primase	rs2277339	0.10	2E-19	Stolk et al. [14], Day 2015
RAD51	Homologous recombination and inter-strand crosslink repair	Recombinase	rs9796	0.46	1E-10	Day 2015
RAD54L	Homologous recombination	DNA helicase	rs12142240	0.68	7E-9	Day 2015
REV3L	Translesion synthesis	DNA polymerase	rs12196873	0.85	3E-8	Day 2015
RPAIN	DNA replication	Nuclear transporter	rs1800932	0.44	6E-05	Perry [61] Day 2015
			rs8070740	0.76	2E-9	
SRSF9	Spliceosome factor		rs551087	0.29	4E-8	Day 2015
SYCP2L	Sister chromatids pairing		rs2153157	0.49	9E-11	He et al. [11], Stolk et al. [14], Perry [61] Day 2015
			rs6899676	0.80	2E-19	
			rs9393800	0.27	4E-13	
TLK1	Regulation of chromatin modification and DNA damage response signalling	Protein kinase	rs10183486	0.36	2E-14	Stolk et al. [14], Day 2015
			rs930036	0.38	3E-19	
UIMC1	Double strand DNA break checkpoint		rs365132	0.51	1E-33	He et al. [11], Stolk et al. [14], Day 2015
			rs2241584	0.38	2E-11	

[a] If multiple genes are located at the SNP region only those associated with genome maintenance are listed.

link with DSB repair and homologous recombination repair (see Table 1).

These studies all contribute to the growing evidence that DNA repair processes instead of intra- or extra-ovarian regulators of folliculogenesis play a key role in ovarian ageing and could be an important therapeutic target for infertility.

3. From gene discovery to functional biology – a prominent role of genome maintenance in ovarian ageing

Biological pathway analysis of the genetic associations with ANM from GWAS using distinct algorithms and databases were in close agreement in emphasizing general biological pathways for

DNA repair i.e. cell cycle and cell death and mitochondrial function as well as immune response [14,20]. By using special techniques, such Ingenuity Pathway Analysis (IPA), MANGENTA and GRAIL to identify networks and pathways that might be involved in regulating age of menopause several networks have been identified. One network containing 12 of all the genes nearest to the 44 menopause GWAS loci, relates to cell cycle, cell death, and cancer. The *ESR1* gene is central in this network, suggesting that genes in this network influence or are influenced by oestrogen signalling. A second network involved in mitochondrial function is similarly, at least in part, related to cell death. The third network relates to infection mechanisms, DNA replication, recombination and DNA repair as well as to gene expression. Of course "immune response" can be triggered by cell death, which in turn can be due to DNA damage. Similarly, mitochondrial function can be influenced by damage to the genome. Only 13 protein-encoding genes are left on the mitochondrial DNA. The nucleus harbours hundreds if not more than 1000 genes, that specify for mitochondrial proteins, and thus damage to nuclear DNA can directly impact on mitochondrial function [27]. Mitochondrial dysfunction in turn could yield elevated levels of reactive oxygen species resulting in increased DNA damage, cell death, and inflammation [28]. Moreover, we and others have found that persistent DNA damage can trigger a metabolic redesign, which also alter the main metabolic pathways, including oxidative phosphorylation of mitochondria [29–31]. Interestingly, several of the 17 input genes included in the fourth network, which is related to lipid metabolism, molecular transport, and small molecule biochemistry are also involved in DNA repair mechanisms [14].

