npj | regenerative medicine

Meeting report

Published in partnership with the Australian Regenerative Medicine Institute

https://doi.org/10.1038/s41536-025-00446-7

Emerging concepts and novel mechanisms in organ fibrosis

Adrián Ruiz-Villalba[1,2,5] ✉ & Ana Pardo-Saganta[3,4,5] ✉

Fibrosis, a maladaptive response characterized by excessive extracellular matrix deposition, disrupts tissue architecture and organ function. Recent advances reveal fibroblast heterogeneity across organs, with shared Postn^{+} activated fibroblast subsets driving fibrogenesis. Emerging evidence links fibrosis to mechanical stress, metabolic rewiring, and non-coding RNA regulation, unveiling novel therapeutic targets. Innovative models and regenerative strategies - including senolytics, metabolic modulation, and in vivo reprogramming – hold promise to reverse fibrosis and promote tissue repair.

Summary of the meeting

The workshop gathered experts in organ fibrosis and tissue repair to discuss emerging concepts and mechanisms in the field to better understand the development of fibrosis and to discover novel therapeutic approaches. Thus, we aimed to 1) understand fibroblast heterogeneity, 2) unravel novel mechanisms of fibrogenesis including aging, mechanotransduction and senescence, 3) study the influence of the microenvironment in tissue fibrosis and repair, and 4) develop strategies to promote regeneration in fibrotic organs. Here, we briefly provide an overview of the scientific content of the meeting, together with the main conclusions, within the context of the current knowledge on the pathophysiology of fibrosis.

Fibrosis: a common response in different contexts

The main hallmark of fibrosis is the exuberant extracellular matrix (ECM) deposition, leading to the loss of the natural tissue architecture. This response can, to some extent, be considered a reversible and adaptative function to different stimulus occurring in different organs[1]. However, when the switch from a physiological wound healing response to pathological fibrosis disables the reversibility of the process, organ structure and function are disrupted, significantly contributing to global morbidity and mortality[2,3]. Across organs, pathological fibrosis follows similar dynamics: aberrant fibroblast activation, excessive ECM deposition, and inadequate tissue repair. This process involves multiple cellular and molecular players that generate a fibrotic niche, characterized by a complex network of cell-to-cell and cell-to-ECM interactions. During the meeting, several aspects of this complexity were highlighted and discussed.

Fibroblast: a semantic problem?

During the workshop, a roundtable entitled *"Fibroblasts: a semantic problem?"* debated the concept of the fibroblast. Fibroblasts exist in every tissue, providing structural support by maintaining ECM architecture, and tissue homeostasis[4]. Given their role, these cells have historically been considered as "sentinel cells" of the organ[5]. In response to tissue injury, resident fibroblasts acquire a set of biological properties, including increased proliferation, excessive ECM secretion, and enhanced environmental responsiveness, that collectively define fibroblast "activation". These activated fibroblasts emerge at injured sites and drive pathologic fibrosis in both acute and chronic disease contexts[6]. Activated fibroblasts have traditionally been identified as *myofibroblasts* based on their increased expression of alpha-smooth muscle actin (α-SMA), distinguishing them from the non-activated fibroblasts[7]. However, one of the most significant advances in the field has been the recognition of fibroblast heterogeneity across organs. These advances have generated controversy regarding the use of α-SMA as a bona fide marker of activated fibroblasts in favour of others such as *Periostin (Postn)* or *Collagen triple helix repeat containing-1 (Cthrc1)*[8,9], which appear to more accurately define pathological fibroblasts contributing to fibrosis initiation and progression.

Fibroblast heterogeneity: unraveling the major subpopulations involved in fibrogenesis

Fibroblast heterogeneity was widely discussed during the workshop, considering multiple perspectives. A longstanding question has been the origin of fibroblasts that respond to tissue damage (Fig. 1). Fiona Watt´s lab demonstrated that dermal fibroblasts derive from distinct cellular lineages, with their origin linked to specific functions during skin development and

[1]Department of Animal Biology, Faculty of Sciences, University of Málaga, Málaga, Spain. [2]Instituto de Biomedicina de Málaga (IBIMA)-Plataforma BIONAND, Campanillas (Málaga), Spain. [3]Institute for Lung Health (ILH), Justus-Liebig University, Universities of Giessen and Marburg Lung Center (UGMLC), German Center for Lung Research (DZL), Giessen, Germany. [4]Cardio-Pulmonary Institute (CPI), Department of Internal Medicine, Justus Liebig University, Giessen, Germany. [5]These authors contributed equally: Adrián Ruiz-Villalba, Ana Pardo-Saganta. ✉e-mail: adruiz@uma.es; ana.pardo-saganta@innere.med.uni-giessen.de

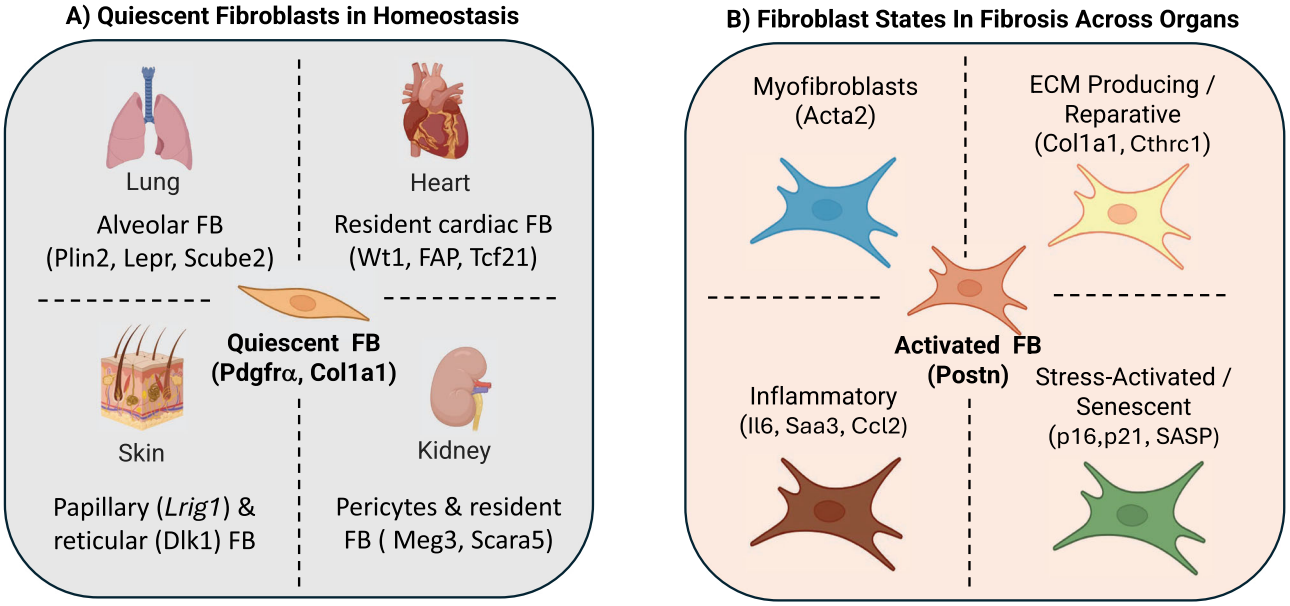

Fig. 1 | Fibroblast subpopulations across organs. A Quiescent fibroblasts in the lung, heart, skin and kidney under homeostatic conditions, characterized by specific transcriptomic signatures/profiles. **B** Activated fibroblasts, including the different states that emerge during activation following injury, all share the expression of *Periostin* (*Postn*). These states are observed across most organs; however, in some cases, they have not yet been fully characterized or identified. Created in *BioRender*.

