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Immuno-regenerative biomaterials for *in situ* cardiovascular tissue engineering – Do patient characteristics warrant precision engineering?

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ABSTRACT

In situ tissue engineering using bioresorbable material implants - or scaffolds - that harness the patient's immune response while guiding neotissue formation at the site of implantation is emerging as a novel therapy to regenerate human tissues. For the cardiovascular system, the use of such implants, like blood vessels and heart valves, is gradually entering the stage of clinical translation. This opens up the question if and to what extent patient characteristics influence tissue outcomes, necessitating the precision engineering of scaffolds to guide patient-specific neo-tissue formation. Because of the current scarcity of human *in vivo* data, herein we review and evaluate *in vitro* and preclinical investigations to predict the potential role of patient-specific parameters like sex, age, ethnicity, hemodynamics, and a multifactorial disease profile, with special emphasis on their contribution to the inflammation-driven processes of *in situ* tissue engineering. We conclude that patient-specific conditions have a strong impact on key aspects of *in situ* cardiovascular tissue engineering, including inflammation, hemodynamic conditions, scaffold resorption, and tissue remodeling capacity, suggesting that a tailored approach may be required to engineer immuno-regenerative biomaterials for safe and predictive clinical applicability.
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Contents

Abbreviations: AGE, Advanced glycation end-products; AP1, Activator protein 1; BMI, Body mass index; BMP, Bone morphogenetic proteins; CABG, Coronary artery bypass graft; CCL-4, Macrophage inflammatory protein-1β; CKD, Chronic kidney disease; CRP, C-reactive protein; CVD, Cardiovascular disease; DAMP, damage-associated molecular pattern; DM, Diabetes mellitus; E2, 17β-Estradiol; EC, Endothelial cell; eNOS, Endothelial nitric oxide synthase; ER, Endoplasmic reticulum; ERK, extracellular signal-regulated kinase; ESKD, end-stage kidney disease; FBR, foreign body response; GM-CSF, Granulocyte-macrophage colony stimulating factor; GUCH, Grown-up congenital heart disease; HDL, High density lipoprotein; IFN-γ, Interferon-γ; IL, Interleukin; LDL, Low density Lipoprotein; LPS, Lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP-1, Monocyte chemoattractant protein 1; MHC-II, Major histocompatibility complex class II; MMP, Matrix metalloproteinase; MNGC, Multinucleated giant cells; NET, Neutrophil extracellular trap; NF-κB, Nuclear factor-κB; NIH, National institutes health; NLRP3, NLR family pyrin domain containing 3; NO, Nitric oxide; Nox, NADPH oxidase; Nrf2, Nuclear factor erythroid2-related factor2; OVX, ovariectomized; PCI, Percutaneous coronary intervention; PCL, Polycaprolactone; PTFE, Polytetrafluoroethylene; RAGE, Receptor for advanced glycation end-products; RNS, Reactive Nitrogen species; ROS, Reactive oxygen species; SMC, Smooth muscle cell; TIMP, Tissue inhibitor of metalloproteinase; TLR, Toll-like receptor; TNF-α, Tumor necrosis factor alpha; VIC, Valve interstitial cell; VSMC, Vascular smooth muscle cell.

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1. Introduction

Cardiovascular diseases (CVD) are a global healthcare burden, with an overall prevalence of about 30% [1]. CVD include heart valve disease, coronary artery disease and atherosclerosis, as well as congenital anomalies and rheumatic heart disease. When progressing into end-stage disease these patients often require replacement of diseased blood vessels or heart valves. In Europe, over 1 million cardiovascular implants (artificial heart valves, vascular by-pass grafts and intravascular stents) are implanted every year [2]. Although these are life-saving procedures, they severely affect life expectancy and quality of life, posing a tremendous financial and societal burden. For the EU economy alone, CVD-related costs are estimated to amount to approximately € 210 billion per year, with more than half deriving from direct healthcare costs (53%), as well as consequential costs due to informal care (21%) and productivity loss (26%) [2]. These alarming numbers emphasize the pressing need for improved and durable alternatives for cardiovascular implants. It is essential that innovations are cost-effective to confine the steep rise in healthcare costs in the coming 50 years, and to keep new cardiovascular treatments broadly applicable and affordable, as recently emphasized by the European Society of Cardiology [2].

One such innovation that has taken flight over the past decade is the use of acellular resorbable materials to regenerate damaged or diseased cardiovascular tissues directly *in situ*. With this technique, commonly termed *'in situ* tissue engineering', off-the-shelf available biomaterials are implanted that immunologically erode while being gradually replaced by autologous new tissue, deposited by endogenously recruited cells [3,4] (Fig. 1). In situ tissue engineering is a clinically attractive concept to replace diseased or damaged cardiovascular tissues, including heart valve replacements [5–11], vascular grafts [12–23], endovascular stents [24], and arteriovenous shunts for renal dialysis [25–28]. It offers an autologous living replacement tissue that can adapt and grow in response to changing hemodynamic conditions, while avoiding costly and lengthy *in vitro* cultures that are necessary for traditional *in vitro* tissue engineering methods [29,30]. This makes it a logistically and economically efficient concept, particularly when using resorbable synthetic materials as the main graft material, as these materials are relatively cheap and simple devices that do not require any *de novo* engineering and/or processing of donor tissue [31,32]. By substantially reducing the risk of reoperations, a living, tissue-engineered substitute would be a cost-effective alternative in terms of cost reduction and increase in quality adjusted life years (QALY), both for paediatric patients and adults, as recently described for tissue-engineered heart valves [33,34].

Although there are still many uncertainties regarding the underlying principles of biomaterial-driven *in situ* tissue engineering, a general, generic temporal course of events can be proposed based on the evidence to date, as described in detail in Section 2 (Fig. 1). Preclinical work in large-animal models has demonstrated the proof-of-principle for *in situ* tissue engineering of blood vessels [16,25,26,35–37] and pulmonary valve replacements [5,6,38] using various classes of biomaterials (natural, synthetic or hybrid materials). For applications in the low-pressure circulation, ongoing and finalized clinical trials have been reported for large venous bypass conduits [39,40], as well as for pulmonary valve replacement [41], both in paediatric patients with congenital malformations. For resorbable synthetic implants, the clinically most sought-after applications, including small-diameter arteries, aortic valves, and arteriovenous shunts for renal dialysis, have not yet reached clinical application. Several challenges are to be overcome for these 'less-forgiving' applications to cope with the more stringent hemodynamic loads to which they are exposed. Important risk factors for these applications include thrombosis and thromboembolic events, adverse remodeling (e.g. intimal hyperplasia, progressive fibrosis, calcification) and structural graft failure (e.g. aneurysm formation, valvular leaflet tearing). Unpredicted variability in outcome has been reported for both vascular [42,43] and valvular grafts [44,45] that were identical at implantation. Variability in the local hemodynamic loads are most likely a contributing factor to this observed variability in outcome [6,13,42]. Nevertheless, these observations are all done in relatively homogenous, healthy laboratory animals in which relevant patient-specific characteristics, such as sex, age or multi-factorial disease profiles are not