Recent advances have identified accumulation of DNA damage as a major driver of ageing [28]. However, there are numerous kinds of DNA lesions each with their own characteristics and cellular outcome, which highly depends on the cellular context: proliferation (different stages of the cell cycle), differentiation, propensity for survival/death, condition of the cell and systemic hormonal and immunological parameters. In addition, DNA damage is strongly influenced by cellular metabolism, anti-oxidant status and exogenous factors, consistent with the multi-factorial nature of ageing. Notably, DNA lesions interfering with replication have very different outcomes compared to those stalling transcription. DNA damage blocking transcription seems to cause widespread accelerated ageing in many organs and tissues, including liver, kidney and most notably the neuronal system. Presumably since most neurons are post-mitotic, DNA damage is not diluted by *de novo* DNA synthesis, and hence accumulates in time causing neuronal dysfunction and cell death, contributing to neurodegeneration [32]. On the other hand, cytotoxic DNA lesions interfering with replication may cause besides cancer, also ageing-associated features particularly in proliferative organs and tissues, such as the bone marrow, but also liver and kidney. Such type of DNA damage may also affect development. Interestingly, several types of DNA damage may affect fertility, gonadal development and long-term gonadal functioning and influence gonadal ageing. The identified menopausal genes involved in genome maintenance cover several DNA repair and response systems primarily replication-related DNA repair processes, such as mismatch repair which corrects replication errors (*MSH6*, *EXO1*, *MSH5*), homologous recombination (notably, the key strand exchange protein *RAD51*, also implicated in meiosis, *BRCA1, RAD54L, HELQ*), crosslink repair (*FANCI*), translesion DNA synthesis (*REV3L*), and base excision repair (*APEX1*, *APTX*). In addition, genes implicated in transcription are highlighted by the GWAS (*POLR2E*, *POLR2H*), which may be relevant for transcription-coupled repair, as well as genes implicated in replication or cell cycle regulation (*PRIM1, CDK2AP1, CHEK2, HELB*).

The strong connection between genome stability and multi-organ ageing was mainly disclosed by extensive analysis of DNA repair deficient mouse mutants that closely mimic rare human DNA repair syndromes, which were found to exhibit many features of severely accelerated but *bona fide* ageing in numerous organs and tissues. The most extreme and widespread premature ageing phenotype is presented by the *Ercc1* mutant mice, which are deficient in at least three repair processes: transcription-coupled repair (TCR), global genome-nucleotide excision repair (GG-NER) as well as interstrand cross-link (ICL) repair, combining transcription-related and replication-related DNA damage consequences [33]. As a result, *Ercc1* mouse mutants exhibit a progressive manner of premature and in some cases even excessive ageing in almost all organs and tissues including brain, bone marrow, liver, kidney, gonads, skeleton, cardiovascular tissue, thymus and retina. Consequently, the resulting phenotype is characterized by wide-spread, progressive premature ageing, including prominent neurodegeneration, cardiovascular disease, osteoporosis, kyphosis, osteosclerosis, early greying, cachexia, sarcopenia, overall frailty and notably infertility with a reduced life-span [21,34]. Ageing features in these mouse models are summarized in a recent paper and showing that genome maintenance and metabolism are closely interconnected, they may constitute the main underlying biology of aging [35]. Interestingly, female mice deplete their follicular pool rapidly within a few weeks after birth. At 4 weeks of age, ovaries are significantly smaller and the primordial follicle pool is nearly completely depleted. Subsequently, also the number of small preantral follicles is strongly reduced, while the number of larger growing follicles is still fairly normal. At 16 weeks of age, the ovaries of *Ercc1* mutant mice have reduced even further in size and are devoid of growing follicles. Similarly, AMH levels were strikingly reduced in Ercc1 mutant mice indicating loss of ovarian function (unpublished data). Notably, also other DNA repair deficient mouse mutants (and the corresponding human DNA repair syndromes) display early infertility, due to accelerated ageing or even compromised sexual development, when the ageing is so early that development is compromised. A clear example is the mouse mutant for the rare disorder trichothiodystrophy (TTD), carrying a specific point mutation in the *Xpd* repair transcription gene, found in several TTD patients [36]. The striking correlation between dose and type of DNA damage and repair and response processes on the one hand and the onset and severity of multiple features of accelerated ageing on the other hand provide a strong experimental basis for the concept that DNA damage is a main contributor of the ageing process in mammals, but that not all damage is equal [21,32].

