Ageing Research Reviews 120 (2026) 103190

Contents lists available at ScienceDirect

Ageing Research Reviews

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

Review article

Misplaced nucleic acids as a trigger of coagul-aging

Angelica Giuliani [a,b,*], Sonia Fantone [c], Matilde Sbriscia [c,**], Maurizio Cardelli [c], Fabiola Olivieri [a,c], Maria Rita Rippo [a], Jacopo Sabbatinelli [a,b]

[a] Department of Clinical and Molecular Sciences, Università Politecnica Delle Marche, Ancona, Italy
[b] Clinic of Laboratory and Precision Medicine, IRCCS INRCA, Ancona, Italy
[c] Advanced Technology Center for Aging Research, IRCCS INRCA, Ancona, Italy

ARTICLE INFO

Keywords:
Coagulation
Inflammaging
Coagul-aging
Extracellular vesicles
Tissue factor
RNA:DNA hybrids

ABSTRACT

Aging is associated with a persistent, sterile inflammatory state called inflammaging, which contributes to endothelial dysfunction, immune dysregulation, and a gradual shift toward a procoagulant phenotype known as coagul-aging. Inflammation and coagulation are now understood as interconnected processes, linked by innate immune activation and thrombin production. Recent evidence highlights the vital role of endogenous nucleic acids, especially cytosolic and extracellular DNA, RNA, and RNA:DNA hybrids, as key mediators at the intersection of these systems. These nucleic acids, often originating from senescent cells and endogenous retroelements, accumulate due to impaired degradation and are detected by pattern recognition receptors such as cGAS–STING, RIG-I, and TLR9. Besides promoting inflammatory cytokine release and tissue factor expression, certain nucleic acid species, particularly when unencapsulated, can directly activate the contact pathway via factor XII (FXII), contributing to thrombin production independently of traditional inflammatory pathways. This dual role makes nucleic acids central players in the convergence of inflammaging and coagul-aging. In this review, we examine the sources, topological forms, and immunothrombotic functions of misplaced nucleic acids in aging. We propose that a cumulative nucleic acid burden acts as a molecular trigger for thrombo-inflammatory responses, offering new insights into age-related vascular risk and novel targets for therapeutic intervention, including the development of biomarker-based risk stratification approaches and novel strategies targeting upstream thromboinflammatory pathways.

1. Introduction

Aging is characterized by a gradual decline in tissue homeostasis and regenerative capacity, accompanied by the emergence of a chronic, low-grade inflammatory state termed inflammaging (Franceschi et al., 2000). This sterile inflammation stems from the accumulation of cellular and molecular damage, defective clearance of self-derived debris, and persistent activation of innate immune pathways (Franceschi et al., 2017). Inflammaging plays a central role in the development of age-related pathologies, including cardiovascular and thrombotic diseases (Franceschi and Campisi, 2014).

One of the major vascular consequences of inflammaging is the establishment of a prothrombotic phenotype, referred here to as coagul-aging. This state results from endothelial dysfunction, platelet hyperreactivity, and altered hemostatic balance. Importantly, inflammation and coagulation are not isolated processes but are functionally intertwined through the concept of thrombo-inflammation, a coordinated response originally evolved to contain infection and repair tissue damage. When chronically activated, however, this crosstalk becomes maladaptive, sustaining vascular injury and thrombotic risk (Jackson et al., 2019). While traditionally studied in overt pathological conditions such as sepsis (Meyer and Prescott, 2024), autoimmune diseases (Menichelli et al., 2023), and cancer (Mack et al., 2024), this reciprocal amplification between the immune system and the coagulation cascade is now gaining attention as a potential contributor to the chronic inflammatory and procoagulant phenotype observed in physiological aging (Zeng et al., 2024).

Emerging evidence suggests that misplaced nucleic acids, including extracellular or cytosolic DNA, RNA, and RNA:DNA hybrids, act as molecular triggers of both innate immune activation and coagulation. These nucleic acids, often derived from endogenous retroelements or senescence-associated damage, are sensed by pattern recognition

* Correspondence to: Department of Clinical and Molecular Sciences, Università Politecnica delle Marche, Via Tronto 10/A, Ancona 60126, Italy.
** Correspondence to: Advanced Technology Center for Aging Research, IRCCS INRCA, Via Santa Margherita 5, Ancona 60124, Italy.
E-mail addresses: angelica.giuliani@staff.univpm.it (A. Giuliani), m.sbriscia@inrca.it (M. Sbriscia).

https://doi.org/10.1016/j.arr.2026.103190
Received 21 November 2025; Received in revised form 11 April 2026; Accepted 26 May 2026
Available online 29 May 2026

receptors such as cGAS–STING, TLR9, and RIG-I-like receptors, promoting type I interferon responses, cytokine release, and Tissue Factor (TF) expression (Chen et al., 2025; Mankan et al., 2014). In parallel, they may directly activate the contact pathway of coagulation via factor XII (FXII), providing a non-inflammatory route to thrombin generation (Fuchs et al., 2010; Kannemeier et al., 2007).

In this review, we examine the role of nucleic acid accumulation and dysregulation in linking inflammaging to coagul-aging. We propose that extracellular nucleic acids act as central effectors of age-associated thrombo-inflammatory circuits, not only by sustaining chronic immune activation, but also by directly triggering coagulation, potentially bypassing classical inflammatory pathways. These properties position nucleic acids as both mechanistic drivers and potential therapeutic targets in vascular aging.

2. Coagulation and aging: a prothrombotic drift

Aging is characterized by a progressive shift toward a prothrombotic state. This phenomenon contributes to the increased incidence of thrombotic events in older adults, which collectively account for a substantial burden of morbidity and mortality in the aging population (Poscablo et al., 2024; Tang et al., 2015; Tschan and Bolliger, 2021). This shift reflects multifactorial changes involving endothelial dysfunction (Fuchs et al., 2010), platelet hyper-reactivity (Davizon-Castillo et al., 2019), altered levels of coagulation and fibrinolytic factors, and chronic low-grade inflammation.

Older individuals exhibit increased levels of coagulation factors such as factor VIII (FVIII), fibrinogen, and von Willebrand factor (vWF), together with reduced activity of natural anticoagulants and impaired fibrinolysis (Wang et al., 2018; Wilkerson and Sane, 2002). These changes increase the basal thrombin potential and predispose individuals to both arterial and venous thrombotic events (Liu et al., 2023; Tschan and Bolliger, 2021). Thrombin, in turn, together with activated factor VII (FVIIa) and activated factor X (FXa), can amplify inflammation by signaling through protease-activated receptors (PARs) on endothelial and immune cells (Heuberger and Schuepbach, 2019). Thrombin and FXa, via PAR−1 and PAR−2, respectively, promote the release of proinflammatory cytokines, adhesion molecules, and chemokines, thereby reinforcing the thromboinflammatory phenotype of aging (Habibi et al., 2025).

At the vascular level, the endothelium undergoes structural and functional remodeling with age. Senescent endothelial cells acquire a proinflammatory and procoagulant phenotype, characterized by increased expression of adhesion molecules (ICAM−1 and VCAM−1) (Honda et al., 2021), upregulation of TF (Kurz et al., 2014), and diminished production of nitric oxide due to reduced eNOS activity (Bochenek et al., 2016; Han and Kim, 2023). This promotes vasoconstriction, platelet adhesion, and further endothelial activation. In parallel, platelets from aged individuals exhibit increased reactivity and enhance thrombin generation by releasing more procoagulant microparticles (Martinez Bravo et al., 2024; Tian et al., 2025). The fibrinolytic system is also affected, with reduced levels of tissue plasminogen activator (tPA) and increased levels of plasminogen activator inhibitor−1 (PAI−1), which favor clot persistence and impair thrombus resolution (Khoddam et al., 2025). Inflammatory cytokines such as IL−1β and TNF-α, commonly elevated in aging tissues, further exacerbate this imbalance by increasing TF and suppressing anticoagulant pathways in endothelial and immune cells (Giuliani et al., 2023, 2024).

Importantly, the complement system, which interacts with both immune and coagulation systems, is also altered in aging. Elevated levels of complement proteins such as C3 and C1q, together with sustained complement activation through the classical and alternative pathways, contribute to vascular inflammation, endothelial dysfunction, and amplify thromboinflammatory responses in aging (Hasegawa et al., 2019; Stephan et al., 2013). Complement-derived anaphylatoxins C3a and C5a can directly activate platelets via their respective receptors, promoting the release of P-selectin and procoagulant microvesicles. Moreover, C5a has been shown to reinforce the thromboinflammatory loop by inducing TF expression in neutrophils and endothelial cells (Kim and Conway, 2019; Skendros et al., 2020). Reciprocally, activated FXII (FXIIa) can directly trigger complement activation by cleaving C1r and C1s, while FXII-driven kallikrein generation further amplifies this crosstalk by promoting C3 and C5 cleavage (Schmaier and Stavrou, 2019). C3a can directly activate platelets, while C5a, together with thrombin released from activated platelets, induces tissue factor expression in neutrophils and promotes the formation of TF-bearing neutrophil extracellular traps (NETs) (Skendros et al., 2020).

With aging, platelets acquire a senescent phenotype characterized by enhanced basal activation, increased reactivity, altered granule secretion, and proinflammatory signaling, which collectively sustain a prothrombotic drift and vascular dysfunction (Anjum et al., 2025; Le Blanc and Lordkipanidze, 2019; Montenont et al., 2019). In parallel, aging drives a progressive remodeling of the megakaryocyte–platelet axis at the level of hematopoietic stem cells (HSCs). This shift leads to the generation of hyperreactive platelets with increased thrombotic potential, contributing to age-related coagulopathy independently of systemic inflammation (Poscablo et al., 2024).

Hemodynamic factors also play a non-negligible role in coagul-aging. Increased arterial stiffness—driven by elastin degradation, collagen cross-linking, and accumulation of advanced glycation end-products (AGEs) - combined with altered shear stress patterns due to reduced physical activity and endothelial dysfunction, establish a prothrombotic biomechanical milieu. These alterations impair endothelial responsiveness and nitric oxide release, foster platelet–endothelial adhesion and consequently lower the threshold for thrombus formation (Ungvari et al., 2018; Zhang et al., 2024).

Together, these age-related alterations establish a prothrombotic environment even in the absence of overt disease (Fig. 1). Clinically, these changes translate into a higher incidence of venous thromboembolism (VTE), ischemic stroke, and myocardial infarction in older individuals. As a result, older patients often require antithrombotic therapies, such as low-dose anticoagulants or antiplatelet agents, both for primary prevention in high-risk populations and for secondary prevention following thrombotic events (Okumura et al., 2020; Spence et al., 2020; Stuby et al., 2024). Understanding the molecular underpinnings of coagul-aging is essential for identifying novel biomarkers of vascular aging and for developing preventive strategies tailored to thromboinflammatory risk in older populations.

