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Review

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ECM formation and degradation during fibrosis, repair, and regeneration

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Imperfect attempts at organ repair after repeated injury result in aberrant formation of extracellular matrix (ECM) and loss of tissue structure. This abnormal ECM goes from being a consequence of cellular dysregulation to become the backbone of a persistently fibrotic cell niche that compromises organic function and ultimately drives systemic disease. Here, we review our current understanding of the structure of the ECM, the mechanisms behind organ-specific fibrosis, resolution, healing and regeneration, as well as the development of anti-fibrotic strategies. We also discuss the design of biomarkers to investigate fibrosis pathophysiology, track fibrosis progression, systemic damage, and fibrosis resolution.

The organized complexity of the extracellular matrix

The mechano-chemical properties of the extracellular matrix (ECM) (Fig. 1) are necessary for cells to differentiate, specialize, locate themselves in relation to other cell populations, and build the functional units that characterize multicellular anatomy. There is a reciprocity between function, developmental stage and ECM structure that results in specialized ECMs, where components are connected in organ- and stage-specific patterns[1]. These ECMs are made of different protein combinations[2] with different turnover cycles, dependent on strictly regulated building, dismantling, and remodeling cycles.

Pioneering work on Mass Spectrometry (MS) has cataloged ECM components (the matrisome), divided in core-matrisome (~300) and matrisome-associated proteins (~1000)[2]. The core-matrisome, or structural ECM proteins, includes 28 collagens, elastin, fibronectin, and laminin isoforms, as well as proteoglycans (like perlecan) and glycoproteins (like nidogens). Matrisome-associated proteins regulate ECM structure (e.g., proteolytic enzymes, matrix metalloproteinases-MMP, etc) but are also controlled by ECM, e.g., transforming growth factor beta, (TGF-β), vascular endothelial growth factor, (VEGF) superfamilies, other growth factors and cytokines[2,3]. The emergence of spatial proteomics and 3D ECM mapping[4–6] is revealing the 3D structure of the ECM, showing that healthy and diseased tissue share ECM components, but their amount, distribution, density, and articulation in space differs. It is likely that functional units within an organ (e.g., nerve trunks and terminals, vessels, specialized structures like follicles, glomeruli, alveoli, or acini) have a function-specific ECM[6]. This seems to be the case of capillary follicles and skin[7,8].

ECM structure is generally divided in two compartments (Fig. 1): Basement Membrane (BM) and Interstitial Matrix (IM). BM is a cloth-like surface, adhesive to epithelia, glandular epithelia, endothelium, myocytes, and adipocytes, among other cells[5]. The BM is based on a Collagen type IV backbone supporting a Laminin surface[9]. Glycoproteins, such as Nidogens and Perlecan, bind the Laminin and Collagen type IV layers. Others, like Netrin-4, regulate BM mechanical properties[10].

IM is structured by fibrillar collagens (type I, II, III, V) and elastin. In turn, collagen fibrils are bridged by Fibril-associated Collagens with Interrupted Triple Helices (reviewed elsewhere[11]) and linked to the BM by non-fibrillar collagens, like Collagen type VII[12]. Fibronectin (reviewed here[13,14]), regulates ECM assembly, collagen fiber assembly, embryo development, and is also critical during wound healing, ECM maturation and cancer progression. Cell-secreted fibronectin is a mediator of scar tissue formation[15]. Upon fibrosis progression, IM undergoes extensive remodeling, notably, abundant cross-linking mediated by enzyme families, like transglutaminases and lysyl-oxidases[16], and collagen glycation, a process associated to diabetes and aging[17]. The overgrowth of crosslinked collagen results in a stiff, more viscoelastic[18], linearized IM with deleterious consequences for disease progression[19].

ECM stores and releases growth factors, cytokines, and bioactive peptides, controlling their location, density, and activity. Fibronectin binds VEGF, hepatocyte growth factor (HGF), platelet-derived growth factors (PDGF), among others, and growth factor-binding domains are abundant in matrisomal proteins[3]. Injury responses can, by increasing binding sites, signaling oligopeptides, and structural domains, enhance fibrogenesis as

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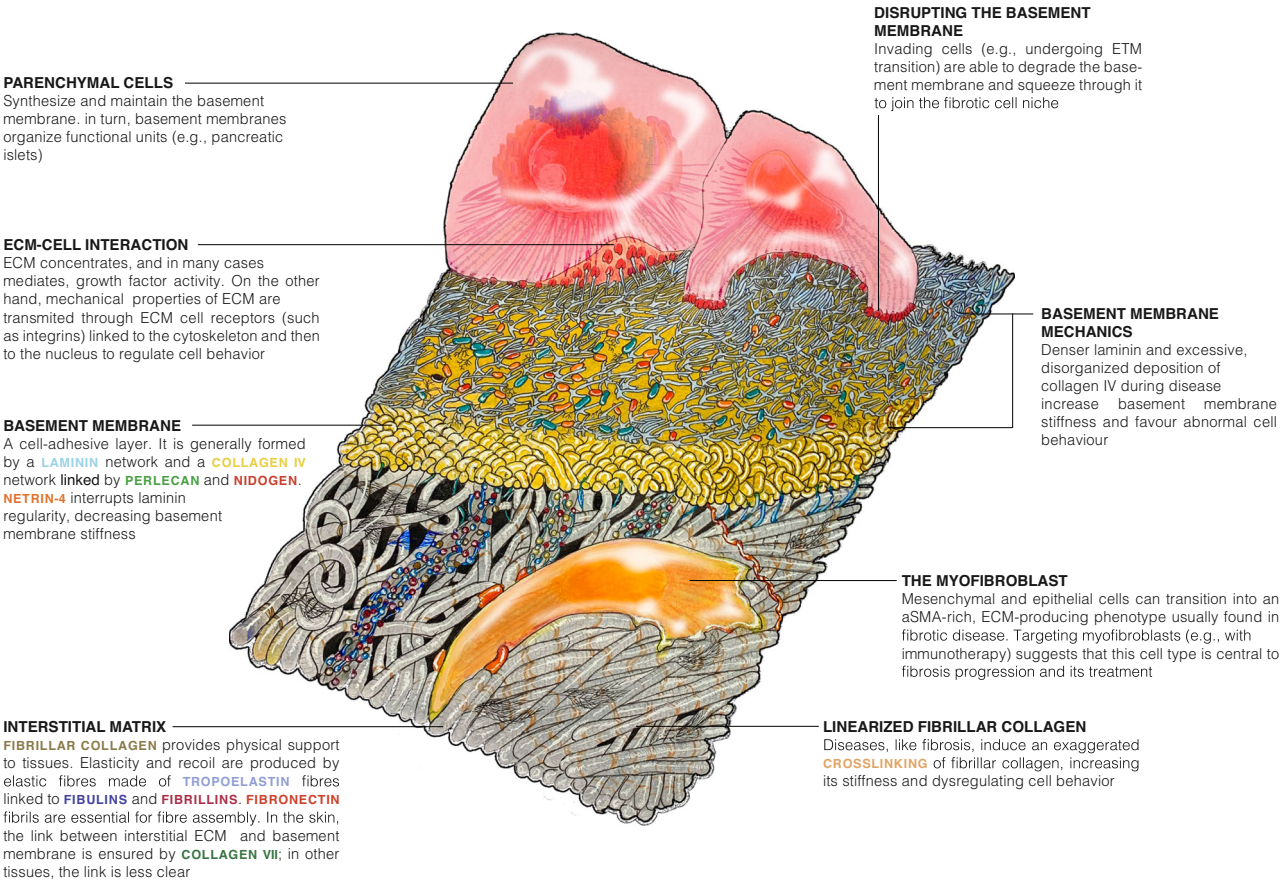

Fig. 1 | A schematic of ECM structure. Although ECM is organ specific, there are characteristics that are common to most tissues, like the presence of a basement membrane and an interstitial matrix. Equally, disease may induce *sui generis* remodeling, abnormal formation and degradation are shared by several conditions (e.g., IPF, MASLD, COPD, etc.).

well as mechanosignaling[20]. Pioneering experiments exposing radiolabeled PDGF isoforms keratinocyte growth factor and HGF to collagen chains demonstrated binding to collagens type I, III, IV, V, and VI as well as preserved growth factor bioactivity[21–23]. The affinity of collagen domains extends to inflammatory mediators and cytokines (e.g., interleukin-2, oncostatin)[24,25]. Isolating cell-ECM structure interactions in an ECM scaffold-based bioreactor shows that kinase activity (including growth-factor activity) and cell-driven ECM remodeling follow anatomical cues, supporting the notion of positional regulation[26]. Therefore, the ECM acts as a spatial regulator of cellular activity.

