




## Review Article

## Barrier breakdown in ageing and age-related diseases: The potential role of hierarchical epigenetic control of microRNAs on surfactant collectins, S100 alarmins and fibronectin

Chiara Bontempo<sup>a,1</sup>, Lucio Publio Gallo<sup>a,1</sup>, Marco Mattiacci<sup>a</sup>, Sabrina Valente<sup>a,c</sup>, Annalisa Astolfi<sup>a,c</sup>, Maria Conte<sup>a</sup>, Gaetano La Manna<sup>a,d</sup>, Gianandrea Pasquinelli<sup>a,e</sup>, Mauro Gargiulo<sup>a,b</sup>, Fabiola Olivieri<sup>f,g</sup>, Miriam Capri<sup>a,h,\*</sup> 

<sup>a</sup> Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum-University of Bologna, Bologna, Italy

<sup>b</sup> Vascular Surgery Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

<sup>c</sup> IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

<sup>d</sup> Nephrology, Dialysis and Kidney Transplant Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

<sup>e</sup> Pathology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

<sup>f</sup> Department of Clinical and Molecular Sciences, Università Politecnica delle Marche, Ancona, Italy

<sup>g</sup> Clinic of Laboratory and Precision Medicine, IRCCS INRCA, Ancona, Italy

<sup>h</sup> Interdepartmental Centre - Alma Mater Research Institute on Global Challenges and Climate Change, University of Bologna, Bologna, Italy

## ARTICLE INFO

## Keywords:

Anatomical barriers  
Exposomes  
Stress response  
Inflammaging  
Age-related diseases  
Surfactant proteins  
S100 protein family  
Fibronectin  
Hierarchical biomarkers

## ABSTRACT

Surfactant proteins, particularly SP-A and SP-D, S100 family members and fibronectin belong to the group of so-called stress-related molecules and share the characteristic of being expressed at anatomical barriers such as the skin, pulmonary/respiratory epithelia, and the intestinal tract. In this context, they constitute part of the body's first line of defence, acting in concert with immune cells to counter a broad spectrum of external and internal stressors (exposomes), potentially fuelling chronic low-grade inflammation (inflammaging). The levels of the above-mentioned molecules in the blood or local tissues result altered in a range of age-associated pathologies and have been proposed as potential diagnostic/prognostic biomarkers, although they generally lack specificity for a single pathological condition. Evidence from *in silico* analyses further suggests that most of these molecules may be regulated by members of the microRNA-29 family, pointing towards hierarchical epigenetic mechanisms that merit detailed investigation as potential contributors to ageing-related biomarker signatures. Despite research advances, the identification of robust biomarkers capable of predicting disease onset at the individual level, an essential prerequisite for precise geromedicine, remains an elusive goal in clinical practice. Although individuals differ biologically, this does not preclude the existence of overarching principles that could be reflected in hierarchical biomarkers. Within this framework, a pragmatic strategy for immediate application may involve the systematic use of currently available longitudinal data, for example, from hospitalised patients or through dedicated software programs utilised by general practitioners.

## 1. Introduction

Anatomical barriers constitute the body's first line of defence, protecting the organism against various stressors. These include not only pathogens or microbiota, but also a wide range of factors collectively termed the external and internal exposomes (Wild, 2012), i.e., allergens, pollutants, excessive or highly processed food, alcohol consumption,

climate changes, psychological disturbances, socio-economic status among others. Stressors trigger a coordinated stress response involving the immune system and the psycho-neuroendocrine system (Capri et al., 2025), enabling the organism to combat single or combined stressors at both cellular and systemic levels.

The response to stressors can be modulated by various factors, including the persistence of the stressor itself, the level and type of

\* Correspondence to: Via San Giacomo, 12, Bologna 40126, Italy.

E-mail address: [miriam.capri@unibo.it](mailto:miriam.capri@unibo.it) (M. Capri).

<sup>1</sup> Authors have equally contributed to the paper

cytokine production, and the concentration of corticosteroids, as well as the production of self-alarmins, also known as damage-associated molecular patterns (DAMPs). Notably, the contribution of non-immune cells to the stress response is increasingly recognized. This involves a wide range of cell types, including epithelial cells, hepatocytes, enterocytes, keratinocytes, fibroblasts, endothelial cells, mesangial cells, glial cells, chromaffin cells, chondrocytes, osteocytes, and cardiomyocytes, among others (Dainichi et al., 2021).

The activation and role of non-immune cells represent the other side of the coin in the context of the response to stressors under both physiological and pathological conditions. This response involves plasma membrane receptors, intracellular and nuclear signalling pathways, gene expression changes, and retrograde signalling from the mitochondria to the nucleus (Liao and Butow, 1993; Muneretto et al., 2024). It also includes adaptive phenomena such as epigenetic modifications and, ultimately, tissue remodeling. Stress-induced molecules, produced by non-immune cells, can act as early danger signals or opsonins against infections, cellular damage, tumour cells, metabolic disturbances, and against other stressors such as radiation, pollutants, and/or oxidative stress. In certain cases, they may directly counteract stressors, while indirectly promoting optimal activation of the immune system. These molecules facilitate the activation of innate and innate-like immune cells among others, which are typically found at anatomical barriers, and concurrently enhance the activation and effector functions of T and B lymphocytes by promoting a pro-inflammatory environment. Therefore, the crosstalk between immune cells and non-immune cells, as well as their regulation, is crucial for balancing immune activation and preventing excessive inflammation/hyper-inflammatory reactions or the risk of autoimmune disease onset (Huang et al., 2024; Kroemer et al., 2024).

This review focuses on certain stress-related molecules that act against pathogens and other types of stressors, such as oxidative stress, chronic inflammation, metabolic stress, and mechanical stress. These specific selected molecules include surfactant proteins (SPs), the S100 protein family, and extracellular or blood-circulating fibronectin. This selection of molecules, among the hundreds encoded by the human genome (Harper and Bennett, 2016) was made based on their key roles within the anatomical barriers having a protective function against external and internal exposomes, as well as the role of non-immune cells as a complementary arm of the immune response. Their presence and function will be examined within the context of various age-related diseases, with particular consideration of their potential microRNAs (miRs) regulation and value as biomarkers.

## 2. Surfactant proteins

Surfactant proteins, including SP-A (encoded by two functional genes, SFTPA1 and SFTPA2, which produce the SP-A1 and SP-A2 proteins), SP-B, SP-C, and SP-D, constitute a small fraction of the surfactant mass, which is enriched in phospholipids and located at interfaces with the external environment. These sites include the skin, tongue papillae and oral epithelium, gastric and intestinal mucosae, joints, peritoneum, pericardium, pleura, middle ear, and lungs (Bourbon and Chailley-Heu, 2001; Mo et al., 2007; Akman et al., 2008; Ujma et al., 2017). In particular, SP-A and SP-D belong to the collectin family of C-type lectins, so named for their amino-terminal collagen-like region and carboxy-terminal lectin, or carbohydrate recognition domain, which binds carbohydrates in a calcium-dependent manner. These collectins function as pattern recognition receptors (PRRs), binding to microbial surfaces, apoptotic cells, and DAMPs, thereby enhancing pathogen clearance and modulating inflammatory responses (Pastva et al., 2007). They play diverse roles in mediating both innate and adaptive immune functions, as well as in the clearance of apoptotic cells, allergens, and other noxious particles that induce oxidative stress (Watson et al., 2020); they are also involved in responses to mechanical stress.

In human skin, SP-A and SP-D bind via their collagen tails to SIRP- $\alpha$

(Signal Regulatory Protein- $\alpha$ ), which acts as an inhibitory receptor, thereby mediating anti-inflammatory responses in the absence of microbial ligands. Conversely, in the presence of microbial ligands, they function as opsonins by binding these ligands and promoting a pro-inflammatory response through recognition by innate immune cells (Watson et al., 2020). SP-A and SP-D are also involved in skin inflammatory and autoimmune diseases such as psoriasis and systemic lupus erythematosus (Hoegh et al., 2009; T. Wang et al., 2021; Elmore et al., 2023). In the latter case, SP-D levels are reduced in the blood, likely due to its engagement in the recognition and clearance of apoptotic bodies. Their role in specific autoimmune diseases, at both local and systemic levels, suggests their potential involvement in regulating disease severity and possible synergistic effects with ageing process, although the literature on this topic remains limited.

In the lungs SP-A and SP-D play a crucial role not only regulating the function of the innate immune cells but also acting as stress sensors, detecting pathogens, allergens, and air pollutants for pulmonary protection. They enhance phagocytosis by macrophages and modulate the inflammatory response, exhibiting both anti-inflammatory and pro-inflammatory activities, also facilitating complement activation. As mentioned above, they function as PRRs, recognizing pathogen-associated molecular patterns (PAMPs) and damaged self-molecules or DAMPs, thereby facilitating their clearance by alveolar macrophages. Alveolar epithelial type II cells (AEC2s) are responsible for producing both SP-A and SP-D (Pastva et al., 2007). However, SP-A is crucial for surfactant metabolism and function, preventing alveolar collapse, whereas SP-D plays a greater role in host defence and contributes to maintaining lung epithelial integrity (Shamim et al., 2024a).

With ageing, the lung is subjected to persistent stressors such as elevated production of reactive oxygen species (ROS), DNA damage, increased cellular apoptosis, and reduced autophagy. These stressors can lead to the injury of AEC2s, likely affecting the production of SP-A and SP-D, while alveolar flooding can further inactivate these SPs (Kuroki et al., 1998; Cho and Stout-Delgado, 2020; Fehrenbach, 2001). Notably, ageing impairs immune function, leading to increased susceptibility to respiratory infections and pneumonia in older adults (Schneider et al., 2021). In this context, recent literature has highlighted the potential role of increased blood-circulating SP-D levels in acute respiratory distress syndrome (ARDS) and lung injury as an evaluable biomarker (Elmore et al., 2023).

Similarly, lung levels of SP-D are reduced in chronic obstructive pulmonary disease (COPD), correlating with a decline in lung function. A decrease in SP-D leads to impaired bacterial clearance and increased inflammation, likely contributing to the disease progression (Obeidat et al., 2017). Conversely, blood-circulating SP-D levels are elevated in association with different gene polymorphisms, highlighting the genetic contribution as a risk factor for COPD onset and supporting the potential use of blood-circulating SP-D as a biomarker (Obeidat et al., 2017).

High levels of SP-D have been found in the airway tissue from individuals with allergic asthma and airway inflammation, indicating its role in both allergic inflammation and immune responses to pathogens (Mackay et al., 2016). Mackay and coauthors also observed a concomitant increase of SP-D in serum, likely due to the increased permeability or compromised airway epithelium integrity, together with the possible cleavage of SP-D by proteases, allowing fragments or intact SP-D to enter the circulation. Additionally, a greater bacterial burden in the airways may contribute to SP-D depletion in the lungs, as SP-D binds to these pathogens, reducing its availability in bronchoalveolar lavage samples for assessment (Mackay et al., 2016). Under physiological conditions, SP-D proteins are normally around 1 microg/mL of fluid.

Expression of SPs has also been identified in the human gastrointestinal tract (Ujma et al., 2017) albeit to a lesser extent than in the lungs. SP-A is expressed in the columnar epithelial cells lining the villi and crypts of the small intestine, as well as in the surface epithelial cells of the large intestine. SP-D is expressed in the epithelial lining of the small intestine and, at lower levels, in the large intestine and stomach.

Although the role of these proteins in these compartments is apparently limited, SP-A and D (Shamim et al., 2024a) appear to act both in the control of pathogens and in the regulation of immunity. Both proteins have been implicated in controlling inflammatory bowel disease (IBD). In particular, SP-A has been found to be overexpressed in the gut (Luo et al., 2008), while a single-nucleotide polymorphism (G/A Ala160Thr) in the SP-D gene has been associated with susceptibility to Crohn's disease (Lin et al., 2011). Interestingly, recent data in mouse model have revealed that SP-D is synthesized in the gallbladder and delivered into intestinal lumen and selectively binds to species of gut commensal bacteria. Noteworthy, SP-D-deficient mice manifest intestinal dysbiosis (Sarashina-Kida et al., 2017). This is not yet investigated in humans and may represent a new perspective for therapeutic approaches in particular with ageing. It is well recognized that ageing process may weaken mucosal immunity and increase susceptibility to gut infections and inflammatory disorders (Branca et al., 2019; Walrath et al., 2021). Thus, a potential reduction in the SP expression could also contribute to age-related gut dysbiosis and chronic inflammation.

SP-D serum levels have been found positively associated with the carotid artery intima-media thickness and the coronary artery calcification in patients with chronic kidney disease (CKD) (Hu et al., 2016), confirming the conceivable role of SP-D as biomarker beyond age-related pulmonary disease with potential applicability for the assessment of the risk of atherosclerosis (Sorensen, 2018). Moreover, higher plasma levels of SP-D have been found in patients affected by both Type 2 Diabetes (T2D) and Chronic Heart Disease (CHD), and in patients with CHD without diabetes (Banfi et al., 2024), thus reinforcing the potential role of SPs as biomarkers in cardiovascular diseases (CVDs).

Furthermore, plasma concentration of SP-D has been found increased in COVID-19 (Corona Virus Infection Disease) patients (Gupta et al., 2020). In fact, inflammatory activation and cytokine release trigger the secretion of SP-D into the bloodstream, and these elevated levels continue to rise in parallel with the progression of lung damage (Salvioni et al., 2022).