3. Nucleic acids as drivers of inflammaging

3.1. Garb-aging and nucleic acid accumulation

Aging and cellular senescence are accompanied by the progressive accumulation of nucleic acid debris, resulting from both enhanced endogenous production and impaired clearance mechanisms. This accumulation is a hallmark of the broader phenomenon known as "garb-aging," in which senescent cells fail to degrade intracellular waste due to compromised autophagy, reduced nuclease activity, and altered chromatin dynamics (Franceschi et al., 2017). Among the most prominent nucleic acid species that accumulate are cytosolic double-stranded DNA (dsDNA), single-stranded DNA (ssDNA), mitochondrial DNA (mtDNA), double-stranded RNA (dsRNA), and RNA:DNA hybrids. These molecules can originate from multiple sources, including nuclear envelope instability, micronuclei rupture, endogenous retroelements such as LINE−1, and mitochondrial dysfunction (Ramini et al., 2024; Storci et al., 2018)

LINE−1 elements, usually silenced by heterochromatin, become transcriptionally derepressed in senescence (Li et al., 2024; Ramini et al., 2022). Moreover, the accumulation of LINE−1–derived RNA contributes to heterochromatin loss and the onset of senescent phenotypes. At the same time, its depletion by antisense oligonucleotides restores epigenetic marks, attenuates senescence-associated secretory

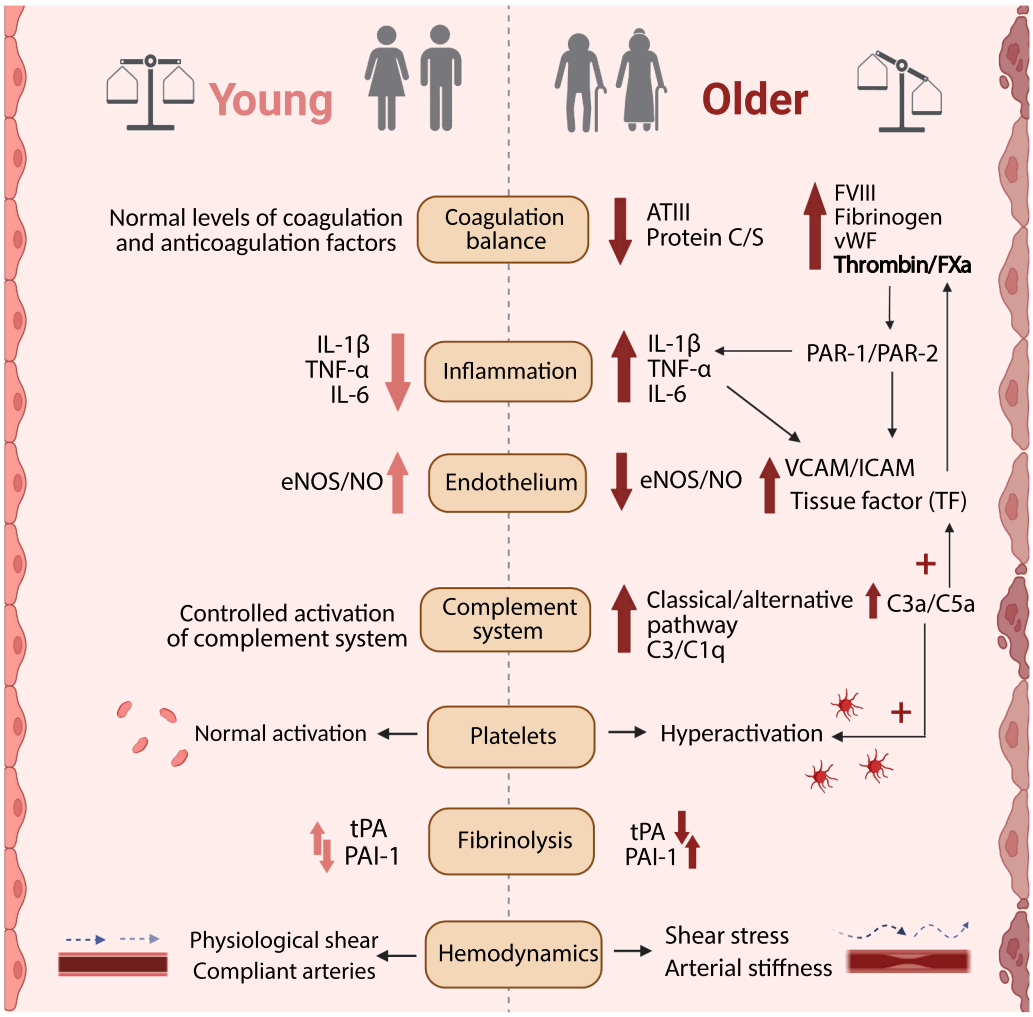

Fig. 1. Age-related alterations promoting a prothrombotic state (coagul-aging). Schematic representation of the main mechanisms contributing to the prothrombotic shift in aging. Increased platelet reactivity and elevated levels of coagulation factors, including factor VIII (FVIII), fibrinogen, and von Willebrand factor (vWF), enhance thrombin generation, while natural anticoagulants, such as antithrombin III (ATIII) and protein C/protein S (PC/PS), are reduced. Impaired fibrinolysis, characterized by decreased tissue plasminogen activator (tPA) and increased plasminogen activator inhibitor−1 (PAI−1), further promotes clot persistence. Proinflammatory cytokines, including interleukin−1 beta (IL−1β), tumor necrosis factor alpha (TNF-α), and interleukin−6 (IL−6), induce tissue factor (TF) expression and protease-activated receptor (PAR−1/PAR−2) signaling. Endothelial dysfunction is associated with increased vascular cell adhesion molecule−1 (VCAM−1) and intercellular adhesion molecule−1 (ICAM−1), and reduced endothelial nitric oxide synthase (eNOS) activity and nitric oxide (NO) availability. Complement activation (C1q, C3, C3a, C5a) and altered hemodynamics, including increased arterial stiffness and shear stress, further contribute to the thromboinflammatory phenotype.

phenotype (SASP) gene expression, and ameliorates progeroid features (Della Valle et al., 2022). LINE−1 RNA transcripts are reverse-transcribed by endogenous reverse transcriptase activity into cDNA, generating RNA:DNA hybrids and cytosolic dsDNA fragments (Beck et al., 2011) that are not efficiently degraded due to reduced expression of nucleases such as RNase H2, TREX1, and DNase1L3 (Guo et al., 2021; Kim et al., 2020b; Ramini et al., 2024). Similarly, nuclear DNA fragments can translocate into the cytoplasm through lamin B1–mediated nuclear envelope alterations (Freund et al., 2012), and mitochondrial stress can lead to the release of immunogenic mtDNA and mtRNA (Gogvadze and Zhivotovsky, 2025; Victorelli et al., 2024)

These misplaced nucleic acids are potent activators of innate immune pathways. Cytosolic DNA is recognized by cGAS, which triggers the STING pathway and induces type I interferon responses (Yu and Liu, 2021). TLR9, localized to endosomes, senses DNA-rich complexes, including RNA:DNA hybrids (Rigby et al., 2014). In parallel, RIG-I and MDA5 detect aberrant or misprocessed cytosolic RNA, especially mitochondrial-derived RNA species (Di Giorgio et al., 2024; Molony et al., 2017). These nucleic acid sensors have evolved to detect non-self-genetic material, such as viral or bacterial genomes, and to trigger appropriate inflammatory and interferon (antiviral) responses. However, under certain conditions, such as cellular senescence, defective nucleic acid metabolism, or autoimmune diseases like systemic lupus erythematosus (SLE), self-derived nucleic acids can accumulate in aberrant cellular compartments (Mustelin et al., 2019). Their inappropriate recognition by these sensors leads to chronic activation of innate immunity, contributing to the maintenance of the SASP and sustaining low-grade, systemic inflammation, a hallmark of inflammaging (Ramini et al., 2024).

Beyond their role in sustaining the SASP, these innate immune pathways also influence coagulation. Activation of cGAS–STING and TLR9 in endothelial and immune cells leads to increased TF expression, endothelial activation, and monocyte recruitment (Yu et al., 2025), all of which promote thrombin generation. Moreover, type I interferons and proinflammatory cytokines induced by nucleic acid sensing (e.g., IL−6, TNF-α) contribute to platelet activation and impair anticoagulant mechanisms (Page et al., 2018).

In sum, garb-aging encompasses a multilayered disruption of nucleic

acid homeostasis: senescent cells accumulate and release DNA and RNA species that are recognized as danger signals, activating inflammatory and procoagulant cascades. This accumulation is both a marker and a mechanistic contributor to the thromboinflammatory phenotype of aging.

3.2. Extracellular nucleic acids and secretory mechanisms

In addition to their intracellular accumulation, senescent and stressed cells actively release nucleic acids into the extracellular environment, where they act as potent proinflammatory and procoagulant signals (Ramini et al., 2024; Teo et al., 2019). These cell-free nucleic acids (cfNAs), including both cell-free DNA (cfDNA) and RNA (cfRNA), can exist in multiple physical forms: either freely circulating as "naked" molecules, or enclosed within extracellular vesicles (EVs) or protein–lipid complexes such as virtosomes (Malkin et al., 2022). This structural diversity is key to understanding the biological roles and immunogenic potential of cfNAs in aging and senescence.

3.2.1. cfDNA

Mechanistically, cfDNA can originate through several pathways: (i) passive release during apoptosis or necrosis, resulting in short nucleosomal fragments; (ii) active secretion of DNA, either nuclear or mitochondrial; and (iii) packaging within EVs, such as exosomes or microvesicles, by living cells (Grabuschnig et al., 2020; Stejskal et al., 2023).

This distinction (naked or EV-associated cfNAs) is not merely structural; it carries important functional implications. While encapsulation can shield nucleic acids from enzymatic degradation and facilitate intercellular communication, naked nucleic acids are directly accessible to extracellular sensors and coagulation factors, and thus more likely to engage in pathological interactions.

Although cfDNA was historically associated with apoptotic and necrotic cell death, emerging evidence suggests that, in addition to DNA packaged within EVs (Mensà et al., 2020; Ramini et al., 2024), senescent cells are a key source of nuclear or mitochondrial cfDNA. Thus, they contribute to the pool of circulating naked cfDNA (possibly bound to nucleosomes or protein complexes), perhaps or probably through active secretion mechanisms or impaired nuclear-cytoplasmic integrity (Lai et al., 2025; Simon et al., 2019; Szilagyi et al., 2020). While earlier studies suggested that exosomes and microvesicles were the major carriers of cfDNA, more recent high-resolution approaches demonstrated that most circulating nuclear cfDNA is in fact associated with nucleosomes rather than vesicles, whereas mitochondrial cfDNA (cf-mtDNA) is frequently protected within membrane structure (Malkin et al., 2022). Consistently, experimental work has demonstrated that the soluble, non-vesicular fraction of cfDNA is able to induce cell transformation and tumorigenesis through horizontal DNA transfer in vitro and in vivo (De La Cruz-Siguenza et al., 2024; Schwartz and Conboy, 2023). Moreover, in senescence, DNA fragments can accumulate in the cytoplasm as cytosolic chromatin fragments (CCFs), which may then be expelled from the cell either as vesicular cargo or in a free soluble form (Schwartz and Conboy, 2023). Interestingly, studies of senescence induced by anticancer therapies suggest that cfDNA release can be modulated, sometimes leading to altered kinetics or reduced release compared to proliferating cells (Rostami et al., 2020).