repair[10–12]. One subset gives rise to the upper dermis, which is required for hair follicle formation. The other subset forms the lower dermis and initiates dermal repair in wounded adult skin by recruiting upper dermal fibroblasts, which expand in response to epidermal β-catenin activation to drive re-epithelialization[10]. More recently, they described how dermal NG2$^+$ perivascular cells originate from two different lineages: papillary fibroblasts (*Lrig1*$^+$ lineage) in the upper dermis and reticular *Dlk1*$^+$ fibroblasts in the lower dermis[12]. This heterogeneity was further explored in adult human skin, where at least four distinct fibroblast populations were identified[11]. Similarities and differences between mouse and human skin, including the presence and frequency of hair follicles, were also highlighted. Unravelling dermal fibroblast heterogeneity may provide insights into physiological wound healing and how its dysfunction contributes to pathological states such as fibrosis and basal cell carcinoma.

Along the same lines, José M. Pérez-Pomares presented evidence for the origin of cardiac fibroblasts from embryonic (pro)epicardial progenitors and reported novel insights into the mechanisms that regulate their specification and expansion in the cardiac interstitium. It is well established that proepicardial cells first form the primitive epicardial epithelium, and that a subset of epicardial cells undergoes an epithelial-to-mesenchymal transition (EMT), giving rise to epicardial-derived-cells (EPDCs), a heterogeneous pool of connective tissue embryonic cells that includes the fibroblasts responsible for the fibrotic response following myocardial infarction (MI) in adulthood[13]. Delving into the nature of proepicardial cells, the Pérez-Pomares lab recently demonstrated that true epicardial and EPDC progenitors can be distinguished based on their combined expression of both Wilm's tumour suppressor 1 gene (*Wt1*) and alpha-4 integrin (*Itga4*) genes. These *Wt1*$^+$/*Itga4*$^+$ progenitors retain a high proliferative rate in the nascent subepicardium, regulated by the Wnt signalling pathway via C-JUN[14]. Taken together, these findings open new avenues for studying the regulation of cardiac fibroblast progenitors from embryonic EPDCs in the postnatal heart and for identifying the mechanisms that trigger their proliferative response.

However, the resolution about adult fibroblast heterogeneity in multiple organs derives from the advent of single-cell and spatial multi-omic approaches. In this context, the research led by Christoph Kuppe has characterized the landscape of kidney and cardiac fibrosis in human tissue. His analyses indicate that most of the scar tissue in these organs originates from *PDGFRα*$^+$/*PDGFRβ*$^+$ fibroblasts. The combination of genetic fate tracing and time course scRNA-seq and ATAC-seq experiments, together with spatial transcriptomics in human kidney fibrosis, has elucidated the origin and regulation of renal myofibroblasts - defined as cells expressing the highest number of ECM-related genes. These cells, identified by *POSTN* expression, predominantly derive from pericytes and resident fibroblasts[15]. Moreover, Kuppe's multi-omic, spatially resolved approaches, enabled the assessment of neighbourhood effects on cardiac fibroblast state and transcriptional regulation, providing a comprehensive map of cardiac remodelling after MI with unprecedented spatial and molecular resolution[16].

In the lung, recent discoveries have also identified the cell of origin of pathological fibroblasts and delineated the cellular transitions and regulatory circuits involved. Dean Sheppard's team described multiple fibroblast subsets with distinct transcriptional profiles and anatomical locations in the healthy mouse lung[17]. Their work revealed the emergence of *Cthrc1*-expressing fibroblasts in fibrotic murine lungs, a subset also detected in human pulmonary fibrosis. Functional analyses provided evidence for the disease relevance of this population. Similarly, Ruiz-Villalba et al. demonstrated that profibrotic *Cthrc1*$^+$ cardiac fibroblasts play a critical role during the early phases of myocardial remodelling[18]. Importantly, multiple studies have suggested *Cthrc1* as a more specific marker of the small subset of fibroblasts producing the highest levels of ECM proteins across different organs in fibrotic disease[19,20].

More recently, Sheppard´s group demonstrated by lineage tracing that *Scube2*$^+$-alveolar fibroblasts are the dominant source of newly formed *Cthrc1*$^+$ profibrotic fibroblasts in response to lung injury[21]. These findings challenge the proposed universal origin of profibrotic fibroblasts in every organ suggested by computational inference, which would rely on *Pi16*$^+$ adventitial ones[22]. Consistently, subsequent work confirmed that *Cthrc1*$^+$/*Postn*$^+$ pathological fibroblasts derive from *Lepr*$^+$ cells that include *Scube2*$^+$ alveolar fibroblasts, and revealed *Runx2* as a key regulator of fibrotic genes essential for their generation[9].

Building upon these findings, inflammatory mediators released after injury induce alveolar fibroblasts to transition into inflammatory fibroblasts, which later differentiate into fibrotic fibroblasts in response to profibrotic cytokines such as TGFβ1[21]. Consistently, Herbert Schiller delineated the transitional path of fibroblast activation following fibrotic lung injury, describing the spatiotemporal evolution of injury-activated fibroblast states towards *Cthrc1*$^+$ fibroblasts and emphasizing early events. His research identified a novel *Sfrp1*$^+$ transitional state that appears early after injury and

becomes invasive only upon TGFβ stimulation, which induces differentiation into *Cthrc1*$^+$ fibroblasts[23], revealing that SFRP1 modulates TGFβ1-driven fibroblast activation. Notably, they found that SFRP1 is highly enriched in fibrotic extracellular vesicles (EVs), which exert a pro-fibrotic effect in vivo[24].

In agreement with previous knowledge showing that Pdgfrα+ lipofibroblasts in alveolar walls are closely associated with alveolar type 2 (AT2) epithelial cells and can support their growth ex vivo[25], Sheppard also demonstrated that, beyond being the cell of origin of fibrotic fibroblasts, alveolar fibroblasts serve as an essential niche for AT2 cell maintenance at homeostasis[21]. Analyses of early-stage pulmonary fibrosis revealed significant differences not only in the stromal compartment but also in epithelial cells compared to healthy tissue[26]. Importantly, epithelial cell injury is considered a trigger for the development of fibrosis, regulated by a pathological feed-forward loop between fibroblasts and alveolar epithelial cells[27,28]. Purushothama Tata's work uncovered the co-emergence of transitional states in both the epithelium and fibroblasts, showing how they influence each other to regulate alveolar injury-repair processes[29]. The coordinated activity of these transitional states determines the repair outcome, with imbalance in epithelial-mesenchymal interactions leading to tissue disorganization and reduced organ function. Tata's findings indicate that transitional cells from both compartments are functionally linked and indispensable for tissue repair. Previous work from his lab described the stepwise process of alveolar regeneration after injury, identifying epithelial intermediate states (PATS) with unique transcriptional signatures enriched in human lung fibrosis[28]. They further demonstrated that induction of epithelial intermediate cells and transitional *Runx1*$^+$ fibroblasts is required to prevent emphysema, while abnormal persistence of these states may cause fibrosis[29]. These results highlight that therapeutic strategies should focus on limiting proliferation or accumulation of *Acta2*$^+$/*Runx1*$^+$-alveolar fibroblasts to treat lung fibrosis, rather than inhibiting their formation, which could impair repair.

