The stroma-vascular compartment: central facilitator of the damage response and repair across organs

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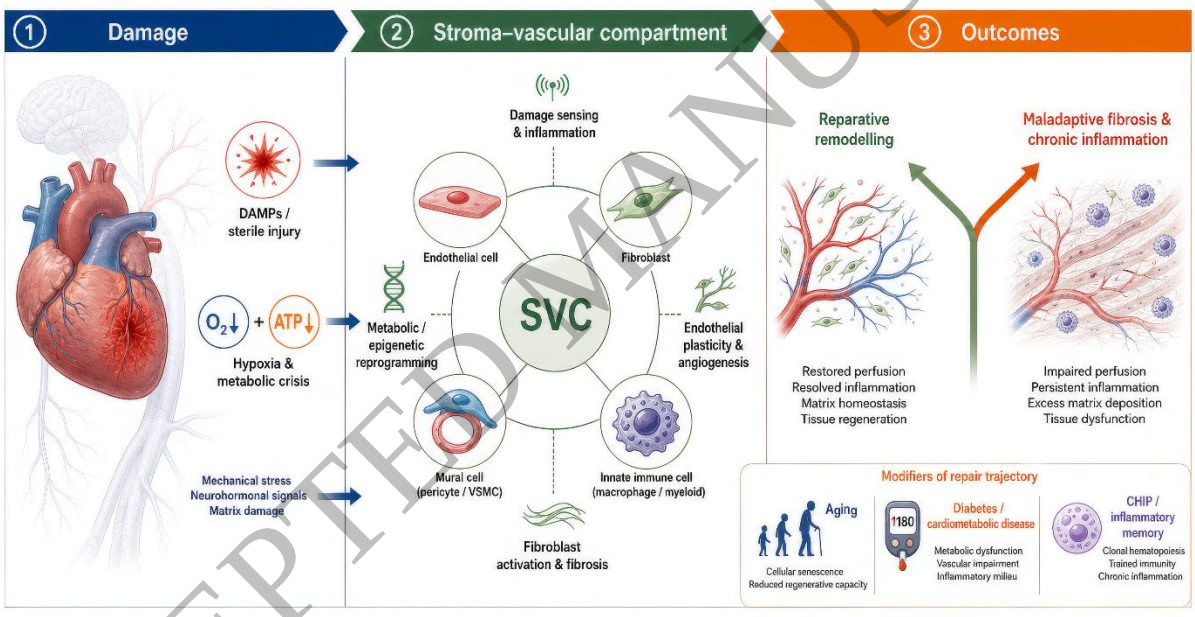
Abstract

Tissue injury initiates a complex, multicellular programme whose outcome i.e. functional repair or irreversible fibrosis, is determined by the coordinated activity of the stroma-vascular compartment (SVC). This network of resident fibroblasts, vascular mural cells, endothelial cells and immune populations acts as a gatekeeper of tissue integrity.

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Following ischaemia, trauma, or mechanical damage, extracellular danger signals are sensed by pattern-recognition receptors and transduced into cell type-specific metabolic and mechanical responses. An initial inflammatory wave clears cellular debris, after which endothelial sprouting and matrix deposition proceed toward scar maturation; a collagen-rich structure whose geometry ultimately governs future perfusion. Epigenetic reprogramming and metabolic rewiring enforce each of these transitions while simultaneously imprinting a memory that skews subsequent responses in the context of ageing, diabetes, chronic inflammation or clonal haematopoiesis. Targeting the SVC, rather than the parenchyma alone, now underpins therapeutic strategies spanning precision senolytics, engineered stromal cell grafts, and biomechanically instructive scaffolds.

Graphical abstract



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1. Introduction

Injuries are unavoidable and the ability to respond to and repair injured tissue is a fundamental requirement of all longer-lived organisms.[1,2] Every myocardial infarction, ischemic stroke or balloon-induced vascular injury confronts the organism with the same dilemma i.e. how can a sterile insult, such as loss of perfusion or barrier integrity, be sensed to mount a protective inflammatory response and resolved with sufficient precision to minimise functional loss? The principal determinant of the extent of functional recovery is the regenerative capacity of parenchymal cells within the affected organ.[1,2] Not all tissues are equal in this regard, as the liver and skin possess substantial regenerative capacity but the heart and brain do not. The functionally significant transdifferentiation of stromal cells into parenchymal cells is a rare event in adult mammals. Once parenchymal cells enter a permanent post-mitotic state and local stem and progenitor pools are exhausted, any injury that results in parenchymal cell loss leads to scar formation and permanent attenuation of function.[3] The situation is markedly different within the stroma-vascular compartment (SVC). Far from being a mere scaffolding structure, the SVC possesses the capacity to orchestrate every phase of the damage response, from the clearance of necrotic debris to capillary reformation, thus functioning as an integrated injury-response unit.[4] The SVC is heterogeneous in both lineage and function. It contains quiescent interstitial fibroblasts capable of instantaneously reactivating embryonic synthetic programmes so that perivascular adventitial fibroblasts differentiate into vascular smooth muscle cells (VSMCs) or macrophage-like cells, and endothelial cells become poised to abandon homeostasis in favour of mesenchymal, immunological or angiogenic phenotypes. Mural pericytes and long-lived tissue macrophages also play key roles in these processes, in part because their epigenetic memory of prior sterile or infectious insults modulates responsiveness to subsequent challenge.[5] Here we summarise recent mechanistic insights into how constituents of the SVC choreograph the transition from acute damage through inflammation, matrix deposition and vascular reconstitution, and how these processes are hampered by comorbidities such as ageing, diabetes, chronic inflammation or clonal haematopoiesis.

2. The damage response within the SVC

In the cardiovascular system, the most prevalent form of damage arises from oxygen and nutrient deprivation following the acute cessation of blood flow. Early restoration of perfusion limits ischemia-induced damage, albeit sometimes at the cost of eliciting ischemia-reperfusion injury. A further relevant category is traumatic injury, including that caused by balloon angioplasty. In such settings, damage is focal; nevertheless,

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transferable signals such as damage-associated molecular patterns (DAMPs) generated by injured cells can induce a state of systemic activation.[6–8] The inflammatory response and its resolution proceed through distinct phases characterised by shifting cell populations, cytokine profiles, and cellular programmes. Such coordination is essential for recruiting phagocytic cells, ensuring their optimal activation and subsequent clearance, and for initiating and resolving inflammation, promoting angiogenesis, as well as activating fibroblasts to drive extracellular matrix (ECM) production. As mechanistic understanding of impaired healing in the context of comorbidities has grown, optimising the SVC damage response has emerged as a promising therapeutic avenue.

2.1 Inflammation

The initial phase of the damage response is characterised by cell death leading to oedema formation, protease activation and inflammation. DAMPs and related signals activate tissue-resident cells, triggering cytokine release that recruits circulating inflammatory cells. Simultaneously, vascular permeability increases, enabling recruited cells to enter the damaged area, phagocytose debris and signal to other SVC constituents to initiate healing. This response must be finely balanced as an inadequate reaction delays debris clearance and prolongs resolution, whereas excessive inflammation destroys additional parenchymal cells and impairs functional recovery.

Immediately after damage, inflammatory signals and TGF-β family cytokines dominate the signalling repertoire, creating conditions that promote endothelial-to-mesenchymal transition (EndMT). EndMT is a cellular reprogramming event in which endothelial cells acquire characteristics typical of mesenchymal cells such as fibroblasts.[9] Cell transplantation studies have demonstrated that endothelial cells placed into wound environments begin expressing EndMT markers, including PDGFRα and factors linked to cartilage and bone formation.[10] This indicates that signals within damaged tissue are sufficient to redirect the fate of resident vascular cells and those recruited from the circulation. The mesenchymal progeny of EndMT deposit ECM that initially stabilises the injured tissue.[11] However, when this response becomes dysregulated or prolonged, it drives excessive scarring that can compromise tissue function. A further underappreciated consequence of EndMT is depletion of the endothelial cell pool, reducing microvessel density and further impairing blood flow and oxygen delivery.[12] This dual effect, i.e. promoting scarring while simultaneously undermining vascular integrity, distinguishes EndMT from conventional fibroblast-mediated repair and marks it as a maladaptive response in adult tissues.[13] Importantly, the transition to a mesenchymal state is not irreversible, as cells may arrest partway, retaining hybrid features or revert toward their

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original identity under appropriate conditions, raising the possibility of therapeutic intervention to limit harmful fibrosis while preserving beneficial aspects of healing.