While the precise contribution of senescent cells to this non-encapsulated cfDNA pool remains to be determined, its presence in circulation has been documented and may have functional relevance in aging-related inflammation and coagulation. In contrast, cf-mtDNA appears more frequently within membrane-protected compartments, although it can also exist as soluble extracellular fragments (Malkin et al., 2022). This duality underscores the complexity of cfDNA biology and the need to differentiate between fractions when studying its origins and functions.

Circulating cf-mtDNA was shown to increase with age in both murine models and human donors, suggesting that senescent cells are a major contributor to the age-associated rise in cfDNA levels (Iske et al., 2020). Similarly, one recent study demonstrated that chemotherapy-induced senescence of tumor cells contributes to paracrine signaling and immune activation via the release of cf-mtDNA in a regulated manner (Lai et al., 2025). Functionally, cfDNA acts as more than a passive by-product. Extracellular DNA is recognized as a damage-associated molecular pattern (DAMP) capable of triggering innate immune pathways. In particular, cf-mtDNA can activate the cGAS-STING axis, driving interferon signaling and pro-inflammatory responses (Daubermann et al., 2025). Furthermore, oxidized cfDNA has been proposed to serve as a long-range stress signal that propagates inflammatory cues to neighboring cells (Glebova et al., 2015).

In summary, although cfDNA has long been associated with tumor biology and liquid biopsy, it is increasingly clear that senescent cells represent an important source of both nuclear and mitochondrial cfDNA and contribute to the pro-inflammatory milieu of senescence and aging through innate immune activation (Daubermann et al., 2025; Iske et al., 2020).

3.2.2. cfRNA

cfRNA encompasses a wide array of RNA species, including messenger RNA (mRNA), microRNAs (miRNAs), long non-coding RNAs (lncRNAs), ribosomal RNA fragments (rRFs), circular RNAs (circRNAs), and mitochondrial RNAs (mtRNAs). Unlike cfDNA, cfRNA is highly labile in extracellular fluids and typically requires stabilization through incorporation into EVs or binding to RNA-binding proteins (e.g., AGO2, HDL particles). Among circulating RNAs, microRNAs are by far the most extensively studied in the context of aging and senescence, serving as well-established biomarkers of inflammaging and vascular dysfunction (Giuliani et al., 2018; Olivieri et al., 2021). Nevertheless, other RNA species, including long non-coding RNAs (He et al., 2018), circular RNAs (Kim et al., 2021), and tRNA-derived fragments (Kim et al., 2021), are increasingly recognized as potential contributors to the aging process, although their roles remain less defined and warrant further investigation. Recent work has demonstrated that extracellular mtRNAs are increased in the plasma and saliva of patients with Sjögren's syndrome, supporting their presence as circulating signals with potential pathophysiological relevance (Ha et al., 2025). Naked cfRNA fragments, including extracellular ribosomal RNAs, have been shown to activate endosomal Toll-like receptors in dendritic cells and macrophages (Castellano et al., 2025). Moreover, mitochondrial double-stranded RNA (mt-dsRNA), either secreted in EVs or released into the cytosol under stress or senescence, can engage key innate immune sensors such as TLR3 and MDA5 (Kim et al., 2022, 2020a).

3.2.3. EVs in cfNA trafficking

EVs represent a major route of cfNA trafficking. Senescent cells, especially endothelial and immune cells, increase their release of EVs as part of the SASP (Buzas, 2023; Mensà et al., 2020). These EVs may carry nucleic acids, including DNA fragments, small RNAs, or retroelement-derived transcripts, along with proteins and lipids. The encapsulation of nucleic acids in vesicles confers protection from enzymatic degradation and allows for targeted delivery to recipient cells, influencing gene expression, inflammation, and immune responses. Moreover, a subset of EVs known as virtosomes has been described as complexes of DNA and RNA associated with lipids and proteins, actively secreted by metabolically active cells. However, beyond their nucleic acid cargo, senescence-associated EVs themselves display a prothrombotic profile, as their surface exposure of phosphatidylserine and enrichment in tissue factor provide catalytic platforms for coagulation (Du et al., 2024; Hanelova et al., 2023; Wright et al., 2023).

Taken together, extracellular nucleic acids in aging display a complex spectrum of origin, structure, and packaging. Their accumulation and altered distribution reflect a combination of increased release and

impaired clearance. While the exact proportions of naked versus vesicle-associated cfNAs remain to be fully defined, both forms are integral components of the senescent secretome and may contribute to the chronic inflammatory milieu characteristic of aging.

4. Disease models linking nucleic acids to thromboinflammation

Several pathological conditions represent amplified settings in which nucleic acid accumulation is markedly increased. In these contexts, a higher nucleic acid burden is consistently associated with enhanced thromboinflammatory activation. These models help clarify mechanisms that may also operate, at lower intensity, during physiological aging.

Systemic Lupus Erythematosus (SLE) is a prototypical autoimmune disease characterized by defective clearance of apoptotic material, excessive activation of endogenous retroelements, and the accumulation of extracellular and intracellular nucleic acids. Patients with SLE often exhibit high levels of circulating cfDNA and RNA:DNA hybrids, which sustain chronic type I interferon production by engaging TLR9 and cGAS–STING signaling pathways (Hartl et al., 2021). These hybrids are generated through transcriptional dysregulation and impaired nucleic acid clearance mechanisms, and increased activity of endogenous retroelements such as LINE−1 (Ukadike et al., 2023). In addition, NETs, which are abundant in SLE, provide a major source of extracellular DNA and TF (Moore et al., 2020). Importantly, an engineered RNase (RSLV−132) designed to degrade extracellular RNA has been evaluated in a phase 2a clinical study in (SLE), showing a trend toward clinical improvement in patients with moderate-to-severe cutaneous disease, and thus highlighting extracellular RNA as a potentially targetable driver of interferon-mediated pathology in SLE (Burge et al., 2024). Clinical studies have shown that thrombotic events in SLE can occur even in the absence of antiphospholipid antibodies. This observation supports the idea that alternative mechanisms, such as nucleic acid–driven innate immune activation and TF induction, may contribute to the prothrombotic state in these patients (Richter et al., 2024). Moreover, in sporadic SLE, particularly in patients with nephritis, neutralizing autoantibodies against DNASE1L3, an enzyme involved in degrading extracellular chromatin, significantly reduce its enzymatic activity, resulting in the accumulation of long polynucleosomal cfDNA fragments within circulating microparticles, a non-genetic mechanism that fosters anti-dsDNA autoimmunity and disease severity (Hartl et al., 2021). Interestingly, patients with SLE have autoantibodies against the L1-encoded open-reading frame 1 protein (ORF1p) (Ukadike et al., 2023), suggesting that aberrant LINE−1 expression and retrotransposition intermediates are not immunologically silent, but may be actively targeted by the immune system.

A similar mechanism has been proposed in Aicardi-Goutières Syndrome (AGS), a monogenic interferonopathy, which results from mutations in genes involved in nucleic acid metabolism, such as TREX1 and RNASEH2 (Liu and Ying, 2023). These defects lead to intracellular accumulation of endogenous nucleic acids, including RNA:DNA hybrids, and spontaneous activation of innate immune responses (Liu and Ying, 2023). Although overt thrombosis is not a typical feature of AGS, affected individuals frequently develop vasculopathy, endothelial damage, and inflammatory neurovascular lesions (Adang et al., 2018; du Moulin et al., 2011). These manifestations may reflect subclinical activation of coagulation cascades in response to chronic sensing of endogenous nucleic acid.

Both SLE and AGS exemplify how genetic variants in innate nucleic acid sensors can predispose to chronic interferon signaling. In particular, single nucleotide polymorphisms and gain-of-function mutations in RIG-I-like receptors, especially MDA5, have been reported in these disorders, enhancing sensitivity to self-RNA and sustaining inappropriate type I interferon responses (Oda et al., 2014; Oliveira et al., 2014)

HIV infection provides a further model where viral nucleic acids, especially reverse-transcribed cDNA and RNA:DNA intermediates, accumulate in host cells and contribute to chronic immune activation (Akiyama et al., 2018). Even under suppressive antiretroviral therapy, people living with HIV (PLWH) exhibit persistently elevated levels of inflammatory and coagulation markers, including D-dimer, and tissue factor–positive microparticles (MP-TF), suggesting a chronic prothrombotic state despite effective viral control (Baker et al., 2013b; Funderburg, 2014). Experimental data suggest that viral nucleic acid debris can activate the cGAS–STING pathway, promote monocyte TF expression, and potentially engage FXII. This raises the question of whether pharmacological suppression of nucleic acid intermediates might modulate thromboinflammation in vivo. Interestingly, nucleoside reverse transcriptase inhibitors (NRTIs), beyond their direct antiviral activity, have been shown to dampen immune activation driven by endogenous RNA:DNA hybrids by reducing their intracellular accumulation and subsequent inflammasome stimulation. By inhibiting the reverse transcription of viral RNA into cDNA, NRTIs reduce the formation of intermediate nucleic acid species, such as cytosolic cDNA and RNA:DNA hybrids, that are known to activate innate immune sensors like cGAS–STING and TLR9 (Olivieri et al., 2025). This immunomodulatory effect may attenuate monocyte TF expression, endothelial activation, and the release of procoagulant microparticles. Consistent with this, active HIV replication has been shown to increase thrombin generation and alter levels of extrinsic coagulation factors such as FVII and FVIII, in association with increased tissue factor expression on monocytes and microparticles (Baker et al., 2013a). Notably, certain NRTIs such as tenofovir disoproxil fumarate (TDF) are associated with a relatively favorable cardiovascular profile, whereas abacavir has been linked to increased risk of thrombotic and major adverse cardiovascular events (MACE) - findings supported by data from the REPRIEVE trial showing approximately twofold higher hazard ratios for MACE in abacavir-treated individuals compared to TDF-based regimens (Davies Smith et al., 2025; Fichtenbaum et al., 2025; Grinspoon et al., 2019) and corroborated by observational cohort analyses in HIV-positive veterans (Choi et al., 2011).

Importantly, this thromboinflammatory state persists even under complete viral suppression. The mechanisms sustaining this residual risk remain unresolved, as current evidence cannot clearly disentangle the contributions of antiretroviral therapy (ART)-related effects, the immunovascular damage established prior to treatment, and the low-grade viral and immune perturbations that continue during suppressive therapy (Perkins et al., 2023). This mechanistic ambiguity is reflected in the persistent elevation of inflammatory and coagulation biomarkers in treated PLWH and in their sustained cardiovascular risk despite viral suppression.