### 3. S100A/B protein family

The S100 proteins (over 20) localize into the cytoplasm and nucleus of a wide range of cells, particularly those involved in inflammation, immunity and barrier function. They consist of calcium-binding proteins that play a role in both intracellular and extracellular signaling. They act as intracellular calcium sensors, exerting regulatory effects on calcium channels and transport systems. In particular, they bind to surface receptors like Receptor for Advanced Glycation End-products (RAGEs), which stimulates NF- $\kappa$ B signalling, a key driver of inflammation, thus promoting the recruitment and activation of inflammatory cells (Leclerc et al., 2009; Dong et al., 2022). Many S100A proteins (e.g., S100A8, S100A9, and S100A12) function as DAMPs, mediating inflammation and immune responses (Donato et al., 2009, 2013). Interestingly, S100B is glial-specific and is expressed primarily by a subtype of mature astrocytes that draw blood vessels and by a subtype of oligodendrocytes (Du et al., 2021).

S100A8 and S100A9 are mostly found as a heterodimer S100A8/S100A9, also named Calprotectin. They are produced by neutrophils, monocytes/macrophages, and dendritic cells, but they are also highly expressed in mucosal surfaces (gut, lung) and in the sites of infection and inflammation. Released during tissue damage or pathogen recognition, they act as pro-inflammatory mediators. Several studies have reported elevated serum levels of S100A8 and S100A9 in patients with COPD. Specifically, the S100A8/S100A9 heterodimer acts as a key mediator in neutrophil recruitment following inflammatory exposure (Newton and Hogg, 1998), suggesting its association with inflammation and its potential involvement in development and progression of COPD. Findings indicate that higher serum levels of the S100A8/S100A9 heterodimer are inversely correlated with pulmonary function in acute exacerbations

of COPD (Huang et al., 2020). Calprotectin has also been found higher in serum obtained from T2D patients than healthy subjects (Hassan et al., 2025). Moreover, S100A9, initially proposed as a marker of inflammation (Swindell et al., 2013), has recently been suggested for diagnosis and treatment of IBD and of microbiome dysbiosis, as its fecal concentration is directly correlated with the level of gut inflammation (Wang et al., 2025).

Noteworthy, the engagement of RAGEs with its ligands, such as S100A/B proteins, is able to induce inflammatory and thrombotic reactions, suggesting a role in the development and progression of atherosclerotic CVDs (Yamagishi and Matsui, 2018). In particular, S100A12 (called both Extracellular Newly identified -EN- RAGE, and calgranulin C) secreted by neutrophils and monocytes, activates membrane RAGEs, amplifying inflammatory responses. Interestingly, S100A12 has been adopted as predictor of mortality in a study performed on hemodialysis patients (HD) (Kalousová et al., 2012) and, high plasma S100A12 has been identified as an independent predictor of increased mortality risk in patients suffering of CKD, stage 5 (Isoyama et al., 2015), reinforcing the hypothesis of the applicative role of these stress-related molecules.

Other S100A proteins (e.g., S100A4, S100A6) are expressed in epithelial cells, fibroblasts, and some tumour cells (Fei et al., 2017; Wang et al., 2023). They are involved in cell migration, differentiation and stress responses which are mechanisms affected by ageing process (Kennedy et al., 2014). In this respect, either interaction or synergistic effects between stress-related S100A proteins and cellular/molecular ageing mechanisms may be envisaged.

As far as S100B is concerned, recent studies have shown the over-expression of S100B in cultured enteric glial cells following exposure to pathogenic bacteria, but not after the exposure to probiotics, thus suggesting an important role for healthy microbiome homeostasis (Grundmann et al., 2019). Di Liddo and coauthors demonstrated the presence of S100B in feces, showing significantly different levels between healthy individuals and IBD patients, thereby supporting its potential as biomarker for this disease (Di Liddo et al., 2020). In fact, S100B levels are reduced in the feces of IBD patients, likely due to a different interaction of S100B with modified gut microbiota, which in turn leads to an altered detection in feces.

Recent findings have identified S100B as a key molecular factor in the myoblasts-brown adipocytes transition (Morozzi et al., 2017). Based on this evidence, it was proposed that S100B acts as stress-related mediator of the harmful effects caused by the accumulation of ROS in myoblasts and, potentially, myofibers, likely playing a role in the pathophysiology of sarcopenia (Riuzzi et al., 2018). In addition, a new study has demonstrated that S100B can compensate for RAGE signaling deficit in myoblasts grown on *ad hoc* substrate containing Advanced Glycation End (AGE) products, being able to restore proliferation and myogenic differentiation, thus highlighting its potential therapeutic role in muscle regeneration and sarcopenia prevention (Olson et al., 2024).

Notably, several S100 proteins, among the 25 known, are expressed in the brain and have been associated to age-related neurodegenerative diseases, such as Alzheimer's disease (AD), Tauopathies and, Parkinson Disease (PD).

As far as AD is concerned, S100B, S100A1, S100A6, S100A7, S100A8, S100A9, and S100A12 are linked to AD pathways (Hagmeier et al., 2019). S100 molecules may act both in the initiation and progression of AD (Cristóvão and Gomes, 2019). In particular, various studies have reported elevated brain levels of S100B in AD patients (Van Eldik and Griffin, 1994; Chaves et al., 2010) and in AD mouse models (Yeh et al., 2015). S100B is implicated in amyloid precursor protein (APP) cleavage and may be considered a cellular stress-response with effect on the pathology development. In fact, elevated expression of S100B enhances BACE1 ( $\beta$ -site amyloid precursor protein cleaving enzyme) activity, leading to the increased production of toxic APP- $\beta$  and C-terminal fragments (CTF) with the amyloidogenic  $\beta$ -CTF (C99) (Mori et al., 2010). Furthermore, many data collectively suggest that S100B

both influences and is influenced by the levels of pro-inflammatory cytokines implicated in AD pathogenesis. S100B upregulates IL-6 mRNA (Mori et al., 2010; Yeh et al., 2015) and IL-1 mRNA levels in microglia and neurons (Mori et al., 2010) through Sp1 and NF- $\kappa$ B signaling pathways (Liu et al., 2005). Similarly, various studies in animal models have also confirmed a role of S100B in tau-accumulation by increasing tau phosphorylation and disrupting the Wnt pathway, which is involved in regulating tau protein stability (Sidoryk-Wegrzynowicz et al., 2017; Moreira et al., 2021).

S100A6 and S100A6/S100B heterodimer are also strongly associated with the AD phenotype and accumulates around amyloid  $\beta$ -protein (A $\beta$ ) deposits in the gray matter (Boom et al., 2004). Interestingly, in PS/APP mice, a double presenilin-1 and APP transgenic mice model with early onset of AD, S100A6 reduces A $\beta$  levels and plaque burden; it binds zinc, thus preventing zinc-induced toxicity and further reducing A $\beta$  plaque load (Tian et al., 2019). Moreover, S100A6 binds the CacyBP/SIP (calyculin binding protein/Siah-1 interacting protein) complex, regulating tau dephosphorylation in neuroblastoma cells (Wasik et al., 2013). However, S100A6 has been recognized in the AD gene signature as one of the proteins most strongly positively correlated with the AD phenotype (Wruck et al., 2016), thus suggesting a complex interaction in the astrocyte signaling pathway as response to inflammatory chronic reaction and “cell-engulfment”-related stress.

As far as PD is concerned, elevated levels of S100B have been found in the brain tissue of PD patients (Rydbirk et al., 2017) as well as in animal models (Sathe et al., 2012). Notably, transient increases in serum S100B levels have been linked to increased disease severity and sleep disturbances in PD patients (Carvalho et al., 2015), while some genetic variants in the S100B gene are associated with differences in the age of PD onset (Fardell et al., 2018).

S100B also promotes microglial activation and migration via RAGE-dependent pathways (Bianchi et al., 2010, 2011) and skews microglia toward a pro-inflammatory M1 state (Zhou et al., 2018). In the cerebrospinal fluid (CSF), S100B levels have been found elevated in early PD (Sathe et al., 2012), but these findings have not been consistently replicated (Dos Santos et al., 2018). Overall, while S100B shows potential as a marker of PD severity and subtype differentiation, especially in early or non-motor manifestations, its diagnostic specificity is limited by inconsistent findings and its elevation in other inflammatory conditions (Angelopoulou et al., 2021).

#### 4. Fibronectins

Fibronectin (FN) exists in two main forms, an insoluble form found in the extra-cellular matrix (ECM), and a soluble form found in plasma (Sicari et al., 2023). Both forms originate from the same gene FN1, even if some isoforms have been identified with extra domain A of FN (EDA) and extra domain B of FN (EDB) (Lemańska-Perek and Adamik, 2019). ECM has been proposed to be an important hallmark of immunosenescence and cell senescence in different tissues/organs and ageing process (Moreau et al., 2017; Statzer et al., 2023).

FN is the second, after collagen, most abundant ECM molecule expressed in submucosal tissues, basement membranes, and interstitial tissues, where different cell types organize the ECM and promote the assembly of other proteins like collagen. The structure of FN contains three repeating modules joined together like beads on a string, called Type I, Type II, and Type III modules and different binding domains for collagen, fibrin, heparin and cells have been recognised.

The soluble and insoluble forms serve different physiological functions, allowing FN to participate in wound healing, immune responses, and ECM remodeling. Plasma fibronectin (pFN) is produced by the liver and circulates in the blood as a soluble dimer. During tissue injury, pFN binds to fibrin clots, helping to stabilize blood coagulation and promote wound healing. It interacts with immune cells, guiding their migration to inflammation sites, it binds integrins ( $\alpha$ 5 $\beta$ 1,  $\alpha$ V $\beta$ 3) and Toll-like receptors (TLRs), thus acting as DAMPs and influencing macrophage

activation and tissue repair (To and Midwood, 2011; Dalton and Lemon, 2021). pFN is a stress-related molecule critical in case of trauma/injuries and inflammatory status, it binds to circulating degradation products and mediates their elimination by the reticuloendothelial system, which leads to its depletion.

FN has a crucial role in the anatomical barriers during ageing. Despite the increased FN expression in skin fibroblasts during ageing process (Kumazaki et al., 1993) the protein is reduced in the reticular dermis of the skin (Perié et al., 2024), thus its incorporation into the ECM scaffold is impaired and likely, this induces an effect on senescent phenotype. In this respect, knockdown expression of FN in senescent cells might delay the onset of senescence and decrease the activation of senescence regulators. Perié and coauthors suggest that senescent fibroblasts might express a FN variant that induces a senescent microenvironment (Perié et al., 2024). Recently, compositional changes of the lung extracellular matrix in ARDS have been observed in early and advanced diffuse alveolar damage, highlighting the role of FN/ECM changes in older subjects (Fan et al., 2025).

Notably, a growing literature is focusing on the role of pFN on endothelial cells during ageing and, particularly in atherosclerotic plaque. In fact, pFN deposited in susceptible regions of the arteries could contribute to early atherosclerotic lesion formation and the recruitment of smooth muscle cells that shape the fibrous cap of advanced lesions. This has been demonstrated in mouse model (Moore and Fisher, 2012). In this perspective, the role of FN at the blood-brain barrier (BBB) has recently obtained an increased attention for age-related neurodegeneration, since TGF- $\beta$  signaling in pericytes supports the BBB integrity by promoting FN expression, basal membrane synthesis, and stimulating tight junction protein expression (Geranmayeh et al., 2019).

However, high blood level of pFN has been found in patients with AD when compared to healthy control groups (Bogdan et al., 2022) and FN1 seems to have a role in senile plaque development (Lepelletier et al., 2017). In fact, a rare human variant of FN1 with loss of function (LOF) is able to reduce gliosis, enhance gliovascular remodeling, and potentiate the microglial response, suggesting that pathological accumulation of FN1 protein could impair toxic protein clearance, which is ameliorated with FN1 LOF in APOE $\epsilon$ 4 AD (Bhattarai et al., 2024). At the opposite side, it has been found that blood concentration of pFN decreases with PD progression and it is in association with BBB disruption (Zhu et al., 2025), even if the mechanisms have not yet been clarified.

A recent study demonstrated that low pFN levels might be an independent predictor of CHD, even if these levels are not yet able to predict the severity of CHD (Peng et al., 2023). Moreover, age-related deamidation of pFN leads to the formation of isoDGR motifs (pFN/isoDGR), which enhance binding to integrins on monocytes, macrophages, and endothelial cells. This interaction promotes inflammatory signaling and may contribute to the development of atherosclerosis. In fact, pFN (isoDGR) has been found associated with human plaque destabilization in carotid endarterectomy patients (Mol et al., 2025) and recent results suggest that an increased FN protein deposition is produced by vascular smooth muscle cells during atherosclerosis development (Pearson-Gallion et al., 2025).

FN1 has also been implicated in the development and progression of COPD. Blood pFN levels of COPD patients were significantly higher than those in the normal group, with negative correlation between pFN levels and lung function parameters, thus suggesting pFN as a potential biomarker for evaluating the prognosis of COPD patients (Wang F et al., 2025).

Interestingly, blood levels of pFN isoforms (EDA-FN) and FN-fragments have been found associated in patients infected with SARS-CoV-2 and suffering of COVID-19. Isoforms were significantly higher in patients who died, than in survivors. Authors suggest FN isoforms are potential biomarkers that can be used in clinical settings to monitor the condition of COVID-19 patients and predict treatment outcomes (Lemańska-Perek et al., 2022).