A comparison of loci associated with follicle number and menopausal age indicates that several variants were clustered in specific genomic regions on chromosomes 20, 13, and 12. The variants on chromosome 20, including one associated with follicle number in Caucasians, one within *MCM8* associated with both follicle number and menopause, and several nearby associated variants, were in a genomic region that comprises long stretches of highly associated SNPs. Moreover, it has been reported that many of the identified variants associated with antral follicle count (AFC) were also associated with AMH. Of the top 16 variants associated with AFC, seven were significantly associated with AMH levels, and again, localized to chromosomes 12, 13 as well as to chromosome 20 harbouring our most significant menopause SNPs [37]. Finally, these authors were able to demonstrate that *MCM8* colocalized with the germ cell-specific marker VASA and was present within the oocytes of primordial, primary, and secondary follicles. In contrast, *MCM8* was not detected in seminiferous epithelium or neuronal tissue indicating that it might be highly specific for the ovary [37]. Interestingly, mice deficient in *MCM8*, or its physical partner *MCM9*, are infertile due to an early block in follicle development leading to atrophied ovaries in adult mice [26], as observed in the

Ercc1 mutant mice. Recently, homozygous mutations in *MCM8* and *MCM9* have been identified in families with members presenting with primary amenorrhoea. Affected individuals presented with ovarian dysgenesis and genomic instability in somatic cells [24,23,38].

Also other, rare human genome instability conditions such as Fanconi's anemia, (caused by defects in interstrand crosslink repair), Blooms syndrome (due to a deficiency in properly resolving sister chromatid recombination intermediates) and Werner syndrome (associated with an ill-defined impairment in replication-associated DNA damage response) are characterized by POI or ovarian deficits and at the same time display multiple symptoms of premature ageing, further strengthening the link between ovarian dysfunction, ageing and genome maintenance [16].

In summary, there is strong functional biological evidence that some of the identified genetic variants are indeed governing processes that might indirectly also determine age at which a woman enters menopause. Consequently, ageing of the soma seems to be a primary driver for the loss of ovarian function in women instead of the current dogma which implies that loss of ovarian function initiates ageing of the soma. In the light of these new findings one might reconsider whether this dogma still holds. Time for a paradigm shift?

3.1. How does the rate of DNA damage accumulation influence ovarian ageing?

Detailed analysis of full genome expression profiles of multiple organs in a variety of DNA repair-deficient, progeroid mouse models has disclosed that these mutants strongly resemble genome-wide expression profiles of normal ageing, capturing a tremendous amount of underlying biological processes, which are shared between accelerated and natural ageing [31,39,40]. This is consistent with the numerous parallels at the pathological, histological, physiological and functional levels, supporting the notion that the accelerated ageing to a large extent resembles the normal ageing process. The expression profile analysis also revealed that repair-deficient, premature ageing mouse mutants systemically suppress key somato-, lacto- and thyrotrophic hormonal axes, including the GH/IGF1 pathway, explaining why all progeroid repair mice – and the corresponding human patients- show dramatic early cessation of growth. Attenuation of the GH/IGF1 axis is also found with normal ageing [41]. Energy appears to be redirected from growth to maintenance and defence mechanisms, such as the NRF2-controlled anti-oxidant system and stress resistance. This so-called 'survival' response resembles the response triggered by dietary restriction, which is for long known to retard the process of ageing and promote longevity in a very wide variety of organisms, ranging from yeast to mammals, including in one study non-human primates [42]. Persistent DNA damage even triggers this response at the level of individual cells in culture, indicating its universal, highly conserved nature [43]. The most plausible interpretation of this response is that organisms facing accelerated ageing due to rapid accumulation of DNA damage, caused by an inborn DNA repair deficiency, attempt in this way to delay ageing in order to extend their short lifespan and live as long as possible. This finding provided a link between high DNA damage loads and the insulin/IGF1 signal transduction pathway, which controls, metabolism, growth and lifespan and influences the ageing process.