Murine models provide additional support, showing that impaired nucleic acid degradation leads to chronic interferon activation, vascular injury, and features of coagulopathy. For example, Trex1 −/− mice, which lack the major cytosolic DNA exonuclease TREX1, accumulate endogenous DNA in the cytosol, triggering chronic cGAS–STING-mediated inflammation and exhibiting signs of vascular damage and endothelial activation-features, that may predispose to thrombotic complications (Stabach et al., 2024; Yan, 2017). Similarly, mice deficient in DNase1L3, show increased levels of circulating RNA:DNA hybrids and develop autoimmunity and vasculopathy, paralleling aspects of human SLE (Gomez-Banuelos et al., 2023). In both models, the presence of nucleic acid debris has been shown to stimulate monocyte activation and tissue factor expression, and in some settings may activate the intrinsic coagulation pathway via FXII, although this remains to be conclusively demonstrated (Jimenez-Alcazar et al., 2017). These preclinical observations reinforce the idea that misplaced nucleic acids are not only immunogenic, but may also directly modulate thrombotic pathways, providing a mechanistic bridge between innate sensing and coagulation in chronic inflammation and aging (Gall et al., 2012; Sisirak et al., 2016).

Together, these disease models demonstrate that the pathological accumulation of self-derived nucleic acids, whether due to genetic

mutations, viral infection, or immune dysregulation, can contribute to thromboinflammatory phenotypes (Ferriere et al., 2020; Klavina et al., 2022). They reinforce the hypothesis that nucleic acids are not merely markers of cell damage, but active drivers of coagulation and vascular inflammation, and suggest that similar mechanisms may contribute to the thromboinflammatory phenotype observed during physiological aging.

5. Nucleic acid burden as a molecular driver of coagul-aging

The evidence discussed above, including both pathological models and aging-related mechanisms, converges on a unifying concept: the accumulation and mislocalization of nucleic acids, both cytosolic and extracellular, constitutes a molecular axis that links cellular senescence, chronic inflammation, and thrombosis. While nucleic acids have long been recognized as potent immunostimulatory DAMPs that activate innate immune pathways and sustain chronic inflammation, accumulating evidence demonstrates that they also possess direct procoagulant potential through activation of FXII and the contact system (Vu et al., 2016). This dual functionality highlights their ability to drive both inflammation and coagulation, thereby challenging the classical notion that coagulation in aging is merely a downstream consequence of inflammation.

Specifically, FXII is a zymogen that becomes autoactivated upon exposure to negatively charged nucleic acids, including dsDNA, RNA:DNA hybrids, and NET-associated DNA (Fuchs et al., 2010; Hothorn et al., 2009; Pavlov et al., 2006; Renne and Stavrou, 2019). Once activated, FXII initiates the intrinsic coagulation cascade, amplifying thrombin generation and fibrin formation, while also engaging the kallikrein–kinin system to promote bradykinin release and vascular permeability (Mailer et al., 2022). In aging, the accumulation of LINE−1–derived cDNA, mitochondrial RNA, RNA:DNA hybrids, and cfDNA, the so-called 'nucleic acid burden', provides a persistent trigger for FXII activation, establishing coagul-aging as a parallel and self-amplifying process that arises from nucleic acid dysregulation rather than being a mere byproduct of inflammaging. The contact activation pathway, centered on FXII, provides a mechanistic link between nucleic acids and coagulation. Experimental studies have shown that cfRNA, particularly ribosomal and mitochondrial RNA, exhibits potent FXII-activating properties (Alharbi et al., 2021). A prototypical example of nucleic acid–driven FXII activation is provided by NETs, which supply a DNA-rich scaffold that promotes contact activation and thrombus formation (McDonald et al., 2017). This mechanism has been extensively documented in pathological conditions such as sepsis, where excessive NETosis fuels both immunothrombosis and organ damage (Gould et al., 2014). Beyond triggering FXII activation, NETs have also been shown to promote FXI activation, thereby amplifying the intrinsic pathway and promoting thrombin generation in sepsis models (Shi et al., 2021). One of the landmark studies in this field demonstrated that both eukaryotic and prokaryotic RNA molecules can directly trigger FXII activation and downstream thrombin generation in vitro and in vivo (Kannemeier et al., 2007). Importantly, RNA was found to be significantly more potent than DNA in activating coagulation, and its prothrombotic effect could be attenuated by treatment with RNase but not DNase (Kannemeier et al., 2007). Subsequent studies confirmed that ribosomal RNA, mitochondrial RNA, and synthetic polyribonucleotides exhibit similar procoagulant properties, suggesting that specific structural features of RNA confer high contact activity (Alharbi et al., 2021; Mareboina et al., 2024). The homeostasis of extracellular RNA is safeguarded by RNase A type ribonucleases, which are constitutively secreted, most prominently by endothelial cells, and degrade circulating RNA to prevent its procoagulant activity (Bedenbender and Schmeck, 2020). Exposure of human umbilical vein endothelial cells (HUVECs) to pro-inflammatory cytokines such as IL−1β and TNF-α leads to a significant downregulation of RNase A at both the mRNA and protein levels, suggesting a diminished capacity of the endothelium to neutralize extracellular RNA (Bedenbender et al., 2019). Although a direct impairment of this regulatory axis has not yet been demonstrated in senescence models, evidence from chronic inflammatory settings indicates that RNase1 expression is suppressed, leading to defective clearance of extracellular RNA and amplifying vascular dysfunction and procoagulant activity (Laakmann et al., 2023). Importantly, this mechanism operates independently of classical cytokine-driven inflammation and may explain the presence of a basal procoagulant state in aging individuals, even in the absence of acute inflammatory stimuli. The co-localization of nucleic acid accumulation, innate immune activation, and thrombin generation in aging tissues supports the concept of a nucleic acid–driven thromboinflammatory axis (Fig. 2).

6. Conclusions and future perspectives

The dysregulation and extracellular release of endogenous nucleic acids emerge as central pathophysiological mechanisms linking senescence, inflammation, and coagulation. Rather than being passive byproducts, these nucleic acids act as active agents capable of stimulating both innate immune receptors and the coagulation system, particularly through direct activation of FXII. This dual function places them at the heart of thromboinflammatory responses observed in aging and in several chronic diseases.

We propose that a "nucleic acid burden," resulting from the combined effects of retroelement activation, defective degradation, and vesicular export, drives a parallel process of inflammaging and coagul-aging. Therapeutic strategies aimed at reducing the accumulation, sensing, or systemic spillover of these nucleic acids, such as nucleases, inhibitors of retrotransposition, or senolytic agents, may offer novel opportunities to mitigate vascular aging and thrombotic risk.

From a clinical perspective, these mechanistic insights reinforce the notion that older individuals display a persistently heightened thromboinflammatory tone, even in the absence of overt cardiovascular disease. In this context, beyond conventional inflammatory markers, greater attention should be given to circulating indicators of coagulation activation. These may include TF activity associated with circulating membranes, such as extracellular vesicles and microparticles, as well as markers of thrombin generation, such as thrombin–antithrombin (TAT) complexes. Notably, experimental models of endothelial senescence have shown increased vesiculation and enhanced TF expression (Holnthoner et al., 2017; Mensà et al., 2020), suggesting that aged individuals may exhibit higher levels of circulating TF activity. In parallel, a more comprehensive assessment of endogenous anticoagulant pathways, including the protein C/protein S and antithrombin systems, which are not routinely evaluated in clinical practice, may provide additional insight into individual thromboinflammatory risk. Together, these parameters may support the development of integrated biomarker panels capturing procoagulant drivers, thrombin generation, and anticoagulant capacity, thereby enabling a more refined stratification of vulnerability to coagul-aging–related complications. This observation naturally raises the question of whether low-intensity anticoagulation might attenuate the vascular consequences of coagul-aging. However, current evidence outside atrial fibrillation remains scarce. Trials evaluating low-dose direct oral anticoagulants (DOACs) in elderly or high-risk populations have so far yielded disappointing results. The COMMANDER HF study, which tested rivaroxaban 2.5 mg twice daily in patients with chronic heart failure and coronary artery disease, failed to reduce the primary composite endpoint of death from any cause, myocardial infarction, or stroke compared with placebo (Zannad et al., 2018). The only significant difference observed was a modest reduction in the incidence of ischemic stroke, with no overall cardiovascular benefit despite acceptable safety. Importantly, the mean age of participants (≈66 years) did not fully capture the biological complexity of the oldest-old, in whom the thrombotic–bleeding balance may differ substantially. Additionally, emerging strategies targeting upstream components of the coagulation cascade, particularly the contact activation

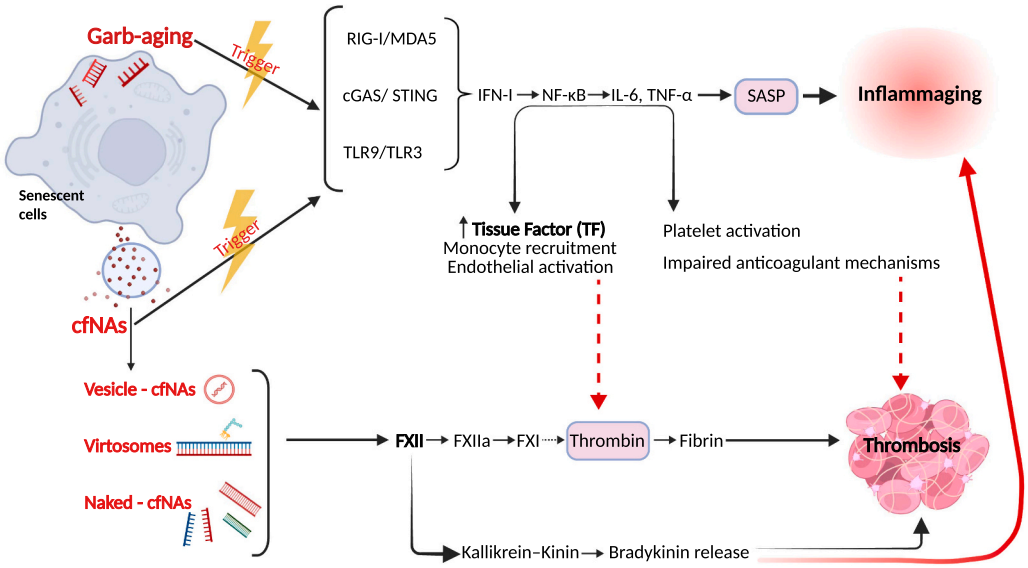

Fig. 2. Misplaced nucleic acids as drivers of thromboinflammation in aging. Accumulation of cell-free nucleic acids (cfNAs), including cell-free DNA (cfDNA) and RNA (cfRNA), in aging results from impaired degradation ("garb-aging") and active release from senescent cells, either as naked molecules or within extracellular vesicles (EVs) or virtosomes. These nucleic acids are sensed by pattern recognition receptors, including cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING), Toll-like receptors (TLR9 and TLR3), and RIG-I–like receptors (RIG-I and melanoma differentiation-associated protein 5, MDA5), leading to type I interferon (IFN-I), nuclear factor kappa B (NF-κB), and cytokine (IL−6, TNF-α) responses, contributing to the senescence-associated secretory phenotype (SASP) and inflammaging.In parallel, extracellular nucleic acids activate the contact pathway via factor XII (FXII), promoting factor XI (FXI), thrombin, and fibrin generation, and engaging the kallikrein–kinin system with bradykinin release. These pathways also induce tissue factor (TF) expression and monocyte recruitment, ultimately linking nucleic acid burden to thrombosis and coagul-aging.

system, may offer additional opportunities. Experimental and early clinical data indicate that inhibition of FXII can attenuate both thrombosis and inflammation without significantly impairing hemostasis, suggesting a promising approach to modulate thromboinflammation while potentially minimizing bleeding risk (Muller et al., 2011; Xu et al., 2024). More broadly, novel antithrombotic approaches aimed at dissociating thrombosis from hemostasis are under active investigation, including targeting factor XI, platelet receptors such as PARs, glycoprotein VI (GPVI), or intracellular signaling pathways, which have shown antithrombotic efficacy with a potentially improved safety profile in preclinical and early clinical studies (Buller et al., 2015; Xu et al., 2024).