By-products of ECM protein synthesis add an additional layer of complexity to ECM dynamics. These by-products can be bioactive, paracrine, and endocrine regulators[27]. Collectively, they are called matrikines[28]. Notable examples of this family[29] include endotrophin, a pro-peptide of collagen type VI, linked to visceral adipose tissue (VAT) dysregulation, including fibrosis, leading to metabolic disorders[30]; endostatin, a pro-peptide of collagen type XVIII that is an endogenous inhibitor of angiogenesis[31] and potentially fibrogenesis[32]; and tumstatin[33], a collagen type IV pro-peptide, that suppresses inflammation and angiogenesis, and therefore has been shown to play a regulatory role in multiple inflammatory and oncogenic conditions.

Balance and imbalance between tissue formation and destruction

All possible combinations of ECM proteins in presence, abundance, and density could suggest high ECM variability[34], yet normal development[35] and adult homeostasis follow predictable patterns. The relative pathological regularity of fibrosis serves as an indicator of disease stage[36] and suggests the existence of organ- and disease-specific (rather than patient-specific) variations of ECM topography. This notion has important implications: there is considerable evidence pointing to the ECM as a key source of cellular regulation, thus, fibrotic ECM has been identified as an actor, not a bystander, of disease progression[37,38]. As the structure of fibrosis is largely predictable, so should be the biological effects of that structure[39,40]. These mechanisms seem to depend on context: an example is the function of the TGF-β superfamily[41]. The latent form of TGF-β1 is bound by ECM structure, however, TGF-β1 signaling is swayed by its binding substrate, e.g., binding to Fibulin 4 decreases TGF-β1 signaling[42], while binding to Fibulin 2 enhances TGF-β1[43]. Moreover, TGF-β1 is also bound and regulated by Fibrillins[44], Fibronectin[45], among others[46,47]. Similarly complex interactions are likely the norm for growth factors[48].

Cumulative damage resulting from aging[49], injury[50,51], acute[52,53], chronic disease[54,55] can interact with reparative reactions, including inflammation[56], metabolic dysregulation[57] and immune response[58], to incline the ECM balance towards fibrogenesis and overgrowth[59]. Some organisms respond to injury by recreating the original tissue[60], mammalians however appear to have only a very partial version of this ability, most of it lost after birth[61]. With few exceptions, skewed ECM formation results in fibrotic scars.

Fibrosis can be staged histologically by scoring it in biopsies[62], or non-invasively by using imaging techniques[63], to measure organ biomechanics[64] and by probing biochemical variables (or biomarkers) that track fibrosis progression[65,66]. Importantly, biomarkers have helped establish a distinction between staging disease severity and assessing the dynamics of disease activity[67]. Staging describes the net result of fibrotic accumulation, while biomarkers of fibrogenesis, a measure of disease activity, open a window on the timing and rhythm of disease progression, revealing periods of quiescence as well as bouts of ECM remodeling or accumulation. In advanced

disease, these bouts may determine the prognosis of a patient. Differences in etiology and fibrogenic activity in advanced fibrosis also reveal patient heterogeneity, leading to further advantages of using biomarkers in a personalized approach: selecting patients according to disease (and fibrosis) endotype and, it follows, determining whether a treatment affects fibrogenesis or fibrous tissue degradation during periods of ECM remodeling (Fig. 2).

Recent progress in drug development, in research and in clinical trials, shows that it is possible to modulate the balance between ECM formation and degradation and removal[68–70], raising new questions about mammalian and human ability to resolve fibrosis, and then initiate a program of functional tissue repair and regeneration. This progress must be matched by biomarkers designed to detect, differentiate, and quantify disparate processes dynamically. Such biomarkers should become useful tools for development and efficacy monitoring of antifibrotic and pro-regenerative therapies.

Core mechanisms of fibrosis

"Core" pro-fibrotic mechanisms[71] are myofibroblast-associated pathways found in different fibroses. A bare bones myofibroblast definition could be that of an "activated" mesenchymal cell characterized by a dense α-smooth muscle actin (αSMA) cytoskeleton, enhanced contractility, and ECM protein overexpression. Myofibroblast progenitors can be traced to be adipocytes[72], pericytes[73], smooth muscle cells[74], immune cells[75], mesenchymal stem cells[76], endothelium[77], epithelia[78], bone-marrow derived and organ-specific fibroblasts[79]. This heterogeneity suggests that more than a cell type, "myofibroblast" may denote a behavior. Myofibroblast activation largely depends on a signaling network that hovers around the TGF-β superfamily[41,79], beginning with the release of TGF-β1 from the TGF-β latency associated peptide (LAP) in the ECM, prompted by multiple mechanisms, including mechanical stress sensing by the LAP-binding integrins αVβ1 on myofibroblasts and αvβ6 on activated epithelia[80,81], binding to TGF-β receptors 1 and 2, canonical SMAD signaling, translocation of SMAD2, SMAD3 and SMAD4 to the nucleus and promotion of the genes encoding αSMA (*ACTA2*) and ECM proteins. Other pathways also lead to activation: TGF-β2[82,83] and TGF-β3[84], and non-canonical TGF-β signaling through mitogen-activated protein (MAP) kinase[85].

Signaling and mechanical changes are linked. Injury attracts fibroblasts, and they contract injured tissue, increasing stiffness. An initially soft ECM is then substituted by scar tissue (discussed below) rich in fibronectin and collagen crosslinked by transglutaminases[86] and lysyl oxidases[87,88]. Myofibroblasts transmit and perceive force through cell surface receptors, notably integrins[87], discoid domain receptors (DDR)[89], vanilloid receptors[90], G-protein coupled receptors[91], and hyaluronan receptor CD44[92] Cell-ECM contact induces the synthesis of cytoskeleton proteins and cell adhesion complexes, calling for further ECM contraction. Integrins αvβ1, αvβ3, αvβ5 and αvβ6 activate latent TGF-β by mechanically pulling LAP[79], thus linking both biochemical and mechanical signaling in one positive activation loop. The ADAMTS (A disintegrin-like and metalloproteinase with thrombospondin motifs) superfamily has 19 members that remodel the ECM, partly by cleaving latent TGF-β complexes, changing cell mechanics, and increasing tension as well as TGF-β release[93]. A subgroup of ADAMTS members bind to fibrillin and fibronectin[94], belong in the fibrillin microfibril niche, a mechanosensing hub, and regulate elastic fiber assembly through TGF-β[95]. ADAMTS-like 2 variants produce geleophysic dysplasia, a syndrome associated to cardiac and interstitial fibrosis[96], and is overexpressed in adults with chronic liver disease[97]. Recessive mutations in ADAMTS10 can cause Weill-Marchesani Syndrome, associated with cardiac fibrosis[98].

The TGF-β superfamily also includes a subgroup of cytokines, activins, that bind to membrane receptors (activin receptors type I and II) to phosphorylate the activin-like kinase 4 (ALK4), which in turn phosphorylates Smad proteins 2 and 3 to transduce activin signaling into the nucleus[99]. Activin action is downregulated by follistatins, which bind to the ECM (e.g., to heparan sulfate proteoglycans)[100] and trap activin, so it can be cleaved by proteolysis. Activin upregulation results in follistatin overexpression and activin attenuation. The activin-follistatin system is implicated in scarring and regeneration across several organs. In the liver, activin is overexpressed in models of liver fibrosis, activating hepatic stellate cells (HSCs)[101], whilst Follistatin blocks activin and inhibits TGF-β signaling as well as collagen production[102]. In the kidneys, activin is overexpressed after injury and during kidney fibrosis, mimicking TGF-β signaling and hampering regeneration[103], but follistatin blockade promotes epithelial proliferation and repair[104]. In the lungs, activin promotes myofibroblast proliferation, ECM formation, and TGF-β overexpression, which in turn induces activin, creating a persistent fibrotic niche[99]. Follistatin gene therapy has been trialed for Becker muscular dystrophy, resulting in reduced muscle fibrosis and muscle performance improvement[105]. Activin A inhibition with a monoclonal antibody (Garetosmab[106]) reduces new heterotopic bone lesion formation in fibrodysplasia ossificans progressive. Sotatercept, an activin inhibitor, reduced the risk of death in patients with pulmonary arterial hypertension[107].