The DNA damage-induced general suppression of hormonal systems, which is linked to ageing, also extends to the oestrogen receptor, which is supported by the early loss of female fertility in DNA repair deficient, progeroid mouse mutants, as discussed above. In line with the parallels between the DNA damage induced 'survival' response and dietary restriction, food restriction also temporarily lowers female fertility. Hence, accumulation of DNA damage in normal and accelerated ageing may affect ovarian function in various manners. First, gradual (or in case of compromised genome maintenance rapid) accumulation of unrepaired DNA damage causes (premature) cell death and cellular senescence, leading to exhaustion of cell renewal capacity, hypo cellularity, cellular dysfunction in affected organs and tissues and eventually ageing in the entire soma. Likely, ovaries do not escape from erosion of the genome, as apparent from e.g. the increased risk for trisomy 21 with age in pregnancies of older women. Secondly, the systemic 'survival' response intentionally suppresses the oestrogen hormonal output, which in turn may contribute to onset of menopause, particularly when age-dependent DNA damage accumulation does not cease. Both effects are expected to synergize to promote ovarian silencing and install menopause. Intriguingly, accumulation of DNA damage has many direct and indirect consequences, including mitochondrial alterations, providing a possible connection with other gene clusters identified by the GWAS on ANM (see Table 1).

3.2. Support from epidemiological studies

Apart from genetic and biological proof there should also be some epidemiological evidence supporting this paradigm shift. Indeed, several data in the literature point into the same direction.

Recently it was shown that symptoms of flushing were not significantly associated with risk of coronary heart disease (CHD). However, the presence of night sweats was associated with a modest but significantly increased risk of CHD. This association was attenuated but not eliminated after correction for body mass index, blood pressure, and total cholesterol. Hence women with menopausal symptoms of night sweats have a significantly increased risk of CHD compared to women of similar age without these vasomotor signs [44]. Similarly, a recent pooled meta-analysis showed that, although vasomotor symptoms in women were not associated with measures of subclinical atherosclerosis, women with vasomotor symptoms had an unfavourable cardiovascular risk profile compared to women not yet suffering from night sweats and hot flashes [45]. Moreover, a recent study showed that in women suffering from vasomotor signs the risk for breast cancer was not increased indicating that different genome maintenance systems are involved in breast cancer [46]. Indeed, there is some epidemiological evidence that links a longer reproductive lifespan to increased risks of hormone-receptor-positive breast cancer [47]. Genetic findings from GWAS and menopause do support that relationship. Probably, women who enter menopause later do have a more efficient DNA repair mechanisms compared to women who undergo menopause earlier. Their increased susceptibility to breast cancer, therefore, probably indicates mechanisms other than DNA repair are involved. Probably the fact that they have been exposed longer to sexsteroids might cause the increased risk of breast cancer [16]. Alternatively, or in addition, these women may have more efficient DSB repair by the non-homologous end-joining (NHEJ) pathway, which repair double strand breaks in G1 and early S-phase when homologous recombination repair cannot work because it depends on the presence of an identical sister chromatid that is made after replication. However, NHEJ is error-prone. Hence this repair system will promote cell survival from DSBs, thereby postponing ageing, but at the expense of mutations which promotes cancer.

Similarly, another Dutch group compared pregnancies conceived through IVF or IVF/ICSI either complicated by pre-eclampsia or being uneventful. Pregnancies were achieved within a similar time frame in both populations. However, these authors were

able to show that a higher amount of total administered FSH and FSH per day, together with a lower number of obtained oocytes during IVF treatment, were associated with an increased risk of pre-eclampsia in the subsequent pregnancy. The administered FSH dose per follicle and per obtained oocyte showed even stronger relationships, the latter having the best predictive value. Since pre-eclampsia is a predictor for cardiovascular disease in later life [48,49] these women seem to be less healthy compared to controls in that study. Consequently, they show a diminished responsiveness of the ovaries to exogenous stimulation, reflecting decreased ovarian reserve, which is associated with earlier menopause [50].

Because vascular disease is closely associated with menopause the question remains how these two are causally interlinked. Therefore, we looked for evidence of ovarian dysfunction in other illnesses. Indeed, there is evidence that in type II Diabetics ovarian function is also compromised. In a Turkish study it was shown that both ovarian volume as well as the antral follicle count were significantly reduced in women with type II Diabetes compared to healthy controls [51]. Moreover, our own group recently showed that ovarian reserve is already severely compromised at the time of diagnosis in young girls with cancer [52].