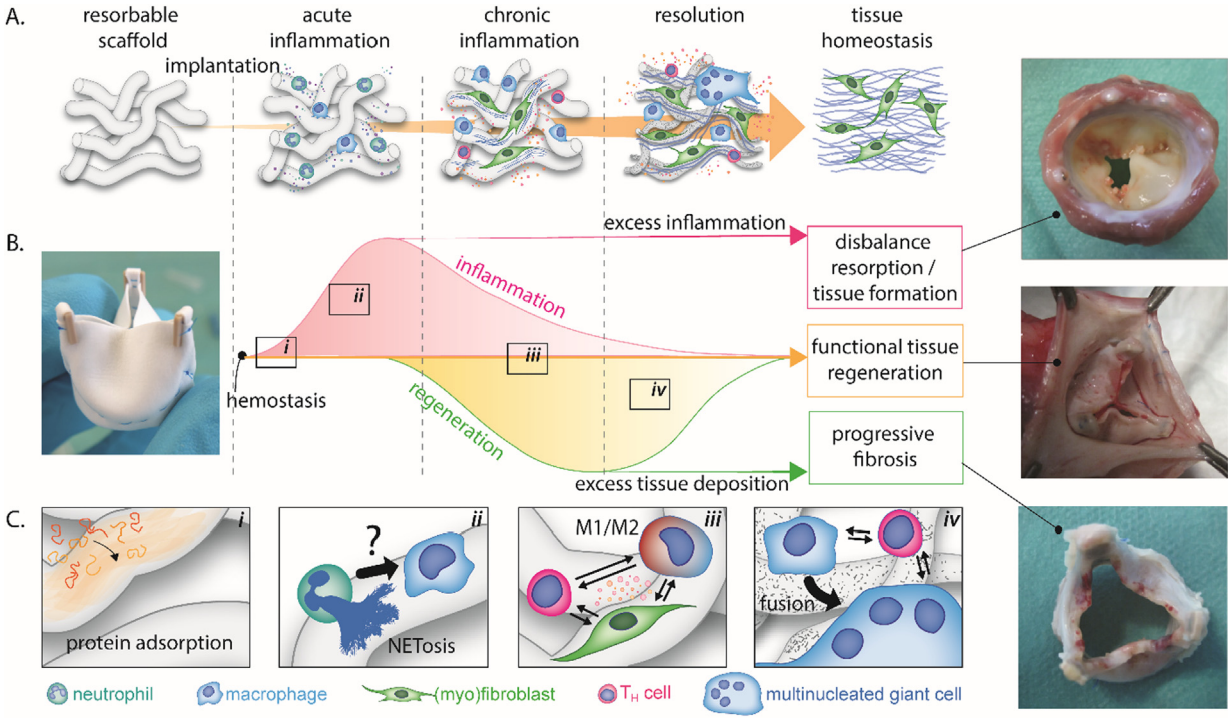

Fig. 1. Schematic overview of the immune-driven *in situ* regeneration of a resorbable scaffold, progressing through stage of acute inflammation, chronic inflammation and resolution to ultimately result in tissue homeostasis (A). When these processes are in balance this results in functional tissue regeneration, however excess inflammation or excess tissue deposition can result in a disbalance between scaffold resorption and tissue formation, which may lead to structural failure or progressive fibrosis (B). Many processes regulate this balance such as (i) protein adsorption, (ii) NETosis, (iii) the balance between pro-inflammatory M1- and pro-regenerative M2-type macrophages, in direct and paracrine cross-talk with T cells and (myo)fibroblasts, and (iv) macrophage fusion into multinucleated giant cells (C). Images adapted from [3,5,45].

taken into account. Given that the *in situ* regenerative response is heavily reliant on the patient's immunological state and regenerative capacity [46,47], systemic patient-specific characteristics may dominantly dictate outcome and, as such, form an even greater source of variability in outcome between patients.

Cardiovascular implants are needed for diverse patient populations and over a broad age range from children and young adults with congenital malformations to elderly with acquired morbidities. This means that there are important differences between patient cohorts, for example in terms of hemodynamic conditions or metabolic activity. Moreover, many patients receiving cardiovascular implants suffer from multi-factorial diseases, such as atherosclerosis, diabetes or chronic kidney disease (CKD). For example, in the US, over 25% of patients who undergo a revascularization procedure, including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), have diabetes [48]. This is caused by the fact that these diseases are systemically linked, for example via a compromised immune system. For example, patients suffering from CKD or diabetes have an increased risk of a CVD-related event due to the systemic effects of CKD and diabetes on the immune system, affecting the cardiovascular system [49–51]. As such, patient-specific factors are important predictors and risk factors for the onset of CVD, as well as the outcome after treatment with cardiovascular substitutes. For example, factors that showed significant increase in restenosis risk after carotid revascularization include diabetes, dyslipidemia, female sex, CKD, hypertension, and smoking [52]. Predictors for patient-prosthesis mismatch of heart valve implants include older age and female sex, as well as pathological comorbidities such as hypertension, diabetes, and kidney failure [53]. These statistics on the currently used clinical prostheses strongly suggest that patient-specific characteristics that underlie CVD will also be an important determinant for the success or failure of *in situ* tissue-engineered grafts.

In order to engineer the 'ideal' scaffold, much research is dedicated to elucidate the influence of scaffold design parameters, such as microstructural design features (e.g. pore size), as well as surface topography and chemistry, on the scaffold immunomodulatory properties [45,54–65] (Fig. 2A). However, so far, relatively little direct data is available regarding the influence of patient characteristics on *in situ* tissue engineering (Fig. 2B). Whereas others have reviewed the potential use of tissue-engineered products for precision medicine [66–69], this review is specifically aimed at pinpointing specific systemic variables and immunological states that may impact design criteria for such tissue-engineered products and (resorbable) biomaterials. We outline the current understanding of *in situ* tissue engineering and the role of the immune response therein, and delineate which patient-specific characteristics, both inherited and acquired, are important to consider in terms of affecting the patient's immunological state and regenerative capacity. To that end, common systemic characteristics will be identified in CVD patient cohorts that are in need of heart valve or blood vessel replacements, followed by analysis of potentially relevant effects of these systemic characteristics on the cellular level. Here, we focus specifically on the effect of patient-specific characteristics on macrophages and tissue formation. Another key mechanism for *in situ* tissue engineering of cardiovascular devices is endothelialization. Given the complexity of *in situ* endothelialization by itself, which is further complicated by patient characteristics, the reader is referred to recent dedicated review articles for a more elaborate view on this aspect of the regenerative cascade specifically [70–76]. Finally, this review will explore the question whether precision treatments will be needed for *in situ* cardiovascular tissue engineering, and identify future directions in shifting to a more patient-centered approach in order to translate *in situ* cardiovascular tissue engineering into a safe and robust clinical treatment option.