The Wnt/ β-catenin pathway can also drive fibrogenesis. Wnt is a homolog of integrase-1 and the wingless gene in *Drosophila*[108]. There are 19 Wnt proteins, essential for development and homeostasis. The canonical Wnt pathway involves binding to the Frizzled (FZD) transmembrane receptors, the translocation of β-catenin into the cell nucleus, and activation of target genes by transcription factors T-cell factor (TCF) and Lymphoid enhancer factor (Reviewed extensively in[109]). The Wnt/β-catenin pathway is activated in fibrogenic diseases. Wnt1, Wnt7b, Wnt10b, FZD2, FZD3, β-catenin are overexpressed during idiopathic pulmonary fibrosis (IPF), a disease marked by the overproduction of ECM. Wnt in pulmonary fibrosis promotes fibroblast proliferation, recruitment and activation[110]. Interestingly, chronic obstructive pulmonary disease (COPD) a disease marked by alveolar ECM destruction, has reduced Wnt/β-catenin activity[111]. Activation of Wnt/β-catenin seems to attenuate COPD progression[112]. Wnt/β-catenin can be controlled by TGF-β and thus promote myofibroblast differentiation[113]. Monoclonal antibodies Vantictumab and Ipafricept block Wnt to FZD receptors and decrease human tumor growth[114]. β-catenin inhibitors, ICG-001 and PRI-724 reduce markers of fibrogenesis and myofibroblast differentiation, collagen, and inflammation[115].

Organ-specific fibrosis, fibrosis resolution, and the perspective of regeneration

Human regenerative capacity is limited, but there are examples of complete regeneration in nature that serve as experimental models and point to the mechanisms humans lack: *Hofstenia miamia*, an Acoel worm, can regenerate its whole body[116], the sea slug *Elysia cf. marginata* self-decapitates to grow a new body[117], the axolotl (*Ambystoma mexicanum*) can grow an exact replica of almost any tissue[118,119], and the Zebra fish (*Danio rerio*) can regenerate organs upon mutilation[120]. Sequencing the Acoel genome uncovered Early Growth Response (*egr*), a master control gene induced by mutilation that epigenetically regulates other wound control response genes (vertebrates bear homologs of *egr*)[116]. Zebra fish respond to amputation with the formation of a "blastema", a mass of undifferentiated cells that proliferate and specialize to regenerate tissue. Remarkably, epigenetic control exerted by the Kdm6b.1 demethylase over zebra fish genes, associated to embryonic patterning, switches on after injury, activating regenerative programs[121].

The discovery of scarless healing[122] established that regeneration exists in mammalians but vanishes as intrauterine development ends[123]. After injury, fetal coagulation forms porous clots that are weakly crosslinked[122], followed by the deposition of an ECM with a higher collagen type III to collagen type I ratio[123]. Fetal wound ECM lacks oxidative stress[15]. TGF-β1 and TGF-β3, regulate the injury response in mammalians but seem to play opposite roles. TGF-β1 is central to the activation of fibroblasts[41], while TGF-β3 can be anti-fibrotic[124]. Both bind to multiple ECM sites[125], but only TGF-β1 becomes activated by increasing ECM stiffness[126]. Moreover, while

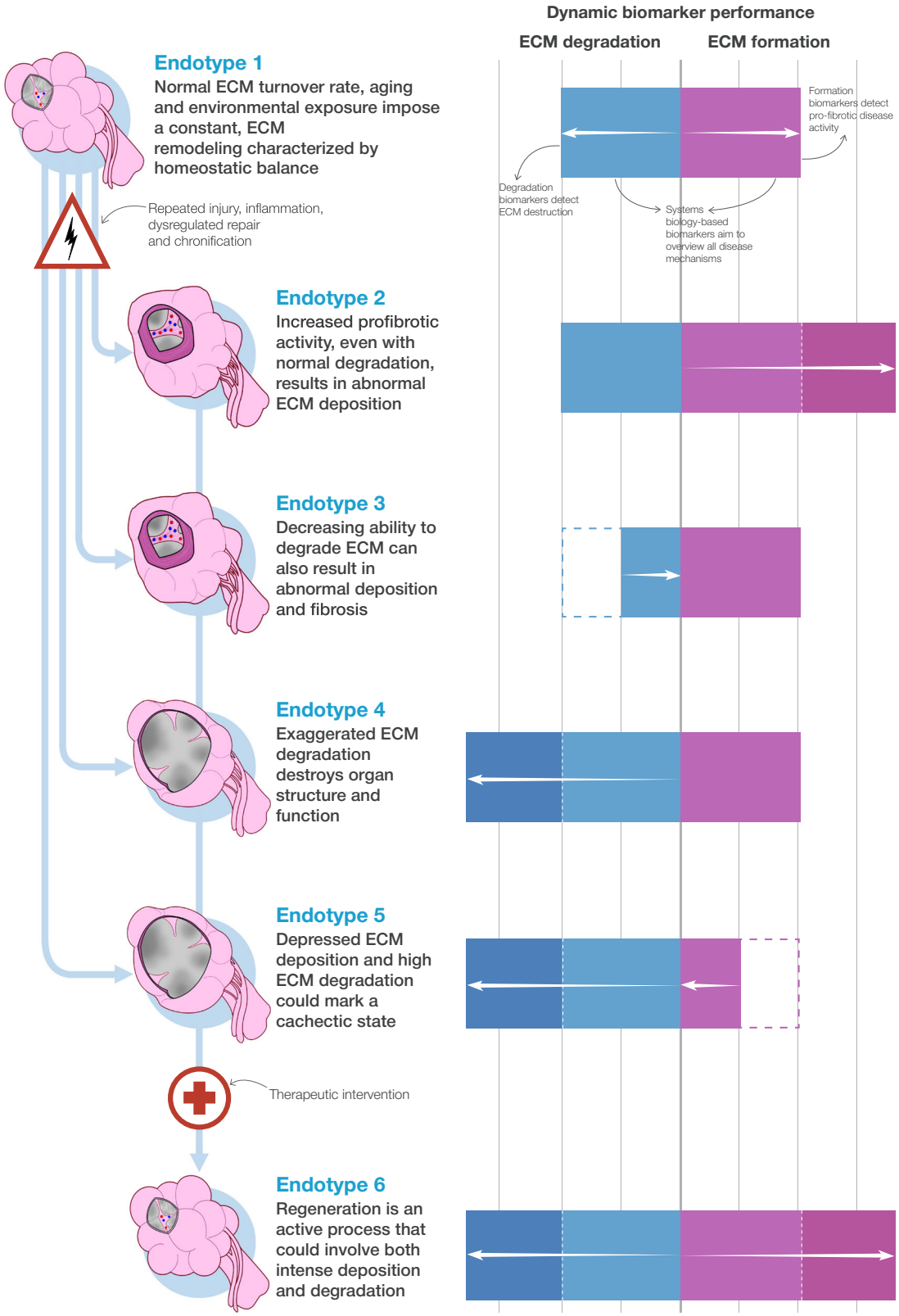

Fig. 2 | The balance between ECM formation and degradation. Homeostatic balance can be broken by repeated injury (infection, environmental exposure, physical or chemical insult, mutations, etc.) and subsequent, insufficient, dysregulated reparative response. How this balance tilts towards determines a distinct functional disruption (endotype). Dynamic biomarkers should identify these endotypes and the activities driving disease as well as a potential regeneration.