It is known that a younger age of natural menopause is determined by a number of parameters i.e. education, age at menarche, menstrual cycle length, a negative health perception and smoking. On the contrary, the use of oral contraceptives as well as parity postpones the age at which natural menopause occurs [53]. However, by far the best predictor for a later age at menopause is the total number of children a woman had. Hence the reproductive success in terms of fecundity as well as in terms of the total number of living children is also a measure for health and longevity. This fitness benefit arises because post-reproductive mothers enhance the lifetime reproductive success of their offspring by allowing them to conceive earlier, more frequently and more successfully. Finally, the fitness benefit of prolonged lifespan diminishes as the reproductive output of offspring declines. This suggests that in females, selection for deferred ageing should wane when one's own offspring becomes post-reproductive and, correspondingly, that rates of female mortality accelerate as their offspring terminate reproduction laden [54]. Moreover, a recent paper of Lahdenpera suggests that menopause evolved, in part, because of age-specific increases in opportunities for intergenerational cooperation and reproductive competition under ecological scarcity [55]. Overall, it appears that age at last childbirth routinely correlates with post-reproductive longevity, suggesting a slower rate of senescence among late fertile women [56]. Interestingly, maternal age at childbirth was neither related to offspring nor to maternal survival. However, females who had their last child at advanced age also lived longest, while maternal age at first childbirth, the time spacing between births, and total fecundity were unrelated to female longevity. Thus, the primary and the most dominant feature that links longevity with fertility is the time of birth of the youngest child. Interestingly, brothers whose sisters gave birth at late age tend to have a significantly longer lifespan as well. This suggests that the link between extended fertility and longevity has a genetic component that is independent of physiologic changes from having offspring [57]. Indeed, many of the 44 genetic variants involved in age at menopause are also pathways important to ageing and longevity. One of the DNA repair genes identified in the menopause GWAS, exonuclease 1 (*EXO1*), was previously reported to be associated with prolonged life expectancy in female centenarians [58]. Moreover, several genetic variants previously identified to be associated with age at menopause such as *FOXO, APOE, LMNA* are also associated with longevity [59]. These results suggest that reproductive and somatic senescence may be coupled in humans and that selection could have favoured late reproduction [60]. The identified genetic variants in the DNA repair system could very well constitute the link between reproductive and somatic senescence.

4. Conclusion

Genetic variants that determine age at menopause seem to be mainly involved in DNA repair and genome maintenance. Interestingly, the identified menopausal genes involved in genome maintenance pathways, are mainly linked with DNA repair processes, which preserve proper genome function and protect from DNA damage induced cell death primarily during replication or by transcription-coupled repair. Hence the link between ageing of the soma on the one hand and fertility and menopause on the other hand implies a common genetic background for these phenomena. Indeed, functional biology data as well as epidemiology data do suggest that it is the ageing soma that determines when reproduction and subsequently menopause will occur. This new paradigm challenges the old dogma that women age as a consequence of menopause. Finally, reproductive performance seems to constitute a very good marker for a woman's general health later on life. This offers new possibilities for developing preventive strategies, which might further improve women's health.

Contributors

JSEL wrote the review, was responsible for the design of the new concept and critical analysis of the existing literature and GWAS data.

JAV was responsible for the design of the new concept and critical analysis of the existing literature and GWAS data. She also critically reviewed the manuscript.

AGU was responsible for the design of the new concept and critical analysis of the existing literature and GWAS data. He also critically reviewed the manuscript.

WPV was responsible for the design of the new concept and critical analysis of the existing literature and GWAS data. He also critically reviewed the manuscript.

JHJH was responsible for the design of the new concept and critical analysis of the existing literature and GWAS data. He also critically reviewed the manuscript.

Conflict of interest

The authors have no conflict of interest to declare.

Funding

No funding was received for this article.

Provenance and peer review

This article has undergone peer review.

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