Table 1 summarises the most significant up- and down-expression of

**Table 1**  
Stress-related molecules both at anatomical barriers and into the blood (plasma or serum) as valuable and shared biomarkers in various age-related diseases.

Stress-related molecules	Age-related Pathology	Tissue/district	Increase/decrease	References
P-A and/or SP-D	ARDS, Asthma	Broncho-alveolar lavage sample	↓	Kuroki et al. (1998); Mackay et al. (2016)
SP-D	ARDS/Lung injury	Serum	↑	Elmore et al. (2023)
SP-D	COPD	Serum	↓ or ↑ due to gene variants	Obeidat et al. (2017)
SP-D	CKD with Atherosclerosis	Serum	↑	Hu et al. (2016)
SP-D	T2D- CHD	Plasma	↑	Banfi et al. (2024)
S100A8/S100A9	COPD	Serum	↑	Huang et al. (2020)
S100A9	Microbiome dysbiosis	Feces	↑	Wang et al. (2025)
S100A	PAD	Artery	↑	Yamagishi et al. (2018)
S100A12	CKD	Plasma	↑	Isoyama et al. (2015)
S100B	IBD	Feces	↑	Di Liddo et al. (2020)
S100B	Sarcopenia	Myoblasts	↑	Riuzzi et al. (2018)
S100B	AD	Hippocampus, Temporal, Occipital, Frontal lobes/ Serum	↑	Van Eldik and Griffin (1994); Chaves et al. (2010)
S100A6/S100B	AD	White Matter/ temporal neocortex	↑	Boom et al. (2004)
S100B	PD	mRNA levels in brain tissue extracts	↑	Rydbirk et al. (2017)
Specific S100B variants	PD	Serum/Frontal Cortex	↑	Fardell et al. (2018)
S100A8-S100A9	T2D	Serum	↑	Hassan et al. (2025)
FN1/ECM	ARDS	Lung	↓	Fan et al. (2025)
pFN	AD	Serum	↑	Bogdan et al. (2022)
pFN	PD	Plasma	↓	Zhu et al. (2025)
pFN	CHD	Plasma	↓	Peng et al. (2023)
pFN isoDGR	CHD	Plaque	↑	Mol et al. (2025)
pFN	COPD	Serum	↑	Wang et al. (2025)

AD, Alzheimer Disease; ARDS, Acute Respiratory Distress Syndrome; CHD, Coronary Heart Disease; CKD, Chronic Kidney Disease; COPD, Chronic obstructive pulmonary disease; IBD, Inflammatory Bowel Disease; PAD, Peripheral Artery Disease; PD, Parkinson's disease; T2D, Type 2 Diabetes.

different stress-related molecules, such as SP-A/-D, S100A6/A8/A9/A12, S100B proteins and pFN1 (including isoforms) as well, highlighting similar trends of decrease or increase in different tissues shared with various age-related diseases.

## 5. microRNAs and potential regulation of SP-A/D, S100 family proteins and FN

It is recognized that non-coding RNAs, including miRs, significantly change their patterns of expression during cellular stress (e.g., oxidative stress, hypoxia, ER stress, heat shock, genotoxic stress) (Emde and

Hornstein, 2014). In particular, some miRs are up-regulated, while others are down-regulated depending on the type of stressor or exposome, the cell type, the duration and severity of the stress (Du et al., 2019; Miguel et al., 2020). In this context, they can suppress pro-apoptotic genes under mild stress to promote survival, suppress cell cycle genes to induce arrest, or promote apoptosis/senescence under severe or unresolved stress by targeting anti-apoptotic genes. Notably, changes of cellular/organ-related miR profile may have systemic effects via exosomes/microvesicles/free blood circulation, thus miRs are increasingly proposed as sensitive biomarkers of exposome exposure (Chaiwangyen et al., 2025) and ageing/longevity process (Morsiani et al., 2021, 2022), beyond their well-known role on either tumour suppressors or oncogenes.

In this context, the current review highlights a bioinformatic analysis performed by the authors by means of the miRNet v2.0 online resource (website: <https://www.mirnet.ca/>) (Chang et al., 2020) able to manage all the genes/mRNAs of FN1, S100A6/8/9, SFTPA1 and SFTPD, in order to reveal common miRs for their effect on specific targets predicted in silico. Findings showed some miRs, such as miR-34a-5p, miR-182-5p, miR-218-5p and miR-29b-3p, able to recognize a few of the above-mentioned molecules. The unique miR able to directly or indirectly regulate 5 out of 6 mRNAs (i.e. FN1, S100A6/8/9, SFTPA1) appears to be miR-29b-3p, belonging to miR-29 family. Through the use of another bioinformatic platform i.e., miRWalk (<http://mirwalk.umm.uni-heidelberg.de/>) (Sticht et al., 2018a), the predicted binding sequences of miR-29 family members to almost all mRNAs of the reviewed stress-related molecules (FN1, S100A6/8/9/12, SFTPA1, SFTPA2 and SFTPD) were further analysed and are reported in Table 2, highlighting the predicted binding site of miR-29 family members on almost all the investigated mRNA targets. A bioinformatic analysis was also performed assessing the GSEA of filtered mRNA targets of the above mentioned three miRs i.e., miR-34a-5p, miR-182-5p, miR-218-5p as showed in supplementary material (Table 1S). Findings suggest cancer pathways at the top of the KEGG analysis. Moreover, the analyses of filtered miR-29 family targets by GSEA and KEGG network have been reported in Table 2S and Fig. 1S, respectively. It is interesting to observe that among the identified pathways ECM-receptor interaction has been revealed, consisting with the role of extracellular matrix and fibronectin molecule at anatomical barriers, among others.

Noteworthy, literature gives evidence for a miR-29 family role on age-related mechanisms. In fact, miR-29 family expression was significantly upregulated in epithelial cells isolated from mouse fetal lung during late gestation and in epithelial cells isolated from human fetal lung explants during type II cell differentiation in culture (Guo et al., 2016). MiR-29b-3p, also found in blood circulating exosomes (Yu et al., 2024), has been highlighted through some studies for its role in cellular stress, fibrosis, hypoxic-inflammatory response and ageing process in different models and age-related diseases (O'Reilly, 2016; Heid et al., 2017; Horita et al., 2021). Some of the mature miR-29 family members can accumulate into the nucleus leading to the up-regulation of transcription factors and genes involved in the mechanisms of cell differentiation, fibrosis, and apoptosis (Horita et al., 2021). In addition, miR-29b-3p has been found highly expressed in human bronchial epithelial cells exposed to particulate matter (PM). MiR-29b-3p promoted PM-induced pro-inflammatory cytokines expression, such as IL-1 $\beta$ , IL-6, and IL-8, via inhibiting the AMPK signaling pathway, likely representing a key regulator of cellular stress against air pollutant in the respiratory tract (Wang et al., 2020). The increase of blood circulating miR-29b-3p in healthy centenarians in comparison with old adults may be interpreted as one of the adaptation phenomena to counteract chronic reaction to the lifelong stressors and inflammation (Morsiani et al., 2021).

Notably, miR-29 is a miR known to be upregulated during both normal and premature ageing. In fact, it has been demonstrated that in an established mouse model of progeria, the partial loss of miR-29 extends the lifespan, whereas its overexpression is sufficient to drive many

**Table 2**  
miR-29 family members targeting the specific stress-associated molecules.

Hsa-miR	Refseq id	Gene symbol	Score	Position	Binding Site
miR-29a-3p	NM_001164647	SFTPA1	0.85	CDS	100,123
miR-29a-3p	NM_005411	SFTPA1	0.85	5UTR	89,106
miR-29a-3p	NM_005411	SFTPA1	0.85	CDS	171,194
miR-29a-3p	NM_001093770	SFTPA1	0.85	CDS	160,183
miR-29a-3p	NM_001093770	SFTPA1	0.85	CDS	160,183
miR-29b-1-5p	NM_001365518	FN1	1.00	CDS	3035,3075
miR-29b-1-5p	NM_002965	S100A9	1.00	CDS	350,366
miR-29b-1-5p	XM_017028424	S100B	0.85	3UTR	1066,1090
miR-29b-1-5p	NM_001093770	SFTPA1	0.92	CDS	113,148
miR-29b-1-5p	XM_005270132	SFTPA2	0.92	5UTR	53,88
miR-29b-1-5p	XM_005270132	SFTPA2	0.85	3UTR	1290,1313
miR-29b-2-5p	NM_001365518	FN1	0.92	CDS	6036,6053
miR-29b-2-5p	NM_001365518	FN1	0.92	CDS	3071,3107
miR-29b-2-5p	NM_001365518	FN1	0.85	CDS	1079,1102
miR-29b-2-5p	NM_002965	S100A9	0.85	CDS	346,366
miR-29b-2-5p	NM_002965	S100A9	1.00	CDS	79,123
miR-29b-2-5p	XM_017028424	S100B	0.87	3UTR	1067,1087
miR-29b-2-5p	XM_017028424	S100B	0.82	3UTR	440,468
miR-29b-2-5p	XM_005270132	SFTPA2	0.85	3UTR	1751,1782
miR-29b-2-5p	XM_005270132	SFTPA2	0.85	CDS	285,302
miR-29b-2-5p	XM_005270132	SFTPA2	0.92	3UTR	1283,1313
miR-29c-5p	NM_003019	SFTPD	0.85	CDS	683,703
miR-29c-5p	NM_005411	SFTPA1	1.00	CDS	521,553
miR-29c-5p	NM_001093770	SFTPA1	1.00	CDS	510,542
miR-29c-5p	NM_001093770	SFTPA1	1.00	CDS	510,542
miR-29c-5p	XM_005270132	SFTPA2	1.00	CDS	462,482
miR-29c-5p	XM_005270132	SFTPA2	0.85	CDS	181,219

Score: Probability (max 1) that the miRNA-target interaction is functional, calculated using the TarPmiR algorithm with a Random Forest model trained on experimental data. Binding site: see the reference (Sticht et al., 2018). CDS: Coding DNA sequence; UTR: untranslated region;

ageing-related phenotypes and leads to early lethality (Swahari et al., 2024). Transcriptomic analysis of both young and old mice revealed shared downregulation of genes associated with extracellular matrix organization and fatty acid metabolism, and shared upregulation of genes in pathways linked to inflammation. When miRs have been analysed at different time points across the lifespan of mice from 2 up to 18 months of age, the RNA content of extracellular vesicles showed a strong association with ageing, especially the miR-29 family in adipose tissue (Kern et al., 2023). These results highlight the functional importance of miR-29 in controlling a gene expression program that drives ageing-related phenotypes.

Overall, miR-29 family appears to be a critical regulator gene for

ageing mechanisms and CVDs (Liu et al., 2021) with potential therapeutic effects, even if not yet achieved. In agreement, GSEA of filtered miR-29 targets reports the most significant pathways related to cardiomyopathy (Table 2S). Recent literature underpins the hierarchical not-clustered network role of miR inside the cells, and among them, miR-29a has been demonstrated to have a hierarchical influence on the control of focal adhesion signaling during muscle regeneration in animal model (Luca et al., 2020).

Other mechanisms, including CpG DNA methylation and demethylation, histone acetylation and deacetylation, and other histone modifications in relation to the aforementioned stress-related molecules, have received only fragmented attention to date, to our knowledge. In this context, studies in normal lung tissue have shown that higher levels of specific unmethylated CpG sites are associated with increased SP-A1 and SP-D transcript expressions, identifying these CpGs as key regulators of gene activity (Lin et al., 2007). In particular, epigenetic regulation under hypoxia, oxidative stress caused by ozone and exposure to particulate matter has been shown to affect the expression of SP-A (Silveyra and Floros, 2012). Epigenetic investigations of the S100 family have been undertaken, particularly for crucial CpG sites and histone modifications of S100A6, both *in vitro* and *in vivo* model (Leśniak et al., 2007). Similar studies have addressed S100B and its role in neurodegeneration (Dali et al., 2025) and cancer (Lindsey et al., 2007; Bresnick et al., 2015). By contrast, FN has attracted considerable attention, with numerous studies focusing on miR-mediated regulation under various conditions (Shan et al., 2009; Tang et al., 2013) including cancer (Gong et al., 2017).