TGF-β1 is only shortly activated after injury in fetuses, it persists in adults. TGF-β3 is only briefly activated at the end of adult scarring. It is notable that scarless healing disappears as the mature immune response emerges[127]. Mechanosignaling plays a role in switching the repair response towards scar formation, via activation of Engrailed 1 (*En1*) in fibroblasts by injury. High stiffness produces fibrotic scars, but low stiffness and inhibition of the Yes-associated protein favors scarless healing and recreation of specialized structures[128]. ECM abnormalities in adult animals (e.g., increasing stiffness)

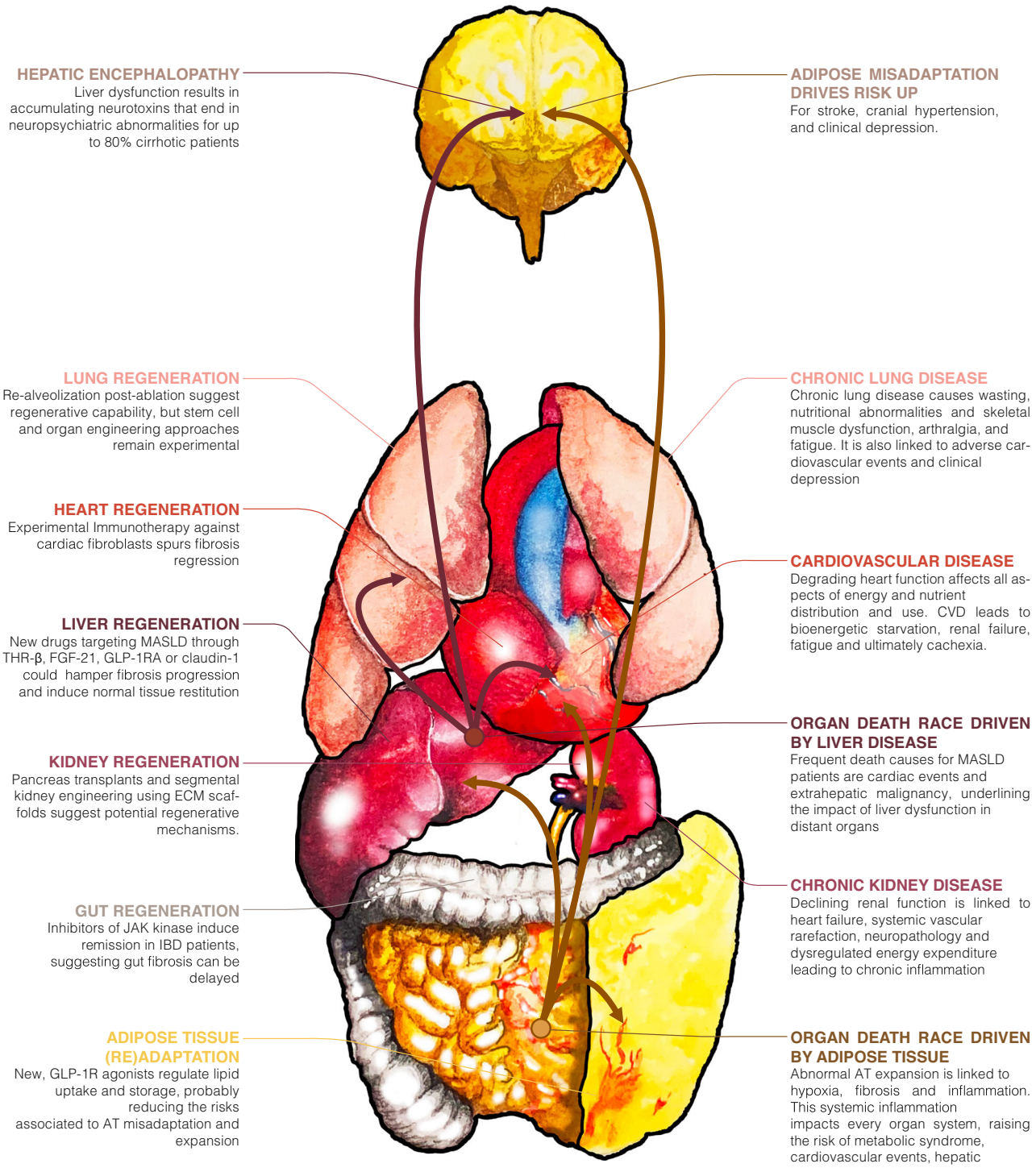

Fig. 3 | Local ECM-associated disease drives systemic dysfunction, but new therapies can revert the course. Schematic highlighting the state-of-the-art of organ regeneration technology (left), and the "Organ death races" that are triggered by local, ECM-associated disease, emphasizing liver and adipose tissue as sources of syndrome-like and ultimately lethal events (right).

deregulate fibroblast signaling, enhancing their survival by activating RAS (derived from rat sarcoma virus) activity[129], while controlling multipotency in epithelial lineages[130]. Regenerative mechanisms seem to be absent in post-fetal mammalians[121] and are certainly lacking in humans, but our regenerative plasticity, while limited, is not non-existent (Fig. 3). Human regeneration is heterogeneous, with high variation along developmental stages and among organs.

Liver

In mammalians, the liver stands out for its ability to regenerate completely from a loss of up to 75% of its mass, until it reaches at least 85% of hepatocyte function[131]. This process can be completed in less than 2 weeks[132]. In contrast, injury to the myocardium frequently results in the formation of a non-functional scar[133]. Livers recur to specialized repair mechanisms to maintain hepatic function after injury or hepatectomy[134]. Liver injury triggers the

urokinase-type plasminogen (uPA) activator[135] and matrix metalloproteinases to start ECM degradation and remodeling[136]. uPA leads to the release of HGF bound to ECM[22,137,138]. A subpopulation of annexin 2 (ANXA2) positive hepatocytes[139] has been shown to respond to HGF and drive the regenerative response to injury. This seems to coincide with a coordinated proliferation of hepatocytes, which proceeds from the portal spaces towards the central vein[140], although tracing reveals proliferating hepatocytes to be more abundant in zone 2 of the hepatic lobule[141]. ECM composition seems to run a parallel course to hepatocytes: pioneering data compiled in rat models[134,142] suggest that ECM gene expression patterns are choreographed, successively increasing proteoglycan expression, tissue inhibitor of metalloproteinase 1 (TIMP-1), and then interstitial collagens type I and III.

A cohort of patients with MASLD and treated with bariatric surgery saw fibrosis regressing in 70% of all participants after 5 years, including resolution in 45% of patients with advanced fibrosis at baseline[143]. Bariatric surgery reduces the expression of pro-fibrotic genes[144] as part of a vast impact on metabolic and endocrine physiology that includes decreased levels of the "hunger hormone" Ghrelin, the "satiety hormone" leptin and pro-inflammatory cytokines like Tumor Necrosis Factor Alpha (TNF-a)[145]. Remarkably, patients with chronic hepatitis B virus and cirrhosis at baseline regressed their histological fibrosis staging and were diagnosed as non-cirrhotic after long-term treatment with tenofovir[146]. Similar results seem to be mirrored in patients with hepatitis C[147]. Together, these results suggest liver fibrosis to be reversible (Fig. 3). Moreover, newer therapies appear on the immediate horizon[148]. Dual agonists of the glucagon receptor and the glucagon-like peptide-1 (GLP-1) produce fibrosis regression in up to one third of MASH patients[149] and fibroblast growth factor 21 (FGF21) analogs also improve fibrosis in MASH[150]. New mechanisms keep being dissected, e.g., targeting claudin-1 a component of tight cell junctions, has been shown to be an anti-fibrotic strategy[151].

Liver biomarkers have advanced apace. The enhanced liver fibrosis test (ELF)[152], a composite biomarker synthesizing blood levels of the tissue inhibitor of metalloproteinase-1 (TIMP-1), procollagen III amino terminal peptide (PIIINP) and hyaluronic acid (HA), and the N-terminal of procollagen type III (PRO-C3)[153] are routinely used in the clinical evaluation of chronic liver disease and in drug development, to diagnose, prognosticate, measure disease activity and evaluate drug effect[70,148,154].