2.3 Resolution of inflammation

The switch from the inflammatory to the proliferative phase of healing is a complex process that involves intercellular signals, like proresolving lipids[14,15] and chemokines such as TGF-β_1 and IL-10[16]. Moreover, the cellular transdifferentiation of immune cells in response to efferocytosis,[17] uptake of apoptotic particles,[18] formation of reactive oxygen species (ROS) and activation of nuclear receptors [19] contribute to the reprogramming process. As the inflammatory response subsides, inflammatory cells release mediators that promote and support angiogenesis and cell growth.[20] Also, the signalling environment shifts to gradually favour vessel formation over mesenchymal conversion. Oxygen deprivation acts as the principal trigger linking tissue damage to new vessel growth by initiating the production of growth factors that stimulate the surviving vasculature at the margins of the damaged zone.[4] Macrophages are required for both angiogenesis and vasculogenesis following injury. Their phenotypic conversion from pro-inflammatory to pro-resolving states favours growth factor over cytokine production; processes reviewed in detail elsewhere.[21] Distinct populations of vessel-associated progenitor cells also participate in rebuilding the vasculature, including the coverage of the nascent vessel with mural cells, such as pericytes. Pro-angiogenic and pro-reparative signals produced in this phase are, among others, VEGF, PDGF, FGF2, IGF-1, CSF1, GM-CSF and CXCL12.[16]

To re-establish perfusion, endothelial cells must exit quiescence and activate a pro-angiogenic gene expression programme in the ischemic border zone. Epigenetic modification at key pro-angiogenic loci gate this transition.[22,23] Altering repressive histone marks and DNA methylation upregulates endothelial pro-angiogenic genes, enhancing neovascularisation and functional recovery after infarction[24,25]. Moreover, different classes of non-coding RNAs contribute to the angiogenic switch.[26–29] For example, PCAT19 governs endothelial quiescence and is down-regulated in vascular disease to promote endothelial proliferation.[30]

Fibroblasts exhibit comparable phenotypic plasticity. Numerous studies have documented that perivascular fibroblasts in particular expand after injury and migrate into the wound to promote healing, though their abundance and activity vary considerably by organ.[12] The brain is almost devoid of parenchymal fibroblasts, whereas these cells constitute 20–30% of all cells in the heart. Reflecting this disparity, damage in the brain and kidney is typically resolved without a solid scar and fibroblasts seal the lesion, which is subsequently resorbed.[31] In the heart and following perivascular injury, by contrast, damage leads to

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overt, rigid scar formation. This difference appears to reflect the distinct functional repertoires of interstitial fibroblasts across organs.[13,14]

2.4 Maturation

Granulation tissue is highly vascularised, and its nascent matrix is largely disorganised and infiltrated by inflammatory cells. During the organisation phase, the capillary plexus matures and vessel density decreases. Thereafter, the ECM progressively condenses and becomes more organised, whilst cell proliferation declines. TGF-β1 and CTGF are important facilitators of this process, which in humans can extend over many months (**Fig. 1**).

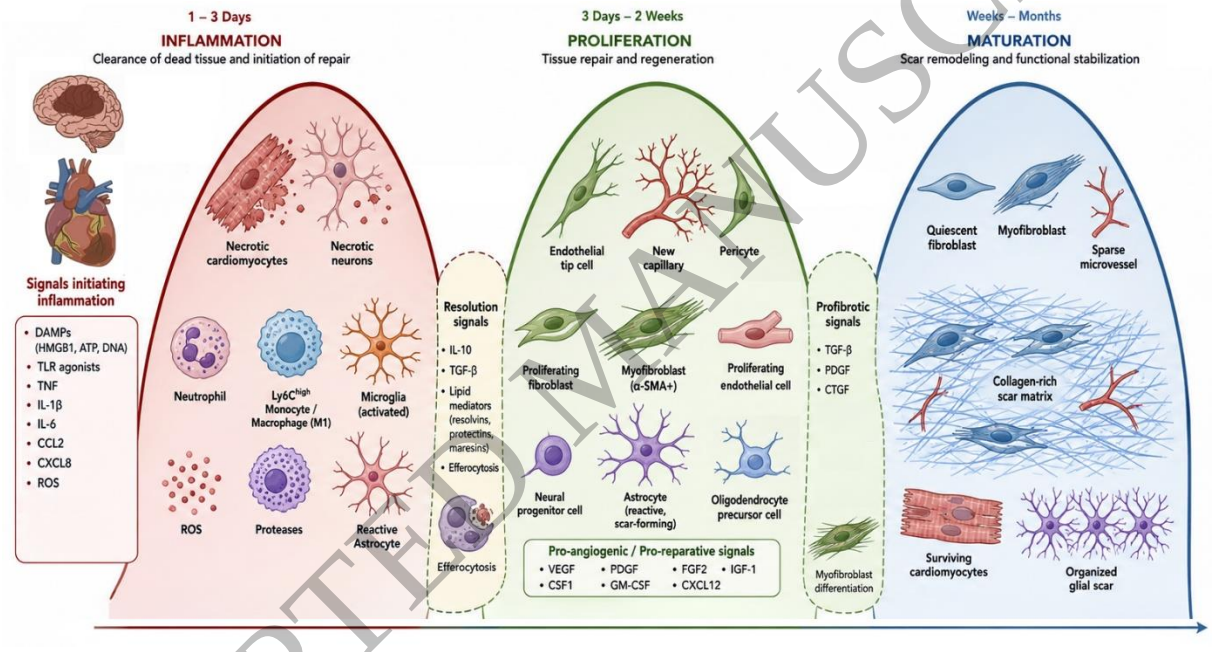


Fig. 1. Phases of the damage response. Damage-associated molecular patterns (DAMPs) released from injured cells initiate an inflammatory phase that clears cellular debris. Inflammatory cell phenotypes and cytokine profiles subsequently shift towards reparative signalling, driving fibroblast and endothelial cell proliferation and the formation of hypervascular granulation tissue, which then matures. ROS: reactive oxygen species

3. The cellular response to damage

3.1 Sensors and responses to damage

The ability of the SVC to respond to damage depends largely on sensing systems that translate biochemical and structural perturbations into defined cellular programmes. In organs with limited regenerative potential, these mechanisms strongly influence whether repair resolves the damage or converts it into chronic inflammation and fibrosis.[32] Damage detection in the SVC is attributable, in large part, to the pattern recognition receptors,

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which detect DAMPs exposed during cellular stress, injury or death.[33] TLRs, particularly TLR2 and TLR4, recognise a diverse set of endogenous ligands, including HMGB1, S100 proteins, heat-shock proteins and ECM fragments such as hyaluronan and fibronectin. The receptor for advanced glycation end products, which is enriched in endothelial and immune cells, binds overlapping ligands and sustains inflammatory signalling over longer time frames. C-type lectin receptors extend the detection repertoire by recognising lipid and glycan structures exposed after damage or stress.[34] Together, these receptors form an integrated sensor network that couples tissue breakdown to inflammatory activation.

A second sensing axis monitors extracellular nucleotide levels, i.e. ATP, which serves as a quantitative indicator of tissue damage.[35] ATP can be released passively during necrosis or actively through pannexin channels under stress to activate purinergic P2X and P2Y receptors, most notably P2X7. Low ATP concentrations support chemotaxis, whereas a sustained elevation drives potassium efflux and assembly of the NLRP3 inflammasome.[35] In parallel, complement activation products generated on damaged surfaces, e.g., C3a and C5a, engage receptors on endothelial, stromal and immune cells to increase vascular permeability as well as promote leukocyte recruitment and cytokine production.[36]

Intracellular stress pathways provide an additional layer of damage surveillance. Endosomal TLRs (TLR3, TLR7/8, and TLR9) detect nucleic acids released from compromised nuclei or mitochondria,[33] while the cGAS-STING pathway is activated by cytosolic DNA to promote type I interferon signalling.[37] DNA strand breaks engage ATM and ATR kinases to coordinate cell cycle arrest, repair, or apoptosis.[38] Oxidative stress is monitored through the KEAP1–NRF2 system[39], and disruption of proteostasis activates endoplasmic reticulum stress sensors including PERK, IRE1 and ATF6.[40] Loss of endothelial cell-derived nitric oxide provides a further example of how failing homeostatic mechanisms feed into these pathways, as the denitrosation of the RNA-editing enzyme ADAR1 perturbs A-to-I editing, leading to accumulation of cytosolic double-stranded RNA and consequent type I interferon induction.[41]

The SVC also responds to mechanical and structural damage. Integrins and focal adhesion kinase signal the loss of ECM continuity and altered force transmission,[42] whereas Piezo1 and Piezo2 respond to changes in membrane tension and shear stress.[43] Collagen fragmentation activates DDR1 and DDR2, linking ECM disruption to intracellular signalling.[44] Ionic imbalance provides a rapid indicator of membrane disturbance, and while potassium efflux promotes inflammasome activation, calcium influx drives cytoskeletal remodelling and TRP channels are activated in response to osmotic and oxidative stress[45] (**Fig. 2**). Collectively, these sensing systems enable the SVC to convert tissue damage into coordinated inflammatory, vascular and stromal responses that determine the trajectory of repair.