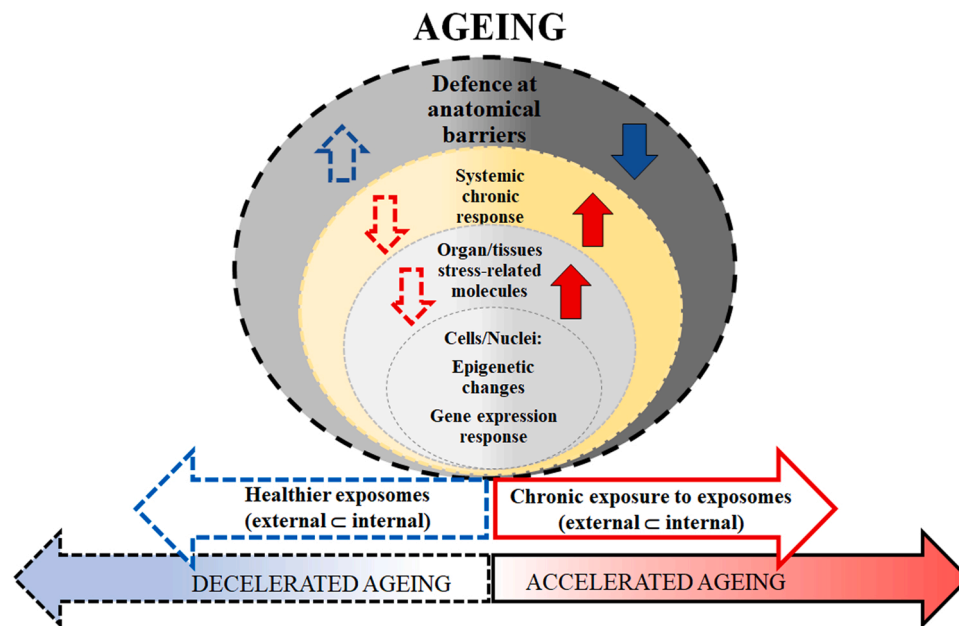
Noteworthy, an emerging body of literature suggests the existence of hierarchical patterns within epigenetic structures, particularly in the context of chromatin remodelling and its influence on cellular senescence (Thanos et al., 2025). More broadly, a recent review points towards a hierarchical model governing epigenetic ageing in mammals (Lehmann et al., 2020). On this basis, age-related epigenetic dysregulation may itself follow a hierarchical, or at least partially hierarchical, structure, although this remains an open question.

Overall, the concept of specific circulating miRs exerting hierarchical epigenetic effects is particularly relevant for understanding pathogenic mechanisms shared by the most common age-related diseases. From a general point of view hierarchical miR regulation refers to the idea that miRs do not all regulate genes equally or independently. Instead, miRs form layers or tiers of regulation, where some miRs act as master regulators, others function at intermediate levels and some play roles only in specific pathways, tissues, or conditions. This may create a hierarchical network. The possibility that also dysregulation may have a hierarchical structure appears a topic to be investigated for the discovery of master regulators likely shared by different organs or anatomical barriers.

We may hypothesise that hierarchically relevant circulating miRs, involved in the regulation of stress-related pathways in different organs and tissues, converge at the systemic level to shape global homeostasis. This raises the intriguing possibility that specific signatures of circulating miRs could serve as integrative biomarkers, simultaneously reflecting local tissue stress and systemic ageing trajectories. Moreover, targeting such hierarchically relevant miRs might represent a novel therapeutic avenue to modulate systemic stress responses, delay age-associated dysfunctions, and reduce the risk of chronic degenerative diseases. To provide robustness to these hypotheses, however, longitudinal studies with repeated measurements of circulating miRs over time will be required, in order to capture their dynamic fluctuations and establish causal relationships with ageing and disease progression.

## 6. The impact of exposome and ageing interactions on anatomical barriers

Continuous exposure to external and internal exposomes can elicit chronic stress responses at the cellular, tissue/organ, and systemic



**Fig. 1.** Stress-related molecules vs Exposomes. The continuous exposure to internal and external ( $\subset$  i.e., **together**) exposomes can induce a chronic stress response both at nuclear/cellular, and systemic levels. The response to stressors modifies gene expression through epigenetic changes and induces an increase of mediators, stress-related molecules, that may synergistically interact with ageing process/inflammaging leading to acceleration of ageing/disease onset. At anatomical barriers, levels of many stress-related molecules may decline with age, resulting in reduced protective functions and weakened barrier integrity. Consequently, environmental exposomes (e.g., pathogens, allergens, pollutants, nano- and microplastics, food-derived antigens, and other non-self molecules) may interact and synergize with internal exposomes (e.g., gut dysbiosis, psychological stress, socioeconomic status among other). Chronic exposure to such combined stressors may pose a greater risk in older individuals compared to younger ones. "Healthier external exposomes" means: decreased exposure to climate changes, decreased infective and pollutant agents i.e., pathogens, food/water contamination or threatening agents including nano-micro-plastic among others; moderate and informed sun exposure for vitamin D production. "Healthier internal exposomes" means: improving life style behaviours i.e., no smoke, no alcohol and drugs; increase of aerobic and resistant physical exercise in a personalised fashion, increase of relaxed activities; balanced diet/MedDiet with proper intake of vitamins/micro-macro-nutrients and normal weight maintenance.

levels, while inducing adaptive phenomena. Stressors modulate gene expression through epigenetic mechanisms and the regulation of stress-related molecules. These effects may act synergistically with ageing processes. In this direction, stressed and dying cells release a variety of bioactive molecules, such as DAMPs. These include small metabolites (e.g., ATP), nucleic acids (e.g., nuclear and mitochondrial DNA), proteins (e.g., cytokines and DAMPs), lipids (e.g., oxidised cardiolipin and oxidised LDL), and molecular debris. Together, they interact with the immune system to trigger chronic inflammatory responses thereby fuelling inflammaging (Franceschi et al., 2017; Conte et al.2020; Kroemer et al., 2022).

In this context, Fig. 1 highlights the critical role of both internal and external exposomes in driving stress responses at the cellular, tissue/organ, and systemic levels, while interacting with ageing process. To mitigate these effects, reducing exposure to harmful external and internal exposomes across the life course should be encouraged; however, such strategy is difficult to adopt. In fact, stressors arising from climate change (e.g., persistently high temperatures in temperate countries), environmental pollutants (air and water), and, not least, spill-over pathogens cannot be entirely avoided. Pragmatic countermeasures therefore lie in lifestyle modifications that improve the internal exposome, such as abstaining from smoking, alcohol, and recreational drugs; engaging in personalised, regular physical activity; maintaining a well-balanced diet with positive effects on gut microbiome (e.g., the Med-Diet) and healthy/regular body weight as well as practising daily cognitive training and stress-reduction physical exercises. These approaches have the potential to attenuate systemic inflammation and promote pro-longevity health benefits (Ghosh et al., 2020; Coperchini et al., 2025).

The present review does not address the well-established field of anti-ageing pharmacological interventions, including senolytics,

senomorphics, geroprotectors, mitophagy enhancers, and glucidic/metabolic regulators. This omission is partly because recent reviews have already detailed their beneficial effects on health and inflammatory status (Petr et al., 2024; Cozza, Boccardi, 2025). However, long-term clinical trial data in humans, spanning several years of treatment, are still lacking, and the impact of these interventions on stress-related molecular alterations requires further investigation.

The combined impact of exposome-related stressors and intrinsic ageing can result in reduced or altered levels of numerous defence-associated molecules, such as SPs, S100 proteins, and fibronectin, among others not discussed in this review (Alvarez-Rodriguez et al., 2012; Shimizu et al., 2022; Quin et al., 2024). This decline weakens barrier integrity and compromises overall host protection, thereby increasing susceptibility to pathogenic infections and maladaptive responses to external noxious agents, exerting more detrimental effects in older individuals compared with younger counterparts.

In this direction, recent findings show that non-industrialised populations exhibit lower levels of systemic inflammation and inflammaging compared to industrialised populations, thus suggesting a reduced burden due to a reduced exposure to stressors/exposomes in such contexts through a decreased blood levels of pro-inflammatory cytokines (Franck et al., 2025).

However, single biomarkers alone are rarely disease-specific, as shown in Table 1 in relation with the current discussed molecules. In addition, blood circulating miRs alone are not able to become diagnostic tools, given the highly variability among subjects and the intrinsic variability of miRs, also observed during the circadian rhythm (Heegaard et al., 2016). Thus, what is the future of biomarker research in the ageing field? The human population genome has both a common core and individual variability (i.e., individuality). Considering the ageing process as a continuum (Franceschi et al., 2018), three types of

investigative approaches can be envisaged: i. To search for early, common and age-associated biomarkers among individuals in a cross-sectional model with cohorts of subjects in conditions of accelerated and decelerated ageing, and not necessarily for age-related diseases (e.g. the European project MARK-AGE; Capri et al., 2015). ii. To search for biomarkers in single individuals as predictors of age-related diseases adopting a longitudinal time course; iii. To search for both i. and ii. where the various models may likely highlight common biomarkers with hierarchical and/or temporarily characteristics.

In this perspective, the considerable effort required to identify personalised molecular signatures of ageing and disease onset remains a distant goal, particularly in terms of their translational application in clinical settings. Such endeavours necessitate longitudinal cohorts, costly omics analyses, and advanced AI methodologies to derive individual-level insights. The use of either various types of omics at different biological layers, such as epigenomics, transcriptomics, proteomics, metabolomics or Computed Tomography(CT)/Imaging analyses for each individual has been mentioned many times by various researchers (Li et al., 2024; Zack et al., 2025), but the cost of this approach is very high and only specific AI application, such as explainable AI may be useful to deeply understand the molecular underpinning mechanisms (Franceschi et al., 2025; Kalyakulina et al., 2025; Vershinina et al., 2025). These approaches would underpin the personalised, continuous adaptation of organs, tissues, and the whole body to lifelong exposure to internal and external exposomes, but currently are not applicable in a clinical setting or from general practitioners. Likely, in a next future CT/Imaging and NMR across life span of patients/individuals may be analysed and interpreted by specific AI methodology together with haemato-biochemical analysis in the clinical setting.

### 6.1. Conclusions

SP-A and SP-D, members of the S100 protein family, and FN are examples, among hundreds encoded in the human genome, of stress-related molecules, some of which are produced by non-immune cells. These molecules reflect both local (cellular/organ) and systemic responses to pathogens and other stressors. Their action is mediated by a complementary mechanism between immune and non-immune cells, particularly relevant at anatomical barriers, which constitute the first line of defence against external and internal exposomes. MiR-epigenetic regulation of these molecules is still a scanty research topic in humans and likely, deserves a deeper attention due to their role at the interface with external environment. Their dysregulation, through either hyperactivation or hypoactivation of the immune system (Fulop et al., 2020), can compromise health over the life course, influenced by individual genetics and exposome interactions that drive personalised epigenetic changes and inflammatory profiles. Probably, age-related epigenetic dysregulation may have hierarchical structure in the population, but this is an open field to be further investigated in order to improve the specificity of age-related and/or disease onset biomarkers. Moreover, chronic dysregulation of stress-related molecules may contribute to organ-specific ageing patterns, or “organ ageotypes.” In this context, the ageing process can affect each organ differently across individuals, both hierarchically and temporally, thereby influencing the timing and nature of age-related disease onset (Prattichizzo et al., 2024). This field of research is particularly promising, and the identification of organ-specific biomarkers capable of detecting accelerated ageing and predicting the onset of age-related diseases is an area of intense study (Cardoso et al., 2018; Sayed et al., 2021; Salvioli et al., 2023; Herzog et al., 2025).

From this perspective, organ-related biomarkers combined with biological clocks at single individual and longitudinal approach could enable the characterisation of personalised ageing trajectories and organ ageotypes. Such an approach can allow the early detection of organ-specific molecular dysfunctions and create opportunities for timely

intervention through preventive medicine. However, the identification of early organ-specific biomarkers associated with disease onset remains a major challenge for combating age-related pathologies and advancing precision geromedicine.

A pragmatic strategy in clinical practice would consist of the systematic use of routinely available haematological, urinary, and biochemical data from individual adults to track parameter changes across successive follow-up visits. Such an approach not only enables the timely detection of emerging or progressive organ-related alterations but also provides an evidence-based foundation for implementing lifestyle interventions as the primary means of mitigation. Pharmacological treatment, in turn, should be reserved for late and complex conditions in which non-pharmacological measures prove insufficient, thereby reinforcing the principle of lifestyle modification as the first-line option.

### CRediT authorship contribution statement

Conceptualization: CB, LPG, FO, MC. Data curation: CB, LPG, SV, AA, MaC. Funding acquisition: FO, MC. Investigation: CB, LPG, SV, AA, MaC. Methodology: CB, LPG, MM, SV, AA, MaC, GLaM, GP, MG, FO, MC. Supervision: GLaM, GP, MG, FO, MC. Visualization: CB, LPG, MaC, MC. Writing the original draft: CB, LPG, GLaM, GP, MG, FO, MC. Writing – review and editing: MaC, FO, MC.

### Funding statement

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The authors acknowledge co-funding from Next Generation EU, in the context of the National Recovery and Resilience Plan, Investment PE8 – Project Age-It: “Ageing Well in an Ageing Society”. This resource was co-financed by the Next Generation EU (DM 1557 11.10. 2022).

### 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.

### Acknowledgements

Authors thank the online resources of both miRNet v. 2 and miRWalk at the website: <https://www.mirnet.ca/> and <http://mirwalk.umm.uni-heidelberg.de/>, respectively. Paper citations have been inserted, accordingly.

### Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.arr.2025.103003](https://doi.org/10.1016/j.arr.2025.103003).