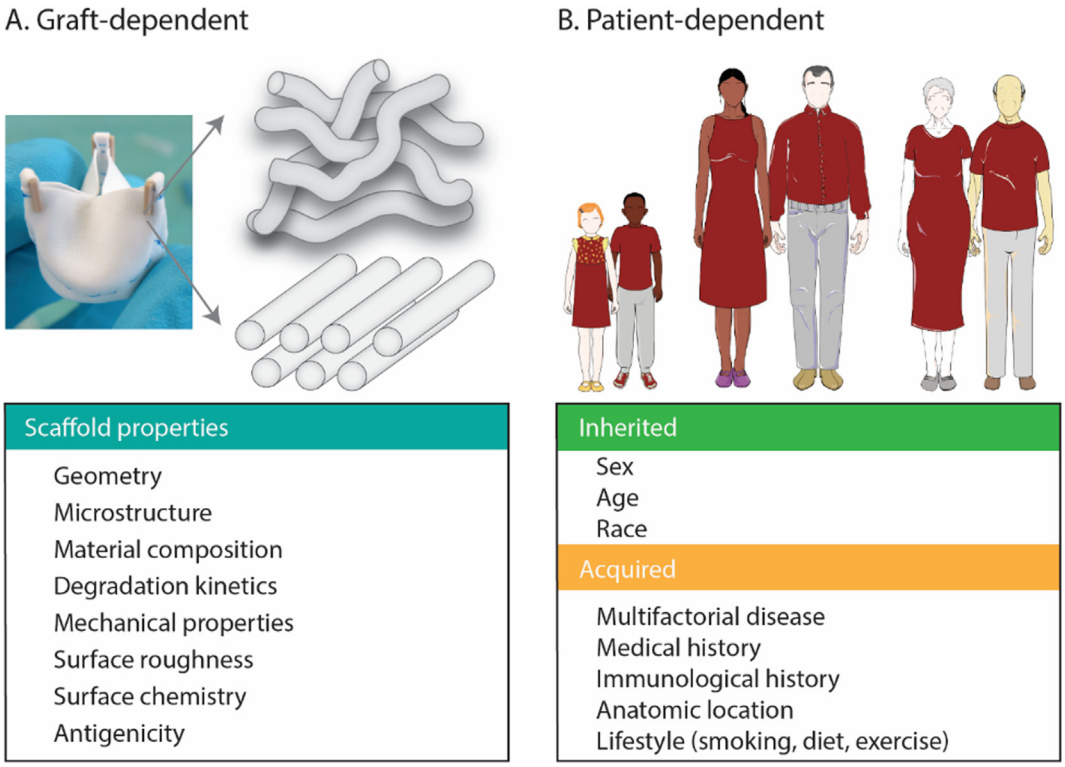

Fig. 2. The immune-driven host response towards a biomaterial graft can be altered by graft dependent properties (A) as well as patient-dependent traits, both inherited and acquired (B). Images adapted from REF [3,45] and Servier medical art (https://smart.servier.com).

2. Inflammation as the driver of *in situ* tissue engineering

The concept of *in situ* cardiovascular tissue engineering in itself is not new; one of the first studies to report on the implantation of a resorbable synthetic vascular graft dates back to 1956 by Harrison & Adler [77], although in that study, graft resorption was reported as a retrospective observation, rather than a preconceived graft design parameter. In the 1980's, there was a surge in reports on the use of resorbable polyurethane scaffolds to replace small arteries (e.g. [78–80]). In 1985, Van der Lei et al. highlighted the importance of multinucleated giant cells (MNGCs) in the process of scaffold resorption and tissue formation [80]. However, the more recent recognition that the host immune response can be actively directed by the scaffold properties to steer the process of tissue formation and material resorption is what has propelled the field over the last decade.

Overall, the process of *in situ* tissue engineering mirrors the wound healing cascade (Fig. 1A, B). Instantaneously after implantation, any biomaterial is coated by proteins (Fig. 1C). This protein layer consists of blood proteins, as well as opsonins and adsorbed danger signals, such as damage-associated molecular patterns (DAMPs) that are released after tissue damage due to the implantation procedure. The composition of the protein layer is dictated by the material properties and it is dynamic due to the Vromann effect [81]. The interaction between the biomaterial with blood clotting components, such as fibrin, provide a provisional matrix which serves as an interface for cells to interact with, and which is a modulator of the subsequent immunological and regenerative response [82–84]. In the acute inflammatory phase, neutrophils are among the first cells to engage with the protein coating on the biomaterials, in response to cytokine release by tissue-resident cells, as well as histamine release by mast cells, with a typical peak in neutrophil numbers within the first 3 days after implantation, [85]. Recent works have demonstrated that neutrophils can deposit neutrophil extracellular traps (NETs) onto a biomaterial by the process of NETosis, and that this is dependent on the scaffold microstructure [86]. To date it is unclear to what extent and in which situations neutrophils and NETs dictate downstream tissue formation (Fig. 1C). Sadtler et al. demonstrated that systemic neutrophil depletion did influence the recruitment of monocytes and macrophages to synthetic scaffolds, when injected in a model of volumetric muscle loss in mice, but it did not significantly affect tissue formation [87]. Li et al. recently suggested an important role for neutrophil polarization in the downstream immunomodulatory and pro-angiogenic effects of gelatin-based scaffolds [88]. Hence, despite the fact that neutrophils are short-lived cells (typical life span < 24 h [89]), their early phenotype and potential NET depositions may influence downstream inflammatory events, with most evidence pointing at an important role in governing angiogenesis (see recent review by Fetz et al. [90]). The secretion of chemokines by degranulating neutrophils leads to the accumulation of monocytes and macrophages at the site of implantation, marking the transition into the chronic inflammatory phase. During this phase, macrophages govern both the resorption of the implanted biomaterial on the one hand, while directing the formation of new tissue on the other, by communicating with tissue-producing cells, such as progenitor/stem cells and (myo)fibroblast-like cells [91–93] (Fig. 1C). The dominant function of macrophages is transient and dependent on their polarization state, which occurs over a continuous spectrum of pro-inflammatory M1 to pro-regenerative M2 phenotypes [94]. Initially, the recruited macrophages attain a pro-inflammatory M1 phenotype under the influence of pro-inflammatory cytokines and DAMPs from the local tissue damage, the latter which activate the cells via their pattern recognition receptors (e.g. Toll-like receptors (TLRs)). Once the initial damage is cleared, the macrophages stimulate the formation of new tissue

by attracting and activating tissue-producing cells, such as (myo)-fibroblasts and vascular smooth muscle cells (VSMCs) [95]. Tissue synthesis is mainly driven by pro-reparative M2 macrophages, under the influence of interleukin-4 (IL-4), which has become a target for biomaterial-based immunomodulation [96–98]. The source of tissue cells in resorbable grafts for cardiovascular applications is not completely known. In blood vessel grafts, various routes of cellularization have been described [15,20,99,100], of which a combination of transmural cell ingrowth complemented with cell recruitment from the circulatory system is likely the most relevant in the human situation [101]. In resorbable heart valves, ingrowth of smooth muscle cells (SMCs), both transmurally and from the adjacent artery have been described [102], suggesting that VSMCs form an important source of cells to reconstitute a valve interstitial cell (VIC)-like population during *in situ* tissue engineering of heart valves, and thus form a relevant population to study.