Fibroblast proliferation and recruitment: expanding the fibroblast foci

Although Idiopathic Pulmonary Fibrosis (IPF) has long been described as a fibroproliferative disease, with fibroblast division presumed to underlie the progressive nature of lung fibrosis, new evidence demonstrates additional mechanisms driving fibrosis initiation and progression[30,31], including fibroblast activation[7], as well as alternative modes of fibroblast recruitment to sites of injury such as chemotaxis (movement directed by chemical gradients)[32] and durotaxis (migration guided by matrix stiffness gradients)[33]. Although fibroblast proliferation has been proposed as a key driver of fibrogenesis, the supporting data remain inconsistent and fail to clarify fundamental questions: how fibroblasts proliferate, where and when this occurs, and which subpopulations are involved. Lineage tracing from the Sheppard group demonstrated that alveolar fibroblasts first differentiate into *Cthrc1*$^+$ fibrotic fibroblasts and subsequently proliferate, with clonal expansion in regions of dense remodeling across two murine models of lung fibrosis[30]. Using EdU incorporation, genetic lineage tracing, and scRNA-seq, they defined this proliferative wave and showed that ablation of proliferating fibroblasts or disruption of cytokinesis mitigated fibrosis and improved lung function[31]. In an influenza injury model, the Morrisey group found that Pdgfrα-lineage (AF1) cells undergo a robust but transient proliferative burst, identified by increased Ki67$^+$ lineage-labeled AF1 cells, decreasing over time with minimal proliferation observed in AF1-derived AF2 cells by day 28 after injury, and similarly observed that blockade of mesenchymal cell division reduced tissue injury and promoted alveolar repair regeneration[31]. Complementary findings from the Lagares lab further refined this model. Using a Collagen-GFP reporter mouse and in vivo BrdU labeling, their data showed that < 1% of GFP^{high}/αSMA$^+$ myofibroblasts were proliferating at day 21 in the bleomycin-induced lung fibrosis model, compared with 6% of GFP^{low}/αSMA$^-$ fibroblasts[33]. These results support a model in which fibroblasts proliferate outside fibrotic foci, then migrate via durotaxis and become mechanically activated to acquire the αSMA$^+$ phenotype[33].

In human IPF lungs, Sheppard's group reported that proliferating fibroblasts with a fibrotic signature are present even in end-stage fibrotic human lungs, exhibiting higher proliferation rates in precision-cut lung slices (PCLS)[30]. In contrast, the Lagares' lab observed virtually no proliferative activity among αSMA$^+$ myofibroblasts by immunohistochemistry across multiple IPF patient samples. While expansion of 'fibroblast foci' in patients with idiopathic pulmonary fibrosis has been attributed to myofibroblast proliferation, Lagares data challenge this view. The use of different markers and sample types to address a similar question in both studies likely accounts for the divergent conclusions.

Taken together, these findings indicate that myofibroblast proliferation is unlikely to be a dominant driver of established fibrosis not fully accounting for the progressive nature of IPF. Future work must define which fibroblast subsets actively divide, their functional outputs (ECM production, contraction, inflammatory signaling, immune evasion), and how these processes can be selectively and safely modulated in chronic fibrotic disease.

Mechanisms of fibrosis (I): the role of the extracellular matrix

Recent work from the Lagares lab demonstrates that mechanical cues, including increased matrix stiffness, promote both fibroblast recruitment and mechano-activation into scar-forming myofibroblasts. Their studies revealed a novel role for 'durotaxis', the directed migration of fibroblasts along stiffness gradients, in directing fibroblast recruitment to sites of fibrosis, expanding fibrotic foci in the lungs and promoting disease progression[32,33]. This process has been also described in fibrosis in the skin, kidney and lungs, highlighting a conserved pathogenic mechanism across organs[33]. Importantly, Lagares' group identified that fibroblast durotaxis and mechano-activation are driven by FAK-Paxillin interaction, a novel mechanosensor upregulated in IPF-derived myofibroblasts. Therapeutically, mice carrying a point mutation (FAK^L994E) that disrupts FAK–Paxillin binding are protected from bleomycin-induced lung and skin fibrosis and pharmacological disruption of FAK-Paxillin with JP-153 mimics these effects[33]. Building on these findings, Herbert Schiller's work further demonstrated stiffness-dependent changes in the phosphoproteome of human lung fibroblasts, identifying phospho-Paxillin and NFATC4 as novel regulators of fibroblast mechano-activation[34]. Additionally, Lagares' lab revealed that matrix stiffness induces cellular senescence in myofibroblasts[35,36]. Importantly, they show that survival and persistence of senescent myofibroblasts depend on stiffness-induced expression of the pro-survival protein Bcl-XL. Accordingly, they had previously reported that therapeutic blockade of Bcl-XL with ABT-263 induces apoptosis of senescent myofibroblasts exposed to high stiffness, and that in vivo ABT-263 treatment reverses skin and lung fibrosis in preclinical models[7,36,37]. Mechanistically, stiffness-induced Bcl-XL expression is dependent on FAK signalling, and targeting FAK-mediated mechanotransduction similarly induces apoptosis of senescent myofibroblasts both in vitro and in vivo. Together, these findings demonstrate that efficiently inducing apoptosis of senescent myofibroblasts can reverse fibrosis and promote tissue regeneration.

The relevance of matrix stiffness in the biology of activated fibroblasts was also highlighted by Giancarlo Forte. He showed that ECM remodelling applies unique mechanical stress on cardiac cells, highlighting that the modifications in the 3D nanostructure and mechanics of human cardiac ECM promote the activation of cardiac fibroblasts in both, ischemic and dilated heart failure[38]. In this context, he introduced the concept of mechanosensitive messenger RNA alternative splicing, a phenomenon which was recently discovered in the failing human heart[39]. After the analysis of different human and murine datasets, Forte´s lab found an RNA binding protein – heterogeneous nuclear ribonucleoprotein C (hnRNPC) –consistently and reproducibly upregulated in the ischemic and non-ischemic heart across species. Interestingly, the cellular localization of hnRNPC depends on the ability of the cell to spread and build intracellular tension. Thus, Forte's lab described for the first time the phenomenon

of mechanosensitive alternative splicing through which ECM remodelling in the failing heart directly impacts on the splicing of relevant mRNAs by inducing the shuttling of hnRNPC out of the nucleus and to the sarcomeres, close to sites of localized translation.

Noteworthy, ECM remodelling is itself a hallmark of pathological fibrosis. Activated fibroblasts downregulate enzymes that are responsible of matrix cross-linking, enhancing stiffness of the fibrotic scar. This promotes self-sustaining activation of the fibrotic process, giving rise to a positive and dangerous feed-back contributing to the chronification of the disease. Fernando Rodriguez-Pascual´s talk highlighted the role of LOX enzymes in this context. In addition to TGF-β1 and hypoxia which are key factors promoting transcription of LOX genes, proteolysis itself has been recognized as a fundamental process for LOX isoforms activation. Recent studies from his group have added ADAMTS2 and ADAMTS14 to the repertoire of proteases capable of processing LOX[40]. More recently, they identified that LOXL1 protein is processed by BMP1 and ADAMTS14[41], suggesting a complex regulation of LOXL1 enzymes with relevance in tissue fibrosis.