### References

- Akman, A., Kankavi, O., Ciftcioglu, M.A., Alpsy, E., 2008. Surfactant proteins in inflammatory skin diseases: controlled study. *Arch. Dermatol. Res.* 300 (7), 353–356. <https://doi.org/10.1007/s00403-008-0846-1>.
- Alvarez-Rodriguez, L., Lopez-Hoyos, M., Garcia-Unzueta, M., Amado, J.A., Cacho, P.M., Martinez-Taboada, V.M., 2012. Age and low levels of circulating vitamin D are associated with impaired innate immune function. *J. Leukoc. Biol.* 91 (5), 829–838. <https://doi.org/10.1189/jlb.1011523>.
- Angelopoulou, E., Paudel, Y.N., Piperi, C., 2021. Emerging role of S100B protein implication in Parkinson’s disease pathogenesis. *Cell. Mol. Life Sci. CMLS* 78 (4), 1445–1453. <https://doi.org/10.1007/s00018-020-03673-x>.
- Banfi, C., Piarulli, F., Ragazzi, E., Ghilardi, S., Greco, A., Lapolla, A., Sartore, G., 2024. Immature surfactant protein type B and surfactant protein type D correlate with coronary heart disease in patients with type 2 diabetes. *Life (Basel Switz.)* 14 (7). <https://doi.org/10.3390/life14070886>.
- Bhattarai, P., Gunasekaran, T.I., Bello, M.E., Reyes-Dumeyer, D., Jülich, D., Tayran, H., Yilmaz, E., Flaherty, D., Turgutalp, B., Sukumar, G., Alba, C., McGrath, E.M., Hupalo, D.N., Bacikova, D., Le Guen, Y., Lantigua, R., Medrano, M., Rivera, D.,



- Recio, P., Vardarajan, B.N., 2024. Rare genetic variation in fibronectin 1 (FN1) protects against APOE $\epsilon$ 4 in Alzheimer's disease. *Acta Neuropathol.* 147 (1), 70. <https://doi.org/10.1007/s00401-024-02721-1>.
- Bianchi, R., Giambanco, I., Donato, R., 2010. S100B/RAGE-dependent activation of microglia via NF-kappaB and AP-1 Co-regulation of COX-2 expression by S100B, IL-1beta and TNF-alpha. *Neurobiol. Aging* 31 (4), 665–677. <https://doi.org/10.1016/j.neurobiolaging.2008.05.017>.
- Bianchi, R., Kastrianaki, E., Giambanco, I., Donato, R., 2011. S100B protein stimulates microglia migration via RAGE-dependent up-regulation of chemokine expression and release. *J. Biol. Chem.* 286 (9), 7214–7226. <https://doi.org/10.1074/jbc.M110.169342>.
- Bogdan, S., Puścion-Jakubik, A., Klimiuk, K., Socha, K., Kochanowicz, J., Gorodkiewicz, E., 2022. The Concentration of Fibronectin and MMP-1 in Patients with Alzheimer's Disease in Relation to the Selected Antioxidant Elements and Eating Habits. *J. Clin. Med.* 11 (21). <https://doi.org/10.3390/jcm11216360>.
- Boom, A., Pochet, R., Authalet, M., Pradier, L., Borghgraef, P., Van Leuven, F., Heizmann, C.W., Brion, J.-P., 2004. Astrocytic calcium/zinc binding protein S100A6 over expression in Alzheimer's disease and in PS1/APP transgenic mice models. *Biochim. Et. Biophys. Acta* 1742 (1–3), 161–168. <https://doi.org/10.1016/j.bbamer.2004.09.011>.
- Bourbon, J.R., Chailley-Heu, B., 2001. Surfactant proteins in the digestive tract, mesentery, and other organs: evolutionary significance. *Comp. Biochem. Physiol. Part A Mol. Integr. Physiol.* 129 (1), 151–161. [https://doi.org/10.1016/s1095-6433\(01\)00312-9](https://doi.org/10.1016/s1095-6433(01)00312-9).
- Branca, J.J.V., Gulisano, M., Nicoletti, C., 2019. Intestinal epithelial barrier functions in ageing. *Ageing Res. Rev.* 54, 100938. <https://doi.org/10.1016/j.arr.2019.100938>.
- Bresnick, A.R., Weber, D.J., Zimmer, D.B., 2015. S100 proteins in cancer. *Nat. Rev. Cancer* 15 (2), 96–109. <https://doi.org/10.1038/nrc3893>.
- Capri, M., Moreno-Villanueva, M., Cevenini, E., Pini, E., Scurti, M., Borelli, V., Palmas, M.G., Zoli, M., Schön, C., Siepmeyer, A., Bernhardt, J., Fiegl, S., Zondag, G., de Craen, A.J.M., Hervonen, A., Hurme, M., Sikora, E., Gonos, E.S., Voutetakis, K., Franceschi, C., 2015. MARK-AGE population: from the human model to new insights. *Mech. Ageing Dev.* 151, 13–17. <https://doi.org/10.1016/j.mad.2015.03.010>.
- Capri, M., Montano, N., Piccirillo, S., Narici, M., Ferranti, F., Maccarrone, M., 2025. Spaceflight exposome/microgravity effects on the psychoimmunoneuroendocrine system. *NPJ Microgravity* 11 (1), 66. <https://doi.org/10.1038/s41526-025-00487-8>.
- Cardoso, A.L., Fernandes, A., Aguiar-Pimentel, J.A., de Angelis, M.H., Guedes, J.R., Brito, M.A., Ortolano, S., Pani, G., Athanasopoulou, S., Gonos, E.S., Schosserer, M., Grillari, J., Peterson, P., Tuma, B.G., Dogan, S., Meyer, A., van Os, R., Trendelenburg, A.-U., 2018. Towards frailty biomarkers: candidates from genes and pathways regulated in aging and age-related diseases. *Ageing Res. Rev.* 47, 214–277. <https://doi.org/10.1016/j.arr.2018.07.004>.
- Carvalho, D.Z., Schönwald, S.V., Schumacher-Schuh, A.F., Braga, C.W., Souza, D.O., Oses, J.P., Donis, K.C., Rieder, C.R., 2015. Overnight S100B in Parkinson's Disease: a glimpse into sleep-related neuroinflammation. *Neurosci. Lett.* 608, 57–63. <https://doi.org/10.1016/j.neulet.2015.10.010>.
- Chaiwangyen, W., Khantamat, O., Kangwan, N., Tipsuwan, W., de Sousa, F.L.P., 2025. MicroRNA expression in response to environmental hazards: implications for health. *Ecotoxicol. Environ. Saf.* 300, 118420. <https://doi.org/10.1016/j.ecoenv.2025.118420>.
- Chang, L., Zhou, G., Soufan, O., Xia, J., 2020. miRNet 2.0: network-based visual analytics for miRNA functional analysis and systems biology. *Nucleic Acids Res.* 48 (W1), W244–W251. <https://doi.org/10.1093/nar/gkaa467>.
- Chaves, M.L., Camozzato, A.L., Ferreira, E.D., Piazenski, I., Kochhann, R., Dall'Igna, O., Mazzini, G.S., Souza, D.O., Portela, L.V., 2010. Serum levels of S100B and NSE proteins in Alzheimer's disease patients. *J. Neuroinflamm.* 7, 6. <https://doi.org/10.1186/1742-2094-7-6>.
- Cho, S.J., Stout-Delgado, H.W., 2020. Aging and Lung Disease. *Annu. Rev. Physiol.* 82, 433–459. <https://doi.org/10.1146/annurev-physiol-021119-034610>.
- Conte, M., Martucci, M., Chiariello, A., Franceschi, C., Salvio, S., 2020. Mitochondria, immunosenescence and inflammaging: a role for mitokines? *Semin. Immunopathol.* 42 (5), 607–617. <https://doi.org/10.1007/s00281-020-00813-0>.
- Coperchini, F., Greco, A., Teliti, M., Croce, L., Chytiris, S., Magri, F., Gaetano, C., Rotondi, M., 2025. Inflamm-aging: how cytokines and nutrition shape the trajectory of ageing. *Cytokine Growth Factor Rev.* 82, 31–42. <https://doi.org/10.1016/j.cytogfr.2024.08.004>.
- Cozza, M., Boccardi, V., 2025. Cognitive impairment in chronic kidney disease: mechanisms, clinical manifestations, and management strategies. *Metab. Brain Dis.* 40 (8), 312. <https://doi.org/10.1007/s11011-025-01735-2>.
- Cristóvão, J.S., Gomes, C.M., 2019. S100 proteins in Alzheimer's disease. *Front. Neurosci.* 13, 463. <https://doi.org/10.3389/fnins.2019.00463>.
- Dainichi, T., Kabashima, K., Ivanov, I.I., Goto, Y., 2021. Editorial: regulation of Immunity by Non-Immune Cells. *Front. Immunol.* 12, 770847. <https://doi.org/10.3389/fimmu.2021.770847>.
- Dali, A., Basnyat, S., Delancey, R., Chopra, N., 2025. MiRNA-mediated regulation of S100B: a review. *Neurosci* 6 (3). <https://doi.org/10.3390/neurosci6030075>.
- Dalton, C.J., Lemmon, C.A., 2021. Fibronectin: molecular structure, fibillar structure and mechanochemical signaling. *Cells* 10 (9). <https://doi.org/10.3390/cells10092443>.
- Di Liddo, R., Piccione, M., Schrenk, S., Dal Magro, C., Cosma, C., Padoan, A., Conran, N., Scapellato, M.L., Pagetta, A., Romano Spica, V., Conconi, M.T., Parnigotto, P.P., D'Inca, R., Michetti, F., 2020. S100B as a new fecal biomarker of inflammatory bowel diseases. *Eur. Rev. Med. Pharmacol.* 24 (1), 323–332. [https://doi.org/10.26355/eurrev\\_202001\\_19929](https://doi.org/10.26355/eurrev_202001_19929).
- Donato, R., Sorci, G., Riuzzi, F., Arcuri, C., Bianchi, R., Brozzi, F., Tubaro, C., Giambanco, I., 2009. S100B's double life: intracellular regulator and extracellular signal. *Biochim. Et. Biophys. Acta* 1793 (6), 1008–1022. <https://doi.org/10.1016/j.bbamer.2008.11.009>.
- Donato, R., Cannon, B.R., Sorci, G., Riuzzi, F., Hsu, K., Weber, D.J., Geczy, C.L., 2013. Functions of S100 proteins. *Curr. Mol. Med.* 13 (1), 24–57.
- Dong, H., Zhang, Y., Huang, Y., Deng, H., 2022. Pathophysiology of RAGE in inflammatory diseases. *Front. Immunol.* 13, 931473. <https://doi.org/10.3389/fimmu.2022.931473>.
- Dos Santos, M.C.T., Scheller, D., Schulte, C., Mesa, I.R., Colman, P., Bujac, S.R., Bell, R., Berteau, C., Perez, L.T., Lachmann, I., Berg, D., Maetzler, W., Nogueira da Costa, A., 2018. Evaluation of cerebrospinal fluid proteins as potential biomarkers for early stage Parkinson's disease diagnosis. *PLoS One* 13 (11), e0206536. <https://doi.org/10.1371/journal.pone.0206536>.
- Du, J., Li, M., Huang, Q., Liu, W., Li, W.-Q., Li, Y.-J., Gong, Z.-C., 2019. The critical role of microRNAs in stress response: therapeutic prospect and limitation. *Pharmacol. Res.* 142, 294–302. <https://doi.org/10.1016/j.phrs.2018.12.007>.
- Du, J., Yi, M., Zhou, F., He, W., Yang, A., Qiu, M., Huang, H., 2021. S100B is selectively expressed by gray matter protoplasmic astrocytes and myelinating oligodendrocytes in the developing CNS. *Mol. Brain* 14 (1), 154. <https://doi.org/10.1186/s13041-021-00865-9>.
- Elmore, A., Almutashiri, A., Wang, X., Almutashiri, S., Zhang, D., 2023. Circulating surfactant protein D: a biomarker for acute lung injury? *Biomedicines* 11 (9). <https://doi.org/10.3390/biomedicines11092517>.
- Emde, A., Hornstein, E., 2014. miRNAs at the interface of cellular stress and disease. *EMBO J.* 33 (13), 1428–1437. <https://doi.org/10.15252/emj.201488142>.
- Fan, Y., Moser, J., Jongman, R.M., Borghuis, T., Vonk, J.M., Timens, W., van Meurs, M., Pillay, J., Burgess, J.K., 2025. Compositional changes of the lung extracellular matrix in acute respiratory distress syndrome. *Am. J. Physiol. Cell Physiol.* 328 (4), C1279–C1292. <https://doi.org/10.1152/ajpcell.01007.2024>.
- Fardell, C., Zettergren, A., Ran, C., Carmine Belin, A., Ekman, A., Sydow, O., Bäckman, L., Holmberg, B., Dizdar, N., Söderkvist, P., Nissbrandt, H., 2018. S100B polymorphisms are associated with age of onset of Parkinson's disease. *BMC Med. Genet.* 19 (1), 42. <https://doi.org/10.1186/s12881-018-0547-3>.
- Fehrenbach, H., 2001. Alveolar epithelial type II cell: defender of the alveolus revisited. *Respir. Res.* 2 (1), 33–46. <https://doi.org/10.1186/rr36>.
- Fei, F., Qu, J., Zhang, M., Li, Y., Zhang, S., 2017. S100A4 in cancer progression and metastasis: a systematic review. *Oncotarget* 8 (42), 73219–73239. <https://doi.org/10.18632/oncotarget.18016>.
- Franceschi, C., Garagnani, P., Vitale, G., Capri, M., Salvio, S., 2017. Inflammaging and "Garb-aging". *Trends Endocrinol. Metab.* TEM 28 (3), 199–212. <https://doi.org/10.1016/j.tem.2016.09.005>.
- Franceschi, C., Garagnani, P., Parini, P., Giuliani, C., Santoro, A., 2018. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat. Rev. Endocrinol.* 14 (10), 576–590. <https://doi.org/10.1038/s41574-018-0059-4>.
- Franceschi, C., Olivieri, F., Moskalev, A., Ivanchenko, M., Santoro, A., 2025. Toward precision interventions and metrics of inflammaging. *Nat. Aging* 5 (8), 1441–1454. <https://doi.org/10.1038/s43587-025-00938-7>.
- Franck, M., Tanner, K.T., Tennyson, R.L., Daunizeau, C., Ferrucci, L., Bandinelli, S., Trumble, B.C., Kaplan, H.S., Aronoff, J.E., Stieglitz, J., Kraft, T.S., Lea, A.J., Venkataraman, V.V., Wallace, I.J., Lim, Y.A.L., Ng, K.S., Yeong, J.P.S., Ho, R., Lim, X., Cohen, A.A., 2025. Nonuniversality of inflammaging across human populations. *Nat. Aging*. <https://doi.org/10.1038/s43587-025-00888-0>.
- Fulop, T., Larbi, A., Hirokawa, K., Cohen, A.A., Witkowski, J.M., 2020. Immunosenescence is both functional/adaptive and dysfunctional/maladaptive. *Semin. Immunopathol.* 42 (5), 521–536. <https://doi.org/10.1007/s00281-020-00818-9>.
- Geramayeh, M.H., Rahbarghazi, R., Farhoudi, M., 2019. Targeting pericytes for neurovascular regeneration. *Cell Communication Signaling CCS* 17 (1), 26. <https://doi.org/10.1186/s12964-019-0340-8>.
- Ghosh, T.S., Rampelli, S., Jeffery, I.B., Santoro, A., Neto, M., Capri, M., Giampieri, E., Jennings, A., Candela, M., Turroni, S., Zoetendal, E.G., Hermes, G.D.A., Elodie, C., Meunier, N., Brugere, C.M., Pujos-Guillot, E., Berendsen, A.M., De Groot, L.C.P.G.M., Feskens, E.J.M., Kaluza, J., Pietruszka, B., Bielak, M.J., Comte, B., Maijo-Ferre, M., Nicoletti, C., De Vos, W.M., Fairweather-Tait, S., Cassidy, A., Brigidi, P., Franceschi, C., O'Toole, P.W., 2020. Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries. *Gut* 69 (7), 1218–1228. <https://doi.org/10.1136/gutjnl-2019-319654>.
- Gong, J., Wang, Z.X., Liu, Z.Y., 2017. miRNA-1271 inhibits cell proliferation in neuroglioma by targeting fibronectin 1. *Mol Med Rep* 16 (1), 143–150. <https://doi.org/10.3892/mmr.2017.6610>.
- Grundmann, D., Loris, E., Maas-Omlor, S., Huang, W., Scheller, A., Kirchhoff, F., Schäfer, K.-H., 2019. Enteric Glia: S100, GFAP, and Beyond. *Anat. Rec. (Hoboken N. J.)* 2007 (302 (8)), 1333–1344. <https://doi.org/10.1002/ar.24128>.
- Guo, W., Benhabib, H., Mendelson, C.R., 2016. The MicroRNA 29 family promotes type II cell differentiation in developing lung. *Mol. Cell. Biol.* 36 (16), 2141. <https://doi.org/10.1128/MCB.00096-16>.
- Gupta, A., Madhavan, M.V., Sehgal, K., Nair, N., Mahajan, S., Sehrawat, T.S., Bikdeli, B., Ahluwalia, N., Ausiello, J.C., Wan, E.Y., Freedberg, D.E., Kirtane, A.J., Parikh, S.A., Maurer, M.S., Nordvig, A.S., Accili, D., Bathon, J.M., Mohan, S., Bauer, K.A., Landry, D.W., 2020. Extrapulmonary manifestations of COVID-19. *Nat. Med.* 26 (7), 1101–1032. <https://doi.org/10.1038/s41591-020-0968-3>.
- Hagmeyer, S., Romão, M.A., Cristóvão, J.S., Villella, A., Zoli, M., Gomes, C.M., Grabrucker, A.M., 2019. Distribution and relative abundance of S100 proteins in the