Heart

Upon insult, the adult myocardium answers with fibrogenesis, not regeneration[155,156]. Nonetheless, adult cardiomyocytes can re-enter the cell cycle, and conclusive evidence emerged from an elegant study that measured carbon-14 incorporation in cardiomyocytes from individuals born around the partial ban in nuclear testing of 1963[157], when environmental isotope levels decreased exponentially. The key finding established that ≈0.5-1% of adult human cardiomyocytes re-enter the cell cycle per year, not enough to sustain regeneration.

The key to heart regeneration may not be in its beating cells, but in those maintaining its structure (Fig. 3). Scar-building cells in the heart come from resident fibroblasts[158], recruited bone marrow progenitors (fibrocytes), and endothelial cells that complete endothelial-mesenchymal transition. They become myofibroblasts under TGF-β signaling[159]. These cells depose ECM after being exposed to hypoxia or inflammatory cytokines like interleukin-2 and tumor necrosis factor[160], but in another example of the contextual nature of fibrosis, the persistence of myofibroblasts is not necessarily damaging. Mice engineered to produce myofibroblast-rich post-infarction tissue showed reduced scar formation[161]. Still, groundbreaking work[162] in cardiac fibroblasts engineered to express ovoalbumin peptide to mark them as targets for CAR (chimeric antigen receptor) CD8+ T-cells (i.e., anti-fibroblast immunotherapy) led to a reduction of cardiac fibrotic injury. Tantalizingly, fibrillar collagen deposition was reduced in treated hearts that showed histologically normal myocardium, suggesting that a restitution of normal architecture could take place after eliminating the cells producing abnormal ECM. The optimal window for such a therapy needs to be determined.

Cardiac biomarkers are extensively reviewed elsewhere[163,164]. Benchmark biomarkers include B-type natriuretic peptide (BNP) and N-terminal BNP (NT-proBNP) (diagnostic and prognostic in heart failure patients), cardiac troponins (myocardial necrosis), Suppression of Tumorigenicity (ST2), an interleukin receptor upregulated in response to injury (prognostic for heart failure), Galectin-3, a lectin, that marks cardiac fibroblastic activity and C-terminal type VIa3 pro-collagen (PRO-C6), prognostic in heart failure with preserved ejection fraction[165].

Lungs

Like the heart, the lungs are subject to constant mechanical demands fulfilled by a highly specialized ECM (Fig. 3). Unlike the heart, the lungs are directly exposed to a variety of environmental irritants that can trigger the destruction of normal ECM structure and its substitution by excessive scar tissue (e.g., interstitial lung disease- ILD) or a protracted dismantling of pulmonary airways and alveoli (emphysema in COPD).

In ILD, functional parenchyma is gradually substituted by an ECM that reduces alveolar area to dysfunctional remnants, while building a fibrotic callus. A prominent form of ILD, idiopathic pulmonary fibrosis (IPF)[166] has so far evaded mechanistic dissection. Repeated micro-injury to the alveolar epithelium[167] can work together with mutations in the surfactant protein gene (*SFTPC*) expressed by Alveolar Type 2 epithelial cells (AT2), intracellular accumulation of abnormal surfactant and cell senescence[168], including telomere dysfunction, to induce fibroblast-to-myofibroblast activation. More specifically, AT2 cells lose regenerative capacity during ILD, leading to their substitution by progenitor airway cells invading the alveoli[169]. These airway cells have basal cell (basaloid) characteristics, including keratin 17 production (KRT5-/KRT17+ cells) and expression of ECM genes[170] and locate on fibrotic lesions. Mechanochemical signaling is also associated to fibrosis development. Loss of the cell division control protein 42 homolog (*Cdc42*) in mice renders them unable to regenerate alveoli after pneumonectomy, which increases mechanical tension and triggers a TGF-β activation loop, driving peripheral fibrosis that advances toward the lung hilum[171].

Basic knowledge is being gradually translated to the clinic. Pirfenidone inhibits TGFB signaling and collagen production[172]. In IPF patients, Pirfenidone slows disease progression and respiratory decline[173]. Nintedanib is a competitive inhibitor of non-receptor and receptor tyrosine kinases, including platelet derived growth factor receptor (PDGFR), fibroblast growth factor receptors 1, 2 and 3 and VEGF receptors 1, 2 and 3[174]. Nintedanib slows lung function decline but is not curative[175].

Functional tests are paramount in pulmonary drug development. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV), and 6-min walk distance are used along lung imaging, arterial gases diffusion and quality of life measurements. A non-invasive biomarker, plasma fibrinogen, was qualified as a drug development tool by the food and drugs administration (FDA)[153]. Another biomarker, Eosinophil count, has been instrumental in the development of new drugs to treat COPD exacerbations[176,177]. Novel markers, sensitive to ECM remodeling during lung disease are increasingly used to evaluate drug performance[66].

Kidney

At homeostasis, the potential plasticity of tubular epithelium translates into a capacity to repair the kidney parenchyma after acute injury, acting in concert with endothelium, fibroblasts, and macrophages, and through the activation of developmental pathways, like Notch, Wnt/B-catenin, SOX9 transcription factor, and the Sonic hedgehog pathway[178]. However, repeated aggression results in a maladaptive response to damage that subverts these pathways and ultimately results in the recruitment of pro-inflammatory cells, and the activation of myofibroblasts (including tubular epithelial cells that undergo mesenchymal-to-epithelial transition, resident mesenchymal cells, and fibroblasts)[179].

Once the bridge to chronic kidney disease (CKD) has been crossed reparative ability diminishes but is not completely erased. In diabetic patients suffering from CKD, pancreas transplantation reverted ECM

remodeling (more specifically, BM thickening, it is unclear if this process extends to the IM) after 10 years[180] (Fig. 3). In a porcine preclinical model, a nephrectomy followed by the implantation of a segment of decellularized ECM results in the recellularization of the matrix with structures reminiscent of glomeruli, vessels, and tubules[181]. Unfortunately, clinical progress toward the reversal of kidney fibrosis is still partial. Blocking TGF-β signaling, the main driver of ECM deposition, has shown no beneficial effect on kidney damage[182]. In type 2 diabetics with CKD however, GLP-1 inhibitors reduce the risk of death, heart and kidney outcomes[183].

Biomarkers of ECM remodeling and turnover assess kidney fibrosis progression[184]. Collagen type III turnover biomarkers PRO-C3 and C3M (a segment resulting from MMP-9 collagen type III cleavage) correlate with kidney fibrosis degree. C3M/creatinine ratio is highly discriminative for advanced kidney fibrosis[185]. Lysyl oxidase (LOX) crosslinks fibrillar collagen and is increased in patients with kidney fibrosis[186]. Dickkopf-related protein 3 (DKK-3) is a glycoprotein secreted upon tubular injury that promotes scarring that significantly predicts estimated glomerular filtration rate (eGFR) decline and identifies patients at high risk of CKD progression[187]. PRO-C6 is associated with kidney fibrosis and outcomes in acute kidney injury[188,189].

Gut

Inflammatory Bowel Disease (IBD, including its variants Crohn's Disease-(CD); and Ulcerative Colitis (UC) progression involves chronic inflammation and mucosal damage leading to abnormal ECM remodeling in the intestine[190–202]. This combination is called Fibro-inflammation, an emerging concept in IBD, covering processes related to immune cell activity, mucosal damage, intestinal fibrogenesis, and fibrosis resolution[203]. In late stages of fibro-inflammation, fibrosis progresses independently of inflammation, accompanied by visceral adipose tissue (creeping fat). Creeping fat has been associated with intestinal fibrosis progression and luminal narrowing[190] Along with fibrosis, CD produces a thickening of the muscularis layer at the expense of submucosal layers, hypertrophic nerve trunks and vessels with hyperplastic muscularity also leading to strictures[204]. Intestinal fibrosis is a clinical feature of UC but rarely causes strictures[205,206]. UC and CD-associated fibrosis has been associated with an absence of clinical response to anti-inflammatory treatments such as biologics and small molecules[207].