While new tissue is being formed, the synthetic scaffold material is being resorbed via hydrolysis and oxidation [103–105]. Prolonged presence of a synthetic biomaterial will lead to a foreign body response (FBR), which is characterized by the fusion of macrophages under the influence of key cytokines, such as IL-13 and IL-4, resulting in MNGC formation [106] (Fig. 1C). The communication between MNGCs, macrophages and T cells is an essential determinant of MNGC function, as pioneeringly established by the group of James Anderson [107–109]. MNGCs create a fibrous capsule to shield off the foreign material form the rest of the body, after which a highly degradative environment is created inside the tissue capsule [110]. Both 'fast' and 'slowly' resorbing materials have been reported [12,111–113], but in reality, scaffold resorption is not simply a matter of degradation rate. Rather, resorption is an active process that can be slowed down or accelerated by the cellular response to the material. Macrophages can persistently secrete proteases and reactive oxygen species (ROS), which can strongly accelerate biomaterial resorption via hydrolysis and oxidation, respectively [103,105]. It has been reported that the rate of resorption is dependent on the scaffold microstructure [65], but also on implant location [114] or the type of animal model [115]. Moreover, the resorption of a biomaterial leads to local changes in the cellular microenvironment (e.g. local mechanical properties [116]) and biomaterial degradation products can induce inflammasome activation in macrophages, leading to a sustained pro-inflammatory environment [117]. We recently reported on the strong spatiotemporal heterogeneity in resorption of supramolecular elastomeric heart valves [102]. Together, these data underline that biomaterial resorption is not a constant, but that it is a transient, heterogenous process, which is reciprocally dependent on the local cellular microenvironment.

Adequately maintaining the balance between scaffold resorption and tissue formation is one of the most challenging aspects for *in situ* cardiovascular tissue regeneration, as it can be a determining factor between premature scaffold failure, functional tissue regeneration and pathological fibrosis (Fig. 1B) [111,112,118,119]. Moreover, once sufficient tissue is deposited and scaffold has been resorbed, it is essential that the inflammation is resolved and that the newly formed tissue is remodelled into a native-like organisation. Tissue maturation encompasses several processes, including the switch from activated myofibroblasts into a quiescent state [120], a transition of a matrix of primarily collagen 3 into a to collagen 1-dominated matrix [102,121,122], collagen reorganisation according to the hemodynamic demand [123], endothelialisation [15], and elastic fiber regeneration, although the latter is still largely elusive [124]. During this tissue maturation phase, IL-10-induced regulatory M2 macrophages play an important role, as they secrete tissue remodeling factors, such as matrix metalloproteinases (MMPs), and govern the resolution of both inflammation and myofibroblast activation by further secretion of key regulatory cytokines, including IL-10 [125]. Moreover, Battiston et al. showed that macrophage-conditioned medium after exposure to a polyurethane biomaterial led to a switch in VSMCs from a synthetic to a contractile phenotype, identifying Monocyte chemoattractant protein 1 (MCP-1) and particularly IL-6 as key signalling cytokines [126], a finding that is confirmed by other studies [127,128].

The pleiotropic functionalities of macrophages make them a central cell type to *in situ* tissue engineering and different macrophage functions are needed at different stages of the regenerative cascade. Moreover, macrophages directly contribute to essential regenerative process such as angiogenesis [129] and endothelialisation [130]. Studies have shown that a systemically induced deficiency in macrophage numbers, but not neutrophils, leads to impaired regeneration and induction of scarring in regenerative species, such as zebrafish and axolotls [131–134]. Similarly, macrophage depletion was shown to inhibit the *in situ* regeneration of resorbable vascular grafts in mice [135]. On the other hand, a study by the same group showed that a deranged macrophage response leads adverse remodeling events, such as intimal hyperplasia [136]. Modulation of the early macrophage response was shown to be an effective tool to steer downstream tissue formation in vascular grafts [19–21,98]. Indeed, macrophage polarization state has been pinpointed as a predictor for downstream tissue regeneration [137,138]. Macrophage polarization state is determined by both the scaffold design parameters, as well as by the local biomechanical and biochemical milieus. The latter is governed by T helper cells (T_H cells) via the secretion of important immunomodulatory cytokines, IL-4 and interferon-γ (IFN-γ). In fact, Sadtler et al. demonstrated that biomaterial-induced M2 macrophage polarization via IL-4 activation requires T_H2 cells [139]. In a follow-up paper by the same group, the dominant presence of scaffold-associated macrophages has been described, which display a high expression of CD86 and major histocompatibility complex class II (MHC-II), making them eminently equipped to communicate with T cells [140].

Although many immunological aspects remain to be clarified, it is evident that the success or failure of *in situ* tissue engineering is dependent on the host immune response. As such, it is imperative to take the patient's immunological state into consideration when developing scaffolds for *in situ* cardiovascular tissue engineering. Several recent *in vivo* studies have directly investigated the influence of specific patient characteristics on the host response to resorbable biomaterials, as summarized in Table 1 (for extended version see Supplementary Table S1). The findings of these studies do suggest the relevance and importance of patient traits for the host immune response to an implanted biomaterial and the outcome of materials-driven *in situ* tissue engineering, which we will describe in more detail in the follow sections. We predominantly focus on macrophages, as their role in *in situ* tissue engineering is most established and investigated. Given their central role in both biomaterial resorption and tissue regeneration, macrophages, as well as their fused counterparts, the MNGCs, are particularly important for the success or failure of *in situ* tissue engineering. Nevertheless, it is evident that their function in the process of *in situ* tissue engineering is inextricably linked to other immune cells, such as mast cells, neutrophils and T cells. For a more in-depth view on these cells, the reader is referred to recent dedicated review papers

[90,150–152]. Next to these immune cells, also endothelial cells (ECs) and endothelial progenitor cells are of equal importance for reaching homeostasis in cardiovascular *in situ* TE applications, as is evident from recent studies on endothelialisation in the context of *in situ* TE [153–155]. EC functionality is complex and ECs are

Table 1
Examples of preclinical studies with focus on the influence of host-specific characteristics on the FBR to resorbable biomaterials and *in situ* tissue engineering.