Altogether, while the pathophysiological framework of coagul-aging strongly supports the rationale for preventive anticoagulation in selected older adults, current evidence remains insufficient to define optimal strategies outside established indications such as atrial fibrillation or venous thromboembolism. Yet, the recognition that a chronic, nucleic acid–driven chronic thromboinflammatory activation underlies vascular aging warrants a re-evaluation of anticoagulant use through the lens of biological aging. Future studies specifically designed to test low-dose or targeted anticoagulant regimens in biologically aged or inflammaging-prone individuals could help determine whether attenuating subclinical thrombin generation translates into tangible vascular benefits, paving the way for a more personalized approach to thromboprophylaxis in aging.

Author contributions

All authors contributed to information gathering, compiling, writing, editing and reviewing the manuscript.

Funding

This work was supported by the Italian Ministry of Health (Ricerca Corrente to IRCCS INRCA) and Università Politecnica delle Marche (RSA Grant).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Figures in this review were created using BioRender.com.

References

Adang, L.A., Frank, D.B., Gilani, A., Takanohashi, A., Ulrick, N., Collins, A., Cross, Z., Galambos, C., Helman, G., Kanaan, U., Keller, S., Simon, D., Sherbini, O., Hanna, B. D., Vanderver, A.L., 2018. Aicardi goutieres syndrome is associated with pulmonary hypertension. Mol. Genet. Metab. 125, 351–358.

Akiyama, H., Miller, C.M., Ettinger, C.R., Belkina, A.C., Snyder-Cappione, J.E., Gummuluru, S., 2018. HIV-1 intron-containing RNA expression induces innate immune activation and T cell dysfunction. Nat. Commun. 9, 3450.

Alharbi, A., Iyer, N., Al Qaryoute, A., Raman, R., Burks, D.J., Azad, R.K., Jagadeeswaran, P., 2021. Role of ribosomal RNA released from red cells in blood coagulation in zebrafish and humans. Blood Adv. 5, 4634–4647.

Anjum, A., Mader, M., Mahameed, S., Muraly, A., Denorme, F., Kliem, F.P., Rossaro, D., Agkol, S., Di Fina, L., Mulkers, M., Laun, L., Li, L., Kupper, N., Yue, K., Hoffknecht, M.L., Akhalkatsi, A., Loew, Q., Pircher, J., Escaig, R., Strasser, E., Wichmann, C., Pekayvaz, K., Nieswandt, B., Schulz, C., Robles, M.S., Kaiser, R., Massberg, S., Campbell, R., Nicolai, L., 2025. Aging platelets shift their hemostatic properties to inflammatory functions. Blood 145, 1568–1582.

Baker, J.V., Brummel-Ziedins, K., Neuhaus, J., Duprez, D., Cummins, N., Dalmau, D., DeHovitz, J., Lehmann, C., Sullivan, A., Woolley, I., Kuller, L., Neaton, J.D., Tracy, R. P., Team, I.S.S., 2013a. HIV replication alters the composition of extrinsic pathway coagulation factors and increases thrombin generation. J. Am. Heart Assoc. 2, e000264.

Baker, J.V., Huppler Hullsiek, K., Bradford, R.L., Prosser, R., Tracy, R.P., Key, N.S., 2013b. Circulating levels of tissue factor microparticle procoagulant activity are reduced with antiretroviral therapy and are associated with persistent inflammation and coagulation activation among HIV-positive patients. J. Acquir. Immune Defic. Syndr. 63, 367–371.

Beck, C.R., Garcia-Perez, J.L., Badge, R.M., Moran, J.V., 2011. LINE-1 elements in structural variation and disease. Annu. Rev. Genom. Hum. Genet. 12, 187–215.

Bedenbender, K., Scheller, N., Fischer, S., Leiting, S., Preissner, K.T., Schmeck, B.T., Vollmeister, E., 2019. Inflammation-mediated deacetylation of the ribonuclease 1 promoter via histone deacetylase 2 in endothelial cells. FASEB J. 33, 9017–9029.