As in other organs, myofibroblasts are held responsible for ECM overproduction, and their activation depends on the interplay between fibroblasts, endothelium, epithelium, and immune cells. Single cell mRNA sequencing has begun to reveal the cellular complexity of these fibrosis/inflammation interactions: M2a macrophages are profibrotic, but regulatory M2c deactivate myofibroblasts and canonically activated M1 and M2a macrophages[208]. Similarly, T helper 2 cells are fibrogenic but T helper 1 cells are antifibrotic. This intricate cell niche is underpinned by a comparably complex molecular landscape, Pro-inflammatory interleukin family members IL-1, IL-6, IL-18, IL-33, and IL-36 have been associated to IBD[209], while TGF-β1 may be anti-inflammatory in IBD[209] but profibrotic, ushering myofibroblast activation and ECM formation[210]. An observational study describes TGF-β2 overexpression in human biopsies of ulcerative colitis patients[211]. Other factors that also stimulate myofibroblast proliferation, platelet derived growth factor subunit A (PDGFA), platelet derived growth factor subunit B (PDGFB), and insulin-like growth factor-1 (IGF-1)[212]. The molecular drivers of gut fibrosis are partly conditioned by the intestinal microbiota and the integrity of the gut barrier. Increased antibacterial antibodies are common in patients with CD[213] and antibiotic treatment leading to reduced bacterial diversity and numbers is anti-inflammatory (e.g., downregulating the expression of NF-κB, TGFβ and αSMA in the intestinal wall)[214]. The nature of the immune reaction invoked also plays a role, for example by downregulating eosinophil frequency and altering their function, resulting in fibrogenesis and defective repair[215]. Neutrophils, and their extracellular traps (NET) have been implicated in IBD[216] and in intestinal fibrogenesis. NETs enhance fibroblast differentiation into myofibroblast and increase collagen production in vitro[217]. *Escherichia coli* sp. exacerbate fibrosis and inflammation in mice, including epithelial-myofibroblast transition[218]. In humans, bacterial products like outer-membrane protein C, flagellin and Saccaromyces cerevisiae are associated with CD progression and surgery[219,220]. Conversely, *Lactobacillus acidophilus* decreases αSMA and collagen deposition in mice[221]. Genetically modified *Lactococcus lactis* carrying Il-10 could impair colitis activity, showing that host-microbiota interaction and a compromised gut barrier could be leveraged to tread IBD[222]. The nature of the microbiome makes it suitable for systems biology biomarker approaches that detect bacterial species with dynamics that could be diagnostic for CD and UC[223], but they haven't substituted established non-invasive biomarkers like calprotectin, CRP, anti-neutrophil, and anti-S cerevisiae antibodies. Janus kinase inhibitor Upadacitinib induces endoscopic remission[224] and ECM remodeling[225], in a clinical trial of CD patients, suggesting the gut can engage repair processes upon treatment[194,226].

Adipose tissue

Fat deposits covering viscera and underlying the skin compose an endocrine organ that regulates metabolism, immunity, and homeostasis. Adipose tissue (AT) dysfunction has wide-ranging, systemic consequences, and fibrosis is both one of its sequels and drivers.

White adipose tissue (WAT) (Fig. 3) stores energy, while brown-beige (BAT) is thermogenic (i.e., it dissipates energy as heat)[227–229]. BAT sits in the paravertebral, axillary, supraclavicular, and periadrenal areas but WAT is widespread: subcutaneous fat lies beneath the dermis and represents ~80% of total body fat; visceral fat surrounds intrathoracic (e.g., pericardial, epicardial) and intraperitoneal organs (e.g., omental, mesenteric). AT secretes signaling polypeptides (adipokines) that regulate metabolism[230], e.g., adiponectin promotes insulin sensitivity[231], whilst resistin and lipocain promote insulin resistance[230]. It produces leptin, an adipokine that signals to the hypothalamus and other brain regions, promoting satiety and energy expenditure. Leptin resistance is associated to obesity[232]. WAT regulates immunity through pro-inflammatory cytokines TNF-a and interleukins 1B, 6, 8, and 18[230]. WAT deposits have different expansion-contraction patterns[233] and transcriptomic profiles[233], but expansion by hypertrophy is associated to hypoxia[234] and hypoxia-factor 1α (HIF1α) secretion, which in WAT calls for the transcription of ECM associated genes[235], fibrosis, and collagen crosslinking. This AT fibrotic response increases the synthesis of collagen type VI and collagen type VI C-terminal pro-collagen, endotrophin[236]. Collagen type VI correlates with insulin resistance in humans (ref), but interestingly, in $COL6^{-/-}$ animals, AT hypertrophy fails to invoke a fibrotic response, leading to a soft ECM, probably due to a decrease in circulating levels of endotrophin[30].

ECM formation in distant organs, downstream of AT expansion, is associated to ECM formation in distant organs. Approximately one third of systemic angiotensinogen is produced by WAT[237], activating angiotensin receptors (e.g., angiotensin 1b receptor) in the kidneys that are inflammatory in mice[238] and humans[239]. Overstimulation of leptin receptors in the kidney is associated to progressing renal disease[240] and overexpression of TGF-β1, collagen type IV, and fibronectin[241,242].

Another example of AT driving disease is gut creeping fat, which surrounds the exterior of the intestines wrapping the intestines. Creeping fat is linked to the release of pro-inflammatory cytokines and fibrotic mediators which enhance ECM remodeling and collagen deposition of the affected intestinal tissue and is highly associated with the development of intestinal fibrosis and strictures[226,243].

Skin

During homeostasis, adult epidermis regenerates continuously, turning over every 4–6 weeks[244,245] under the control of epidermal stem cells in the basal layer of the skin[246], however, upon injury, post-natal skin forms scar tissue, while fetal skin heals faster and regenerates completely[247]. Hypertrophic scars resulting from trauma (e.g., surgery, physical injury or loss of tissue integrity), are filled with parallelized collagen fibers in the upper skin, while another form of abnormal repair, keloids, proliferate beyond wound limits, accumulating disorganized collagen fibers sustained by angiogenesis[248–250]. Hypertrophic scars are amenable to surgical, laser,

physical or anti-inflammatory therapies. The same treatments are less effective in keloids. Both hypertrophic scars and keloids form exaggerated ECM structures, but different collagen organization, composition and proliferation dynamics suggest different cross-linking and pro-fibrotic mechanisms. Keloids are driven by persistent VEGF and TGF- β1 signaling accompanied by dysregulated syndecan and integrin signaling along with inflammation, but inflammation and fibrosis in hypertrophic scars are self-limiting[247,251,252].

Excessive collagen deposition and cross-linking are also characteristic of skin fibrosis during systemic sclerosis (SSc)[253]. SSc produces a thick dermis with remodeled hair follicles, sweat glands, and cutaneous blood vessels, accompanying systemic manifestations like adipose fibrosis[254,255]. The complex systemic progression of SSc, with multi-organ involvement and diffuse fibrosis, highlight the importance of biomarkers that predict disease evolution. SSc is an autoimmune disease, autoantibodies like Anti-topoisomerase I (ATAs) and anticentromere antibodies (ACAs) are found in around 95% of all SSc patients upon diagnosis[256–258]. ATAs (Anti-Scl-70 antibodies) have been associated with poorer prognosis, increased mortality, pulmonary fibrosis, and cardiac involvement[259–263]. However, auto-antibodies do not evaluate disease activity or its correlation to progressing fibrosis. Composite biomarkers like ELF[152], correlated with modified Rodnan Skin Score, a measure of skin fibrosis and thickness[264]. Blood MMP-12 is an indicator of skin fibrosis severity and blood IL-6 has been associated with pulmonary fibrosis, FVC decline, and increased mortality[265–267].

Biomarkers quantifying degraded collagens (C3M, C4M, C6M, and C7M), and Chemokine (C-C-motif) ligand 18 (CCL18), are lower in SSC patients treated with the autotaxin inhibitor Ziritazestat, showing impaired disease activity and fibrosis improvement[268]. Similarly, C3M, C4M and collagen synthesis biomarkers PRO-C4 and PRO-C3 were prognostic for worsening skin thickness in patients treated with an anti-IL-6 Ab (Tocilizumab)[269].

