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Spatially Organized Immune Remodeling in Menopause: Single-Cell and Spatial Transcriptomic Evidence from Ovarian Aging and Atherosclerosis

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Abstract. As the proportion of people in their mid-to-late years increases around the world, so too does the prevalence of multiple long-term illnesses associated with menopause, many of which involve changes in the immune system. Bulk RNA sequencing averages expression in heterogeneous cell populations and thus cannot identify which cells are changing or where those changes occur. Collectively, single-cell RNA sequencing and spatial transcriptomics have provided two major examples of menopausal changes, ovarian aging and atherosclerosis, showing that the immune remodeling during menopause is not a general increase in inflammation but a spatially organized process characterised by cell state, anatomical location and a local microenvironment. In the aging ovary, pyroptotic macrophages and senescent granulosa and stromal cells establish a self-reinforcing pro-inflammatory niche, while immunoglobulin-expressing cells accumulate at the ovarian periphery. In atherosclerotic plaques, activated T cells accompany macrophages that concentrate around the necrotic core, and immune recruitment localizes to discrete vascular microregions such as the vasa vasorum. Comparing the two settings shows that shared mechanisms, including cytokine and chemokine elevation, produce tissue-specific outcomes. Recognizing this spatial organization helps explain why lesion location, rather than inflammatory magnitude alone, may govern the severity of atherosclerotic disease, and identifies spatially defined immune niches as candidate targets for intervention.

Keywords: menopause, immune remodeling, single-cell RNA sequencing, spatial transcriptomics, ovarian aging

1. Introduction

Menopause is one point in a continuum of life stages for women which is caused by the loss of ovarian follicular function and a decline in circulating blood estrogen levels, marking the end of women's reproductive years. With an aging population, an increasing number of women will experience menopause. By 2030, the world population of menopausal and postmenopausal women is projected to reach 1.2 billion [1], and 85% of them will face problematic menopause symptoms [2]. The transition itself is not a single event but a staged process spanning the late reproductive

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years, the menopausal transition, and early and late postmenopause, each defined by distinct endocrine and menstrual criteria [3].

During this period, age-related ovarian aging is a natural and inevitable physiological process [4], which is highly related to diseases such as osteoporosis: about 27.4% (95% CI, 22.9–32.1%) of postmenopausal women suffer from it [5]. In addition, the lower risk of cardiovascular diseases such as atherosclerosis observed in premenopausal women relative to age-matched men diminishes substantially after menopause, an effect attributed to the change in estrogen level [6].

Accumulating evidence has shown that some of these menopause-induced diseases are associated with immune remodeling. McCarthy et al. reported menopause transition as an inflammatory phase, during which inflammasome activation and elevated proinflammatory cytokines such as IL-6, TNF-α, and IL-1β occur [7]. A plausible mechanistic basis for this shift is that estrogen receptors are expressed across innate and adaptive immune lineages and directly regulate their transcriptional programs, so that estrogen withdrawal may alter immune cell behavior rather than merely being associated with it [8].

Traditionally, bulk RNA sequencing is widely used to analyze transcriptomics and gene expression, which sequences the total RNA of all cells in a sample to obtain the average gene expression level. While it is cost-effective and high-throughput, its broad nature makes it unable to identify the differences between cells [9]. Thus, in recent years, an emerging technology, single-cell RNA sequencing (scRNA-seq), compensates for the flaws of bulk RNA sequencing very well, by zooming the perspective to individual cells, identifying transitional states and revealing cellular heterogeneity at a higher resolution [10]. Meanwhile, when integrating with spatial transcriptomics, not only can the single-cell-level gene expression be observed, but also the distribution trend of cells in the sample, allowing a more comprehensive and precise insight into spatial gene expression [11].