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3.2 Metabolic consequences of, and responses to, damage

Acute injury imposes an oxygen debt and ATP crisis that triggers a coordinated metabolic response across stromal and parenchymal cell populations. As the oxygen tension falls, oxidative phosphorylation collapses, intracellular ATP levels decrease and the AMP/ATP ratio increases.[46] These changes stabilize HIF-1α[47] and activate the AMPK,[48] two cellular fuel sensors that collectively reprogram cellular metabolism to favour survival over other functions. HIF-1α stabilisation induces transcription of glycolytic enzymes and suppresses pyruvate oxidation, shunting pyruvate away from mitochondria towards lactate production.[47] AMPK activation inhibits mTOR-dependent anabolic processes, suppresses protein and lipid synthesis and stimulates autophagy, reallocating resources toward essential ATP-requiring pathways.[49] Critically, this glycolytic switch is not merely a passive stress adaptation: it actively shapes downstream signalling, including redox balance, inflammatory priming and cell fate decisions.[50–52]

A hallmark of acute ischaemia is the accumulation of succinate, driven by reversal of the tricarboxylic acid cycle via fumarate reductase activity. Upon reperfusion, rapid oxidation of succinate at complex II causes electrons to flow backwards through complex I via reverse electron transport,[53] thus generating a burst of mitochondrial ROS that amplifies injury, promotes necrosis, and disrupts the endothelial barrier.[54] An underappreciated consequence of succinate accumulation is protein succinylation, a post-translational modification whose functional significance remains incompletely understood.[55]

Despite being continuously exposed to high concentrations of oxygen, healthy quiescent endothelial cells largely rely on glycolysis for energy production.[56] This metabolic preference confers a dual advantage, i.e. protection against oxidative stress and enhanced tolerance of hypoxia.[57] Moreover, under physiological conditions, endothelial nitric oxide inhibits mitochondrial complex IV,[58,59] further restraining respiratory chain activity. Inflammation amplifies this glycolytic bias.[60–62] Endothelial cells also oxidise fatty acids via CPT1A, however, rather than generating energy, this pathway provides carbon for nucleotide biosynthesis to sustain proliferation.[63]

The transition from quiescence to angiogenesis requires activation of a programme that directs endothelial cells into hypoxic zones and drives phenotypic polarisation into motile, gradient-sensing tip cells and proliferating stalk cells.[64] Perturbation of either glycolysis or fatty acid oxidation impairs angiogenesis, compromises barrier function and promotes maladaptive vascular remodelling.[65] Amino acid uptake constitutes an additional regulatory layer in vascular repair, influencing endothelial chromatin[66] and protein translation control.[67] Metabolites such as S-2-hydroxyglutarate further contribute to the re-establishment of endothelial quiescence by regulating epigenetic remodelling.[68]

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In injured tissue, fibroblasts also undergo metabolic transformation characterised by coordinated activation of glycolysis, glutaminolysis and the proline biosynthesis pathway. This rewiring facilitates the rapid conversion of glucose and glutamine into proline, a key building block for the collagen needed to repair damaged tissue. The process is of therapeutic relevance as reducing glutaminase activity diminishes collagen production, reverses fibrosis, and improves tissue function,[69,70] while interfering with glutamine–proline metabolism can alter scar geometry and vascular stiffness.[71]

Perivascular cells such as pericytes, VSMCs and astrocytes also demonstrate a high level of metabolic plasticity.[72] Under ischaemic conditions, astrocytes mobilise glycogen stores, upregulate glycolysis, and shuttle lactate to neurons, functioning simultaneously as metabolite suppliers and signalling hubs.[73,74] Immune cells follow an analogous pattern; during acute inflammation they rapidly upregulate glycolysis and succinate-driven HIF-1α signalling to amplify cytokine production. During resolution, they shift to oxidative phosphorylation, fatty acid oxidation, and itaconate-mediated antioxidant programmes.[75,76] This stereotypic metabolic sequence, i.e. glycolytic priority under acute stress, mitochondrial modulation to limit ROS, and nutrient routing into biosynthetic pathways, is a unifying feature of the SVC injury response, and metabolic flexibility is its enabling mechanism (**Fig. 2**).

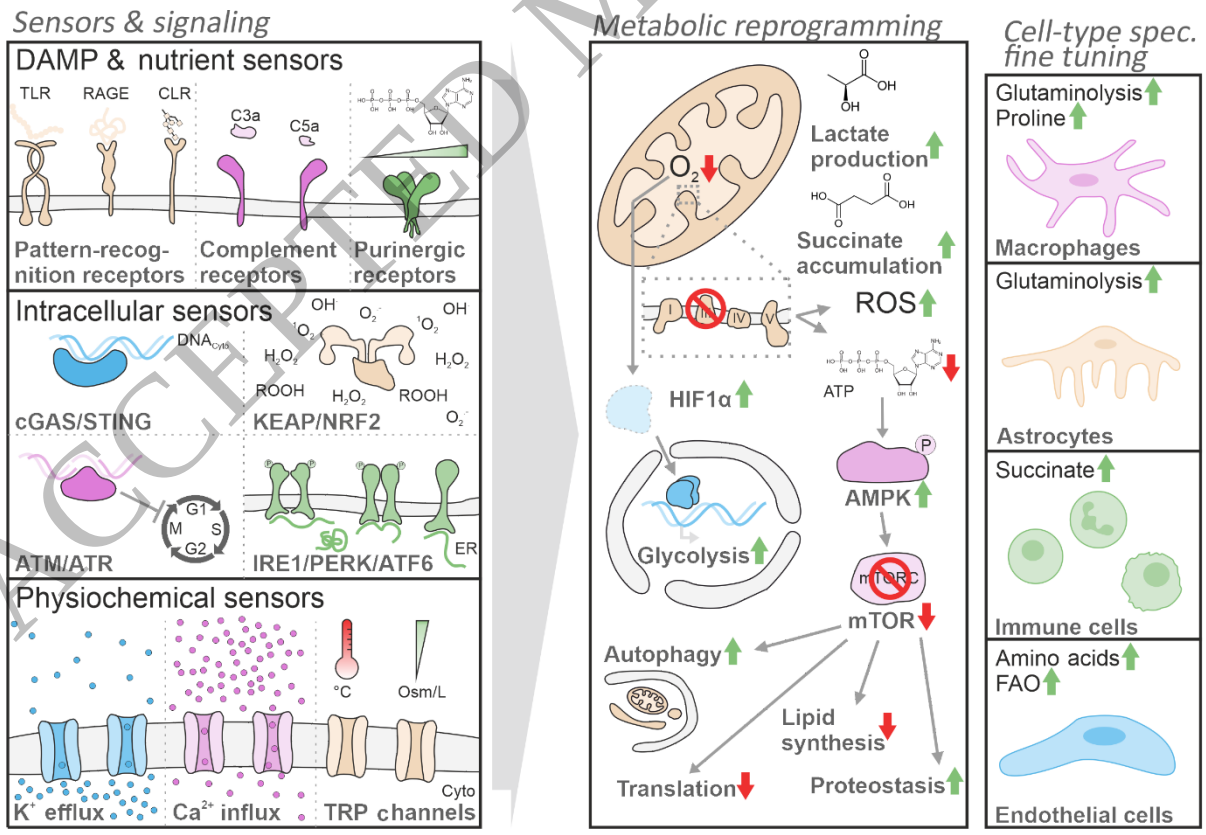


Fig. 2. Sensing and metabolic consequences of damage. **Left:** Cellular damage is detected

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by multiple sensing mechanisms responding to physicochemical and molecular cues, as well as intracellular signals. **Right**: Damage also induces metabolic reprogramming, reflecting both damage-induced signalling and profound alterations in metabolite levels and composition.

4. Cell types contributing to the damage response

4.1 The innate immune system

The innate immune system orchestrates a conserved damage response across organs, yet organ-specific stromal niches determine whether this response restores function or promotes chronic tissue damage.[77] The heart provides a prototypical example, with notable parallels to the microglia-driven responses of the brain.[78] In both myocardium and brain, tissue-resident macrophages and microglia act as first responders that produce chemokines to shape leukocyte recruitment, clear debris and set the balance between repair and maladaptive remodelling.[77,79] Their early polarisation along inflammatory versus reparative programmes critically influences long-term tissue integrity.[80] Lineage-tracing studies and high-dimensional transcriptomic profiling have shown that monocyte-derived macrophages transition into transcriptionally distinct states. Depending on the cues obtained from the local environment, these cells can possess tissue-damaging or inflammation-resolving functions, including the regulation of angiogenesis and matrix remodelling.[79,81]

4.1.1 The innate immune system after myocardial infarction

Following myocardial infarction (MI), the injured myocardium is rapidly invaded by neutrophils, which secrete factors that may directly injure cardiomyocytes, triggering cell death, membrane instability and arrhythmias.[82] Neutrophils also recruit and polarise inflammatory monocytes, which constitute the dominant cardiac leukocyte population during the early inflammatory phase, a response linked to emergency myelopoiesis in the bone marrow and spleen.[83] In the days thereafter, a transition to inflammation-resolving reparative macrophages occurs, the depletion or disruption of which alters scar composition and ventricular remodelling.[77,79]