Collectively, these and other studies highlight the pivotal role of ECM in the development and progression of fibrosis across organs. However, an equally critical component in ECM remodeling during the fibrotic response is the cellular compartment of the fibrotic niche

Mechanisms of fibrosis (II): cellular components of the fibrotic niche

Cellular components and their interactions within the fibrotic microenvironment, significantly influence the injury-repair process. In this regard, Suphansa Sawamiphak identified a mechanism by which the nervous and immune systems orchestrate scarless heart repair in zebrafish: a specific cluster of adrenergic macrophages switch to ECM remodelling macrophages in response to neural input through the adrenergic receptor *Adra1* following myocardial damage. This macrophage phenotypic switch is required to induce pro-regenerative fibroblasts that contribute to ECM turnover, vascular growth and cardiomyocyte proliferation at the lesion site[42]. Interestingly, their data demonstrated that this transition is disrupted in hyperlipidemic obesity and consequently, repair is affected. Thus, compromised macrophage activation could underlie worsen reparative ability of the human heart with metabolic perturbation, as highly prevalent in human MI and when associated with a sympathetic nervous system activation[43].

Metabolic alterations are commonly observed in cells comprising the fibrotic niche. In fact, metabolic changes are key in both the activation of fibroblasts and the biosynthesis of fibrillary collagens by myofibroblasts, processes that also require a remarkable high consumption of energy[44]. Therefore, elucidating the role of cellular metabolism in fibrogenesis will deepen our understanding and may reveal novel strategies to prevent or attenuate fibrosis. Santiago Lamas´s group has shown that mitochondrial dysfunction and defective fatty acid oxidation (FAO) are fundamental contributors to the development and progression of kidney fibrosis[45], thus reinforcing FAO as a key metabolic pathway to support the high energetic requirements of kidney tubules. Restoring the capacity of FAO via enhanced overexpression of carnitine palmitoyl-transferase 1 A (CPT1A), the rate-limiting enzyme for fatty acid metabolism that is necessary to transport long-chain fatty acids into mitochondria, could reverse tissue fibrosis[46]. Further, Lamas' team has recently demonstrated that time-restricted feeding, a dietary strategy to enhance circadian rhythm, reduces inflammation and fibrosis preventing downregulation of genes involved in FAO and mitochondrial function (unpublished data), establishing the connection between metabolism and circadian clock in kidney injury[47]. Based on all his findings, Santiago Lamas proposed a metabolic boost as a therapeutic option for COVID19-induced lung and renal damage. In this regard, they showed that enhanced FAO through metformin and Baicalin treatment, decreased inflammation, epithelial damage and fibrosis[48].

Interestingly, FAO plays an opposite role in mediating heart and kidney repair. During postnatal maturation, cardiomyocytes lose their proliferative potential and regenerative capacity, and undergo a metabolic switch from glycolysis to FAO. Thomas Braun's work demonstrated that cardiomyocyte metabolism correlates with the ability for heart regeneration. Specifically, abrogation of FAO in mature cardiomyocytes through inactivation of carnitine palmitoyl-transferase 1B (CPT1B) markedly increased their cell numbers in the heart[49]. Moreover, Braun established a mechanistic link between metabolism and epigenetics, showing that loss of Cpt1b in cardiomyocytes elevated intracellular concentrations of α-ketoglutarate, a key co-substate of various demethylases, which in turn induced demethylation of H3K4 at promotor regions of genes required to maintain differentiated cardiomyocyte features. The resulting reduction of H3K4me3 decreased transcription and shifted cardiomyocytes towards a less mature, more proliferative state. These findings clearly demonstrate that metabolic maturation shapes the epigenetic landscape of cardiomyocytes, creating a barrier to further cell division. Importantly, reversal of this process promoted cardiac repair, as therapeutic inhibition of Cpt1b following infarction prevented scar formation, allowing hearts to fully regain contractility and restore cardiac function[49].

Extending this concept to other organs, Tata Nageswara Rao studies the effect of cell metabolism in bone marrow fibrosis or myelofibrosis (MF). To investigate this, his group established a model to introduce a single point mutation in JAK2, associated with MF, in hematopoietic stem cells (HSC)[50,51]. This mutation induced metabolic alterations, reduced adipose tissue and body weight. Mass spectrometry analysis identified GDF15 as a potential mediator of these effects, and, consistently, GDF15 levels were elevated in MF patients. Importantly, treatment with JAK inhibitors decreased GDF15 in MF cells and in JAK2 mutant mice, while direct targeting of GDF15 ameliorated disease progression in these mice by reducing inflammation. These findings provide compelling evidence for the critical role of this cytokine in MF pathogenesis. Collectively, Tata's work highlights GDF15 not only as a potential biomarker but also as a novel therapeutic target for myelofibrosis, offering an elegant proof of concept that modulation of cellular metabolism can be leveraged to control fibrotic disease.

Along these lines, Melissa García-Caballero underscored the importance of metabolic reprogramming in endothelial cells (ECs) as a potential therapeutic strategy for pathological fibrosis. Upon injury conditions, quiescent ECs are prompted to become proliferative and angiogenic, contributing to fibrosis by promoting immune cell recruitment, driving vascular rarefaction and impaired angiogenesis, or by secreting profibrotic mediators[52]. Moreover, ECs can undergo endothelial-to-mesenchymal transition (EndoMT), losing their specific endothelial characteristics and acquiring the expression of α-SMA and type I collagen[53] - a process that has attracted increased attention in recent years in both organ fibrosis and cancer[54]. Accordingly, García-Caballero highlighted the relevance of EndoMT in tissue remodelling across heart, lung, and liver fibrosis[55], and revealed a novel EndoMT mechanism driven by endothelial cell metabolism.

An alternative approach to regulate cellular metabolism in the context of fibrosis involves the study of non-coding RNAs. In recent years, growing evidence on the role of microRNAs (miRNAs), which regulate gene expression post-transcriptionally, has revolutionized our understanding of the mechanisms underlying tissue injury and repair. Santiago Lamas highlighted their involvement in the progression of chronic kidney disease and demonstrated that the program of renal fibrogenesis is controlled by miRNAs regulating oxidative metabolism[45,56]. In addition to miRNAs, long non-coding RNAs (lncRNAs), a class of non-coding RNAs capable of interacting with DNA, RNA and proteins to regulate global gene expression patterns, have also been implicated in tissue injury and repair. In this context, Marta Varela-Rey described the functional and mechanistic role of lncRNAC1 in liver disease. Expression of lncRNAC1 is increased in patients with cholestasis and Non-Alcoholic Fatty Liver Disease (NAFLD), as well as in animal models of liver injury. Its inhibition exacerbated liver damage by enhancing hepatocyte apoptosis in a bile duct ligation model of hepatic cholestasis and induced the expression of profibrotic genes in TGFβ-treated Hepatic Stellate Cells (HepSCs) in vitro. Altogether, their

data suggest that lncRNAC1 may play a protective role in liver fibrosis by preventing cell death and attenuating the profibrogenic response of HepSCs.