Therefore, this review combines scRNA-seq and spatial transcriptomics to analyze the role of immune remodeling in the two major menopause-induced problems, ovarian aging and atherosclerosis, and may provide a useful framework for the immunological basis of menopause-related pathologies. Section 2 examines immune remodeling and its spatial organization in the aging ovary, Section 3 turns to atherosclerosis as the major vascular manifestation, and Section 4 compares the two settings to identify shared mechanisms and tissue-specific outcomes.

2. Immune remodeling and spatial organization in ovarian aging

Ovarian aging provides the most direct context for investigating menopause-associated immune remodeling, as follicular exhaustion is accompanied by not only endocrine change, but also the remodeling of the microenvironment, regional immune cell accumulation, and transcriptomic changes of ovarian cells.

2.1. Immune cell expansion and stromal remodeling

During ovarian aging, immune remodeling can be represented by both the increasing population of immune cells and the changes in their states. Isola et al. used scRNA-seq to reveal the doubling of immune cells in the aged ovary of mice, as well as the downregulation of collagenase pathways in stromal fibroblasts, supported by a decreased expression of matrix metalloproteinase 2 (*Mmp2*) that is a key enzyme for collagen degradation, and an increasing collagen deposition, which corresponds to the rising ovarian fibrosis [12].

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2.2. Pyroptosis, senescence, and the pro-inflammatory microenvironment

Additionally, ovarian aging is also associated with immune microenvironment changes. By using scRNA-seq, Zhou et al. discovered that pyroptotic macrophages can switch the ovary into a pyroptotic monocyte-derived macrophage (MDM)-involved pro-inflammatory microenvironment, by analyzing two groups (young versus middle-aged) of women divided based on ages. Additionally, they found that the MDMs from the middle-aged group had increased expression of pyroptosis genes such as *IL1B*, *CASP1*, and *NLRP3*. The MDMs with high pyroptosis activity had lower expression of *SPP1*, whose protein product can be secreted to maintain cells in a younger state. Thus, this weakens the communication of stromal cells (SCs) with T cells and promotes effector-T-cell activation, which means the number of effector T cells increases with advancing age. Collectively, these changes promote the establishment of a pro-inflammatory ovarian microenvironment, and eventually contribute to the senescence of SCs [13].

Meanwhile, the findings of Wu et al.'s group supported this conclusion. Using scRNA-seq, they revealed that aging ovaries exhibit progressive accumulation of senescent granulosa cells (GCs) and SCs, accompanied by activation of DNA damage responses and increased expression of senescence markers such as *CDKN1A*. Subsequently, these senescent cells acquire a senescence-associated secretory phenotype (SASP), characterized by the secretion of pro-inflammatory cytokines, chemokines, and growth factors, which is further amplified by inflammatory signaling pathways, establishing a chronic pro-inflammatory ovarian microenvironment that reinforces cellular senescence through a feed-forward cycle. Beyond revealing inflammatory remodeling, by integrating scRNA-seq and spatial transcriptomics, the study characterized three major types of cells in the human ovary, namely oocytes centrally located in follicles, GCs at the follicle periphery, and theca and stroma (T&S) cells widely distributed along blood vessels. The combination of cell type-specific gene expression profiles and spatial transcriptomics further showed that some subtypes of these cells have higher DNA damage levels and SASP, which corresponds to the previous scRNA-seq results [14].

2.3. Spatial organization of ovarian aging

Ovarian aging is accompanied by spatially organized immune remodeling. Russ et al. applied spatial transcriptomics to identify differences between aged and young mouse ovaries. In young ovaries, granulosa cells are located in two positions: closer to the oocyte (inner GCs) and at the follicle perimeter (outer GCs). Both of them highly expressed inhibins and activins (*Inha*, *Inhba*, *Inhbb*) and gap-junction genes such as *Gja1*, while oocytes maintained normal subpopulations. In contrast, aged ovaries showed follicle depletion, the emergence of distinct GC subpopulations, loss of specific oocyte subpopulations, disrupted gap junction regulation, and suppressed mTOR, EIF2 and mitochondrial pathways which are associated with follicle development and oocyte maturation. These findings demonstrate that ovarian aging is not uniform but spatially organized [15].