Basophils, mast cells and T cells also critically shape innate immune responses and healing after MI. Basophils infiltrate infarcted murine hearts, with numbers peaking roughly 3 - 7 days post-infarction. Antibody-mediated and genetic depletion experiments have established a protective role for these cells, and their absence impairs cardiac function, increases scar thinning and shifts the balance from reparative Ly6C^{low} macrophages toward inflammatory Ly6C^{high} monocytes.[84] Adoptive transfer and cytokine-deficient models have identified basophil-derived IL-4 and IL-13 as essential drivers of reparative macrophage polarisation. Consistent with this, low baseline basophil counts in patients with acute infarction predict larger scars and poorer outcomes.[84] Mast cells are an underappreciated

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cell population that reside in the myocardium, valves and pericardium and can also have a marked impact on post-infarct inflammation. For example, mast cell-derived proteases, histamine and cytokines enhance leukocyte recruitment, matrix degradation and adverse remodelling. On the other hand, mast cell-derived IL-10, IL-13 and angiogenic factors support vascularisation and healing.[85] T cells add a further regulatory layer and following infarction $CD4^+$ regulatory T cells accumulate in the heart and draining lymph nodes, suppressing pro-inflammatory responses and directly protecting cardiomyocytes, thus limiting adverse remodelling.[86] In contrast, cytotoxic $CD8^+$ T cells and T helper 1-skewed responses promote cardiomyocyte apoptosis, fibroblast activation and fibrosis, impairing regenerative potential.[87]

4.1.2 Brain microglia and shared principles

In the brain, in vivo imaging and fate-mapping studies have established microglia as long-lived resident innate immune cells that rapidly respond to ischemic or traumatic insults by altering their morphology, proliferating and adopting diverse transcriptional states.[78,88] Like cardiac macrophages, microglia are essential for debris clearance and synaptic remodelling following traumatic brain or spinal cord injury. However, when activated over longer periods, they produce cytokines and ROS that exacerbate secondary injury and drive neurodegeneration.[78] Also in common with cardiac macrophages, microglia exist across a spectrum of polarised states and exhibit time-dependent waves of pro- and anti-inflammatory gene expression after injury.[78]

Across heart and brain, the principal determinants of tissue loss include the magnitude and duration of damage-associated signalling, the timing and cellular composition of leukocyte influx, the efficiency of efferocytosis and resolution, and the resilience of stromal niches.[79,84] In the heart, excessive early myeloid recruitment, insufficient type 2 and regulatory signals, detrimental T-cell polarisation and persistent stromal activation collectively favour wall thinning, dilation and arrhythmogenic remodelling.[84,87] In the brain, analogous skewing towards chronic microglial and infiltrating macrophage activation promotes white-matter damage, dendritic pruning and cognitive decline.[89,90]

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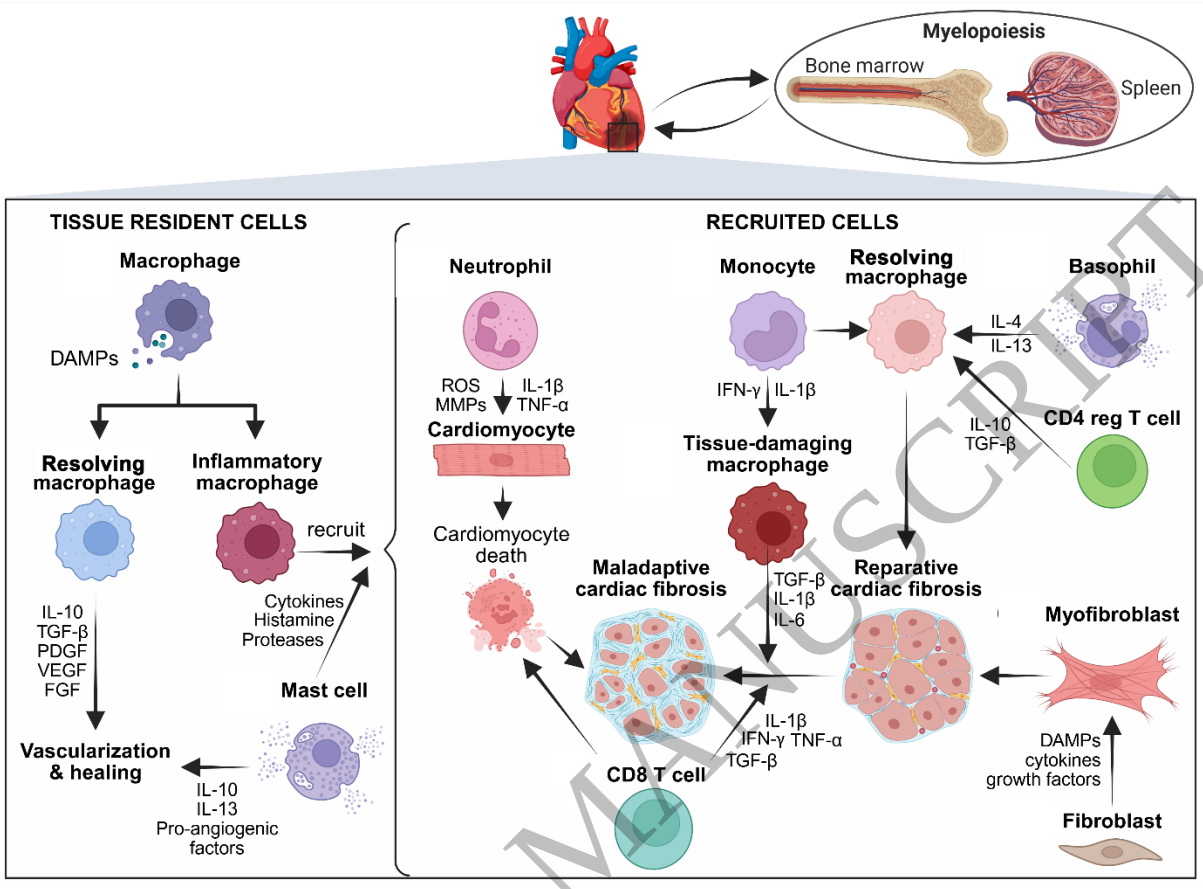


Fig. 3. Impact of damage on components of the immune system. **Left:** DAMPs activate tissue-resident immune cells. Resolving macrophages promote vascularisation and repair, whereas inflammatory macrophages recruit additional myeloid cells to the injury site. Mast cells release factors that promote both processes. **Right:** Recruited immune cells modulate the balance between reparative and maladaptive fibrosis. Factors released by these cells can exacerbate damage by promoting parenchymal cell death and fibrotic progression yet are also required to drive matrix formation and reparative fibrosis.

4.2 Fibroblasts and smooth muscle cells.

Fibroblasts and VSMCs share several functional and phenotypic features that make them key effectors of physiological repair as well as pathological remodelling. Both cell types contribute to ECM production, respond to mechanical as well as biochemical cues and, in response to injury or stress, can undergo phenotypic transition, e.g., between contractile and synthetic states. Indeed, myofibroblasts, which are a hallmark of fibrosis, exemplify this overlap, co-expressing α-smooth muscle actin (α-SMA) and contractile cytoskeletal bundles characteristic of both lineages.[91,92] Nevertheless, the two populations differ in the mechanisms governing their activation and in their specific roles across different damage.[92]

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4.2.1 Fibroblasts

Fibroblasts generate and degrade the ECM that provides structural support to parenchymal and other cells, distribute mechanical force, and support cell growth as well as differentiation.[93] Although highly active during organ development, they are generally quiescent in adult tissues, maintaining only low-level ECM turnover.[91] As with other SVC constituents, fibroblast populations from different organs display distinct gene expression profiles, reflecting topographical heterogeneity.[94]

In response to damage, fibroblasts rapidly re-acquire an activated synthetic phenotype, characterised by proliferation, increased matrix deposition and, if sustained, fibrosis.[93,95] Key signalling cascades implicated in damage-induced fibroblast activation include TGF-β/SMAD, PDGFRα and inflammatory mediators such as IL-1/IL-6/CCL2.[93,95] Activated fibroblasts upregulate contractile proteins, notably α-SMA - the defining feature of myofibroblasts,[96] and produce proteases and matricellular proteins that remodel the existing ECM,[93,95] as well as chemokines that recruit and polarise immune cells.[97] This repertoire positions fibroblasts as central arbiters of the balance between pro-inflammatory and reparative processes. Lineage-tracing studies and single cell transcriptomic analyses have revealed considerable heterogeneity within the fibroblast population,[93] with the phenotype of individual activated fibroblasts shaped by developmental origin, tissue-specific microenvironment and context-dependent activation signals.