Research goal	Experimental set-up	Main findings	Ref
Aging			
Host response in young vs old	Polypropylene (subcutaneous) mesh in young and old mice	Old mice showed delayed resolution of inflammation, more M1 macrophages, lower migration of mononuclear cells.	[141]
Functionalized implant young vs old	Polypropylene (subcutaneous) mesh eluting MCP-1 and IL-4 in young and old mice	Old mice required double MCP-1/IL-4 coating to shift macrophage response to M2, leading to decreased implant scarring. In contrast, in young mice IL-4 alone was more effective to achieve this effect.	[142]
ECM-donor age on graft remodeling	SIS-ECM derived from young and aged pigs as abdominal wall muscle reconstruction in rats	ECM scaffold from young pigs showed dominant M2 macrophage response and resulted in robust constructive remodeling.	[143]
Aorta graft remodelling adult vs old	Heparin impregnated PCL as aorta interposition in adult and old rats	In old rats local narrowing of graft lumen was observed, with extensive flow incongruence with disoriented and less dense collagen fibers in the graft.	[144]
Sex			
Sex-specific host response to TEVG	PGA + PCLA grafts as IVC interposition in male and female mice	Male mice showed lower cellularity, less collagen deposition and maturation, higher graft degradation but lower MNGCs compared to females.	[145]
Diabetes			
Functionalized graft in diabetes	PCL (+/− RGD functionalization) grafts as aorta interposition in diabetic and non-diabetic rats	In diabetic rats an increased macrophage presence, increased platelet adhesion and slower EC and SMC graft coverage was found. The beneficial impact of the RGD in healthy rats, was lost in diabetic rats.	[146]
ASC seeding on scaffold remodeling in diabetes	Decellularized arterial elastin (subcutaneous) scaffolds +/− ASCs seeding, in diabetic and non-diabetic rats	Diabetic rats showed impaired remodeling and healing with increased inflammatory response and a failure to make a phenotypic switch from M1 to M2.	[147]
TEVG seeding with human AD-MSCs from healthy/diseased/aged donors	PEUU grafts +/− AD-MSCs seeding from young/old, (non-)diabetic donors as aortic interposition in rats.	Grafts seeded with cells from diabetic donor showed lower patency rates and reduced fibrinolytic factors production leading to acute thrombosis.	[148]
Foreign body response to subcutaneous discs in diabetes	Polyether-polyurethane sponge discs as subcutaneous discs in diabetic and non-diabetic rats	In diabetic rats, inflammatory parameters were higher, except for macrophage activation which was lower. All fibrogenic markers were lower in diabetic rats. Hyperglycemia downregulates the main features of the FBR.	[149]

Abbreviations: adipose-derived mesenchymal stem cells (AD-MSCs), endothelial cell (EC), foreign body response (FBR), inferior vena cava (IVC), interleukin-4 (IL-4), monocyte chemoattractant protein-1 (MCP-1), multinucleated giant cells (MNGCs), polycaprolactone (PCL), poly(ester urethane)urea (PEUU), poly(glycolic acid) (PGA), poly (lactic-co-glycolic acid) (PCLA), Arg-Gly-Asp motif (RGD), small intestinal submucosa (SIS), smooth muscle cell (SMC), tissue engineered vascular graft (TEVG).

highly sensitive to patient-specific conditions, such as disturbed immunological state or hemodynamics. For a detailed reflection of patient-specific characteristics on EC function, the reader is referred to excellent reviews dedicated to this topic [70–76].

3. Patient demographics and patient-specific systemic variabilities

Patients that are in need of a cardiovascular replacement can be generally divided into two main subgroups: patients with congenital heart disease (Section 3.1) and patients with acquired diseases (Section 3.2). Each of these subgroups has their own specific needs in terms of clinical application (i.e. type of implant), as well as their own span of patient characteristics that may affect intrinsic regenerative potential and, with that, the potential for *in situ* tissue engineering (Fig. 3). Hallmark manifestations of the patient specific systemic variabilities on tissue regeneration as observed in clinical and pre-clinical studies will be discussed below: the influence of ethnicity and socio-demographics (Section 3.2.1), age (Section 3.2.2), sex and gender (Section 3.2.3), and multifactorial diseases, like atherosclerosis, diabetes mellitus and CKD (Section 3.2.4).

3.1. In situ cardiovascular tissue engineering for congenital heart disease

Congenital abnormalities to the heart and/or large vessels are a major cause of death for infants below the age of 1 year [156], with a prevalence of approximately 1 to 2% of all births worldwide [157,158]. Common interventions include the Fontan procedure, in which a large-diameter venous conduit is used to connect the pulmonary artery to the inferior vena cava, and Tetralogy of Fallot, in which the pulmonary valve typically needs to be replaced. So far, all clinical trials for *in situ* tissue-engineered heart valves and blood vessels using resorbable synthetic scaffolds have been conducted on paediatric patients, either as part of the Fontan procedure [13,40,159,160] or pulmonary valve replacement [41]. It is suggested that paediatric patients would benefit most from a living, tissue-engineered graft that is capable of growth and remodeling, as it prevents the need for reoperations that is associated with the current, non-viable substitutes [161]. However, somatic growth of this younger patients also warrants additional complexities in the design of *in situ* TE prosthesis, as described in several recent studies [8,38,162,163]. For example, Feins et al. reported on the development of a growth-accommodating mitral valve annuloplasty ring by combining a braided sleeve around a resorbable core to enable growth of the device upon gradual resorption of the core [162]. In another study by the same research group, they describe the development of (non-degradable) heart valve prostheses that are able to sustain function throughout patient growth by applying an innovative geometrical valve design [163].

In biological sense, paediatric patients represent the 'ideal' patient population for endogenous tissue regeneration, as they are typically free of multifactorial diseases, and thus least compromised. Nevertheless, some sex-specific differences in the manifestation of congenital malformations have been reported, with girls displaying a higher prevalence of atrial septal and atrioventricular septal defects, while boys display a higher prevalence of aortic malformations and Tetralogy of Fallot among other conditions [164]. There have been interesting exploratory studies on the potential for prenatal delivery of an *in situ* tissue-engineered heart valve [165,166]. Besides, due to the improved early treatment and diagnosis, there is also an increasing number of grown-ups with