- brain of the APP23 Alzheimer's disease model mice. *Front. Neurosci.* 13, 640. <https://doi.org/10.3389/fnins.2019.00640>.
- Harper, J.W., Bennett, E.J., 2016. Proteome complexity and the forces that drive proteome imbalance. *Nature* 537 (7620), 328–338. <https://doi.org/10.1038/nature19947>.
- Hassan, H.N., Shamran, S.G., Albady, M.A.Z., Al Fahham, A.A., 2025. Evaluation of serum levels of calprotectin, lactoferrin and zinc in patients with type II diabetes mellitus. *Wiadomosci Lek. (Wars. Pol. 1960)* 78 (2), 288–294. <https://doi.org/10.36740/WLek/201198>.
- Heegaard, N.H.H., Carlsen, A.L., Lilje, B., Ng, K.L., Rønne, M.E., Jørgensen, H.L., Sennels, H., Fahrenkrug, J., 2016. Diurnal variations of human circulating cell-free micro-RNA. *PLoS One* 11 (8), e0160577. <https://doi.org/10.1371/journal.pone.0160577>.
- Heid, J., Cencioni, C., Ripa, R., Baumgart, M., Atlante, S., Milano, G., Scopece, A., Kuenen, C., Guenther, S., Azzimato, V., Farsetti, A., Rossi, G., Braun, T., Pompilio, G., Martelli, F., Zeiber, A.M., Cellierino, A., Gaetano, C., Spallotta, F., 2017. Age-dependent increase of oxidative stress regulates microRNA-29 family preserving cardiac health. *Sci. Rep.* 7 (1), 16839. <https://doi.org/10.1038/s41598-017-16829-w>.
- Herzog, C., Poganik, J.R., Barzilai, N., Basisty, N., Beerman, L., Belsky, D.W., de Cabo, R., Candia, J., Faghri, F., Horvath, S., Maier, A.B., Perez, V., Sen, P., Moqri, M., Gladyshev, V.N., Ferrucci, L., 2025. Biomarkers of aging-NIA joint symposium 2024: new insights into aging biomarkers. *Aging Cell*, e70124. <https://doi.org/10.1111/acef.70124>.
- Hoegh, S.V., Voss, A., Sorensen, G.L., Høj, A., Bendixen, C., Junker, P., Holmskov, U., 2009. Circulating surfactant protein D is decreased in systemic lupus erythematosus. *J. Rheumatol.* 36 (11), 2449–2453. <https://doi.org/10.3899/jrheum.090069>.
- Horita, M., Farquharson, C., Stephen, L.A., 2021. The role of miR-29 family in disease. *J. Cell. Biochem.* 122 (7), 696–715. <https://doi.org/10.1002/jcb.29896>.
- Hu, F., Zhong, Q., Gong, J., Qin, Y., Cui, L., Yuan, H., 2016. Serum surfactant protein D is associated with atherosclerosis of the carotid artery in patients on maintenance hemodialysis. *Clin. Lab.* 62 (1–2), 97–104. <https://doi.org/10.7754/clin.lab.2015.150536>.
- Huang, S.-J., Ding, Z.-N., Xiang, H.-X., Fu, L., Fei, J., 2020. Association between serum S100A8/S100A9 heterodimer and pulmonary function in patients with acute exacerbation of chronic obstructive pulmonary disease. *Lung* 198 (4), 645–652. <https://doi.org/10.1007/s00408-020-00376-9>.
- Huang, Y., Jiang, W., Zhou, R., 2024. DAMP sensing and sterile inflammation: intracellular, intercellular and inter-organ pathways. *Nat. Rev. Immunol.* 24 (10), 703–719. <https://doi.org/10.1038/s41577-024-01027-3>.
- Isoyama, N., Leurs, P., Qureshi, A.R., Bruchfeld, A., Anderstam, B., Heimbürger, O., Bárány, P., Stenvinkel, P., Lindholm, B., 2015. Plasma S100A12 and soluble receptor of advanced glycation end product levels and mortality in chronic kidney disease Stage 5 patients. In: *Nephrology, Dialysis, Transplantation*, 30. Official Publication of the European Dialysis and Transplant Association, *European Renal Association*, pp. 84–91. <https://doi.org/10.1093/ndt/gfu259>.
- Kalousová, M., Kuběna, A.A., Benáková, H., Dusilová-Sulková, S., Tesar, V., Zima, T., 2012. EN-RAGE (extracellular newly identified receptor for advanced glycation end-products binding protein) and mortality of long-term hemodialysis patients: a prospective observational cohort study. *Clin. Biochem.* 45 (7–8), 556–560. <https://doi.org/10.1016/j.clinbiochem.2012.02.014>.
- Kalyakulina, A., Yusipov, I., Trukhanov, A., Franceschi, C., Moskalev, A., Ivanchenko, M., 2025. EplnflammAge: epigenetic-inflammatory clock for disease-associated biological aging based on deep learning. *Int. J. Mol. Sci.* 26 (13). <https://doi.org/10.3390/ijms26136284>.
- Kennedy, B.K., Berger, S.L., Brunet, A., Campisi, J., Cuervo, A.M., Epel, E.S., Franceschi, C., Lithgow, G.J., Morimoto, R.I., Pessin, J.E., Rando, T.A., Richardson, A., Schadt, E.E., Wyss-Coray, T., Sierra, F., 2014. Geroscience: linking aging to chronic disease. *Cell* 159 (4), 709–713. <https://doi.org/10.1016/j.cell.2014.10.039>.
- Kern, F., Kuhn, T., Ludwig, N., Simon, M., Gröger, L., Fabis, N., Aparicio-Puerta, E., Salhab, A., Fehlmann, T., Hahn, O., Engel, A., Wagner, V., Koch, M., Winek, K., Soreq, H., Nazarenko, I., Fuhrmann, G., Wyss-Coray, T., Meese, E., Keller, A., 2023. Ageing-associated small RNA cargo of extracellular vesicles. *RNA Biol.* 20 (1), 482–494. <https://doi.org/10.1080/15476286.2023.2234713>.
- Kroemer, G., Galassi, C., Zitvogel, L., Galluzzi, L., 2022. Immunogenic cell stress and death. *Nat. Immunol.* 23 (4), 487–500. <https://doi.org/10.1038/s41590-022-01132-2>.
- Kroemer, G., Montégut, L., Kepp, O., Zitvogel, L., 2024. The danger theory of immunity revisited. *Nat. Rev. Immunol.* 24 (12), 912–928. <https://doi.org/10.1038/s41577-024-01102-9>.
- Kumazaki, T., Kobayashi, M., Mitsui, Y., 1993. Enhanced expression of fibronectin during in vivo cellular aging of human vascular endothelial cells and skin fibroblasts. *Exp. Cell Res.* 205 (2), 396–402. <https://doi.org/10.1006/excr.1993.1103>.
- Kuroki, Y., Takahashi, H., Chiba, H., Akino, T., 1998. Surfactant proteins A and D: disease markers. *Biochim. Et. Biophys. Acta* 1408 (2–3), 334–345. [https://doi.org/10.1016/s0925-4439\(98\)00079-9](https://doi.org/10.1016/s0925-4439(98)00079-9).
- Leclerc, E., Fritz, G., Vetter, S.W., Heizmann, C.W., 2009. Binding of S100 proteins to RAGE: an update. *Biochim. Et. Biophys. Acta* 1793 (6), 993–1007. <https://doi.org/10.1016/j.bbamcr.2008.11.016>.
- Lehmann, M., Canatelli-Mallat, M., Chiavellini, P., Goya, R.G., 2020. A hierarchical model for the control of epigenetic aging in mammals. *Ageing Res. Rev.* 62, 101134. <https://doi.org/10.1016/j.arr.2020.101134>.
- Lemańska-Perek, A., Adamik, B., 2019. Fibronectin and its soluble EDA-FN isoform as biomarkers for inflammation and sepsis. *Adv. Clin. Exp. Med. Off. Organ Wrocław Med. Univ.* 28 (11), 1561–1567. <https://doi.org/10.17219/acem/104531>.
- Lemańska-Perek, A., Krzyżanowska-Gołąb, D., Dragan, B., Tyszkowski, M., Adamik, B., 2022. Fibronectin as a Marker of Disease Severity in Critically Ill COVID-19 Patients. *Cells* 11 (9). <https://doi.org/10.3390/cells11091566>.
- Lepelletier, F.-X., Mann, D.M.A., Robinson, A.C., Pinteaux, E., Boutin, H., 2017. Early changes in extracellular matrix in Alzheimer's disease. *Neuropathol. Appl. Neurobiol.* 43 (2), 167–182. <https://doi.org/10.1111/nan.12295>.
- Leśniak, W., Słomnicki, Ł.P., Kuźnicki, J., 2007. Epigenetic control of the S100A6 (calcylin) gene expression. *J. Invest. Dermatol.* 127 (10), 2307–2314. <https://doi.org/10.1038/sj.jid.5700879>.
- Li, X., Ding, R., Liu, Z., Teixeira, W.M.S., Ye, J., Tian, L., Li, H., Guo, S., Yao, K., Ma, Z., Liu, Z., 2024. A predictive system comprising serum microRNAs and radiomics for residual retroperitoneal masses in metastatic nonseminomatous germ cell tumors. *Cell Rep. Med.* 5 (12), 101843. <https://doi.org/10.1016/j.xcrm.2024.101843>.
- Liao, X., Butow, R.A., 1993. RTG1 and RTG2: two yeast genes required for a novel path of communication from mitochondria to the nucleus. *Cell* 72 (1), 61–71. [https://doi.org/10.1016/0092-8674\(93\)90050-z](https://doi.org/10.1016/0092-8674(93)90050-z).
- Lin, Z., Thomas, N.J., Bibikova, M., Seifart, C., Wang, Y., Guo, X., Wang, G., Vollmer, E., Goldmann, T., Garcia, E.W., Zhou, L., Fan, J.-B., Floros, J., 2007. DNA methylation markers of surfactant proteins in lung cancer. *Int. J. Oncol.* 31 (1), 181–191.
- Lin, Z., John, G., Hegarty, J.P., Berg, A., Yu, W., Wang, Y., Kelly, A.A., Peterson, B.Z., Poritz, L.S., Floros, J., Koltun, W.A., 2011. Genetic variants and monoallelic expression of surfactant protein-D in inflammatory bowel disease. *Ann. Hum. Genet.* 75 (5), 559–568. <https://doi.org/10.1111/j.1469-1809.2011.00662.x>.
- Lindsey, J.C., Lusher, M.E., Anderton, J.A., Gilbertson, R.J., Ellison, D.W., Clifford, S.C., 2007. Epigenetic deregulation of multiple S100 gene family members by differential hypomethylation and hypermethylation events in medulloblastoma. *Br. J. Cancer* 97 (2), 267–274. <https://doi.org/10.1038/sj.bjc.6603852>.
- Liu, L., Li, Y., Van Eldik, L.J., Griffin, W.S.T., Barger, S.W., 2005. S100B-induced microglial and neuronal IL-1 expression is mediated by cell type-specific transcription factors. *J. Neurochem.* 92 (3), 546–553. <https://doi.org/10.1111/j.1471-4159.2004.02909.x>.
- Liu, M.-N., Luo, G., Gao, W.-J., Yang, S.-J., Zhou, H., 2021. miR-29 family: a potential therapeutic target for cardiovascular disease. *Pharmacol. Res.* 166, 105510. <https://doi.org/10.1016/j.phrs.2021.105510>.
- Luca, E., Turcekova, K., Hartung, A., Mathes, S., Rehrauer, H., Krützfeldt, J., 2020. Genetic deletion of microRNA biogenesis in muscle cells reveals a hierarchical non-clustered network that controls focal adhesion signaling during muscle regeneration. *Mol. Metab.* 36, 100967. <https://doi.org/10.1016/j.molmet.2020.02.010>.
- Luo, J., Liu, Z., Eugene, C.Y., 2008. Overexpression of pulmonary surfactant protein A like molecules in inflammatory bowel disease tissues. *Zhong Nan Da Xue Xue Bao. Yi Xue Ban = Journal of Central South University. Med. Sci.* 33 (11), 979–986.
- Mackay, R.-M.A., Grainge, C.L., Lau, L.C., Barber, C., Clark, H.W., Howarth, P.H., 2016. Airway Surfactant Protein D Deficiency in Adults With Severe Asthma. *Chest* 149 (5), 1165–1172. <https://doi.org/10.1016/j.chest.2015.11.012>.
- Miguel, V., Lamas, S., Espinosa-Diez, C., 2020. Role of non-coding-RNAs in response to environmental stressors and consequences on human health. *Redox Biol.* 37, 101580. <https://doi.org/10.1016/j.redox.2020.101580>.
- Mo, Y.-K., Kankavi, O., Masci, P.P., Mellick, G.D., Whitehouse, M.W., Boyle, G.M., Parsons, P.G., Roberts, M.S., Cross, S.E., 2007. Surfactant protein expression in human skin: evidence and implications. *J. Invest. Dermatol.* 127 (2), 381–386. <https://doi.org/10.1038/sj.jid.5700561>.
- Mol, B.M., Motsak, T., Hoekstra, J.K.R., Zuluaga, V.O., Rumpff-Derksen, S., Paspali-Strik, I., Ngan, S.C., Pasterkamp, G., de Borst, G.J., Sze, S.K., de Kleijn, D.P.V., 2025. High Levels of Plasma and Plaque IsoDGR-Modified Fibronectin are Associated with Rupture Prone Plaque Characteristics in Carotid Endarterectomy Patients. *Eur. J. Vasc. Endovasc. Surg. Off. J. Eur. Soc. Vasc. Surg.* <https://doi.org/10.1016/j.ejvs.2025.04.067>.
- Moore, K.J., Fisher, E.A., 2012. The double-edged sword of fibronectin in atherosclerosis. *EMBO Mol. Med.* 4 (7), 561–563. <https://doi.org/10.1002/emmm.201200238>.
- Moreau, J.-F., Pradeu, T., Grignolio, A., Nardini, C., Castiglione, F., Trieri, P., Capri, M., Salvioli, S., Taupin, J.-L., Garagnani, P., Franceschi, C., 2017. The emerging role of ECM crosslinking in T cell mobility as a hallmark of immunosenescence in humans. *Ageing Res. Rev.* 35, 322–335. <https://doi.org/10.1016/j.arr.2016.11.005>.
- Moreira, E.A., Yamauchi, Y., Matthias, P., 2021. How Influenza Virus Uses Host Cell Pathways during Uncoating. *Cells* 10 (7). <https://doi.org/10.3390/cells10071722>.
- Mori, T., Koyama, N., Arendash, G.W., Horikoshi-Sakuraba, Y., Tan, J., Town, T., 2010. Overexpression of human S100B exacerbates cerebral amyloidosis and gliosis in the Tg2576 mouse model of Alzheimer's disease. *Glia* 58 (3), 300–314. <https://doi.org/10.1002/glia.20924>.
- Morozzi, G., Beccafico, S., Bianchi, R., Riuzzi, F., Bellezza, I., Giambanco, I., Arcuri, C., Minelli, A., Donato, R., 2017. Oxidative stress-induced S100B accumulation converts myoblasts into brown adipocytes via an NF-κB/YY1/miR-133 axis and NF-κB/YY1/BMP-7 axis. *Cell Death Differ.* 24 (12), 2077–2088. <https://doi.org/10.1038/cdd.2017.132>.
- Morsiani, C., Terlecki-Zaniewicz, L., Skalicky, S., Bacalini, M.G., Collura, S., Conte, M., Sevini, F., Garagnani, P., Salvioli, S., Hackl, M., Grillari, J., Franceschi, C., Capri, M., 2021. Circulating miR-19a-3p and miR-19b-3p characterize the human aging process and their isomiRs associate with healthy status at extreme ages. *Ageing Cell* 20 (7), e13409. <https://doi.org/10.1111/acef.13409>.
- Morsiani, C., Bacalini, M.G., Collura, S., Moreno-Villanueva, M., Breusing, N., Bürkle, A., Grune, T., Franceschi, C., De Eguileor, M., Capri, M., 2022. Blood circulating miR-28-5p and let-7d-5p associate with premature ageing in Down syndrome. *Mech. Ageing Dev.* 206, 111691. <https://doi.org/10.1016/j.mad.2022.111691>.
- Muneretto, G., Plazzi, F., Passamonti, M., 2024. Mitochondrion-to-nucleus communication mediated by RNA export: a survey of potential mechanisms and