While the pro-fibrotic response is initially beneficial and helps to stabilise and reinforce the structurally damaged tissue, excessive ECM deposition results in organ stiffening, loss of organ structure, altered perfusion, and molecular diffusion, all of which promote functional deterioration.[77,98] Containing adverse fibroblast activation is therefore a therapeutic objective across multiple pathologies; however, systemic modulation of fibroblast function risks disrupting normal healing.[98] A more selective strategy would be to target specific fibroblast subpopulations and deplete or reprogram pro-fibrotic fibroblast subsets while sparing cells involved in repair and regeneration.[95,97]

4.2.2 Vascular smooth muscle cells

The primary function of VSMCs is to regulate vascular tone and thereby organ perfusion. In healthy adult vessels, VSMCs are highly differentiated and quiescent but in response to inflammation and damage they switch to a “synthetic” phenotype. The latter is characterised by reduced expression of contractile proteins, increased migration and proliferation, and induction of inflammatory genes.[92] Depending on the pathophysiological context, such synthetic VSMCs can adopt characteristics of other cell types, becoming fibroblast-like, macrophage-like, or osteochondrogenic.[99] The mechanisms regulating

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VSMC dedifferentiation are complex. The transcription factor serum response factor (SRF) plays a central role: interactions with myocardin family co-activators support contractile gene expression,[100] whereas binding to ternary complex factor family co-activators has the opposing effect, facilitating dedifferentiation.[100] These two classes of SRF co-activators are in turn regulated by multiple signalling cascades, including mitogen-activated protein kinases, PI3-K/Akt, YAP/TAZ, and NF-κB, that collectively promote dedifferentiation, whilst the differentiated state is maintained by cAMP/CREB-, RhoA-, and TGF-β-dependent signalling.[100–102]

Following traumatic vascular injury, VSMCs contribute to wound healing by migrating to the site of injury, where they support wound closure by proliferation and matrix production. Dedifferentiation can also be triggered by endothelial dysfunction, e.g., following angioplasty or in atherosclerosis.[103] In such cases, VSMCs migrate from the media into the intima where their proliferation and matrix production progressively narrow the vessel lumen and impair blood flow. Therapeutic strategies aimed at limiting maladaptive VSMC proliferation/migration or redirecting the VSMC phenotype towards a reparative state have been studied in detail.[103] In atherosclerosis, however, VSMC dedifferentiation is a double-edged sword and while dedifferentiated VSMCs contribute to plaque formation, foam cell formation and calcification, they also generate fibrous caps that stabilise plaques[103] (**Fig. 4**).

4.3 Endothelial cells

The vascular endothelium coordinates immune cell trafficking during the damage response but also plays a determinant role in remodelling and regeneration, with angiogenesis and lymphangiogenesis representing key events in any regenerative process. Following MI, endothelial cells must expand clonally and form capillary sprouts in the border zone to limit cardiomyocyte death and infarct expansion.[104,105] Similarly, after stroke, angiogenesis in the peri-infarct region promotes cell survival and recovery in the penumbra.[106] Hypoxia drives this angiogenic reprogramming through stabilisation of HIF-1α and HIF-2α, initiating a gene expression program that includes VEGF[107] and angiopoietin-2,[108] as well as chemokines such as CXCL12 that recruit pro-angiogenic myeloid cells to the injury site.[109] In sprouting angiogenesis, tip cells extend filopodia into the injured tissue, while stalk cells proliferate to allow formation of a primitive endothelial tube that is ultimately stabilised by mural cells; principally pericytes differentiating from mesenchymal precursors. The nascent capillary plexus matures into a functional network through the resumption of flow and a pruning process that optimises tissue perfusion, limits fluid extravasation and consolidates granulation tissue.[110] Maturation of the vascular network has been shown to limit cardiac maladaptive remodelling after MI.[111,112]

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As introduced above, EndMT is a central component of the endothelial injury response, during which endothelial cells lose classical markers such as CD144 and CD31 while acquiring mesenchymal traits including α-SMA and vimentin.[113,114] Early EndMT is thought to aid repair by promoting endothelial cell proliferation, whereas persistent EndMT generates fibroblast-like cells that deposit ECM and promote maladaptive fibrosis.[9,115] The molecular machinery driving EndMT involves several converging pathways.[116] TGF-β acts as the dominant initiating signal, engaging both canonical SMAD-dependent pathways and additional kinase cascades including MEK, PI3K, and p38 MAPK. Downstream, the transcription factors Snail, Slug, Twist and ZEB family members coordinate the suppression of endothelial genes and activation of mesenchymal programs.[11] Inflammatory mediators amplify these signals. TNF-α, for example, promotes the nuclear translocation of NF-κB and engages TGF-β signalling through chromatin-level modifications.[12] Not all endothelial populations respond in the same manner to these cues. Cells lining heart valves transition readily when exposed to TGF-β alone, whereas those from the intestinal or skin microvasculature require co-stimulation with inflammatory cytokines.[117] Such heterogeneity means the degree of EndMT following damage varies between vascular beds.

The inflammatory milieu within the damage area also induces an immunomodulatory endothelial phenotype characterised by chemokine secretion, immune cell-like marker expression, and upregulation of antigen processing and presentation machinery. These immunomodulatory endothelial cells (IMECs) emerge transiently after acute MI from tissue-resident $CD144^+$ cells and colocalise with T cells.[118] In inflammatory conditions associated with atherosclerosis driven by interferon-γ, IL-1β and TGF-β, IMECs can activate T cells through paracrine signalling and present antigens via MHC class II molecules, suggesting a role as non-professional antigen-presenting cells.[119]

4.3.1 Lymphatic endothelial cells

Lymphatic vessels drain interstitial fluid and clear immune cells from injured tissue. Damage to the lymphatic network results in oedema and may trap immune cells within the injury zone, perpetuating inflammation and fibrosis.[120] Lymphangiogenesis, i.e. the formation of new lymphatic vessels, is therefore a critical component of the damage response. While MI triggers robust lymphangiogenesis within the infarct zone, epicardial collecting lymphatics undergo adverse remodelling, becoming dilated and dysfunctional, which paradoxically impairs overall lymphatic transport and sustains myocardial oedema.[121] Key molecular drivers of lymphangiogenesis include the VEGF-C/VEGFR-3 axis, inflammatory cytokines and mechanical cues triggered by tissue injury.[122] Endogenous VEGF-C upregulation drives capillary lymphangiogenesis but is insufficient to prevent collecting vessel dysfunction. Preclinical studies demonstrate that exogenous VEGF-C

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delivery at therapeutic concentrations preserves the structure of collecting lymphatics, improves fluid balance, enhances macrophage clearance and limits adverse cardiac remodelling.[121] While some studies have reported that lymphatics are required for macrophage clearance, this point is somewhat controversial, as studies assessing the impact of post-MI lymphangiogenesis in mice in which lymphangiogenesis had been blocked revealed no impact on left ventricular function or on immune cell infiltration and clearance.[123,124]

Collectively, these endothelial processes, i.e. angiogenesis, EndMT, immunomodulation and lymphangiogenesis, form an integrated response network whose balance ultimately determines whether the outcome is regeneration, fibrosis, or chronic inflammation. Targeting specific endothelial mechanisms and subpopulations therefore holds considerable therapeutic potential to limit scarring and improve healing after MI (**Fig. 4**).

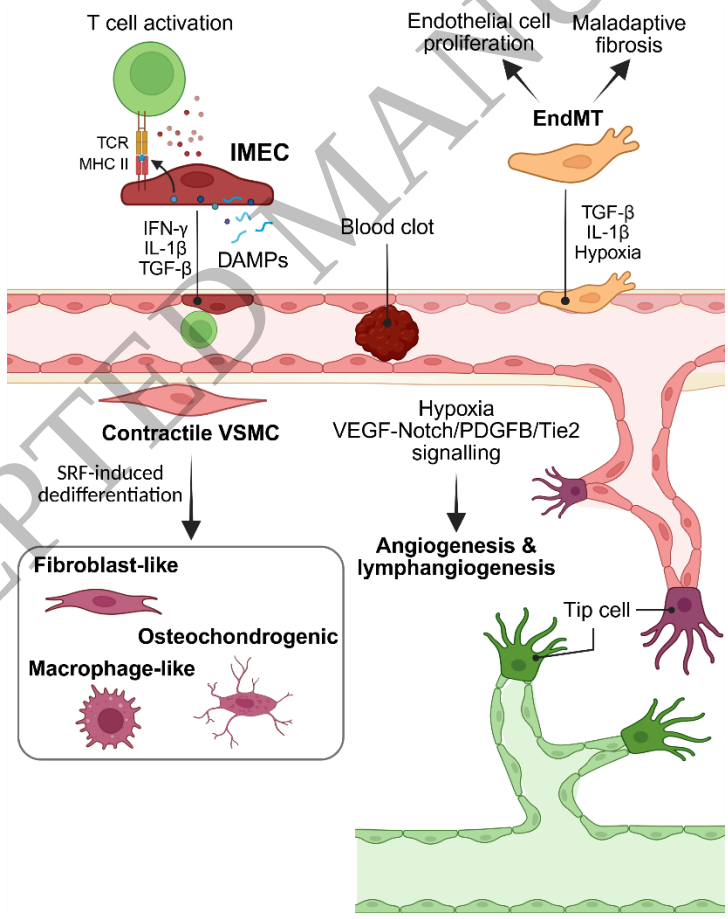


Fig. 4. Impact of damage on endothelial and smooth muscle cell function. Following tissue injury, DAMPs, cytokines, growth factors and hypoxia induce phenotypic switching in endothelial cells and VSMCs. While these changes are essential for reparative processes such as angiogenesis and vascular maturation, specific phenotypes (e.g. IMEC) may further propagate damage or promote maladaptive healing, including excessive fibrosis or osteogenic

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transformation. IMEC: Immune modulatory endothelial cells, VSMC: vascular smooth muscle cells.