Building on the expanding understanding of the non-coding genome, Maria Abad presented on the emergent field of microproteins, small proteins encoded by regions previously assumed to be non-coding and historically overlooked due to their size. Although largely uncharacterized, microproteins have been linked to cell plasticity and pathology. Her lab identified MIDORI, a novel microprotein encoded by ZEB2-AS1 lncRNA, which is upregulated under stress and promotes mesenchymal-epithelial transition (MET). Overexpression of MIDORI suppresses the mesenchymal phenotype, reducing cell migration, invasion, and proinflammatory cytokine production, and it also blocks TGFβ-induced EMT. Importantly, MIDORI expression is lost in fibrotic lesions, supporting its role in preventing fibrosis. These findings highlight the therapeutic potential of microproteins like MIDORI for pro-regenerative strategies and suggest that additional microproteins may be discovered in the future to treat inflammatory and fibrotic disorders.

Taken together, the identification of individual cellular and molecular targets is essential for the understanding of the mechanisms of several fibrotic processes. However, fibrosis is not a single-factor process. Because of that, it is necessary to explore and develop different models to study it.

Novel models for studying pathological fibrosis

Modelling fibrosis is particularly challenging due to its complex, multifactorial nature. In vivo models can provide valuable insights into fibroblast activation and, in some cases, resolution, such as the single-dose bleomycin model in lung and skin. However, when applied to aged mice, fibrosis becomes irreversible[57,58]. Many diseases, such as IPF, are age-related and exhibit most of the hallmarks of aging such as chronic inflammation, stem cell exhaustion and cellular senescence[59]. To address these limitations, Mareike Lehmann has developed advanced technologies, including multicellular alveolar organoids and Precision Cut Lung Slices (PCLS) from mouse and human tissues, which display aging-associated features and enable the study of chronic lung disease pathophysiology, including fibrosis[60–62]. Using these models, Lehmann's group recently identified a novel senescence-associated secretory phenotype (SASP) factor produced by senescent AT2 cells, which mediates fibroblast reprogramming in senescence-associated pulmonary fibrosis and can be blocked by senolytic drugs, thereby attenuating the fibrotic response[63].

PCLS have been proposed as a more reliable ex vivo system in biomedical research, as they include all the cellular compartments of the tissue of interest, despite lacking circulation and mechanical cues[62,64]. Recently, optimization of an ex vivo model to induce early fibrosis-like changes using a fibrotic cocktail has facilitated the study of IPF pathomechanisms[60]. This organotypic model has also been employed by Schiller's team, confirming that these changes closely resemble those observed in early-stage human IPF lungs and enabling the identification novel cell states and cell circuits involved in fibrogenesis[26]. In addition, PCLS models have proven to be valuable platform for drug testing and for the discovery of novel targets aimed at reversing fibrosis and promoting tissue regeneration, thereby helping to bridge the gap between basic research and clinical application[26,62].

Similarly, Forte's group developed an isogenic in vitro model of cardiac fibrosis using decellularized ECM (dECM) obtained from iPSC-derived cardiac fibroblasts exposed to pro-fibrotic stimuli, which served as a culture substrate for cardiomyocytes derived from the same iPSC line. They demonstrated that cardiomyocytes could spontaneously beat on dECMs for over 30 days, and observed that fibrotic matrices influenced cardiomyocyte behaviour in multiple ways, including induction of mechanosensing responses, enhanced sarcomere organization and changes in calcium handling that resulted in shorter relaxation times[65].

In summary, nowadays exist several in vivo and ex vivo models that mimic, at least partially, the complexity that underlie fibrosis. These models have allowed researchers to develop different approaches for addressing therapeutical strategies against fibrosis or even reactivate internal regenerative programs.

Strategies to tackle tissue fibrosis and promote regeneration

In addition to identifying novel targets in fibrotic disease, an important challenge is developing methods to efficiently deliver drugs to achieve their therapeutic effect. Ana V. Villar has generated highly innovative approaches, including in vivo tracking visualization tools and nano-delivery systems, to inhibit fibrotic processes. Villar's group recently demonstrated that a promising protein-nanomaterial hybrid (CTPRAu), a fluorescent gold nanocluster stabilized by an engineered CTPR (Consensus Tetratricopeptide Repeat) protein and containing an Hsp90-inhibiting module (CTPR390), exhibited efficient antifibrotic effects[66,67], highlighting its potential for both therapeutic intervention and monitoring of cardiac fibrosis. Moreover, this antifibrotic drug can be detected in non-apoptotic extracellular vesicles (EVs) inside fibroblasts[68]. Further, Villar showed that engineered fibroblast-derived EVs can serve as trackable transporters of antifibrotic nanodrugs, efficiently targeting both the heart and the lung[69]. These findings underscore the clinical potential of next-generation therapies, including versatile EV-based drug encapsulation and delivery systems carrying protein-based hybrid nanomaterials with antifibrotic activity.

While antifibrotic therapies aim to halt disease progression, complementary strategies focus on restoring tissue function by promoting regeneration. Although virtually every organ can be affected by fibrosis, their regenerative capacity differs significantly. Whereas the skin and the intestine exhibit a high regenerative potential, the heart and the brain display very limited capacity for self-repair[70]. One of the strategies to promote heart regeneration is to stimulate cardiomyocyte proliferation in situ. Adult cardiomyocytes are terminally differentiated, postmitotic cells, while a proliferative state is characteristic of embryonic and neonatal cardiomyocytes. Thomas Braun demonstrated that cell cycle re-entry of cardiomyocytes can be promoted through inhibition of the Hippo signalling pathway, resulting in YAP activation which regulates several cell cycle genes[71]. Nevertheless, he also pointed out that sustained YAP activation induces massive cardiac fibrosis, indicating that additional strategies are required to promote cardiomyocyte proliferation without triggering adverse fibrotic responses.

Another strategy to enhance tissue regeneration involves the use of endogenous stem cells present in adult tissues with regenerative potential[72]. For instance, AT2 cells serve as lung stem cells, maintaining tissue homeostasis and contributing to alveolar repair after injury[73]. However, in human IPF, a significant fraction of AT2 cells is lost or dysfunctional[74]. Preclinical studies by Anna Serrano-Mollar demonstrated the therapeutic effect of intratracheal transplantation of AT2 cells, which reduced experimental pulmonary fibrosis by decreasing fibroblasts proliferation and ECM accumulation, restoring surfactant levels, and improving lung function[75,76]. Furthermore, Serrano-Mollar showed that administration of human AT2 cells to IPF patients was safe, well tolerated, and free of significant adverse effects in individuals with moderate and progressive disease[74]. While it has not yet been established whether this treatment improves lung structure and functionality, these findings pave the way for clinical trials to evaluate the potential benefits of AT2-cell therapy in IPF.