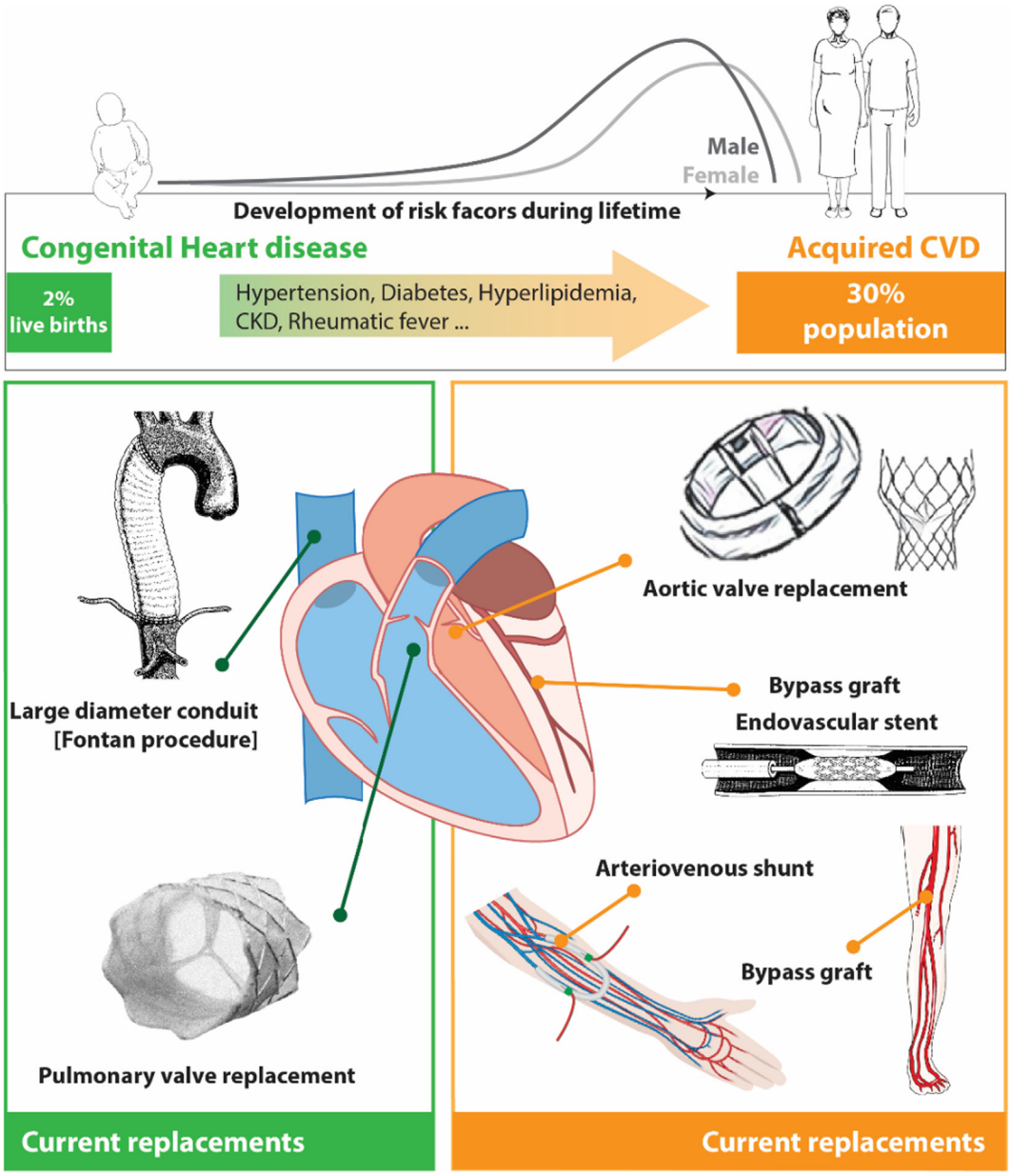

Fig. 3. Patient populations requiring cardiovascular replacements can be subdivided in young patients with congenital heart disease, with a prevalence of 2% of the live births, and adult patients with acquired cardiovascular disease, estimated at 30% of the population. The latter develops risk factors during lifetime, increasing CVD prevalence. Generally, prevalence is higher in the male population, although with old age the female population has a higher prevalence of CVD. Common current replacements for patients with congenital heart disease are large diameter conduits and pulmonary valve replacements, whereas patient with acquired cardiovascular disease often require aortic valve replacements, endovascular stents, coronary and peripheral bypass grafting and in case of CKD arteriovenous shunts. Pulmonary valve adapted from [168]; Aortic valve adapted from [169]; other images adapted from Servier medical art (https://smart.servier.com) or created with Biorender (https://biorender.com/).

congenital heart disease (GUCH) that are in need of cardiovascular replacements [167], thereby broadening the age range of this patient cohort.

3.2. In situ cardiovascular tissue engineering for acquired heart disease

Although paediatric patients represent a highly important target group for tissue-engineered cardiovascular grafts, this is only a relatively small fraction of the total patient population receiving cardiovascular substitutes. Cardiovascular graft implantation in adults is mainly disease-acquired. The population of CVD patients is growing due to aging of the general population as well as behavioural changes, often associated with the development of multifactorial disease [2]. Importantly, in adults, the main clinical need for tissue-engineered implants lies in different anatomical applications when compared to paediatric patients. Unlike for paediatric patients who undergo somatic growth, the current replacement options for large-diameter blood vessels, and to a less extent for pulmonary valves, perform relatively well in adult patients. There, the clinical demand for living implants is largest for small-diameter arteries and the aortic valve for which the current artificial alternatives (i.e. synthetic blood vessel grafts, artificial heart valves) are underperforming. These shortcomings could be overcome by tissue-engineered replacements, due to their intrinsic hemocompatibility (warranted by a regenerated endothelial layer) and their ability to grow and remodel in analogy with their native counterparts.

Creating an *in situ* tissue-engineered heart valve or blood vessel for the adult population is particularly challenging giving the large

diversity in patient-specific characteristics, such as ethnicity and socio-demographic variability (Section 3.2.1), age (Section 3.2.2), sex and gender (Section 3.2.3), and multifactorial diseases (Section 3.2.4).

3.2.1. Ethnicity and socio-demographic considerations

In the American population, age-adjusted prevalence of heart disease differs amongst whites (11.0%), blacks (9.7%), Hispanics (7.4%), and Asians (6.1%) [170]. Socio-demographic variability in CVD prevalence can be attributed to genetic background, region-specific differences in prevalence of CVD risk factors, as well as access to health care [171]. For heart valve replacements, there is an important distinction in patient demographics between high-income countries (mainly Western Europe and the United States) when compared to low-/medium-income or developing countries in Africa and Asia. Whereas calcific aortic valve disease is the most common cause for valve replacement in high-income countries, the major cause of heart valve disease in developing countries is rheumatic heart disease, with a prevalence of 40.5 million patients in 2019 [172,173]. Another important consideration in this matter is that, whereas calcific aortic valve disease predominantly manifests in elderly patients, valve disease due to rheumatic heart disease affects patients over a broad age range, from young adult to elderly [174]. There are no studies to investigate the influence of ethnicity or disease state (e.g. valve calcification versus rheumatic heart disease) on cardiovascular *in situ* tissue engineering. However, the recognition of socio-demographic differences has led to the recent scientific and clinical demand to develop valve replacement options that are affordable and can be implanted without a state-of-the-art operating facilities [175].

3.2.2. Age

One of the most important risk factors for CVD and the need for a blood vessel or heart valve replacement is age. Epidemiological studies have shown that the prevalence of CVD in adults increase with progressing aging [1,176], and old age has been pinpointed as a strong predictor of complications after placement of a cardiovascular prosthesis [177,178]. Moreover, concomitant risk factors for CVD (e.g. valve degeneration and vascular disfunction), including hypertension, hyperlipidemia, and kidney failure, are often present in elderly patients [179]. Aging is a complex process generally characterized by functional and regenerative decline. Alterations associated with aging range from the cell level (e.g. epigenetic change and cellular senescence) [180] to the tissue level (e.g. vascular matrix stiffening due to crosslinking induced by increased advanced glycation end-products (AGE) [181] and a reduced tissue remodeling capacity [182]). Additionally, on a hemodynamic level, aging is associated with elevated blood pressure in Western societies, marked by high levels of stress, high salt intake and obesity [183], whereas in other cultures this age-dependent rise in blood pressure is not necessarily observed [184]. Furthermore, the immune system is also affected by advanced aging, which can be defined by two main processes: (1) immunosenescence, which is characterized by decreased levels of circulating immune cells, delayed migration of immune cells and a disrupted cytokine response, and (2) inflammaging, which is characterized by systemic low-grade chronic inflammation, including elevated serum levels of pro-inflammatory cytokines and ROS, and decreased levels of IL-10 [185,186]. Consequences of this aging immune system clinically manifest themselves in the form of delayed wound healing in the elderly, with a slower immune cell recruitment and decreased collagen deposition [187,188]. Correspondingly, Anstine et al. demonstrated that the recruitment of monocytes and macrophages in murine heart valves was dependent on the age of the animals, and that the cellular composition in the valves changed with age [189].