- players across eukaryotes. *Biol. Lett.* 20 (7), 20240147. <https://doi.org/10.1098/rsbl.2024.0147>.
- Newton, R.A., Hogg, N., 1998. The human S100 protein MRP-14 is a novel activator of the beta 2 integrin Mac-1 on neutrophils. *Journal Immunology (Baltimore Md. 1950 160 (3))*, 1427–1435.
- O'Reilly, S., 2016. MicroRNAs in fibrosis: opportunities and challenges. *Arthritis Res. Ther.* 18, 11. <https://doi.org/10.1186/s13075-016-0929-x>.
- Obeidat, M., Li, X., Burgess, S., Zhou, G., Fishbane, N., Hansel, N.N., Bossé, Y., Joubert, P., Hao, K., Nickle, D.C., van den Berge, M., Timens, W., Cho, M.H., Hobbs, B.D., de Jong, K., Boezen, M., Hung, R.J., Rafaels, N., Mathias, R., International COPD Genetics Consortium, L. eQTL, C.L.H.S., 2017. Surfactant protein D is a causal risk factor for COPD: results of Mendelian randomisation. *Eur. Respir. J.* 50 (5). <https://doi.org/10.1183/13993003.00657-2017>.
- Olson, L.C., Nguyen, T., Sabalewski, E.L., Puetzer, J.L., Schwartz, Z., McClure, M.J., 2024. S100b treatment overcomes RAGE signaling deficits in myoblasts on advanced glycation end-product cross-linked collagen and promotes myogenic differentiation. *Am. J. Physiol. Cell Physiol.* 326 (4), C1080–C1093. <https://doi.org/10.1152/ajpcell.00502.2023>.
- Pastva, A.M., Wright, J.R., Williams, K.L., 2007. Immunomodulatory roles of surfactant proteins A and D: implications in lung disease. *Proc. Am. Thorac. Soc.* 4 (3), 252–257. <https://doi.org/10.1513/pats.200701-018AW>.
- Pearson-Gallion, B., Finney, A.C., Scott, M.L., Connelly, Z., Alam, S., Peretik, J.M., Ben Dhau, C., Bhuiyan, M.S., Traylor, J.G., DeGrado, W.F., Jo, H., Yu, X., Rom, O., Pattillo, C.B., Dhanesha, N., Yurdagul, A., Orr, A.W., 2025. Fibronectin-dependent integrin signaling drives EphA2 expression in vascular smooth muscle cells. *Am. J. Physiol. Cell Physiol.* 328 (5), C1623–C1636. <https://doi.org/10.1152/ajpcell.01021.2024>.
- Peng, L., Deng, H., Li, J., Lu, G., Zhai, Y.-S., 2023. Plasma Fibronectin as a Novel Predictor of Coronary Heart Disease: A Retrospective Study. *J. Cardiovasc. Dev. Dis.* 10 (10). <https://doi.org/10.3390/jcdd10100415>.
- Perié, L., Houél, C., Zambon, A., Guere, C., Vié, K., Leroy-Dudal, J., Vendrely, C., Agniel, R., Carreiras, F., Picot, C.R., 2024. Impaired incorporation of fibronectin into the extracellular matrix during aging exacerbates the senescent state of dermal cells. *Exp. Cell Res.* 442 (2), 114251. <https://doi.org/10.1016/j.yexcr.2024.114251>.
- Petr, M.A., Matiyevskaya, F., Osborne, B., Berglund, M., Reves, S., Zhang, B., Ezra, M.Ben, Carmona-Marin, L.M., Syadzha, M.F., Mediavilla, M.C., Keijzers, G., Bakula, D., Mkrtychyan, G.V., Scheibye-Knudsen, M., 2024. Pharmacological interventions in human aging. *Ageing Res. Rev.* 95, 102213. <https://doi.org/10.1016/j.arr.2024.102213>.
- Prattichizzo, F., Frigé, C., Pellegrini, V., Scisciola, L., Santoro, A., Monti, D., Rippon, M.R., Ivanchenko, M., Olivieri, F., Franceschi, C., 2024. Organ-specific biological clocks: ageotyping for personalized anti-aging medicine. *Ageing Res. Rev.* 96, 102253. <https://doi.org/10.1016/j.arr.2024.102253>.
- Quin, C., Breznik, J.A., Kennedy, A.E., DeJong, E.N., Andary, C.M., Ermolina, S., Davidson, D.J., Ma, J., Surette, M.G., Bowdish, D.M.E., 2024. Monocyte-driven inflamm-aging reduces intestinal barrier function in females (1 & A). *Immun. Ageing* 21 (1), 65. <https://doi.org/10.1186/s12979-024-00469-6>.
- Riuzzi, F., Sorci, G., Arcuri, C., Giambanco, I., Bellezza, I., Minelli, A., Donato, R., 2018. Cellular and molecular mechanisms of sarcopenia: the S100B perspective. *J. Cachex. Sarcopenia Muscle* 9 (7), 1255–1268. <https://doi.org/10.1002/jcsm.12363>.
- Rydbirk, R., Elfving, B., Andersen, M.D., Langbøl, M.A., Folke, J., Winge, K., Pakkenberg, B., Brudek, T., Aznar, S., 2017. Cytokine profiling in the prefrontal cortex of Parkinson's Disease and Multiple System Atrophy patients. *Neurobiol. Dis.* 106, 269–278. <https://doi.org/10.1016/j.nbd.2017.07.014>.
- Salvioli, S., Basile, M.S., Bencivenga, L., Carrino, S., Conte, M., Damanti, S., De Lorenzo, R., Fiorenzato, E., Gialluisi, A., Ingannato, A., Antonini, A., Baldini, N., Capri, M., Cenci, S., Iacoviello, L., Nacmias, B., Olivieri, F., Rengo, G., Querini, P.R., Lattanzio, F., 2023. Biomarkers of aging in frailty and age-associated disorders: state of the art and future perspective. *Ageing Res. Rev.* 91, 102044. <https://doi.org/10.1016/j.arr.2023.102044>.
- Salvioni, L., Testa, F., Sulejmani, A., Pepe, F., Giorgio Lovaglio, P., Berta, P., Domini, R., Leoni, V., Prosperi, D., Vittadini, G., Colombo, M., Fiandra, L., 2022. Surfactant protein D (SP-D) as a biomarker of SARS-CoV-2 infection. *Clin. Chim. Acta Int. J. Clin. Chem.* 537, 140–145. <https://doi.org/10.1016/j.cca.2022.10.013>.
- Sarashina-Kida, H., Negishi, H., Nishio, J., Suda, W., Nakajima, Y., Yasui-Kato, M., Iwasako, K., Kang, S., Endo, N., Yanai, H., Asagiri, M., Kida, H., Hattori, M., Kumonogoh, A., Taniguchi, T., 2017. Gallbladder-derived surfactant protein D regulates gut commensal bacteria for maintaining intestinal homeostasis. *Proc. Natl. Acad. Sci. USA* 114 (38), 10178–10183. <https://doi.org/10.1073/pnas.1712837114>.
- Sathe, K., Maetzler, W., Lang, J.D., Mounsey, R.B., Fleckenstein, C., Martin, H.L., Schulte, C., Mustafa, S., Synofzik, M., Vukovic, Z., Itoharu, S., Berg, D., Teismann, P., 2012. S100B is increased in Parkinson's disease and ablation protects against MPTP-induced toxicity through the RAGE and TNF- $\alpha$  pathway. *Brain A J. Neurol.* 135 (Pt 11), 3336–3347. <https://doi.org/10.1093/brain/aws250>.
- Sayed, N., Huang, Y., Nguyen, K., Krejcirova-Rajaniemi, Z., Grawe, A.P., Gao, T., Tibshirani, R., Hastie, T., Alpert, A., Cui, L., Kuznetsova, T., Rosenberg-Hasson, Y., Ostan, R., Monti, D., Lehallier, B., Shen-Orr, S.S., Maecker, H.T., Dekker, C.L., Wyss-Coray, T., Furman, D., 2021. An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging. *Nat. Aging* 1, 598–615. <https://doi.org/10.1038/s43587-021-00082-y>.
- Schneider, J.L., Rowe, J.H., Garcia-de-Alba, C., Kim, C.F., Sharpe, A.H., Haigis, M.C., 2021. The aging lung: physiology, disease, and immunity. *Cell* 184 (8), 1990–2019. <https://doi.org/10.1016/j.cell.2021.03.005>.
- Shamim, A., Abdul Aziz, M., Saeed, F., Kumari, R., Mary Joseph, A., Ponnachan, P., Kishore, U., Masmoudi, K., 2024a. Revisiting surfactant protein D: an immune surveillance molecule bridging innate and adaptive immunity. *Front. Immunol.* 15, 1491175. <https://doi.org/10.3389/fimmu.2024.1491175>.
- Shan, S.W., Lee, D.Y., Deng, Z., Shatseva, T., Jayapalan, Z., Du, W.W., Zhang, Y., Xuan, J.W., Yee, S.-P., Siragam, V., Yang, B.B., 2009. MicroRNA MIR-17 retards tissue growth and represses fibronectin expression. *Nat. Cell Biol.* 11 (8), 1031–1038. <https://doi.org/10.1038/ncb1917>.
- Shimizu, Y., Nakamura, K., Kikuchi, M., Ukawa, S., Nakamura, K., Okada, E., Imae, A., Nakagawa, T., Yamamura, R., Tamakoshi, A., Ayabe, T., 2022. Lower human defensin 5 in elderly people compared to middle-aged is associated with differences in the intestinal microbiota composition: the DOSANCO Health Study. *GeroScience* 44 (2), 997–1009. <https://doi.org/10.1007/s11357-021-00398-y>.
- Sicari, Brian M., Londono, Ricardo, Dziki, Jenna L., Badylak, Stephen F., 2023. Extracellular matrix as a bioscaffold for tissue engineering. *Tissue Engineering. Academic Press, an imprint of Elsevier*, pp. 132–172.
- Sidoryk-Wegrzynowicz, M., Gerber, Y.N., Ries, M., Sastre, M., Tolkovsky, A.M., Spillantini, M.G., 2017. Astrocytes in mouse models of tauopathies acquire early deficits and lose neurosupportive functions. *Acta Neuropathol. Commun.* 5 (1), 89. <https://doi.org/10.1186/s40478-017-0478-9>.
- Silveyra, P., Floros, J., 2012. Air pollution and epigenetics: effects on SP-A and innate host defence in the lung. *Swiss Med. Wkly.* 142, w13579. <https://doi.org/10.4414/smw.2012.13579>.
- Sorensen, G.L., 2018. Surfactant Protein D in Respiratory and Non-Respiratory Diseases. *Front. Med.* 5, 18. <https://doi.org/10.3389/fmed.2018.00018>.
- Statzer, C., Park, J.Y.C., Ewald, C.Y., 2023. Extracellular matrix dynamics as an emerging yet understudied hallmark of aging and longevity. *Aging Dis.* 14 (3), 670–693. <https://doi.org/10.14336/AD.2022.1116>.
- Sticht, C., De La Torre, C., Parveen, A., Gretz, N., 2018a. miRWalk: an online resource for prediction of microRNA binding sites. *PLoS One* 13 (10), e0206239. <https://doi.org/10.1371/journal.pone.0206239>.
- Swahari, V., Nakamura, A., Hollville, E., Hung, Y.-H., Kanke, M., Kurtz, C.L., Caravia, X.M., Roiz-Valle, D., He, S., Krishnamurthy, J., Kapoor, S., Prasad, V., Flowers, C., Beck, M., Baran-Gale, J., Sharpless, N., López-Otín, C., Sethupathy, P., Deshmukh, M., 2024. miR-29 is an important driver of aging-related phenotypes. *Commun. Biol.* 7 (1), 1055. <https://doi.org/10.1038/s42003-024-06735-z>.
- Swindell, W.R., Johnston, A., Xing, X., Little, A., Robichaud, P., Voorhees, J.J., Fisher, G., Gudjonsson, J.E., 2013. Robust shifts in S100a9 expression with aging: a novel mechanism for chronic inflammation. *Sci. Rep.* 3, 1215. <https://doi.org/10.1038/srep01215>.
- Tang, O., Chen, X.-M., Shen, S., Hahn, M., Pollock, C.A., 2013. miRNA-200b represses transforming growth factor- $\beta$ -induced EMT and fibronectin expression in kidney proximal tubular cells. *Am. J. Physiol. Ren. Physiol.* 304 (10), F1266–F1273. <https://doi.org/10.1152/ajprenal.00302.2012>.
- Thanos, D.-P., Ntintas, O.A., Athanasiadis, E.L., Pappaspyropoulos, A., Petty, R., Gorgoulis, V.G., 2025. Interrogating the regulatory epigenome of cellular senescence. *Cell. Mol. Life Sci. CMLS* 82 (1), 328. <https://doi.org/10.1007/s00018-025-05848-w>.
- Tian, Z.-Y., Wang, C.-Y., Wang, T., Li, Y.-C., Wang, Z.-Y., 2019. Glial S100A6 Degrades  $\beta$ -amyloid Aggregation through Targeting Competition with Zinc Ions. *Aging Dis.* 10 (4), 756–769. <https://doi.org/10.14336/AD.2018.0912>.
- To, W.S., Midwood, K.S., 2011. Plasma and cellular fibronectin: distinct and independent functions during tissue repair. *Fibrogenes. Tissue Repair* 4, 21. <https://doi.org/10.1186/1755-1536-4-21>.
- Ujma, S., Horsnell, W.G.C., Katz, A.A., Clark, H.W., Schäfer, G., 2017. Non-Pulmonary Immune Functions of Surfactant Proteins A and D. *J. Innate Immun.* 9 (1), 3–11. <https://doi.org/10.1159/000451026>.
- Van Eldik, L.J., Griffin, W.S., 1994. S100 beta expression in Alzheimer's disease: relation to neuropathology in brain regions. *Biochim. Et. Biophys. Acta* 1223 (3), 398–403. [https://doi.org/10.1016/0167-4889\(94\)90101-5](https://doi.org/10.1016/0167-4889(94)90101-5).
- Vershinina, O., Sabbatinelli, J., Bonfigli, A.R., Colombaretti, D., Giuliani, A., Krivonozov, M., Trukhanov, A., Franceschi, C., Ivanchenko, M., Olivieri, F., 2025. Explainable artificial intelligence model predicting the risk of all-cause mortality in patients with type 2 diabetes mellitus. *Front. Endocrinol.* 16, 1689312. <https://doi.org/10.3389/fendo.2025.1689312>.
- Walrath, T., Dyamenahalli, K.U., Hulsebus, H.J., McCullough, R.L., Idrovo, J.-P., Boe, D.M., McMahan, R.H., Kovacs, E.J., 2021. Age-related changes in intestinal immunity and the microbiome. *J. Leukoc. Biol.* 109 (6), 1045–1061. <https://doi.org/10.1002/JLB.3RI0620-405RR>.
- Wang, J., Zhu, M., Ye, L., Chen, C., She, J., Song, Y., 2020. miR-29b-3p promotes particulate matter-induced inflammatory responses by regulating the C1QTNF6/AMPK pathway. *Aging* 12 (2), 1141–1158. <https://doi.org/10.18632/aging.102672>.
- Wang, T., Li, K., Xiao, S., Xia, Y., 2021. A plausible role for collectins in skin immune homeostasis. *Front. Immunol.* 12, 594858. <https://doi.org/10.3389/fimmu.2021.594858>.
- Wang, W., Cao, W., Zhang, S., Chen, D., Liu, L., 2025. The role of calprotectin in the diagnosis and treatment of inflammatory bowel disease. *Int. J. Mol. Sci.* 26 (5). <https://doi.org/10.3390/ijms26051996>.
- Wang, Y., Kang, X., Kang, X., Yang, F., 2023. S100A6: molecular function and biomarker role. *Biomark. Res.* 11 (1), 78. <https://doi.org/10.1186/s40364-023-00515-3>.
- Wasik, U., Schneider, G., Mietelska-Porowska, A., Mazurkiewicz, M., Fabczak, H., Weis, S., Zabke, C., Harrington, C.R., Filippek, A., Niewiadomska, G., 2013. Calyculin binding protein and Siah-1 interacting protein in Alzheimer's disease pathology: neuronal localization and possible function. *Neurobiol. Aging* 34 (5), 1380–1388. <https://doi.org/10.1016/j.neurobiolaging.2012.11.007>.
- Watson, A., Madsen, J., Clark, H.W., 2020. SP-A and SP-D: dual functioning immune molecules with antiviral and immunomodulatory properties. *Front. Immunol.* 11, 622598. <https://doi.org/10.3389/fimmu.2020.622598>.