5. The tissue-specific damage response and how it is altered by comorbidities

Advanced age and comorbidities such as diabetes, hyperlipidaemia, prior infection, clonal haematopoiesis and chronic inflammatory activation alter the inflammatory response.[125] These effects arise from changes in both cellularity and gene expression driven by epigenetic alterations. Ageing and repeated damage promote the induction of senescence and the resulting state of "inflamm-ageing" is mediated in part by senescence-associated secretory products.[126] This heightens the initial hyperinflammatory phase after injury, delays resolution and increases tissue loss.

5.1 The heart

The repair process after MI is shaped by unique structural and hemodynamic constraints that favour fibrotic stabilisation over regeneration to preserve organ integrity. Unlike the kidney or brain, where necrotic parenchyma is resorbed, the heart must form a solid, collagen-rich scar to maintain tensile strength and prevent ventricular rupture.[127]

Interstitial fibroblast networks, the epicardium and endocardium, and terminal vasculature anatomy all influence the damage response, with stromal vascular cells integrating immune and mechanical signals into structural repair. Crosstalk between fibroblasts, endothelial cells, pericytes and macrophages determines cardiac scar composition and the balance between reparative and maladaptive remodelling.[128] Pericytes are critical for vascular stability and angiogenesis; their loss or dysfunction in the aged heart leads to increased capillary fragility and pro-fibrotic TGF-β2 signalling.[129] When this crosstalk is balanced, ventricular geometry is preserved and rupture is prevented. However, comorbidities can have a substantial impact on this healing response, promoting excessive fibrosis and heart failure progression.

The coronary microvasculature is a functional end-arterial circulation with few significant collateral connections, meaning that arterial occlusion rapidly renders the supplied tissue ischaemic and impairs regeneration. Beyond the processes of EndMT and angiogenesis outlined above, the epicardium and endocardium are also activated after MI and contribute to the post-injury stromal and vascular response. Epicardial cells undergo epithelial-to-mesenchymal transition and secrete paracrine mediators, including Wnt ligands, FGF and VEGF, that influence both angiogenesis and fibroblast activation.[130] The endocardium, which is essentially a specialised endothelium, in turn contributes to subendocardial fibrosis through TGF-β and NRG-1 signalling pathways.[131]

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Fibroblasts form the structural backbone of the cardiac interstitium and constitute a heterogeneous cell population which also contains cells with pro- as well as anti-fibrotic signatures.[132,133] The myocardium contains distinct interstitial and perivascular fibroblast populations; interstitial fibroblasts maintain ECM organisation within the myocardial matrix, while perivascular fibroblasts support vessel stability and contribute to perivascular fibrosis. Upon activation by DAMPs and cytokines, fibroblasts differentiate into α-SMA+ myofibroblasts[134] and fibroblast-derived collagen I and III replace the provisional fibrin matrix. This dense collagen network ensures mechanical strength but increases stiffness, impairing diastolic filling and predisposing to heart failure.[135] Activated fibroblasts also secrete matricellular mediators such as connective tissue growth factor, periostin and decorin that regulate ECM stabilisation and cross-linking. Ageing and comorbidities such as, obesity, hypertension, diabetes, chronic kidney disease and clonal haematopoiesis of indeterminate potential (CHIP) further shape the behaviour of the SVC and predispose to adverse remodelling.[136]

Myocardial injury also reprogrammes the bone marrow to alter innate immune responsiveness. Trained immunity, i.e. a form of innate immune memory in which prior exposure to a stimulus epigenetically and metabolically programmes cells to respond faster and more intensely to subsequent challenge, has been demonstrated in experimental MI models.[137] For example, the transfer of bone marrow from mice post-MI accelerates atherosclerosis development in naïve recipients.[138] Consistent with this, monocytes from patients with coronary artery disease are hyper-responsive to secondary stimulation, indicative of an epigenetically encoded inflammatory memory.[138]

Ageing, although not strictly a comorbidity, profoundly alters the stromal cell phenotypes and ECM composition of the heart.[139] Aged cardiac fibroblasts exhibit pro-fibrotic properties that promote diastolic dysfunction,[140] while their proliferative and migratory capacity and responsiveness to TGF-β are reduced.[141] Aged endothelial cells develop senescence and secrete factors such as semaphorin 3A, a neuro-repulsive factor that decreases cardiac sympathetic innervation.[142] An increase in decorin generation, on the other hand, sustains inflammatory signalling.[139] Ageing is further associated with a decline in pericyte coverage, resulting in the destabilisation of the microvasculature and contributing to microvascular rarefaction and interstitial fibrosis.[129] CHIP exacerbates these effects, impairs prognosis and favours adverse remodelling.[143] Also, CHIP mutations in hematopoietic stem cells drive the expansion of pro-inflammatory myeloid clones that infiltrate infarcted myocardium and, via the HB-EGF–EGFR axis, polarise macrophages towards a pro-fibrotic state, impairing prognosis and favouring adverse remodelling.[144]

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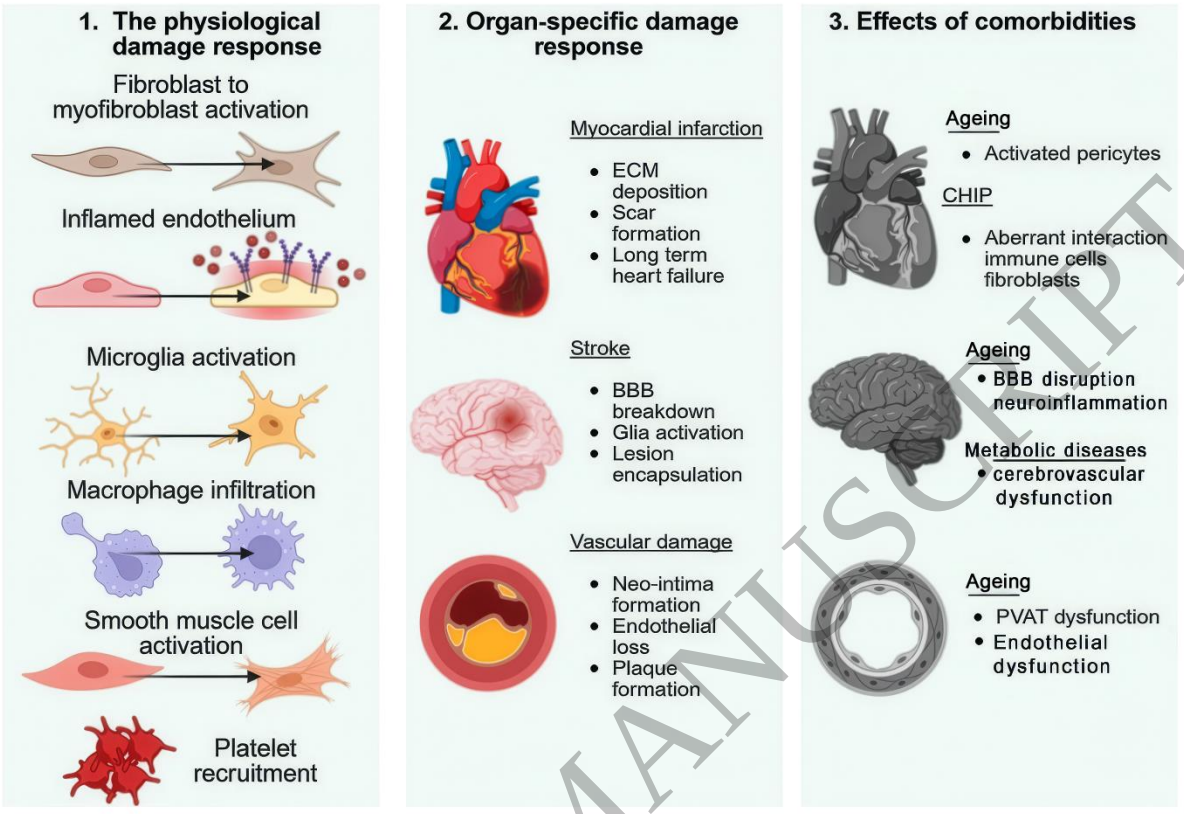


Fig. 5. The multiple facets of the damage response. **Left**: Damage affects all cellular components of the SVC, leading to activation, inflammation, phenotypic changes and cellular recruitment. **Middle**: Although the damage response is broadly stereotypic, organ-specific features are evident, as illustrated for heart, brain and vasculature. **Right**: Comorbidities and ageing impair healing, with heightened inflammation, cellular dysfunction, and tissue loss, delayed repair and a shift towards fibrosis and scarring rather than restitutio ad integrum in aged individuals with comorbid conditions. BBB: blood–brain barrier; ECM: extracellular matrix; CHIP: clonal haematopoiesis of indeterminate potential; PVAT: perivascular adipose tissue.