Regenerative capacity declines with aging and is particularly inefficient in fibrotic tissues. One strategy to restore this capacity is to revert aged cells to a younger state through a process known as "rejuvenation", which can be achieved by cellular reprogramming[77]. The ectopic expression of the four transcription factors OCT4, SOX2, KLF4 and MYC (OSKM) enables the conversion of differentiated cells into induced pluripotent stem cells (iPSCs)[78]. In pioneering work, Manuel Serrano's group achieved in vivo reprogramming in adult mice using inducible transgenic OSKM expression[79–81], deciphering the roadmap of cellular reprogramming in living organisms[82]. Interestingly, they showed that natural killer (NK) cells recognize and eliminate reprogrammed cells, and that supplementation with vitamin B12 enhances the efficiency of in vivo reprogramming and

tissue repair[83]. While sustained OSKM expression drives cells towards embryonic pluripotency and teratoma formation[79,80], partial reprogramming represents an intermediate stage in which temporal OSKM expression induces a reversible loss of cellular identity and formation of dysplastic areas across multiple tissues[79,80]. Serrano's group found that partial reprogramming in aged mice was sufficient to reverse aging-associated DNA methylation changes in the pancreas, liver, spleen, and blood[84], restoring transcriptional profiles, protein homeostasis and collagen composition. Moreover, OSKM expression induced senescence in many cells in vivo, which in turn promoted reprogramming in neighbouring cells, thereby contributing to tissue repair[81].

Extending the concept of partial reprogramming to organs with limited regenerative potential, the feasibility of in vivo reprogramming in the heart has been recently demonstrated[85]. Thomas Braun showed that cardiomyocyte-specific, temporally restricted OSKM expression induces a foetal-like state (dedifferentiation), enabling cell cycle re-entry, metabolic rewiring, and cardiomyocyte division. Transient OSKM expression in transgenic mice, before or immediately after MI, reduced scar size, promoted heart regeneration and improved cardiac function[85]. Consistent with Serrano's findings, Braun's group also observed that prolonged OSKM expression leads to irreversible dedifferentiation of cardiomyocytes, resulting in heart failure. Extended OSKM expression further drives full reprogramming of cardiomyocytes to iPSCs, with subsequent teratoma formation[71,85].

Taken together, various strategies have been proposed to counteract fibrosis and enhance the intrinsic regenerative capacity of different organs. However, further research is needed to translate these approaches into clinical practice.

Conclusions and future perspectives

Recent advances uncovering novel mechanisms underlying fibrogenesis have reshaped our understanding of fibrosis as an organ-spanning process driven by conserved yet heterogeneous fibroblast populations. The identification of Cthrc1$^+$/Postn$^+$ fibroblasts as key effectors shared across multiple organs underscores the importance of delineating lineage-specific trajectories and regulatory circuits that govern their activation and persistence. However, defining the specific behaviors of fibroblast subsets - such as their proliferative or migratory dynamics at distinct disease stages- remains essential to evaluate their relevance as therapeutic targets aimed at halting fibroblast activation and limiting fibrosis progression. In particular, unraveling the major drivers of fibroblast foci expansion - whether through fibroblast proliferation or recruitment - is urgently needed.

Integration of single-cell and spatial multi-omic approaches has revealed that fibrosis arises from dynamic cellular transitions involving not only stromal cells but also other cellular compartments, such as the epithelium, highlighting early epithelial-mesenchymal crosstalk as a critical intervention window. Mechanotransduction and metabolic rewiring converge to sustain fibroblast activation, suggesting that targeting stiffness-sensing pathways, energy metabolism, or senescent cell survival may enable organ-specific antifibrotic strategies. Moreover, long-term persistence mechanisms, such as mechanical activation, survival signaling, and senescence-associated resistance to apoptosis require further exploration.

From a translational perspective, combining ex vivo models such as PCLS and multicellular organoids with multi-omic profiling provides a valuable platform for testing therapies in human-relevant contexts. Emerging antifibrotic strategies, including senolytics, metabolic modulators, and mechanotherapeutics, together with approaches that stimulate stem and progenitor cell activity, hold particular promise for reversing fibrosis and promoting tissue repair. Integrating these mechanistic insights with innovative delivery systems -such as nanocarrier- and EV-based systems- will be key to developing targeted, regenerative antifibrotic therapies.

Ultimately, blocking pathological fibroblasts or targeting dysregulated pathways may provide effective strategies to halt or even reverse fibrosis. This will require the identification of a therapeutic window with high specificity at the mechanistic, cellular, and pathway levels to avoid interfering with physiological tissue repair and regeneration. Complete restoration of tissue architecture and function remains essential for durable repair. Therefore, combining antifibrotic and pro-regenerative approaches will likely be necessary to achieve true functional recovery. Still, critical questions remain as to whether endogenous cells within fibrotic tissues can reestablish proper architecture within a remodeled extracellular matrix, or whether the microenvironment must first be normalized. Deciphering the cellular, molecular, and physical cues that define the fibrotic niche will be crucial to overcome these barriers and translate current mechanistic insights into effective clinical therapies for fibrotic diseases.

Data availability

No datasets were generated or analysed during the current study.

Received: 17 June 2025; Accepted: 1 December 2025;
Published online: 17 December 2025

References

1. Thannickal, V. J., Zhou, Y., Gaggar, A. & Duncan, S. R. Fibrosis: ultimate and proximate causes. *J. Clin. Invest.* **124**, 4673–4677 (2014).
2. Lurje, I., Gaisa, N. T., Weiskirchen, R. & Tacke, F. Mechanisms of organ fibrosis: Emerging concepts and implications for novel treatment strategies. *Mol. Aspects Med.* **92**, 101191 (2023).
3. Atabai, K., Yang, C. D. & Podolsky, M. J. You Say You Want a Resolution (of Fibrosis). *Am. J. Respir. Cell Mol. Biol.* **63**, 424–435 (2020).
4. Plikus, M. V. et al. Fibroblasts: Origins, definitions, and functions in health and disease. *Cell* **184**, 3852–3872 (2021).
5. Smith, R. S., Smith, T. J., Blieden, T. M. & Phipps, R. P. Fibroblasts as sentinel cells. Synthesis of chemokines and regulation of inflammation. *Am. J. Pathol* **151**, 317–322 (1997).
6. Henderson, N. C., Rieder, F. & Wynn, T. A. Fibrosis: from mechanisms to medicines. *Nature* **587**, 555–566 (2020).
7. Hinz, B. & Lagares, D. Evasion of apoptosis by myofibroblasts: a hallmark of fibrotic diseases. *Nat. Rev. Rheumatol.* **16**, 11–31 (2020).
8. Amrute, J. M. et al. Targeting immune–fibroblast cell communication in heart failure. *Nature* **635**, 423–433 (2024).
9. Fang, Y. et al. RUNX2 promotes fibrosis via an alveolar-to-pathological fibroblast transition. *Nature* **640**, 221–230 (2025).
10. Driskell, R. R. et al. Distinct fibroblast lineages determine dermal architecture in skin development and repair. *Nature* **504**, 277–281 (2013).
11. Philippeos, C. et al. Spatial and Single-Cell Transcriptional Profiling Identifies Functionally Distinct Human Dermal Fibroblast Subpopulations. *J. Invest. Dermatol.* **138**, 811e825 (2018).
12. Goss, G., Rognoni, E., Salameti, V. & Watt, F. M. Distinct Fibroblast Lineages Give Rise to NG2+ Pericyte Populations in Mouse Skin Development and Repair. *Front. Cell Dev. Biol.* **9**, 675080 (2021).
13. Ruiz-Villalba, A. et al. Interacting resident epicardium-derived fibroblasts and recruited bone marrow cells form myocardial infarction scar. *J. Am. Coll. Cardiol.* **65**, 2057–2066 (2015).
14. Perez-Pomares J. M. et al. Wt1 + /Itga4+ progenitors drive epicardial-derived cell expansion via non-canonical Wnt signaling. *Research Square*, preprint https://doi.org/10.21203/rs.3.rs-4842079/v1 (2024).
15. Kuppe, C. et al. Decoding myofibroblast origins in human kidney fibrosis. *Nature* **589**, 281–286 (2021).
16. Kuppe, C. et al. Spatial multi-omic map of human myocardial infarction. *Nature* **608**, 766–777 (2022).
17. Tsukui, T. et al. Collagen-producing lung cell atlas identifies multiple subsets with distinct localization and relevance to fibrosis. *Nat. Commun.* **11**, 1920 (2020).
18. Ruiz-Villalba, A. et al. Single-Cell RNA Sequencing Analysis Reveals a Crucial Role for CTHRC1 (Collagen Triple Helix Repeat Containing 1) Cardiac Fibroblasts After Myocardial Infarction. *Circulation* **42**, 1831–1847 (2020).
19. Buckley, C. D. & Midwood, K. S. Tracing the origins of lung fibrosis. *Nat. Immunol.* **25**, 1517–1519 (2024).