In contrast to SSc, Stiff skin syndrome (SSS) is non-inflammatory. SSS is characterized by thickened, indurated skin, and limited joint movement in the absence of systemic symptoms (such as Raynaud's phenomenon, peri-ungual changes, or visceral involvement)[270]. SSS also suffer persistent TGF-β1 signaling, leading to increased expression of COL1A1 and COL3A1[271]. SSS is extremely rare and no established guidelines for patient care exist, most patients are treated with immunosuppressive agents, with a high variation in treatment results.

Designing biomarkers for fibrosis, fibrosis-driven organ death races, and fibrosis resolution

The dysfunction that produces and sustains ECM structural alterations in an organ reverberates in the body, damaging distant tissues and triggering adverse events (Figs. 3, 4). Fibrotic disease in an organ can drive end-stage disease in distant organs, characterized by simultaneous ECM remodeling, albeit at different rates, and with considerable individual variation. Consider how Metabolic dysfunction-associated steatotic liver disease (MASLD, Fig. 4), closely linked to metabolic syndrome, and characterized by excess accumulation of lipids in the liver, inflammation/hepatocyte ballooning degeneration, and hepatic fibrosis[272,273] impacts multiple systems. Before developing cirrhosis, MASLD patients die of cardiovascular disease and extrahepatic cancer with more frequency than from a liver-related event[274,275] (Fig. 4).

Liver disease is by no means unique. Fibrotic progression in WAT is correlated with higher risks of infection[276], cancer (including breast, uterus, ovaries, colon, stomach, esophagus, rectum, liver, pancreas, kidney, meninges, and blood), metabolic, kidney, cardiovascular, and psychiatric disease.

Detecting, predicting, and tracking ECM formation or degradation is challenging. There are multiple molecular mechanisms and proteins involved, affecting tissues with different shape, function, resilience, and regenerative potential. Conceptually, a pharmacodynamic biomarker should either measure fibrogenic activity, i.e., determine the de novo formation of ECM proteins, or fibrolysis, i.e., ECM degradation and removal. A combination of such biomarkers could mirror the balance between fibrogenesis and fibrolysis. ECM biomarkers measure ECM component synthesis dynamically, reflecting how active fibrosis progression pathways are during measurement. They can discriminate between cumulative damage (which is the parameter assessed by a biopsy) and an actual snapshot of the biological status of the disease. Dynamic biomarkers would reflect distinct patient endotypes, characterized by different formation-degradation balances represented by different ECM parameters (Fig. 2).

There are different technological paths to build a biomarker strategy. One passes by combining large-scale biological data and data mining. Omics-based biomarker research have been gaining momentum with the establishment of national biobanks (including the UK Biobank[277], and Biobank Japan[278]) and disease specific international patient registries (including the European MASLD Registry[279]). These large databases have increased the depth, quality, and availability of Omics data as the cost of large-scale data generation has decreased, creating a conducive background for biomarker discovery. Mapping the human proteome[280,281] was a significant step towards assessing multiple molecular pathways simultaneously, opening a conceptual window into complex biological processes. Recently, leveraging RNA-seq and plasma proteomics resulted in organ-specific protein profiles that reveal tissue aging, thus building a proteomics-based biomarker strategy[282]. Plasma proteomics, used in Alcohol-related Liver Disease (ALD), detected circulating proteins associated to fibrosis and metabolic dysfunction, predictive of future liver-related events and all-cause mortality[283]. Complementary approaches in MASLD utilizing a proteo-transcriptomic strategy to characterize the liver-derived circulating proteome across the full disease spectrum[284]. However, there is evidence to suggest that different technologies (i.e., based on aptamers or antibodies) may affect protein quantification and comparability[285,286]. Epigenetics and metabolomics can also perform to a similar level: mapping DNA methylation in whole blood has found associations between disease, age, ancestry and all-cause mortality and specific cytosine-phosphate-guanine sequences, with substantial prognostic improvement for neoplasia-associated death[287]. A metabolomic platform found prognosticators all-cause mortality in a diverse population[288], identifying a panel of 14 metabolic biomarkers that could perform as well as conventional risk factors of mortality.

These panoramic approaches stand in contrast to individual and composite biomarkers supported by mechanistic research. Sensing post translational changes in a fundamental disease pathway is an effective biomarker strategy, with direct clinical impact. This is made evident by the FDA list of approved companion diagnostic devices, where single genetic biomarkers underpin decisions that have reduced disease burden and mortality for millions of cancer patients (e.g., BRCA1, BRCA2, HER1, HER2, KRAS, PD-L1, etc.[289]). A central feature of fibrosis is the formation of ECM, therefore, detecting fibrogenesis and ECM remodeling should be an obvious goal to assess disease activity. In particular, the intracellular synthesis of fibrillar procollagens is often followed by the cleavage of propeptides that are then released into the bloodstream. These procollagens have been proven to be a surrogate of several complex pathophysiological events involving increased ECM synthesis and turnover. PRO-C3[290], produced by fibroblasts as they deposit collagen type III, predicts fibrosis progression[153], reflects fibrosis stage[291], and can predict future lethal events[292], disease outcome[293], and importantly, monitors disease activity during and after therapeutic intervention[154] across cohorts subject to different diseases or treatments. Another example of a composite biomarker centered on ECM biology is the Enhanced Liver Fibrosis (ELF) score[152,294]. ELF measures the tissue inhibitor of metalloproteinases 1 (TIMP-1), hyaluronic acid (HA), and the N-terminal propeptide of procollagen type III (PIIINP). ELF predicts clinical outcome and event-free survival[295,296].

By-products of ECM remodeling can act as signaling messengers, driving fibrosis and metabolic dysfunction. Collagen type VI is a minor but ubiquitous, microfilamentous interstitial collagen of most organs, including the cardiovascular system and WAT, where it plays a role in the regulation of tissue expansion and WAT fibrosis[297]. In mice, a collagen V1(α1) knockout protects against WAT fibrosis[235] and myocardial infarction[298], suggesting a