Bedenbender, K., Schmeck, B.T., 2020. Endothelial ribonuclease 1 in Cardiovascular and Systemic Inflammation. Front. Cell. Dev. Biol. 8, 576491.
Bochenek, M.L., Schutz, E., Schafer, K., 2016. Endothelial cell senescence and thrombosis: Ageing clots. Thromb. Res. 147, 36–45.
Buller, H.R., Bethune, C., Bhanot, S., Gailani, D., Monia, B.P., Raskob, G.E., Segers, A., Verhamme, P., Weitz, J.I., Investigators, F.-A.T., 2015. Factor XI antisense oligonucleotide for prevention of venous thrombosis. N. Engl. J. Med. 372, 232–240.
Burge, D.J., Werth, V.P., Boackle, S.A., Posada, J., 2024. Evaluation of RNase therapy in systemic lupus erythematosus: a randomised phase 2a clinical trial of RSLV-132. Lupus Sci. Med. 11.
Buzas, E.I., 2023. The roles of extracellular vesicles in the immune system. Nat. Rev. Immunol. 23, 236–250.
Castellano, M., Blanco, V., Li Calzi, M., Costa, B., Witwer, K., Hill, M., Cayota, A., Segovia, M., Tosar, J.P., 2025. Ribonuclease activity undermines immune sensing of naked extracellular RNA. Cell. Genom. 5, 100874.
Chen, Z., Behrendt, R., Wild, L., Schlee, M., Bode, C., 2025. Cytosolic nucleic acid sensing as driver of critical illness: mechanisms and advances in therapy. Signal. Transduct. Target. Ther. 10, 90.
Choi, A.I., Vittinghoff, E., Deeks, S.G., Weekley, C.C., Li, Y., Shlipak, M.G., 2011. Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons. AIDS 25, 1289–1298.
Daubermann, C., Herhaus, B., Neuberger, E.W.I., Simon, P., Petrowski, K., 2025. Methodological influences on circulating cell-free-mitochondrial and nuclear DNA concentrations in response to chronic stress. Mol. Biol. Rep. 52, 303.
Davies Smith, E., Malvestutto, C., Ribaudo, H.J., Fichtenbaum, C.J., Aberg, J.A., Watanabe, M., Bloomfield, G.S., Currier, J.S., Chu, S.M., Fitch, K.V., Diggs, M.R., Bedimo, R., Valencia, J., Gomez-Ayerbe, C., Brar, I., Madruga, J.V., Lu, M.T., Douglas, P.S., Zanni, M.V., Grinspoon, S.K., 2025. Cardiovascular hazards of abacavir- versus tenofovir-containing antiretroviral therapies: insights from an analysis of the REPRIEVE trial cohort. Open. Forum Infect. Dis. 12, ofaf177.
Davizon-Castillo, P., McMahon, B., Aguila, S., Bark, D., Ashworth, K., Allawzi, A., Campbell, R.A., Montenont, E., Nemkov, T., D'Alessandro, A., Clendenen, N., Shih, L., Sanders, N.A., Higa, K., Cox, A., Padilla-Romo, Z., Hernandez, G., Wartchow, E., Trahan, G.D., Nozik-Grayck, E., Jones, K., Pietras, E.M., DeGregori, J., Rondina, M.T., Di Paola, J., 2019. TNF-alpha-driven inflammation and mitochondrial dysfunction define the platelet hyperreactivity of aging. Blood 134, 727–740.
De La Cruz-Siguenza, D.A., Reyes-Grajeda, J.P., Velasco-Velazquez, M.A., Trejo-Becerril, C., Perez-Cardenas, E., Chavez-Blanco, A., Taja-Chayeb, L., Dominguez-Gomez, G., Ramos-Godinez, M.P., Gonzalez-Fierro, A., Duenas-Gonzalez, A., 2024. The non-vesicle cell-free DNA (cfDNA) induces cell transformation associated with horizontal DNA transfer. Mol. Biol. Rep. 51, 174.
Della Valle, F., Reddy, P., Yamamoto, M., Liu, P., Saera-Vila, A., Bensaddek, D., Zhang, H., Prieto Martinez, J., Abassi, L., Celii, M., Ocampo, A., Nunez Delicado, E., Mangiavacchi, A., Aiese Cigliano, R., Rodriguez Esteban, C., Horvath, S., Izpisua Belmonte, J.C., Orlando, V., 2022. LINE-1 RNA causes heterochromatin erosion and is a target for amelioration of senescent phenotypes in progeroid syndromes. Sci. Transl. Med. 14, eabl6057.
Di Giorgio, E., Ranzino, L., Tolotto, V., Dalla, E., Burelli, M., Gualandi, N., Brancolini, C., 2024. Transcription of endogenous retroviruses in senescent cells contributes to the accumulation of double-stranded RNAs that trigger an anti-viral response that reinforces senescence. Cell. Death Dis. 15, 157.
Du, Z., Wang, H., Shao, Y., Wu, W., Tong, D., Xie, F., Li, J., Xia, W., Zhou, Y., 2024. Procoagulant effect of phosphatidylserine exposed to extracellular vesicles, blood cells and endothelial cells in patients with aortic stenosis. medRxiv 2024, 24308758, 2006.2011.
Ferriere, A., Santa, P., Garreau, A., Bandopadhyay, P., Blanco, P., Ganguly, D., Sisirak, V., 2020. Self-nucleic acid sensing: a novel crucial pathway involved in obesity-mediated metaflammation and metabolic syndrome. Front. Immunol. 11, 624256.
Fichtenbaum, C.J., Malvestutto, C.D., Watanabe, M.G., Davies Smith, E., Ribaudo, H.J., McCallum, S., Fitch, K.V., Currier, J.S., Diggs, M.R., Chu, S.M., Aberg, J.A., Lu, M.T., Valencia, J., Gomez-Ayerbe, C., Brar, I., Valdez Madruga, J., Bloomfield, G.S., Douglas, P.S., Zanni, M.V., Grinspoon, S.K., Investigators, R., 2025. Effects of antiretrovirals on major adverse cardiovascular events in the REPRIEVE trial: a longitudinal cohort analysis. Lancet HIV 12, e496–e505.
Franceschi, C., Bonafe, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., De Benedictis, G., 2000. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann. N. Y Acad. Sci. 908, 244–254.
Franceschi, C., Campisi, J., 2014. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J. Gerontol. A Biol. Sci. Med. Sci. 69 (1), S4–S9.
Franceschi, C., Garagnani, P., Vitale, G., Capri, M., Salvioli, S., 2017. Inflammaging and 'Garb-aging. Trends Endocrinol. Metab. 28, 199–212.
Freund, A., Laberge, R.M., Demaria, M., Campisi, J., 2012. Lamin B1 loss is a senescence-associated biomarker. Mol. Biol. Cell. 23, 2066–2075.
Fuchs, T.A., Brill, A., Duerschmied, D., Schatzberg, D., Monestier, M., Myers Jr., D.D., Wrobleski, S.K., Wakefield, T.W., Hartwig, J.H., Wagner, D.D., 2010. Extracellular DNA traps promote thrombosis. In: Proc Natl Acad Sci U S A, 107, pp. 15880–15885.
Funderburg, N.T., 2014. Markers of coagulation and inflammation often remain elevated in ART-treated HIV-infected patients. Curr. Opin. HIV AIDS 9, 80–86.
Gall, A., Treuting, P., Elkon, K.B., Loo, Y.M., Gale Jr., M., Barber, G.N., Stetson, D.B., 2012. Autoimmunity initiates in nonhematopoietic cells and progresses via lymphocytes in an interferon-dependent autoimmune disease. Immunity 36, 120–131.
Giuliani, A., Cirilli, I., Prattichizzo, F., Mensa, E., Fulgenzi, G., Sabbatinelli, J., Graciotti, L., Olivieri, F., Procopio, A.D., Tiano, L., Rippo, M.R., 2018. The mitomiR/Bcl-2 axis affects mitochondrial function and autophagic vacuole formation in senescent endothelial cells. Aging 10, 2855–2873.
Giuliani, A., Giudetti, A.M., Vergara, D., Del Coco, L., Ramini, D., Caccese, S., Sbriscia, M., Graciotti, L., Fulgenzi, G., Tiano, L., Fanizzi, F.P., Olivieri, F., Rippo, M. R., Sabbatinelli, J., 2023. Senescent endothelial cells sustain their senescence-associated secretory phenotype (SASP) through enhanced fatty acid oxidation. Antioxid. 12.
Giuliani, A., Ramini, D., Sbriscia, M., Crocco, P., Tiano, L., Rippo, M.R., Bonfigli, A.R., Rose, G., De Luca, M., Olivieri, F., Sabbatinelli, J., 2024. Syndecan 4 is a marker of endothelial inflammation in pathological aging and predicts long-term cardiovascular outcomes in type 2 diabetes. Diabetol. Metab. Syndr. 16, 203.
Glebova, K., Veiko, N., Kostyuk, S., Izhevskaya, V., Baranova, A., 2015. Oxidized extracellular DNA as a stress signal that may modify response to anticancer therapy. Cancer Lett. 356, 22–33.
Gogvadze, V., Zhivotovsky, B., 2025. Mitochondrial DNA: how does it leave mitochondria? Trends Cell. Biol. 35, 819–822.
Gomez-Banuelos, E., Yu, Y., Li, J., Cashman, K.S., Paz, M., Trejo-Zambrano, M.I., Bugrovsky, R., Wang, Y., Chida, A.S., Sherman-Baust, C.A., Ferris, D.P., Goldman, D. W., Darrah, E., Petri, M., Sanz, I., Andrade, F., 2023. Affinity maturation generates pathogenic antibodies with dual reactivity to DNase1L3 and dsDNA in systemic lupus erythematosus. Nat. Commun. 14, 1388.
Gould, T.J., Vu, T.T., Swystun, L.L., Dwivedi, D.J., Mai, S.H., Weitz, J.I., Liaw, P.C., 2014. Neutrophil extracellular traps promote thrombin generation through platelet-dependent and platelet-independent mechanisms. Arterioscler. Thromb. Vasc. Biol. 34, 1977–1984.
Grabuschnig, S., Bronkhorst, A.J., Holdenrieder, S., Rosales Rodriguez, I., Schliep, K.P., Schwendenwein, D., Ungerer, V., Sensen, C.W., 2020. Putative origins of cell-free DNA in humans: a review of active and passive nucleic acid release mechanisms. Int. J. Mol. Sci. 21.
Grinspoon, S.K., Fitch, K.V., Overton, E.T., Fichtenbaum, C.J., Zanni, M.V., Aberg, J.A., Malvestutto, C., Lu, M.T., Currier, J.S., Sponseller, C.A., Waclawiw, M., Alston-Smith, B., Cooper-Arnold, K., Klingman, K.L., Desvigne-Nickens, P., Hoffmann, U., Ribaudo, H.J., Douglas, P.S., Investigators, R., 2019. Rationale and design of the randomized trial to prevent vascular events in HIV (REPRIEVE). Am. Heart J. 212, 23–35.
Guo, D., Ma, D., Liu, P., Lan, J., Liu, Z., Liu, Q., 2021. DNASE1L3 arrests tumor angiogenesis by impairing the senescence-associated secretory phenotype in response to stress. Aging 13, 9874–9899.
Ha, Y.J., Choi, Y.S., Choi, S.R., Yoon, J., Ku, D., Kim, Y., Kang, E.H., Kim, K.S., Jeong, W. J., Hyon, J.Y., Cha, S., Lee, Y.J., 2025. Association of mitochondrial RNA expression levels in saliva and plasma with interferon signature gene expression and disease activity in patients with Sjogren disease. RMD Open. 11.
Habibi, A., Ruf, W., Schurgers, L., 2025. Protease-activated receptors in vascular smooth muscle cells: a bridge between thrombo-inflammation and vascular remodelling. Cell. Commun. Signal. 23, 57.
Han, Y., Kim, S.Y., 2023. Endothelial senescence in vascular diseases: current understanding and future opportunities in senotherapeutics. Exp. Mol. Med. 55, 1–12.
Hanelova, K., Raudenska, M., Kratochvilova, M., Navratil, J., Vicar, T., Bugajova, M., Gumulec, J., Masarik, M., Balvan, J., 2023. Autophagy modulators influence the content of important signalling molecules in PS-positive extracellular vesicles. Cell. Commun. Signal. 21, 120.
Hartl, J., Serpas, L., Wang, Y., Rashidfarrokhi, A., Perez, O.A., Sally, B., Sisirak, V., Soni, C., Khodadadi-Jamayran, A., Tsirigos, A., Caiello, I., Bracaglia, C., Volpi, S., Ghiggeri, G.M., Chida, A.S., Sanz, I., Kim, M.Y., Belmont, H.M., Silverman, G.J., Clancy, R.M., Izmirly, P.M., Buyon, J.P., Reizis, B., 2021. Autoantibody-mediated impairment of DNASE1L3 activity in sporadic systemic lupus erythematosus. J. Exp. Med. 218.
Hasegawa, N., Fujie, S., Horii, N., Uchida, M., Toyama, Y., Inoue, K., Sanada, K., Hamaoka, T., Iemitsu, M., 2019. Aging-induced elevation in circulating complement C1q level is associated with arterial stiffness. Exp. Gerontol. 124, 110650.
He, J., Tu, C., Liu, Y., 2018. Role of lncRNAs in aging and age-related diseases. Aging Med. 1, 158–175.
Heuberger, D.M., Schuepbach, R.A., 2019. Protease-activated receptors (PARs): mechanisms of action and potential therapeutic modulators in PAR-driven inflammatory diseases. Thromb. J. 17, 4.
Holnthoner, W., Bonstingl, C., Hromada, C., Muehleder, S., Zipperle, J., Stojkovic, S., Redl, H., Wojta, J., Schochl, H., Grillari, J., Weilner, S., Schlimp, C.J., 2017. Endothelial cell-derived extracellular vesicles size-dependently exert procoagulant activity detected by thromboelastometry. Sci. Rep. 7, 3707.
Honda, S., Ikeda, K., Urata, R., Yamazaki, E., Emoto, N., Matoba, S., 2021. Cellular senescence promotes endothelial activation through epigenetic alteration, and consequently accelerates atherosclerosis. Sci. Rep. 11, 14608.
Hothorn, M., Neumann, H., Lenherr, E.D., Wehner, M., Rybin, V., Hassa, P.O., Uttenweiler, A., Reinhardt, M., Schmidt, A., Seiler, J., Ladurner, A.G., Herrmann, C., Scheffzek, K., Mayer, A., 2009. Catalytic core of a membrane-associated eukaryotic polyphosphate polymerase. Science 324, 513–516.
Iske, J., Seyda, M., Heinbokel, T., Maenosono, R., Minami, K., Nian, Y., Quante, M., Falk, C.S., Azuma, H., Martin, F., Passos, J.F., Niemann, C.U., Tchkonia, T., Kirkland, J.L., Elkhal, A., Tullius, S.G., 2020. Senolytics prevent mt-DNA-induced inflammation and promote the survival of aged organs following transplantation. Nat. Commun. 11, 4289.
Jackson, S.P., Darbousset, R., Schoenwaelder, S.M., 2019. Thromboinflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. Blood 133, 906–918.

Jimenez-Alcazar, M., Rangaswamy, C., Panda, R., Bitterling, J., Simsek, Y.J., Long, A.T., Bilyy, R., Krenn, V., Renne, C., Renne, T., Kluge, S., Panzer, U., Mizuta, R., Mannherz, H.G., Kitamura, D., Herrmann, M., Napirei, M., Fuchs, T.A., 2017. Host DNases prevent vascular occlusion by neutrophil extracellular traps. Science 358, 1202–1206.

Kannemeier, C., Shibamiya, A., Nakazawa, F., Trusheim, H., Ruppert, C., Markart, P., Song, Y., Tzima, E., Kennerknecht, E., Niepmann, M., von Bruehl, M.L., Sedding, D., Massberg, S., Gunther, A., Engelmann, B., Preissner, K.T., 2007. Extracellular RNA constitutes a natural procoagulant cofactor in blood coagulation. In: Proc Natl Acad Sci U S A, 104, pp. 6388–6393.