5.2 The brain

Injury to the central nervous system (CNS) — e.g. because of stroke, traumatic brain injury and spinal cord injury — is a leading cause of long-term disability, reflecting the brain's limited regenerative capacity. Rather than regenerating lost tissue, the injured brain forms a compact scar.[145] While this scarring limits lesion expansion, it also establishes structural and biochemical barriers that restrict axonal regrowth and functional recovery.[146]

The organ-specific damage response in the CNS is shaped by its unique cytoarchitecture and tightly regulated neurovascular unit.[147] Cerebral vessels are ensheathed by mural cells (pericytes and VSMC) and astrocytic end feet, which together represent the functional unit of the blood-brain barrier (BBB).[148] Under homeostatic conditions, SVC stromal cells, i.e. pericytes and fibroblasts in the perivascular and meningeal space, are quiescent yet poised for rapid activation following injury.[149] Although sparse, these cells play a crucial

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role in structural repair and revascularisation of the injured brain.[150] Endothelial cells, astrocytes and microglia, while not stromal in origin, act in concert within this stromal niche to coordinate the neurovascular injury response.[151]

As is the case in other organs, the response to damage in the CNS progresses through well-defined phases. In the acute phase, BBB disruption permits immune cell infiltration and drives microglial activation.[30] In the subacute phase, reactive astrocytes assemble a glial scar around the lesion,[152] while stromal pericytes and fibroblasts proliferate and migrate into the injury core. During the maturation phase, fibroblasts and glia stabilise the scar and the lesion core becomes encapsulated by reactive astrocytes and stromal fibroblast-like cells that contain the inflammation and limit the expansion of cytotoxic damage.[153] Resident stromal cells differentiate into myofibroblasts and deposit ECM components such as fibronectin, laminins, and collagens,[31] while astrocytes and microglia form an outer glial border that demarcates inflammatory from intact parenchymal zones.[154] Peripheral immune cell integration influences scar maturation and the balance between repair and chronic inflammation.[155] In the chronic phase, myofibroblast–immune cell interactions critically regulate long-term neuroinflammatory status.[31] Although the regenerative capacity in the adult CNS is limited, sprouting of spared axons and recruitment of neural progenitors partially restores connectivity.[156,157] In parallel, angiogenesis generates new capillaries that progressively mature and re-establish a functional, albeit structurally abnormal, barrier.[158] Blood vessels serve as trophic and structural guides for migrating neural progenitors and regenerating axons,[159] directly linking vascular to neuronal repair. Recovery therefore depends on a finely tuned interplay between vascular remodelling, stromal activation and neuronal plasticity within the neurovascular microenvironment.

Comorbidities profoundly worsen outcomes after CNS injury. Ageing is associated with increased neuro-inflammation, impaired BBB integrity, reduced neuroplasticity and diminished repair capacity, leading to less favourable functional recovery.[160] Metabolic comorbidities, including diabetes and obesity, exacerbate injury through cerebrovascular dysfunction and impaired repair mechanisms, such as scar formation and neurogenesis.[161,162] Together, these conditions create a maladaptive systemic and cerebral environment that amplifies injury, disrupts the physiological damage response and constrains recovery.

5.3 Large vessels

Conduit vessels do not contain parenchymal cells. The classic ischemic mode of damage, typical for myocardial infarction and ischemic stroke, does not apply to conduit vessels. Rather, vascular damage is a consequence of mechanical injury, as in the case of

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angioplasty or thrombosis. Given the tremendous relevance of these conditions, the damage aspect of large vessels is discussed here. In contrast to the heart and the brain, conduit vessels are intrinsic components of the SVC. Nevertheless, larger conduit arteries are supplied by a dedicated adventitial SVC containing vasa vasorum, which can contribute to certain pathologies, e.g. intraplaque haemorrhage and overt plaque rupture.[163,164] The damage response in large conduit arteries is therefore central to some of the most important pathologies.[165,166] Once regarded as a passive structural element for vessel insulation and protection against motion, the adventitia is now recognised as a reservoir of immune and vascular progenitor cells that can be activated following injury.[166]

The hallmark of vascular injury is the formation of a neointima, particularly following angioplasty and stent implantation, both conditions in which the endothelium is acutely destroyed and where platelet activation and blood coagulation contribute to the stimulation of VSMC and fibroblast proliferation.[167] Mechanical vascular injury also induces inflammation and therefore follows the classic phases of the damage response.[168] Inflammatory cell recruitment generates an oxidative environment that drives ECM protein modification and impairs the activity of enzymes involved in repair. Chronically elevated oxidative stress and the irreversible inactivation of phosphatases (among many other events) may drive uncontrolled VSMC proliferation by abolishing counter-regulatory control of growth factor receptor signalling. In fact, the importance of specific phosphatases like PTP1B for neointima formation has been demonstrated experimentally.[169,170] Perivascular adipose tissue also plays an important role here as it is a source of adipokines and regulates vascular biology via paracrine crosstalk signals that can modulate inflammatory cell recruitment and may promote vascular disease in obesity.[171] Although the contribution of perivascular fat to the damage response in the vessel is difficult to establish in patients, studies employing PVAT transplantation or perivascular overexpression of leptin, CCL2, or ANGPTL2 support an important functional role.[172] Signalling within the vascular wall can also reprogram the perivascular fat compartment, e.g. via the generation of 4-hydroxynonenal, which can trigger the repolarisation of adipocytes from passive lipid stores to a more synthetic phenotype that produces anti-inflammatory adipokines such as adiponectin.[171]

Diabetes, hypertension, obesity and ageing also impact on the damage response within the vessel wall and alter the ability of vascular cells to contribute to healing. Metabolic risk factors, like diabetes and obesity, promote platelet hyperresponsiveness and activate cysteine proteases that alter platelet-derived protein function, thus contributing to sterile vascular inflammation.[173,174] Platelet-derived products such as PDGF, microRNAs, TGF-β and CCL5 further promote EndMT, monocyte recruitment and VSMC proliferation.[175] Phenotypic switching of VSMCs in the absence of overt injury occurs in parallel with altered

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vascular cell metabolism driven by elevated levels of insulin,[176] glucose[177] or lipids.[178] Metabolic post-translational modifications have been reported for mitogens such as PDGF,[179] glycolytic enzymes, e.g. PKM2,[180] and transcription factors e.g. KLF4, FoxO4 and MYOCD.[181] In obesity, altered DNA methyltransferase activity produces aberrant DNA methylation patterns, resulting in dysregulated gene activation and suppression.[182] Chronic inflammation, oxidative stress, and elevated circulating metabolic mediators, including insulin, TNF-α, leptin and resistin, affect vascular cell types at multiple levels. Ageing additionally alters the adventitia and PVAT, reducing their contribution to neointima formation.[164] As is the case in other progenitor niches, an age-associated decline in the regenerative capacity of the adventitia occurs.[183]

6. Therapeutic approaches targeting the SVC

Recognising the SVC as a central orchestrator of post-injury responses opens multiple therapeutic avenues. Effective interventions should modulate intercellular networks within the SVC, shifting the balance from pathology toward repair and regeneration rather than targeting isolated cell types alone.

Fibroblast plasticity is both a challenge and opportunity. Single-cell sequencing studies have identified numerous distinct fibroblast subpopulations, some supportive of regeneration and others driving fibrosis.[184] Therapeutic strategies aimed at shifting fibroblast phenotypes toward regenerative subsets while suppressing pro-fibrotic ones are therefore attractive. Anti-fibrotic strategies targeting TGF-β signalling, YAP/TAZ mechanotransduction, or epigenetic regulators have shown promise in preclinical models.[185] Precision approaches, e.g. using fibroblast subset–specific markers for CAR-T cell-mediated elimination,[186] may minimise off-target suppression of beneficial stromal functions.

The development of pro-angiogenic therapies has proven challenging, with multiple clinical trial failures.[187] A major limitation is that such interventions must be precisely timed as premature angiogenesis during acute inflammation can exacerbate oedema. Moreover, many approaches increase capillary density without achieving stable, functional vascular networks characterised by luminal patency, smooth muscle cell coverage and effective perfusion.[187] Growth factor combinations, microRNAs, or enhanced metabolic support for endothelial sprouting may improve the quality of revascularisation.[188] However, these strategies must be carefully balanced to avoid aberrant vessel growth. Preventing pathological EndMT represents a complementary strategy, with the potential to limit fibrosis across multiple organs whilst preserving vascular integrity; an increasingly recognised imperative given the contribution of EndMT to maladaptive remodelling.[9]

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Promoting lymphangiogenesis offers a further therapeutic avenue to enhance inflammation resolution and interstitial fluid clearance, particularly in chronic cardiovascular disease.[189] VEGF-C improves clearance of the post-MI inflammatory response by facilitating immune cell trafficking to draining mediastinal lymph nodes.[189] However, other pre-clinical studies failed to demonstrate a therapeutic benefit,[123] underscoring the need for a deeper understanding of context-dependent effects and coordinated vascular-lymphatic remodelling.