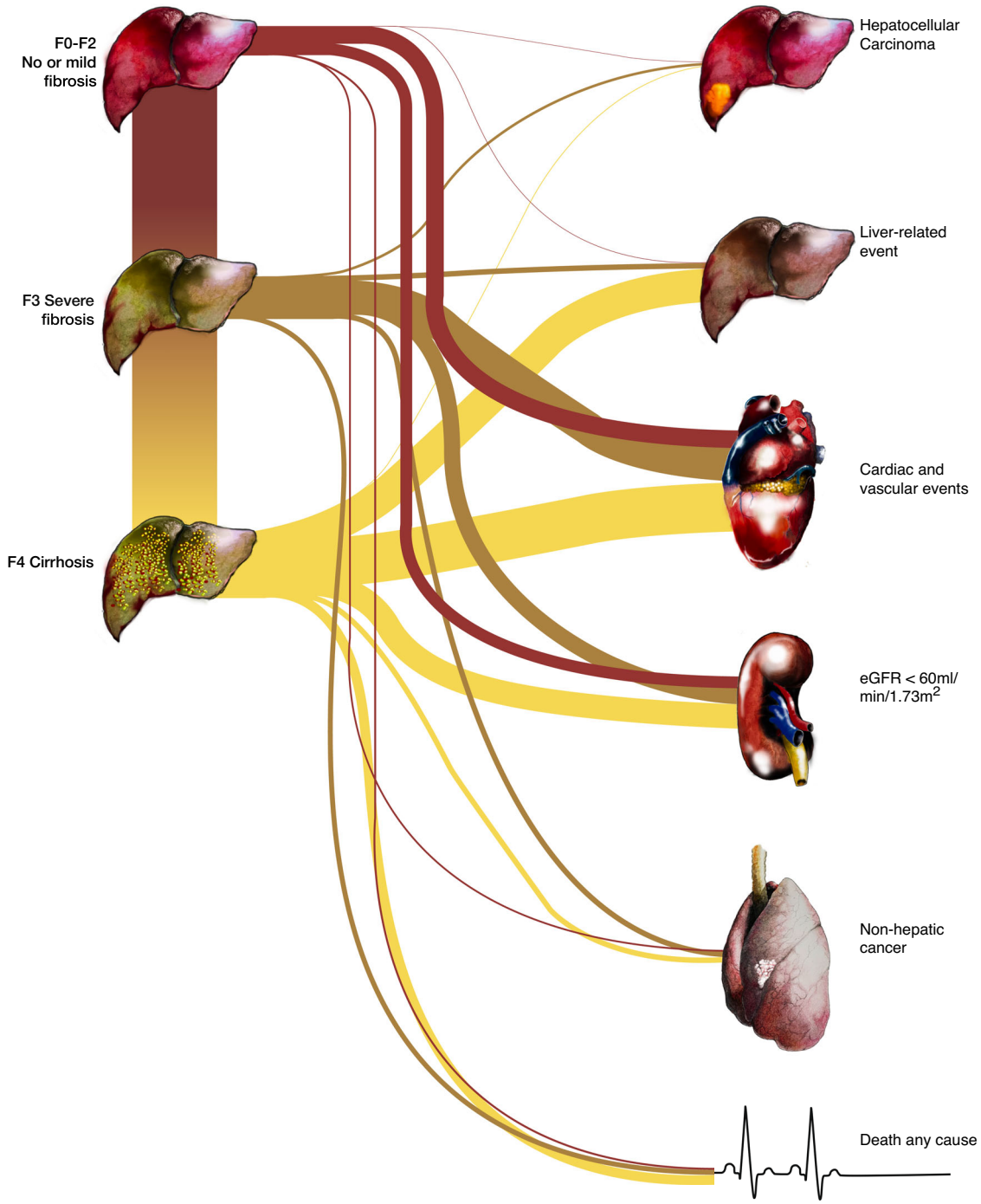

Fig. 4 | Outcomes in adults with MASLD. According to Sanyal AJ et al.[160], patients with chronic steatohepatitis are at higher risk of cardiovascular and renal adverse events than liver-related events. This schematic illustrates the organ death race driven by MASLD progression. (Line thickness represent probability of event per 100 patients).

mechanistic role for collagen type VI remodeling in the chain of events during systemic disease. Endotrophin, a cleavage product of the C-terminal propeptide of the α) chain of procollagen type VI(α3) chain[297,299], is a potent adipokine, activating fibroblasts and recruiting immune and endothelial cells to trigger and promote fibrosis progression. Increased expression of collagen type VI(α3) chain has also been demonstrated to enhance the adhesion of T-cells in tissues from UC and CD[299], indicating a potential link to sustaining chronic inflammation in IBD. It also reduces energy expenditure, increases triglycerides, leads to hepatic steatosis, and ultimately metabolic disease[30]. Endotrophin, lying at the center of fundamental disease pathways, opens a window into organ death races driven by ECM dysregulation. An endotrophin-derived biomarker, PRO-C6, is associated to outcome in COPD[300,301], chronic liver disease[302], acute kidney disease[189], kidney transplant[303], heart failure with preserved ejection fraction[165], multiple solid neoplasias[304–306], and metabolic disease[307–309]. Although more research is required, the mechanisms of collagen type VI synthesis are a bellwether of disease activity and a potential drug target[310].

The deepening knowledge about, and emergence of successful drugs against, fibrosis[311–314] announce a new challenge: how to measure the dismantling of scarred, defective ECM that would determine fibrosis resolution, and healing. Collagen degradation fragments (e.g., by matrix metalloproteinases) released into the bloodstream could indicate the turning of the tide, the tipping of the ECM balance towards fibrotic scar resolution. Developing biomarkers of ECM degradation is a complex task, as the

progression of fibrotic and inflammatory diseases (including rheumatoid[315] and neoplastic diseases[316]) involves the destruction of normal ECM, and so a degradation-inclined ECM balance could rather be interpreted as high disease activity associated with enhanced ECM turnover. However, during fibrosis, fibrillar collagen is abnormally and abundantly crosslinked[317], thus, fibrosis resolution would imply the degradation of crosslinked fibrillar collagen. Biomarkers of degraded, crosslinked collagen could therefore be a successful surrogate of beneficial ECM degradation and repair. The recent development of an ELISA to detect a crosslinked fragment of collagen type III cleaved by MMPs[318] suggests that noninvasive measurement of release of a fragment of a "bad" collagen into the bloodstream is possible and could provide a valid surrogate for scar resolution, thus complementing the armamentarium to assess the balance between fibrogenesis, e.g., represented by PRO-C3, and fibrolysis.

The FDA biomarker qualification program (reviewed in[319]) sets the path for analytes to be considered drug development tools. It includes, at this point, eight biomarkers, three of them non-clinical. Apart from scientific obstacles (e.g., an insufficient knowledge of the mechanistic bases of a particular disease process), one of the main barriers for a sound validation of novel biomarkers of disease is methodological: the development of standardized, replicable measurement methods. Systems biology-based biomarkers often suffer from a lack of comparability[285] that hampers the transition from being research platforms to clinical tools. Single and composite biomarkers are making inroads, and ELF was given a marketing authorization for enriching MASLD patients with advanced fibrosis by the FDA, while markers like PRO-C3 and PRO-C6 have received FDA letters of support or intent, to continue research towards full qualification.

Conclusions

More than three decades of fibrosis research have established that fibrogenesis and scar-formation are not the only possible paths towards advanced disease after a loss of tissue structure. It is increasingly clear that fibrosis resolution, and possibly regeneration, can be coaxed out of mammalian tissues by disrupting profibrotic mechanosignaling, and by eliminating, inhibiting, or manipulating myofibroblast activity directly or by several 'upstream' interventions[311,313]. The arrival of treatments like anti-myofibroblast immunotherapy, GLP-1 agonists, FGF21 analogs and integrin inhibitors, among others, may be a harbinger of a wave of anti-fibrotic therapies and the beginning of the end for the "death races" that are spurred by organ-specific fibroses. To support this progress, powerful drug development tools will be increasingly necessary, to evaluate therapeutic effect and effectivity, and more specifically to measure the balance of ECM remodeling, inflammation, and reparative response in early and late clinical developments. Two approaches, one guided by big data-driven scanning of biological products, the other based on probing critical pathways active in disease progression, are opening windows into fibrosis activity, regression, and systemic damage. In conclusion, accelerated translational medicine and advanced non-invasive diagnosis may be gradually bringing fibrosis, a condition associated with a heavy healthcare burden, poor prognosis and systemic disease, into the realm of manageable diseases.

Data availability

No datasets were generated or analyzed during the current study.

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Author contributions

A.E.M.-G. wrote and edited the manuscript and prepared Figs. 1–4. D.J.L. wrote and edited the manuscript. K.H. wrote and edited the manuscript. J.H.M. wrote and edited the manuscript. Q.M.A. wrote and edited the manuscript, A.J.S. wrote and edited the manuscript. M.A.K. conceived, wrote and edited the manuscript. D.S. wrote and edited the manuscript. S.H.N. wrote and edited the manuscript.

Competing interests

A.E.M.-G., D.J.L., K.H., J.H.M., and M.A.K. are employees of Nordic Bioscience A/S. D.J.L., K.H., J.H.M., S.H.N., and M.A.K. are Nordic Bioscience A/S stockholders. A.J.S.: has stock options in Durect, Inversago, Tiziana, Rivus, Exhalenz, Genfit. He has served as a consultant to Intercept, Gilead, Takeda, Meck, Eli Lilly, Novo Nordisk, Astra Zeneca, Boehringer Ingelheim, Alnylam, Regeneron, Histoindex, Path AI, Pfizer, 89Bio, Altimmune, Northsea, Akero, Madrigal, Salix, Myovant, Poxel, Surrozen, Hanmi, Aligos, Promed, Zydus. His institution has received grants from Intercept, Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Echosens, Hanmi, Madrigal, Gilead, Salix, Meck, Takeda. He receives royalties from Elsevier and Wolter Kluwers. D.S.: is CMO, co-CEO/CSO for ImmuneNTech, and consults for Falk Pharma, Takeda, Boehringer-Ingelheim, Resalis, Immunic, Sanofi, Northsea Bioscirences.

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