20. Cao, M., Ke, D. & Zhou, H. The role and molecular mechanism of CTHRC1 in fibrosis. *Life Sci* **350**, 122745 (2024).
21. Tsukui, T., Wolters, P. J. & Sheppard, D. Alveolar fibroblast lineage orchestrates lung inflammation and fibrosis. *Nature* **631**, 627–634 (2024).
22. Buechler, M. B. et al. Cross-tissue organization of the fibroblast lineage. *Nature* **593**, 575–579 (2021).
23. Mayr, C. H. et al. Sfrp1 inhibits lung fibroblast invasion during transition to injury-induced myofibroblasts. *Eur. Respir. J.* **63**, 2301326 (2024).
24. Burgy, O. et al. Fibroblast-derived extracellular vesicles contain SFRP1 and mediate pulmonary fibrosis. *JCI Insight* **9**, e168889 (2024).
25. Barkauskas, C. E. et al. Type 2 alveolar cells are stem cells in adult lung. *J. Clin. Invest.* **123**, 3025–3036 (2013).
26. Lang, N. J. et al. Ex vivo tissue perturbations coupled to single-cell RNA-seq reveal multilineage cell circuit dynamics in human lung fibrogenesis. *Sci. Trans. Med.* **15**, eadh0908 (2023).
27. Wang, F. et al. Regulation of epithelial transitional states in murine and human pulmonary fibrosis. *J. Clin. Invest.* **133**, e165612 (2023).
28. Kobayashi, Y. et al. Persistence of a regeneration-associated, transitional alveolar epithelial cell state in pulmonary fibrosis. *Nat. Cell Biol.* **22**, 934–946 (2020).
29. Konkimalla, A. et al. Transitional cell states sculpt tissue topology during lung regeneration. *Cell Stem Cell* **30**, 1486–1502.e9 (2023).
30. Molina, C. et al. Clonal expansion of alveolar fibroblast progeny drives pulmonary fibrosis in mouse models. *J. Clin. Invest. Aug.* **28**, e191826 (2025).
31. Jones, D. L. et al. An injury-induced mesenchymal-epithelial cell niche coordinates regenerative responses in the lung. *Science* **386**, eado5561 (2024).
32. Tager, A. M. et al. The lysophosphatidic acid receptor LPA1 links pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak. *Nat. Med.* **14**, 45–54 (2008).
33. Al-Hilal, T. A. et al. Durotaxis is a driver and potential therapeutic target in lung fibrosis and metastatic pancreatic cancer. *Nat. Cell Biol.* **27**, 1543–1554 (2025).
34. Mattner, L. F. et al. Phosphoproteomics of cellular mechanosensing reveals NFATC4 as a regulator of myofibroblast activity. bioRxiv 2023.02.13.528335; https://doi.org/10.1101/2023.02.13.528335.
35. Santos, A. & Lagares, D. Matrix stiffness: The conductor of organ fibrosis. *Curr. Rheumatol. Rep.* **20**, 2 (2018).
36. Merkt, W., Bueno, M., Mora, A. L. & Lagares, D. Senotherapeutics: Targeting senescence in idiopathic pulmonary fibrosis. *Semin. Cell Dev. Biol.* **101**, 104–110 (2020).
37. Lagares, D. et al. Targeted apoptosis of myofibroblasts with the BH3 mimetic ABT-263 reverses established fibrosis. *Sci. Transl. Med.* **9**, 420 (2017).
38. Perestrelo, A. R. et al. Multiscale analysis of extracellular matrix remodeling in the failing heart. *Circ. Res.* **128**, 24–38 (2021).
39. Martino, F. et al. The mechanical regulation of RNA binding protein hnRNPC in the failing heart. *Sci. Transl. Med.* **14**, eabo5715 (2022).
40. Rosell-García, T. et al. Differential cleavage of lysyl oxidase by the metalloproteinases BMP1 and ADAMTS2/14 regulates collagen binding through a tyrosine sulfate domain. *J. Biol. Chem.* **294**, 11087–11100 (2019).
41. Rosell-García, T., Rivas-Muñoz, S., Colige, A. & Rodriguez-Pascual, F. Cleavage of LOXL1 by BMP1 and ADAMTS14 Proteases Suggests a Role for Proteolytic Processing in the Regulation of LOXL1 Function. *Int. J. Mol. Sci.* **23**, 3285 (2022).
42. Apaydin, O., Altaikyzy, A., Filosa, A. & Sawamiphak, S. Alpha-1 adrenergic signaling drives cardiac regeneration via extracellular matrix remodeling transcriptional program in zebrafish macrophages. *Dev. Cell* **58**, 2460–2476.e7 (2023).
43. Masuo, K. & Lambert, G. W. Relationships of adrenoceptor polymorphisms with obesity. *J. Obes.* **2011**, 609485 (2011).
44. Gibb, A. A. et al. Glutaminolysis is essential for myofibroblast persistence and in vivo targeting reverses fibrosis and cardiac dysfunction in heart failure. *Circulation* **145**, 1625–1628 (2022).
45. Miguel, V., Ramos, R., García-Bermejo, L., Rodríguez-Puyol, D. & Lamas, S. The program of renal fibrogenesis is controlled by microRNAs regulating oxidative metabolism. *Redox Biol.* **40**, 101851 (2021).
46. Miguel, V. et al. Renal tubule Cpt1a overexpression protects from kidney fibrosis by restoring mitochondrial homeostasis. *J. Clin. Invest.* **131**, e140695 (2021).
47. Rey-Serra, C. et al. Reciprocal regulation between the molecular clock and kidney injury. *Life Sci. Alliance* **6**, e202201886 (2023).
48. Miguel, V. et al. Enhanced fatty acid oxidation through metformin and baicalin as therapy for COVID-19 and associated inflammatory states in lung and kidney. *Redox Biol.* **68**, 102957 (2023).
49. Li, X. et al. Inhibition of fatty acid oxidation enables heart regeneration in adult mice. *Nature* **622**, 619–626 (2023).
50. Rao, T. N. et al. JAK2-mutant hematopoietic cells display metabolic alterations that can be targeted to treat myeloproliferative neoplasms. *Blood* **134**, 1832–1846 (2019).
51. Rao, T. N. et al. JAK2-V617F and interferon-α induce megakaryocyte-biased stem cells characterized by decreased long-term functionality. *Blood* **137**, 2139–2151 (2021).
52. Sun, X., Nkennor, B., Mastikhina, O., Soon, K. & Nunes, S. S. Endothelium-mediated contributions to fibrosis. *Semin. Cell Dev. Biol.* **101**, 78–86 (2020).
53. Lu, D. et al. Endothelial-to-mesenchymal transition: New insights into vascular calcification. *Biochem. Pharmacol.* **213**, 115579 (2023).
54. Piera-Velazquez, S., Mendoza, F. A. & Jimenez, S. A. Endothelial to Mesenchymal Transition (EndoMT) in the Pathogenesis of Human Fibrotic Diseases. *J. Clin. Med.* **5**, 45 (2016).
55. Yoshimatsu, Y. & Watabe, T. Emerging roles of inflammation-mediated endothelial–mesenchymal transition in health and disease. *Inflamm. Regen.* **42**, 9 (2022).
56. Miguel, V., Lamas, S. & Espinosa-Diez, C. Role of non-coding-RNAs in response to environmental stressors and consequences on human health. *Redox Biol* **37**, 101580 (2020).
57. Hecker, L. et al. Reversal of persistent fibrosis in aging by targeting Nox4-Nrf2 redox imbalance. *Sci. Transl. Med.* **6**, 231ra47 (2014).
58. Kato, K. et al. Impaired myofibroblast dedifferentiation contributes to non-resolving fibrosis in aging. *Am. J. Respir. Cell Mol. Biol.* **62**, 633–644 (2020).
59. Meiners, S., Eickelberg, O. & Konigshoff, M. Hallmarks of the ageing lung. *Eur. Respir. J.* **45**, 807–827 (2015).
60. Alsafadi, H. N. et al. An ex vivo model to induce early fibrosis-like changes in human precision-cut lung slices. *Am. J. Physiol. Lung Cell Mol. Physiol.* **312**, L896–L902 (2017).
61. Lehmann, M. et al. Differential effects of Nintedanib and Pirfenidone on lung alveolar epithelial cell function in ex vivo murine and human lung tissue cultures of pulmonary fibrosis. *Respir. Res.* **19**, 175 (2018).
62. Lehmann, M. et al. Precision cut lung slices: emerging tools for preclinical and translational lung research. An Official American Thoracic Society Workshop Report. *Am. J. Respir. Cell Mol. Biol.* **72**, 16–31 (2024).
63. Melo-Narváez, M. C. et al. Stimuli-specific senescence of primary human lung fibroblasts modulates alveolar stem cell function. *Cells* **13**, 1129 (2024).
64. Graaf, I. A., Groothuis, G. M. & Olinga, P. Precision-cut tissue slices as a tool to predict metabolism of novel drugs. *Expert Opin. Drug Metab. Toxicol.* **3**, 879–898 (2007).
65. Niro, F. et al. Fibrotic extracellular matrix impacts cardiomyocyte phenotype and function in an iPSC-derived isogenic model of cardiac fibrosis. *Transl. Res.* **273**, 58–77 (2024).
66. Cáceres, R. A. et al. Reduction of cardiac TGFβ-mediated profibrotic events by inhibition of Hsp90 with engineered protein. *J. Mol. Cell Cardiol.* **123**, 75–87 (2018).