This is further supported by Zhang et al.'s study in aged human ovaries, which identified a novel endothelial cell (EDC) subtype, *CLDN5*-positive blood EDCs. Most importantly, they used spatial mapping to reveal accumulation of immunoglobulin-expressing (*IGHG1*- and *IGKC*-positive) cells in the ovarian periphery, correlating with advancing age, reinforcing the spatially organized nature of ovarian aging [16].

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3. Menopausal immune remodeling and atherosclerosis

3.1. Estrogen decline, lipid dysregulation, and plaque initiation

Atherosclerosis is the major vascular manifestation of menopausal immune remodeling. The endocrine shifts during menopause, especially the decline in estrogen, are related to endothelial dysfunction and the disorder of lipid metabolism, including elevations in total cholesterol and low-density lipoprotein cholesterol. Combined with the involvement of immune cells, these changes collectively contribute to the initiation and progression of atherosclerotic plaques [17].

Hormonal changes in menopause cause the immune system to enter a state of inflammation (inflammaging) due to the loss of estrogen's anti-inflammatory effects; thus, subendothelial lipid accumulation and oxidation of low-density lipoprotein occur. Monocyte recruitment, foam cell formation, T-cell infiltration, and a switch in vascular smooth muscle cell (VSMC) phenotype from contractile to synthetic, proliferative and migratory states are triggered; thus, plaque growth and fibrous cap remodeling occur [18]. Inflammaging refers to a persistent, low-grade state of inflammation in older age that occurs due to all sorts of factors such as damaged cells, abnormal molecular distribution, nutrients, and alterations in the gut microbiome. This idea provides the general circumstances for the effects of reduced estrogen in menopause [19].

3.2. Immune cell heterogeneity within plaques

Immune cells are also present in the atherosclerotic plaques. Fernandez et al. used scRNA-seq to dissect plaque heterogeneity and obtained high-resolution transcriptomic profiles of individual cells in the plaques. They showed activated T-cell states and increased expression of chemokines and cytokines, such as *IFNG*, *TNF*, *CCL5*, and *CCL4*, thus revealing an inflammatory microenvironment associated with plaque progression [20].

At the same time, Transforming Growth Factor-beta (TGF-β) may also be involved in the induction of endothelial-to-mesenchymal transition in endothelial cells and further promote extracellular matrix (ECM) remodeling of VSMCs, which also promotes plaque progression [21]. The above processes have been shown in fibrous plaques of postmenopausal women. Although direct evidence linking menopausal hormonal changes to elevated systemic TGF-β remains scarce, TGF-β signalling has been associated with vascular remodeling and fibrosis in atherosclerosis, promoting endothelial-to-mesenchymal transition and ECM modification, and thus affecting plaque morphology in postmenopausal women [22].

3.3. Spatial organization of plaque inflammation

Based on the previous single-cell data, spatial transcriptomics can also determine the location of immune cell infiltration, such as in the vasa vasorum or specific areas of a plaque. Therefore, to some extent, the severity of atherosclerosis is not only caused by the overall extent of inflammation but also strongly related to particular locations of inflammatory changes [23].

Integrated single-cell spatial transcriptomics has revealed the morphological heterogeneity of atherosclerotic carotid arteries. Macrophages at the edge of the necrotic core promote further expansion of the core by increasing macrophage death and impairing efferocytosis; thus, secondary necrosis occurs and cellular debris accumulates. Debris contains damage-associated molecular patterns (DAMPs) and is thus chronically inflammatory and damaging to tissue; it significantly raises the risk of plaque rupture and thrombosis [23, 24]. The capacity of phagocytes to carry out

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efferocytosis is also reduced in atherosclerosis; thus, apoptotic and necrotic material accumulates in the plaque, expands the necrotic core, and increases the risk of plaque rupture or erosion [25].