- Wild, C.P., 2012. The exposome: from concept to utility. *Int. J. Epidemiol.* 41 (1), 24–32. <https://doi.org/10.1093/ije/dyr236>.
- Wruck, W., Schröter, F., Adjaye, J., 2016. Meta-Analysis of Transcriptome Data Related to Hippocampus Biopsies and iPSC-Derived Neuronal Cells from Alzheimer's Disease Patients Reveals an Association with FOXA1 and FOXA2 Gene Regulatory Networks. *J. Alzheimer's Dis. JAD* 50 (4), 1065–1082. <https://doi.org/10.3233/JAD-150733>.
- Yamagishi, S.-I., Matsui, T., 2018. Role of ligands of receptor for advanced glycation end products (RAGE) in peripheral artery disease. *Rejuvenation Res.* 21 (5), 456–463. <https://doi.org/10.1089/rej.2017.2025>.
- Yeh, C.-W., Yeh, S.H.-H., Shie, F.-S., Lai, W.-S., Liu, H.-K., Tzeng, T.-T., Tsay, H.-J., Shiao, Y.-J., 2015. Impaired cognition and cerebral glucose regulation are associated with astrocyte activation in the parenchyma of metabolically stressed APPsw/PS1dE9 mice. *Neurobiol. Aging* 36 (11), 2984–2994. <https://doi.org/10.1016/j.neurobiolaging.2015.07.022>.
- Yu, T., Liu, H., Gao, M., Liu, D., Wang, J., Zhang, J., Wang, J., Yang, P., Zhang, X., Liu, Y., 2024. Dexmedetomidine regulates exosomal miR-29b-3p from macrophages and alleviates septic myocardial injury by promoting autophagy in cardiomyocytes via targeting glycogen synthase kinase 3 $\beta$ . *Burns Trauma* 12, tkae042. <https://doi.org/10.1093/burnst/tkae042>.
- Zack, M., Stupichev, D.N., Moore, A.J., Slobodchikov, I.D., Sokolov, D.G., Trifonov, I.F., Gobbs, A., 2025. Artificial intelligence and multi-omics in pharmacogenomics: a new era of precision medicine. *Mayo Clin. Proc. Digit. Health* 3 (3), 100246. <https://doi.org/10.1016/j.mcpdig.2025.100246>.
- Zhou, S., Zhu, W., Zhang, Y., Pan, S., Bao, J., 2018. S100B promotes microglia M1 polarization and migration to aggravate cerebral ischemia. *Inflamm. Res. Off. J. Eur. Histamine Res. Soc.* ... [Et. Al.] 67 (11–12), 937–949. <https://doi.org/10.1007/s00011-018-1187-y>.
- Zhu, S., Li, H., Huang, Z., Zeng, Y., Huang, J., Li, G., Yang, S., Zhou, H., Chang, Z., Xie, Z., Que, R., Wei, X., Li, M., Liang, Y., Xian, W., Li, M., Pan, Y., Huang, F., Shi, L., Wang, Q., 2025. Plasma fibronectin is a prognostic biomarker of disability in Parkinson's disease: a prospective, multicenter cohort study. *NPJ Park. 'S. Dis.* 11 (1), 1. <https://doi.org/10.1038/s41531-024-00865-1>.