In the context of the *in vivo* response to a biomaterial, few preclinical studies have been conducted specifically focussing on the effect of aging on the FBR. Implantation of polycaprolactone (PCL) small-diameter vascular grafts resulted in local narrowing of graft lumen in 75% of aged rats, whereas limited narrowing was found when implanted in young adult rats [144]. In addition, deposited collagen fibers were disoriented and less dense within constructs of the old rats [144]. Hachim et al. implanted a polypropylene mesh subcutaneously in 8-week and 18-months old mice. The aged animals showed a delay in macrophage recruitment, combined with a more pro-inflammatory response and lack of resolution of inflammation at later stages (Fig. 4A). Moreover, in follow-up research the efficacy of biomaterial functionalization with MCP-1 and/or IL-4 was different in old mice compared to young mice[142], indicating the necessity for distinct strategies for effective functionalization within an aging population

3.2.3. Sex and gender

The cardiovascular system exhibits differences based on sex and gender, with the sex represents the biological classification, while gender is defined as the social identity. In terms of variability between biological sexes, females have more compliant blood vessels with a smaller diameter compared to males [190–193]. Additionally, males exhibit higher blood pressures when compared to females throughout, independent of race and ethnicity. On the other hand, the rise in blood pressure accelerates in females post-menopause, leading to a higher hypertension rate in females compared to males by the age of 65–70 [183]. The age-adjusted prevalence for a variety of CVD conditions is higher in males than in females: heart disease (male 11.8% vs female 9.5%), coronary artery disease (7.2% vs 4.2%), hypertension (26.0% vs 23.1%), and stroke (3.3% vs 2.5%) [194]. Although CVD are initially less prevalent in females, the risk for CVD increases in females after menopause, and by the age of 80 prevalence is higher in females than males [158]. In addition, CVD exhibit strong sexual dimorphisms in development and progression as described by Arnold et al. [195]. For example, sexual dimorphism in incidence, plaque burden, progression, and complications of atherosclerosis are being observed [196]. Male patients more often suffer from occlusive coronary artery disease, whereas the cause of coronary artery disease in female patients is more often microvascular disfunction such as pathological vasoreactivity [197]. In addition, males have a higher risk for aortic valve stenosis, with especially more calcification compared to females [198]. However, in females, the same amount of aortic valve calcification leads to more severe aortic stenosis when compared to males [199].

In addition to differences in disease incidence and progression between males and females, the outcome of cardiovascular interventions varies as well. For example, outcomes are less favourable for adult female patients after aortic valve and combined aortic valve-coronary artery surgery, as well as percutaneous coronary interventions when compared to male patients [200–202]. Moreover, certain risk factors might not contribute to the disease process equally in males and females. For example, diabetes was found to be a higher risk for CVD in females compared to males, as reviewed in [203]. Cardiovascular research has classically been male-oriented, however awareness in sex and gender differences in the timing of diagnosis, the disease process, as well as the disease presentation is increasing [204,205].

Sex-based differences in wound healing and immune response are generally described as females exhibiting a more reactive immune response against infection and immunization when compared to males [206]. In murine models, macrophage activity and phagocytosis was increased in young female animals when compared to male animals [207]. Additionally, neutrophils from healthy young adult females were reported to have a more acti-

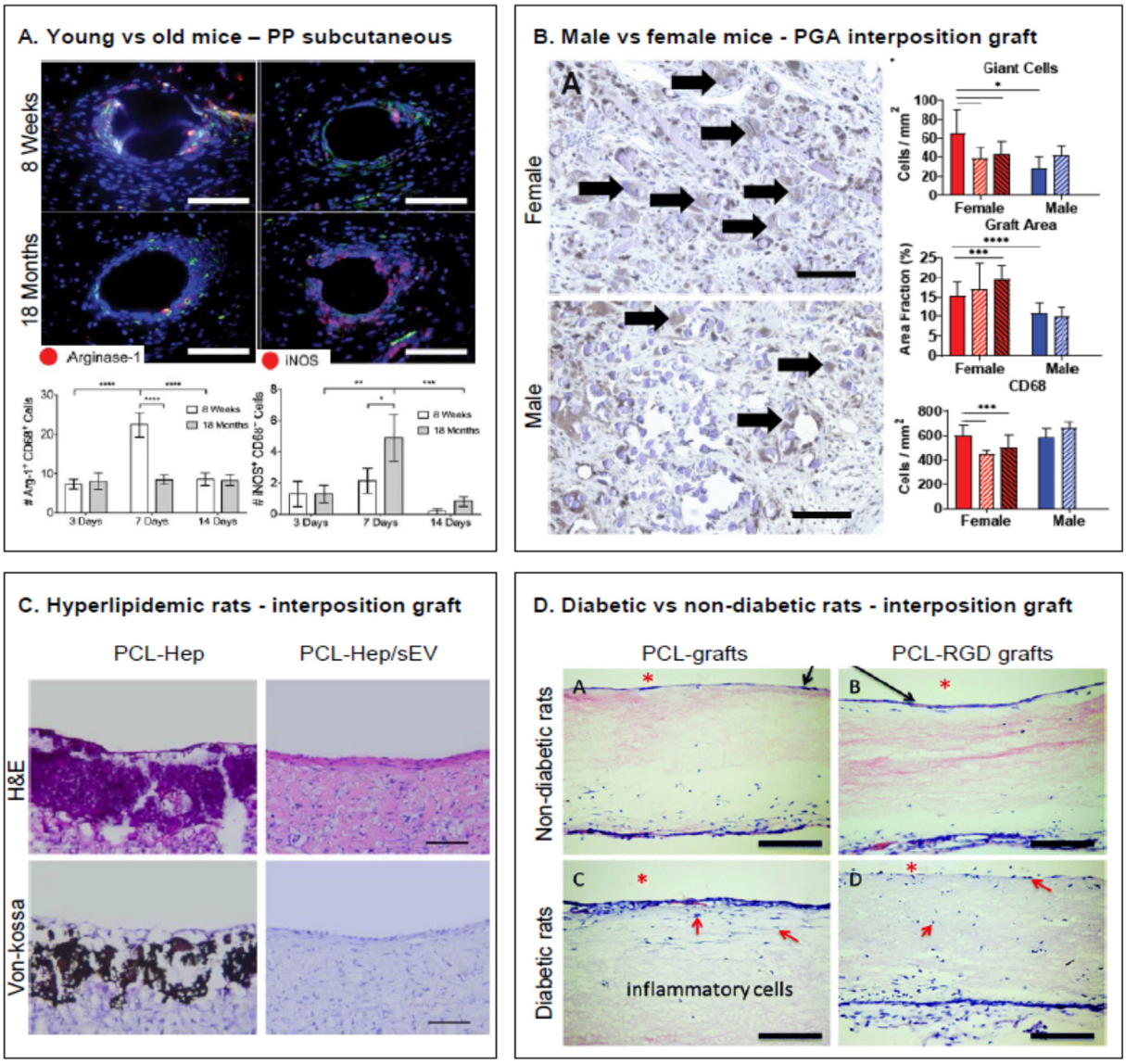

Fig. 4. Examples of recent research investigating the effect of patient characteristics on the host response to a biomaterial. Increased pro-inflammatory macrophages was observed in aged mice when compared to young mice after subcutaneous implantation of a polypropylene (PP) mesh (**A**) (adapted from [141]). Within polyglycolic acid-based (PGA) vascular interposition grafts, more MNGCs were present in female mice compared to male mice, although more graft resorption was present in male mice and CD68 + cell presence was similar (**B**) (adapted from [145]). Within hyperlipidemic rats, functionalization of polycaprolactone (PCL) vascular interposition grafts with heparin (Hep) and stem cell-derived extracellular vesicles (sEV) reduced fibrosis and calcification (**C**) (adapted from [263]). Within diabetic rats, PCL vascular interposition grafts attracted more inflammatory cells and RGD functionalization did not result in similarly functional remodeling as in non-diabetic mice (**D**) (adapted from [146]).