Khoddam, A., Miyata, T., Vaughan, D., 2025. PAI-1 is a common driver of aging and diverse diseases. Biomed. J., 100892

Kim, H., Conway, E.M., 2019. Platelets and complement cross-talk in early atherogenesis. Front. Cardiovasc. Med. 6, 131.

Kim, E., Kim, Y.K., Lee, S.V., 2021. Emerging functions of circular RNA in aging. Trends Genet. 37, 819–829.

Kim, S., Lee, K., Choi, Y.S., Ku, J., Lee, Y.J., Kim, Y., 2020a. Mitochondrial dsRNAs activate PKR and TLR3 to promote chondrocyte degeneration in osteoarthritis. bioRxiv 2020, 156323, 2006.2017.

Kim, S., Lee, K., Choi, Y.S., Ku, J., Kim, H., Kharbash, R., Yoon, J., Lee, Y.S., Kim, J.H., Lee, Y.J., Kim, Y., 2022. Mitochondrial double-stranded RNAs govern the stress response in chondrocytes to promote osteoarthritis development. Cell. Rep. 40, 111178.

Kim, S.Y., Yang, E.J., Lee, S.B., Lee, Y.S., Cho, K.A., Park, S.C., 2020b. Global transcriptional downregulation of TREX and nuclear trafficking machinery as pan-senescence phenomena: evidence from human cells and tissues. Exp. Mol. Med. 52, 1351–1359.

Klavina, P.A., Leon, G., Curtis, A.M., Preston, R.J.S., 2022. Dysregulated haemostasis in thrombo-inflammatory disease. Clin. Sci. 136, 1809–1829.

Kurz, D.J., Payeli, S., Greutert, H., Briand Schumacher, S., Luscher, T.F., Tanner, F.C., 2014. Epigenetic regulation of tissue factor inducibility in endothelial cell senescence. Mech. Ageing Dev. 140, 1–9.

Laakmann, K., Eckersberg, J.M., Hapke, M., Wiegand, M., Bierwagen, J., Beinborn, I., Preusser, C., Pogge von Strandmann, E., Heimerl, T., Schmeck, B., Jung, A.L., 2023. Bacterial extracellular vesicles repress the vascular protective factor RNase1 in human lung endothelial cells. Cell. Commun. Signal. 21, 111.

Lai, P., Liu, L., Bancaro, N., Troiani, M., Cali, B., Li, Y., Chen, J., Singh, P.K., Arzola, R.A., Attanasio, G., Pernigoni, N., Pasquini, E., Mosole, S., Rinaldi, A., Sgrignani, J., Qiu, S., Song, P., Li, Y., Desbats, M.A., Angel, A.R., Mestre, R.P., Cavalli, A., Barile, L., de Bono, J., Alimonti, A., 2025. Mitochondrial DNA released by senescent tumor cells enhances PMN-MDSC-driven immunosuppression through the cGAS-STING pathway. Immunity 58, 811–825 e817.

Le Blanc, J., Lordkipanidze, M., 2019. Platelet function in aging. Front. Cardiovasc. Med. 6, 109.

Li, X., Yu, H., Li, D., Liu, N., 2024. LINE-1 transposable element renaissance in aging and age-related diseases. Ageing Res. Rev. 100, 102440.

Liu, D., Xu, C., Gong, Z., Zhao, Y., Fang, Z., Rao, X., Chen, Q., Li, G., Kong, W., Chen, J., 2023. GRSF1 antagonizes age-associated hypercoagulability via modulation of fibrinogen mRNA stability. Cell. Death Dis. 14, 717.

Liu, A., Ying, S., 2023. Aicardi-Goutieres syndrome: a monogenic type I interferonopathy. Scand. J. Immunol. 98, e13314.

Mack, A., Vanden Hoek, T., Du, X., 2024. Thromboinflammation and the Role of Platelets. Arterioscler. Thromb. Vasc. Biol. 44, 1175–1180.

Mailer, R.K., Rangaswamy, C., Konrath, S., Emsley, J., Renne, T., 2022. An update on factor XII-driven vascular inflammation. Biochim. Biophys. Acta Mol. Cell. Res. 1869, 119166.

Malkin, E.Z., De Michino, S., Lambie, M., Gill, R., Zhao, Z., Rostami, A., Arruda, A., Minden, M.D., Bratman, S.V., 2022. Cell-free DNA topology depends on its subcellular and cellular origins in cancer. JCI Insight 7.

Mankan, A.K., Schmidt, T., Chauhan, D., Goldeck, M., Honing, K., Gaidt, M., Kubarenko, A.V., Andreeva, L., Hopfner, K.P., Hornung, V., 2014. Cytosolic RNA: DNA hybrids activate the cGAS-STING axis. EMBO J. 33, 2937–2946.

Mareboina, M., Deng, E., Mouratidis, I., Yee, N.S., Pitteloud, N., Georgakopoulos-Soares, I., Chartoumpekis, D.V., 2024. A review on cell-free RNA profiling: insights into metabolic diseases and predictive value for bariatric surgery outcomes. Mol. Metab. 87, 101987.

Martinez Bravo, G., Annarapu, G., Carmona, E., Nawarskas, J., Clark, R., Novelli, E., Mota Alvidrez, R.I., 2024. Platelets in thrombosis and atherosclerosis: a double-edged sword. Am. J. Pathol. 194, 1608–1621.

McDonald, B., Davis, R.P., Kim, S.J., Tse, M., Esmon, C.T., Kolaczkowska, E., Jenne, C.N., 2017. Platelets and neutrophil extracellular traps collaborate to promote intravascular coagulation during sepsis in mice. Blood 129, 1357–1367.

Menichelli, D., Cormaci, V.M., Marucci, S., Franchino, G., Del Sole, F., Capozza, A., Fallarino, A., Valeriani, E., Violi, F., Pignatelli, P., Pastori, D., 2023. Risk of venous thromboembolism in autoimmune diseases: A comprehensive review. Autoimmun. Rev. 22, 103447.

Mensà, E., Guescini, M., Giuliani, A., Bacalini, M.G., Ramini, D., Corleone, G., Ferracin, M., Fulgenzi, G., Graciotti, L., Prattichizzo, F., Sorci, L., Battistelli, M., Monsurro, V., Bonfigli, A.R., Cardelli, M., Recchioni, R., Marcheselli, F., Latini, S., Maggio, S., Fanelli, M., Amatori, S., Storci, G., Ceriello, A., Stocchi, V., De Luca, M., Magnani, L., Rippo, M.R., Procopio, A.D., Sala, C., Budimir, I., Bassi, C., Negrini, M., Garagnani, P., Franceschi, C., Sabbatinelli, J., Bonafe, M., Olivieri, F., 2020. Small extracellular vesicles deliver miR-21 and miR-217 as pro-senescence effectors to endothelial cells. J. Extracell. Vesicles 9, 1725285.

Meyer, N.J., Prescott, H.C., 2024. Sepsis and septic shock. N. Engl. J. Med. 391, 2133–2146.

Molony, R.D., Nguyen, J.T., Kong, Y., Montgomery, R.R., Shaw, A.C., Iwasaki, A., 2017. Aging impairs both primary and secondary RIG-I signaling for interferon induction in human monocytes. Sci. Signal. 10.

Montenont, E., Rondina, M.T., Campbell, R.A., 2019. Altered functions of platelets during aging. Curr. Opin. Hematol. 26, 336–342.

Moore, S., Juo, H.H., Nielsen, C.T., Tyden, H., Bengtsson, A.A., Lood, C., 2020. Role of neutrophil extracellular traps regarding patients at risk of increased disease activity and cardiovascular comorbidity in systemic lupus erythematosus. J. Rheumatol. 47, 1652–1660.

du Moulin, M., Nurnberg, P., Crow, Y.J., Rutsch, F., 2011. Cerebral vasculopathy is a common feature in Aicardi-Goutieres syndrome associated with SAMHD1 mutations. In: Proc Natl Acad Sci U S A, 108 author reply E233.

Muller, F., Gailani, D., Renne, T., 2011. Factor XI and XII as antithrombotic targets. Curr. Opin. Hematol. 18, 349–355.

Mustelin, T., Lood, C., Giltiay, N.V., 2019. Sources of pathogenic nucleic acids in systemic lupus erythematosus. Front. Immunol. 10, 1028.

Oda, H., Nakagawa, K., Abe, J., Awaya, T., Funabiki, M., Hijikata, A., Nishikomori, R., Funatsuka, M., Ohshima, Y., Sugawara, Y., Yasumi, T., Kato, H., Shirai, T., Ohara, O., Fujita, T., Heike, T., 2014. Aicardi-Goutieres syndrome is caused by IFIH1 mutations. Am. J. Hum. Genet. 95, 121–125.

Okumura, K., Akao, M., Yoshida, T., Kawata, M., Okazaki, O., Akashi, S., Eshima, K., Tanizawa, K., Fukuzawa, M., Hayashi, T., Akishita, M., Lip, G.Y.H., Yamashita, T., Committees, E.-A., Investigators, 2020. Low-dose edoxaban in very elderly patients with atrial fibrillation. N. Engl. J. Med. 383, 1735–1745.

Oliveira, L., Sinicato, N.A., Postal, M., Appenzeller, S., Niewold, T.B., 2014. Dysregulation of antiviral helicase pathways in systemic lupus erythematosus. Front. Genet. 5, 418.

Olivieri, F., Giuliani, A., Bonafe, M., 2025. Nucleoside reverse transcriptase inhibitors as a therapeutic opportunity to counteract inflammaging and age-related diseases: new evidence from epidemiological data. Ageing Res. Rev. 112, 102878.

Olivieri, F., Prattichizzo, F., Giuliani, A., Matacchione, G., Rippo, M.R., Sabbatinelli, J., Bonafe, M., 2021. miR-21 and miR-146a: the microRNAs of inflammaging and age-related diseases. Ageing Res. Rev. 70, 101374.

Page, M.J., Bester, J., Pretorius, E., 2018. The inflammatory effects of TNF-alpha and complement component 3 on coagulation. Sci. Rep. 8, 1812.

Pavlov, V., Zorn, M., Kramer, R., 2006. Probing single-stranded DNA and its biomolecular interactions through direct catalytic activation of factor XII, a protease of the blood coagulation cascade. Biochem. Biophys. Res. Commun. 349, 1011–1015.

Perkins, M.V., Joseph, S.B., Dittmer, D.P., Mackman, N., 2023. Cardiovascular disease and thrombosis in HIV infection. Arterioscler. Thromb. Vasc. Biol. 43, 175–191.

Poscablo, D.M., Worthington, A.K., Smith-Berdan, S., Rommel, M.G.E., Manso, B.A., Adili, R., Mok, L., Reggiardo, R.E., Cool, T., Mogharrab, R., Myers, J., Dahmen, S., Medina, P., Beaudin, A.E., Boyer, S.W., Holinstat, M., Jonsson, V.D., Forsberg, E.C., 2024. An age-progressive platelet differentiation path from hematopoietic stem cells causes exacerbated thrombosis. Cell 187, 3090–3107 e3021.