67. Aires, A. et al. Engineering multifunctional metal/protein hybrid nanomaterials as tools for therapeutic intervention and high-sensitivity detection. *Chem. Sci.* **12**, 2480–2487 (2020).
68. Groen, J. et al. Correlative 3D cryo X-ray imaging reveals intracellular location and effect of designed antifibrotic protein-nanomaterial hybrids. *Chem. Sci.* **12**, 15090–15103 (2021).
69. RuizdelRio, J. et al. Fibroblast-derived extracellular vesicles as trackable efficient transporters of an experimental nanodrug with fibrotic heart and lung targeting. *Theranostics* **14**, 176–202 (2024).
70. Poss, K. D. & Tanaka, E. M. Hallmarks of regeneration. *Cell Stem Cell* **31**, 1244–1261 (2024).
71. Yuan, X. & Braun, T. Amending the injured heart by in vivo reprogramming. *Curr. Opin. Genet. Dev.* **81**, 102098 (2023).
72. Lu, Q. & El-Hashash, A. H. K. Cell-based therapy for idiopathic pulmonary fibrosis. *Stem Cell Investig* **6**, 22 (2019).
73. Konkimalla, A., Tata, A. & Tata, P. R. Lung regeneration: cells, models, and mechanisms. *Cold Spring Harb. Perspect. Biol.* **14**, a040873 (2022).
74. Serrano-Mollar, A. et al. Safety and tolerability of alveolar type II cell transplantation in idiopathic pulmonary fibrosis. *Chest* **150**, 533–543 (2016).
75. Guillamat-Prats, R., Gay-Jordi, G., Xaubet, A., Peinado, V. I. & Serrano-Mollar, A. Alveolar type II cell transplantation restores pulmonary surfactant protein levels in lung fibrosis. *J. Heart Lung Transplant* **33**, 758–765 (2014).
76. Serrano-Mollar, A. et al. Intratracheal transplantation of alveolar type II cells reverses bleomycin-induced lung fibrosis. *Am. J. Respir. Crit. Care Med.* **176**, 1261–1268 (2007).
77. Yücel, A. D. & Gladyshev, V. N. The long and winding road of reprogramming-induced rejuvenation. *Nat. Commun.* **15**, 1941 (2024).
78. Takahashi, K. & Yamanaka, S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* **126**, 663–676 (2006).
79. Abad, M. et al. Reprogramming in vivo produces teratomas and iPS cells with totipotency features. *Nature* **502**, 340–345 (2013).
80. Ohnishi, K. et al. Premature termination of reprogramming in vivo leads to cancer development through altered epigenetic regulation. *Cell* **156**, 663–677 (2014).
81. Mosteiro, L. et al. Tissue damage and senescence provide critical signals for cellular reprogramming in vivo. *Science* **354**, aaf4445 (2016).
82. Chondronasiou, D. et al. Deciphering the roadmap of in vivo reprogramming toward pluripotency. *Stem Cell Rep.* **17**, 2501–2517 (2022).
83. Kovatcheva, M. et al. Vitamin B_{12} is a limiting factor for induced cellular plasticity and tissue repair. *Nat. Metab.* **5**, 1911–1930 (2023).
84. Chondronasio, D. et al. Multi-omic rejuvenation of naturally aged tissues by a single cycle of transient reprogramming. *Aging Cell* **21**, e13578 (2022).
85. Chen, Y. et al. Reversible reprogramming of cardiomyocytes to a fetal state drives heart regeneration in mice. *Science* **373**, 1537–1540 (2021).

Acknowledgements

We thank all of the speakers of the workshop for their contribution at the meeting kindly sharing their research and knowledge and for their committed revision of the manuscript. We wish to extend our thanks to our institutions (University of Málaga /IBIMA and Institute for Lung Health, JLU Giessen) that supported the workshop, as well as all the sponsors of the workshop (BonsaiLab, Dicsa, Proquinorte, Izasa Scientific, The Company of Biologists, and Fibrosis) and all the personnel involved in its organization.

Author contributions

A.R-V. and A.P-S. equally wrote and edit the manuscript summarizing the content presented and discussed at the workshop.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Adrián. Ruiz-Villalba or Ana Pardo-Saganta.