Broad anti-inflammatory strategies have had limited success in clinical settings. In cardiovascular disease, inhibition of TNF-α, low-dose colchicine, and targeted interference with leukocyte recruitment have all failed to improve outcomes after MI and, in some cases, impaired repair by disrupting key immune functions.[190] Because stromal-immune crosstalk critically governs repair outcomes, selective modulation of this interface may offer a more effective therapeutic approach than systemic immunosuppression. Proposed strategies include enhancing efferocytosis to accelerate clearance of dying cells, promoting reparative macrophage polarisation via stromal-derived mediators or inhibiting pro-fibrotic immune–fibroblast signalling. Emerging evidence further suggests that trained immunity may extend beyond classical immune cells to stromal and vascular cell populations. This raises the possibility that early, context-specific interventions could durably shape SVC responses to subsequent insults, thereby improving long-term tissue resilience rather than merely attenuating acute inflammation.

6.1 Emerging therapeutic modalities

Several emerging therapeutic strategies aim to restore coordinated tissue repair by modulating SVC interactions rather than individual cell types in isolation.

6.1.1 Cell therapy

Bone marrow-derived mononuclear cells were among the first cell products widely tested for their ability to promote cardiovascular repair, and early results appeared promising. With broader experience, however, efficacy proved variable and the benefits were often incremental.[191] Such observations underscore the fact that bone marrow-derived mononuclear cell activity is largely paracrine and immunomodulatory rather than driven by durable engraftment. Current efforts focus on CAR T cells,[192] mesenchymal stromal cells and engineered fibroblasts with pro-regenerative properties.[193] By selectively deleting harmful cell subpopulations that secrete cytokines, growth factors, extracellular vesicles, and metabolites, these cells can modulate endothelial activation and sprouting, dampen excessive inflammation, and promote reparative macrophage polarisation. Next-generation engineered stromal cells may function as transient “bio-generators” that deliver

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pro-reparative cues or extracellular vesicles while minimising risks associated with uncontrolled proliferation or permanent integration.

6.1.2 Gene and RNA based therapeutics

Rather than permanent genetic alteration, transient expression of regenerative factors or the silencing of pro-fibrotic mediators is a particularly attractive strategy to improve recovery after injury. Such approaches may be beneficial in situations where the therapeutic window is finite and prolonged pathway activation may become maladaptive. RNA modalities, including siRNA, antisense oligonucleotides and mRNA, can suppress drivers of fibrotic remodelling, blunt maladaptive immune–fibroblast signalling or transiently enhance pro-angiogenic and pro-resolving programmes in vascular and stromal cells.[194,195] Progress in delivery systems, e.g. lipid nanoparticles, engineered viral vectors, or biomaterial-assisted local release, is bringing cell type-biased targeting within the SVC closer to clinical translation while enabling dose and duration control.[196,197] Central challenges remain the limited efficiency of current delivery vehicles in targeting the SVC. Another challenge is the lack of specificity needed to avoid off-target immune activation and to ensure that the kinetics of gene expression or knockdown are appropriately matched to the phase of repair being targeted.[198] Indeed, the same signal may be beneficial during the early days after injury but become detrimental if sustained into chronic remodelling.

6.1.3 Targeting senescence

Senolytic strategies address a distinct but convergent bottleneck, i.e. the accumulation of senescent cells within SVC compartments that accompanies ageing and chronic disease.[199] Senescent cells impair repair not only through loss of function but also via the senescence-associated secretory phenotype that promotes chronic inflammation, endothelial dysfunction and fibroblast activation.[200,201] Clearing these cells, or attenuating the production of secreted factors via senomorphic interventions, is a potential way to rejuvenate the tissue microenvironment and restore responsiveness to regenerative cues.[199] Conceptually, senolytics may improve the "starting conditions" for repair by removing a self-sustaining source of inflammatory and pro-fibrotic signalling, thereby enhancing the effectiveness of other regenerative interventions. However, as with all SVC-targeting approaches, timing and selectivity are critical. Indeed, senescence can have context-dependent roles in wound containment and remodelling, and indiscriminate clearance may disrupt protective functions if applied at inappropriate stages.[202]

6.1.4 Metabolic Interventions

Metabolic reprogramming within SVC cells during injury responses also represents a therapeutic avenue. For example, activated fibroblasts rely on enhanced glycolytic flux to

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support both proliferation and collagen synthesis. Targeting key glycolytic enzymes (including distal steps such as PGK1) has been reported to reduce α-SMA induction and collagen output in vitro and to attenuate fibrosis in vivo, indicating that glycolysis represents a selective vulnerability of the activated fibroblast phenotype.[203] Likewise, endothelial cells undergo distinct metabolic switches during angiogenesis. Highly glycolytic tip cells and β-oxidation-dependent stalk cells exemplify how metabolic checkpoints govern proliferation, migration and quiescence. Partial modulation of these pathways can reduce excessive sprouting and normalise vessel architecture, suggesting that targeting endothelial metabolism could promote angiogenesis while avoiding maladaptive neovascularisation.[204] In both fibroblasts and endothelial cells, metabolic state imprints longer-term transcriptional programmes through metabolite-driven histone and protein modifications. These changes generate a form of "metabolic memory" that can lock in activated or dysfunctional SVC phenotypes after injury. Manipulating these metabolic–epigenetic nodes in a cell-type-specific manner appears difficult, yet feasible. Supplementing metabolites with cell-specific uptake mechanisms due to tissue-specific SLC-transporter expression is conceivable. Also, the cell-specific activation of metabolites by esterases[205] and cytochrome P450 enzymes[206] appears possible. Finally, cell-specific delivery of metabolites through encapsulation into nanoparticles carrying specific surface receptor ligands is another seemingly feasible route of administration. Collectively, these approaches may help reboot metabolic memory, bolster resilience against recurrent damage and restore SVC responsiveness to regenerative cues.[207]

6.1.5 Biomaterials

Biomaterials provide a complementary route to reprogram the SVC niche by combining mechanical support with instructive bioactive cues. Injectable hydrogels, porous scaffolds and engineered matrices can be designed to stabilise injured tissue, reduce adverse dilation and simultaneously guide cell behaviour via the localised presentation of ligands, the provision of support and degradability.[208] Because stromal activation states and immune recruitment are highly sensitive to biomechanical signals, materials that recreate permissive ECM properties can dampen pathological myofibroblast conversion while supporting endothelial organisation and vessel stabilisation.[209] Biomaterials can also serve as spatiotemporally controlled delivery vehicles for proteins, small molecules, or nucleic acids, thus enabling local and phase-specific modulation of SVC programmes.[210] Such approaches may enhance early debris clearance and resolution while avoiding prolonged inflammatory recruitment or fostering vascular maturation rather than simply increasing capillary density.[211] These emerging strategies parallel broader efforts to harness stromal vascular fraction-based therapies for tissue regeneration.[212]

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7. Conclusion and Outlook

The SVC functions as an integrated repair unit in which stromal-immune crosstalk, endothelial gatekeeping and shared metabolic programs jointly shape regenerative versus fibrotic outcomes. Durable restoration of organ function ultimately requires regeneration or replacement of the parenchymal cells that execute tissue-specific work. Emerging therapeutic strategies converge on a central principle: effective tissue repair cannot be achieved by forcing a single dominant pathway. Instead, effective repair requires restoring the ability of the SVC to coordinate inflammation resolution, vascular remodelling and matrix adaptation. Technological advances are helping to identify approaches to achieve these goals. Spatial and temporal omics can map SVC interactions and state transitions in situ, revealing actionable therapeutic windows. Human organoid and engineered tissue platforms provide increasingly relevant systems for mechanistic studies and screening, while machine learning applied to multi-omic datasets can help predict SVC trajectories and guide intervention timing. Nevertheless, key challenges remain as the molecular switches governing regenerative versus maladaptive SVC programs are incompletely defined, particularly in ageing and cardiometabolic disease. Even where therapeutic targets have been identified, achieving cell state-specific delivery to discrete SVC populations without off-target effects and understanding or therapeutically resetting SVC "memory" after injury remain major hurdles. Despite these challenges, the SVC has emerged as an important target to improve healing and regeneration. Massive roadblocks have to be removed before parenchymal cells of the heart and the brain can be exploited for true tissue regeneration after MI and stroke. Till then, optimising the damage-response of the SVC appears to be the more accessible way to promote healing.

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