Ramini, D., Giuliani, A., Kwiatkowska, K.M., Guescini, M., Storci, G., Mensà, E., Recchioni, R., Xumerle, L., Zago, E., Sabbatinelli, J., Santi, S., Garagnani, P., Bonafè, M., Olivieri, F., 2024. Replicative senescence and high glucose induce the accrual of self-derived cytosolic nucleic acids in human endothelial cells. Cell. Death Discov. 10, 184.

Ramini, D., Latini, S., Giuliani, A., Matacchione, G., Sabbatinelli, J., Mensà, E., Bacalini, M.G., Garagnani, P., Rippo, M.R., Bronte, G., Bonafè, M., Cardelli, M., Olivieri, F., 2022. Replicative Senescence-associated LINE1 Methylation and LINE1-Alu expression levels in human endothelial cells. Cells 11.

Renne, T., Stavrou, E.X., 2019. Roles of Factor XII in innate immunity. Front. Immunol. 10, 2011.

Richter, P., Badescu, M.C., Rezus, C., Ouatu, A., Dima, N., Popescu, D., Burlui, A.M., Bratoiu, I., Mihai, I.R., Rezus, E., 2024. Antiphospholipid antibodies as key players in systemic lupus erythematosus: the relationship with cytokines and immune dysregulation. Int. J. Mol. Sci. 25.

Rigby, R.E., Webb, L.M., Mackenzie, K.J., Li, Y., Leitch, A., Reijns, M.A., Lundie, R.J., Revuelta, A., Davidson, D.J., Diebold, S., Modis, Y., MacDonald, A.S., Jackson, A.P., 2014. RNA:DNA hybrids are a novel molecular pattern sensed by TLR9. EMBO J. 33, 542–558.

Rostami, A., Lambie, M., Yu, C.W., Stambolic, V., Waldron, J.N., Bratman, S.V., 2020. Senescence, necrosis, and apoptosis govern circulating cell-free DNA release kinetics. Cell. Rep. 31, 107830.

Schmaier, A.H., Stavrou, E.X., 2019. Factor XII - What's important but not commonly thought about. Res. Pract. Thromb. Haemost. 3, 599–606.

Schwartz, R.E., Conboy, I.M., 2023. Non-intrinsic, systemic mechanisms of cellular senescence. Cells 12.

Shi, Y., Gauer, J.S., Baker, S.R., Philippou, H., Connell, S.D., Ariens, R.A.S., 2021. Neutrophils can promote clotting via FXI and impact clot structure via neutrophil extracellular traps in a distinctive manner in vitro. Sci. Rep. 11, 1718.

Simon, M., Van Meter, M., Ablaeva, J., Ke, Z., Gonzalez, R.S., Taguchi, T., De Cecco, M., Leonova, K.I., Kogan, V., Helfand, S.L., Neretti, N., Roichman, A., Cohen, H.Y., Meer, M.V., Gladyshev, V.N., Antoch, M.P., Gudkov, A.V., Sedivy, J.M., Seluanov, A., Gorbunova, V., 2019. LINE1 Derepression in Aged Wild-Type and SIRT6-deficient mice drives inflammation. Cell. Metab. 29, 871–885 e875.

Sisirak, V., Sally, B., D'Agati, V., Martinez-Ortiz, W., Ozcakar, Z.B., David, J., Rashidfarrokhi, A., Yeste, A., Panea, C., Chida, A.S., Bogunovic, M., Ivanov, I.I., Quintana, F.J., Sanz, I., Elkon, K.B., Tekin, M., Yalcinkaya, F., Cardozo, T.J., Clancy, R.M., Buyon, J.P., Reizis, B., 2016. Digestion of chromatin in apoptotic cell microparticles prevents autoimmunity. Cell 166, 88–101.

Skendros, P., Mitsios, A., Chrysanthopoulou, A., Mastellos, D.C., Metallidis, S., Rafailidis, P., Ntinopoulou, M., Sertaridou, E., Tsironidou, V., Tsigalou, C., Tektonidou, M., Konstantinidis, T., Papagoras, C., Mitroulis, I., Germanidis, G., Lambris, J.D., Ritis, K., 2020. Complement and tissue factor-enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis. J. Clin. Invest. 130, 6151–6157.

Spence, J.D., Azarpazhooh, M.R., Larsson, S.C., Bogiatzi, C., Hankey, G.J., 2020. Stroke prevention in older adults: recent advances. Stroke 51, 3770–3777.

Stabach, P.R., Sims, D., Gomez-Banuelos, E., Zehentmeier, S., Dammen-Brower, K., Bernhisel, A., Kujawski, S., Lopez, S.G., Petri, M., Goldman, D.W., Lester, E.R., Le, Q., Ishaq, T., Kim, H., Srivastava, S., Kumar, D., Pereira, J.P., Yarema, K.J., Koumpouras, F., Andrade, F., Braddock, D.T., 2024. A dual-acting DNASE1/DNASE1L3 biologic prevents autoimmunity and death in genetic and induced lupus models. JCI Insight 9.

Stejskal, P., Goodarzi, H., Srovnal, J., Hajduch, M., van 't Veer, L.J., Magbanua, M.J.M., 2023. Circulating tumor nucleic acids: biology, release mechanisms, and clinical relevance. Mol. Cancer 22, 15.

Stephan, A.H., Madison, D.V., Mateos, J.M., Fraser, D.A., Lovelett, E.A., Coutellier, L., Kim, L., Tsai, H.H., Huang, E.J., Rowitch, D.H., Berns, D.S., Tenner, A.J., Shamloo, M., Barres, B.A., 2013. A dramatic increase of C1q protein in the CNS during normal aging. J. Neurosci. 33, 13460–13474.

Storci, G., De Carolis, S., Olivieri, F., Bonafe, M., 2018. Changes in the biochemical taste of cytoplasmic and cell-free DNA are major fuels for inflamm-aging. Semin. Immunol. 40, 6–16.

Stuby, J., Haschke, M., Tritschler, T., Aujesky, D., 2024. Oral anticoagulant therapy in older adults. Thromb. Res. 238, 1–10.

Szilagyi, M., Pos, O., Marton, E., Buglyo, G., Soltesz, B., Keseru, J., Penyige, A., Szemes, T., Nagy, B., 2020. Circulating cell-free nucleic acids: main characteristics and clinical application. Int. J. Mol. Sci. 21.

Tang, W., Bell, E.J., Roetker, N.S., Folsom, A.R., Cushman, M., 2015. Epidemiology of thrombosis in aging. Blood 126. SCI–6–SCI–6.

Teo, Y.V., Capri, M., Morsiani, C., Pizza, G., Faria, A.M.C., Franceschi, C., Neretti, N., 2019. Cell-free DNA as a biomarker of aging. Aging Cell. 18, e12890.

Tian, Y., Zong, Y., Pang, Y., Zheng, Z., Ma, Y., Zhang, C., Gao, J., 2025. Platelets and diseases: signal transduction and advances in targeted therapy. Signal. Transduct. Target. Ther. 10, 159.

Tschan, S.L., Bolliger, D., 2021. Coagulation and Aging: implications for the anesthesiologist. Curr. Anesthesiol. Rep. 11, 387–395.

Ukadike, K.C., Najjar, R., Ni, K., Laine, A., Wang, X., Bays, A., Taylor, M.S., LaCava, J., Mustelin, T., 2023. Expression of L1 retrotransposons in granulocytes from patients with active systemic lupus erythematosus. Mob. DNA 14, 5.

Ungvari, Z., Tarantini, S., Donato, A.J., Galvan, V., Csiszar, A., 2018. Mechanisms of vascular aging. Circ. Res. 123, 849–867.

Victorelli, S., Eppard, M., Woo, S.H., Everts, S.P.A., Martini, H., Pirius, N., Franco, A.C., Han, Y., Saul, D., Splinter, P.L., O'Hara, S.P., Valenzuela-Perez, L., Lee, H.S.K., Jurk, D., LaRusso, N.F., Hirsova, P., Passos, J.F., 2024. Mitochondrial RNA cytosolic leakage drives the SASP. Res. Sq.

Vu, T.T., Leslie, B.A., Stafford, A.R., Zhou, J., Fredenburgh, J.C., Weitz, J.I., 2016. Histidine-rich glycoprotein binds DNA and RNA and attenuates their capacity to activate the intrinsic coagulation pathway. Thromb. Haemost. 115, 89–98.

Wang, M., Hao, H., Leeper, N.J., Zhu, L., Early Career, C., 2018. Thrombotic regulation from the endothelial cell perspectives. Arterioscler. Thromb. Vasc. Biol. 38, e90–e95.

Wilkerson, W.R., Sane, D.C., 2002. Aging and thrombosis. Semin. Thromb. Hemost. 28, 555–568.

Wright, A., Snyder, O.L., He, H., Christenson, L.K., Fleming, S., Weiss, M.L., 2023. Procoagulant activity of umbilical cord-derived mesenchymal stromal cells' extracellular vesicles (MSC-EVs). Int. J. Mol. Sci. 24.

Xu, P., Zhang, Y., Guo, J., Li, H., Konrath, S., Zhou, P., Cai, L., Rao, H., Chen, H., Lin, J., Cui, Z., Ji, B., Wang, J., Li, N., Liu, D.P., Renne, T., Wang, M., 2024. A single-domain antibody targeting factor XII inhibits both thrombosis and inflammation. Nat. Commun. 15, 7898.

Yan, N., 2017. Immune diseases associated with TREX1 and STING dysfunction. J. Interferon Cytokine Res. 37, 198–206.

Yu, T., Fleishman, J.S., Wang, H., Liu, X., Huo, L., 2025. cGAS-STING targeting offers novel therapeutic regimen in sepsis-associated organ dysfunction. Cell. Biol. Toxicol. 41, 113.

Yu, L., Liu, P., 2021. Cytosolic DNA sensing by cGAS: regulation, function, and human diseases. Signal. Transduct. Target. Ther. 6, 170.

Zannad, F., Anker, S.D., Byra, W.M., Cleland, J.G.F., Fu, M., Gheorghiade, M., Lam, C.S. P., Mehra, M.R., Neaton, J.D., Nessel, C.C., Spiro, T.E., van Veldhuisen, D.J., Greenberg, B., Investigators, C.H., 2018. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. N. Engl. J. Med. 379, 1332–1342.

Zeng, Y., Buonfiglio, F., Li, J., Pfeiffer, N., Gericke, A., 2024. Mechanisms Underlying Vascular Inflammaging: current insights and potential treatment approaches. Aging Dis. 16, 1889–1917.

Zhang, S., Xia, B., Kalionis, B., Li, H., Zhang, X., Zhang, X., Xia, S., 2024. The role and mechanism of vascular aging in geriatric vascular diseases. Aging Dis. 16, 2237–2249.