4. Discussion

4.1. A shared immune remodeling framework across tissues

Menopause-associated immune remodeling should not be viewed as an increase in the number of immune cells or the degree of inflammation; rather, it refers to changes in the state, location and formative microenvironment of all kinds of immune cells in tissues. Menopause is primarily characterized by ovarian aging and its functional decline. Studies using scRNA-seq show that aging ovaries develop a pro-inflammatory microenvironment driven by pyroptotic macrophages and senescent GCs and SCs, which acquire a SASP, creating a feed-forward cycle that accelerates senescence [13, 14]. Meanwhile, the estrogen decline driven by ovarian aging will disrupt immune stability and metabolism throughout the body, thus increasing the risk of atherosclerosis [17, 18]. This is also supported by the activation of T cells and participation of cytokines and chemokines such as *IFNG*, *TNF*, and *CCL5* in atherosclerotic plaques, further supporting the significance of immune remodeling in atherosclerosis [20]. Therefore, ovarian aging and atherosclerosis during menopause are not mutually independent. Instead, they should be understood under the same immune remodeling framework.

4.2. The methodological contribution of single-cell and spatial approaches

In traditional bulk RNA sequencing and blood tests, only the overall change of inflammation can be detected. However, scRNA-seq and spatial transcriptomics allow more detailed and comprehensive analysis of which cells change, where they are located, and their interactions at the single-cell level. For instance, scRNA-seq is used to reveal the transition of macrophages to a pyroptotic state in middle-aged ovaries, leading to a pyroptotic MDM-involved pro-inflammatory microenvironment [13]. Similarly, in atherosclerosis, single-cell approaches resolve the endothelial and smooth muscle cell states that underlie TGF-β-driven ECM remodeling [21].

scRNA-seq and spatial transcriptomics can also be combined to explore the spatial distribution of cells in immune niches. Studies have shown spatially organized changes in ageing ovaries, such as follicle depletion and peripheral accumulation of immunoglobulin-expressing cells [15, 16]. Spatial analysis of atherosclerotic plaques also showed that the recruitment of immune cells and the accumulation of macrophages are concentrated in some vascular areas, such as the vasa vasorum, discrete plaque microregions and areas around the necrotic core [23].

Finally, scRNA-seq and spatial transcriptomics have been combined to find a common disease path but also to show how this disease affects different tissues. For instance, cytokines and chemokines are increased in both the ageing ovary and atherosclerosis, but they result in chronic immune activation and senescence of the ageing ovary versus T-cell activation and instability of atherosclerotic plaques. Therefore, although the immune remodeling in menopause shares some fundamental pathological reasons, scRNA-seq and spatial transcriptomics can reveal different tissue-specific results of the same causes.

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4.3. Limitations and future directions

There are still some deficiencies. First, many studies use only young and older groups and do not strictly divide them into premenopause, perimenopause, early postmenopause and late postmenopause, even though standardised criteria for these stages are available [3]. This design cannot determine whether some single-cell alterations are due to the hormonal changes of menopause or are the result of a genetic background and natural ageing. Second, most studies use mice as models; their reproductive senescence is not the same as human menopause, and human ovarian tissue is difficult to obtain and often affected by hormone therapy, disease background, and sampling errors. Third, most atherosclerosis samples are from advanced plaques, which may not represent early menopausal single-cell changes, and generally, plaque studies do not classify samples by the stage of menopause.

A further limitation concerns scope. Although ovarian aging and atherosclerosis are two major conditions associated with menopause, many other menopause-related diseases exist, including osteoporosis, breast cancer, and type 2 diabetes. Future studies should therefore extend single-cell and spatial analyses to these other menopause-related diseases to determine whether comparable patterns of immune remodeling are shared.

A final limitation is inferential. While scRNA-seq and spatial transcriptomics excel at identifying cell-specific gene expression and spatial distribution, causality cannot be established. For example, scRNA-seq shows the activation of inflammation-associated pathways in older ovarian cell populations, but this does not prove that ovarian aging is driven by these pathways.

Therefore, although scRNA-seq and spatial transcriptomics are powerful tools, more rigorous research designs are still needed. On the one hand, to obtain more accurate data, longitudinal research should be established. Future studies should not be limited to comparing young and old groups but should track and compare different menopause stages. On the other hand, because menopausal immune remodeling involves multi-tissue changes, future research should not focus merely on local tissues such as the ovary and atherosclerotic plaques, but should also examine surrounding tissues, for example, single-cell changes around the ovary and vascular changes associated with atherosclerotic plaques. To establish more definitive causal links, more experiments should be designed, such as randomized hormone-intervention trials and targeted functional studies.

5. Conclusion

Menopause affects more than a billion women worldwide and is associated with multiple chronic conditions and diseases, and among the major consequences of menopause are ovarian aging and atherosclerosis [6]. These conditions and diseases often involve multi-tissue changes; therefore, traditional bulk RNA sequencing, which is more appropriate for homogeneous cell populations, is insufficient for dissecting the cellular and spatial complexity of menopause-related processes [9]. Thus, scRNA-seq and spatial transcriptomics are needed to deeply analyze cell-type-specific transcriptomic changes and to map their precise anatomical locations [10, 11].

This review integrates scRNA-seq and spatial transcriptomic findings to examine menopause-related immune remodeling in two major settings, ovarian aging and atherosclerosis, and concludes that both are associated with immune cell accumulation, microenvironment changes, and transcriptome shifts. The significance of the locations where immune remodeling occurs is also emphasized. Regarding immune cell accumulation, the aging ovary shows progressive expansion of pyroptotic macrophages and effector T cells that is accompanied by a shift toward pro-inflammatory states [13], while atherosclerotic plaques are characterized by activated T cells and macrophage

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accumulation around the necrotic core [20, 23, 24]. Regarding microenvironment changes, ovarian aging establishes a chronic pro-inflammatory microenvironment through SASP by GCs and SCs [14], whereas in atherosclerosis, defective efferocytosis promotes secondary necrosis and the release of DAMPs that sustain local inflammation [24]. Moreover, regarding transcriptomic shifts, ovarian cells exhibit upregulation of pyroptosis- and senescence-related genes such as *IL1B*, *CASP1*, and *NLRP3* [13], while plaque cells show elevated expression of chemokines and cytokines such as *IFNG*, *TNF*, *CCL5*, and *CCL4* [20].

These immune alterations are not the same everywhere. They are spatially organized instead. Immunoglobulin-expressing cells are located at the periphery of the aged ovary [16], and macrophages have gathered around the necrotic core or within isolated vascular niches, such as the vasa vasorum [23]. Therefore, the specific locations of immune remodeling are closely related to the severity and progression of the disease, and different locations and cellular partners can result in different outcomes.

The above results offer more explicit support for understanding how menopause promotes multi-tissue pathology through spatially organized immune remodeling, and put forward future intervention directions that target specific immune subsets or spatial niches, such as modulating pyroptosis or SASP in the ovary [13, 14], improving efferocytosis [24, 25], or regulating TGF-β signalling in atherosclerotic plaques [21, 22]. In addition to exploring the mechanism of immune system changes in menopause, the above studies have also highlighted the value of new single-cell and spatial technologies for modern medical research. As research questions have shifted from observing changes at the tissue level to identifying heterogeneous cells and dynamic cell states, high-end equipment and technologies are now required for these in-depth studies of microenvironments. With the continued development of single-cell sequencing, spatial multi-omics and integrated computational methods, deeper characterization of immune remodeling in tissues can be achieved, new biomarkers and spatially informed therapeutic targets identified, and thus the translation of mechanistic discoveries into personalised medicine accelerated.

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