vated/mature phenotype, characterized by an increased pro-inflammatory response, enhanced activity of type I interferons, and an increased ability to form NETs when compared to males [208,209]. The impact of these differences on the inflammatory response to an implanted biomaterial and the FBR is often overlooked. In *in vitro* studies, only 10.3% of the studies within this field reported the sex of the used primary cell source [210]. However, awareness is increasing also in other tissue engineering-related fields, as illustrated by a recent reflection on sex bias in the field of 3D-bioprinting for kidneys [211]. Pre-clinical studies now increasingly report animal sex as a biological variable due to changes in National Institutes health (NIH) policy, however, studies specifically focusing on sex differences are few. Recently, sex-specific differences were described in response to non-degradable stent implantation in mini-pigs, in terms of the initial injury and inflammation, as well as tissue formation (neointimal fibrin deposition and adventitial fibrosis). In addition, subtle differences in timing and extent of resolution of inflammation and fibrin clearance were reported and suggested that these difference, although subtle, might be very influential when using degradable materials [212]. When focusing specifically on *in situ* cardiovascular tissue engineering, only one study reports on the direct comparison in the *in vivo* regenerative response between male and female animals [145]. They reported on decreased MNGC formation in female mice when compared to male mice in response to implantation of resorbable polyglycolic acid with poly(lactic-co-glycolic acid) composite grafts as interposition graft in the inferior vena cava (Fig. 4B). Sex hormones represent one important cause of these differences between sexes, and especially estrogen, which is suggested to have an anti-inflammatory effect [213]. Additionally, estrogen is thought to create a favourable systemic environment, for example in terms of a favourable lipid balance, reduced oxidative stress and a reduced blood pressure in pre-menopausal females [214–218]. Additional sources of sexual dimorphisms in

cardiovascular disease and the immune system may be due to dimorphisms in sex chromosomes, such as specific genes encoded only in Y gene, incomplete X chromosome inactivation, and differences in epigenetic changes, as reviewed elsewhere [219,220]. The need of a deeper understanding is especially illustrated within the transgender population, for whom hormone therapy is shown to increase the risk for CVD [221–223]. This indicates that sex differences cannot be explained by hormonal variation by itself, and emphasizes that a more holistic approach is needed to truly unravel this biological variability and how to translate this to tailored treatments.

3.2.4. Multifactorial diseases

CVD often occurs as a result of or in conjunction with other diseases, such as diabetes mellitus (DM) or chronic kidney disease (CKD) [224]. These multifactorial diseases often are associated with systemic metabolic disorders, also referred to as metabolic syndrome. Metabolic syndrome is defined as a set of conditions, like hypertension, hyperglycaemia, obesity and dyslipidemia, which increase the risk of developing CVD like pathological atherosclerosis, as well as diabetes type II, and CKD [225,226]. For a large part these diseases have shared risk factors, related to genetics or lifestyle [227]. This is illustrated by the population-attributable fraction for CVD mortality, which have been reported to be high blood pressure (41%), smoking (14%), poor diet (13%), insufficient physical activity (12%), and abnormal glucose levels (9%) [227]. Metabolic syndrome manifestations, such as hyperglycemia and hyperlipidemia collectively contribute to oxidative stress and moderate chronic inflammation, which results in accelerated atherosclerosis, fibrosis, excessive inflammation, vascular wall stiffening, calcification, macro- and microvascular dysfunction and early implant failure [228–234]. Moreover, metabolic disturbances impair all stages of the natural wound healing response, characterized by endothelial dysfunction and aberrant tissue formation resulting in thrombosis, intimal hyperplasia and fibrosis, aneurysm formation and indications of atherosclerotic disease progression [235–240].

3.2.4.1. Diabetes mellitus. DM is an umbrella term that describes a group of metabolic disorders which are characterized by hyperglycaemia, with DM type 1 being characterized by deficient insulin secretion and DM type 2 by insulin resistance [241]. Diabetes is an important risk factor for developing CVD and a substantial part of the patients requiring cardiovascular implants suffer from diabetes. With respect to interventional outcome, type 2 diabetes is an independent predictor of long-term mortality after coronary artery bypass grafting (10-year mortality diabetic (47.3%) compared to non-diabetic (29.6%); 553 non-diabetic and 1213 diabetic patients included) [242]. Other studies showed that diabetic patients undergoing PCI show an increased risk of intimal hyperplasia and restenosis when compared to non-diabetic patients [243,244], as well as decreased long-term survival [245]. Multiple studies report an association between diabetes and bioprosthetic heart valve dysfunction, with increased risk for earlier reoperation and increased mortality in diabetics when compared to non-diabetic patients [246,247]. Another compromising factor is the observed calcification levels in arteries of diabetic patients [248].

These clinical observations of failing cardiovascular implants in diabetic patients stress the additional challenges faced for *in situ* cardiovascular tissue engineering in diabetic patients. On a more fundamental level, the largest part of the preclinical studies in diabetic animal models revolves around the disturbed (sub)cutaneous (implant) wound healing. Overall, the diabetic animal models tend to show a delayed inflammatory response around implants and increased infectious complications. This is not unexpected, since, in the clinic, diabetic patients show an increased susceptibility to infections [249]. The immune deficiencies in the diabetic patients seem to mainly involve the innate immune system (reduced function of polymorphonuclear cells and monocytes/macrophages) and to a lesser extent also the adaptive immune system (decreased T lymphocyte function) [249,250]. Wound tissue from diabetic patients show a higher M1/M2 macrophage ratio compared to wound tissue from non-diabetics [251].

Several studies have directly investigated the influence of diabetes on *in situ* vascular tissue engineering in animals (also listed in Table 1). Exemplary is a series of studies by the group of Deling Kong. They reported on the improved remodeling and regeneration of RGD-functionalized PCL vascular grafts, when compared to non-functionalized PCL grafts, after 1 month of implantation as carotid artery replacement in healthy rabbits [252]. With the same RGD-functionalized vascular grafts, a second study was performed in diabetic rats, in which the grafts were implanted as abdominal aorta interposition grafts in diabetic and non-diabetic rats. After 1 month, the PCL grafts in the diabetic rats showed high rates of inflammation, plenty of platelet aggregates and some calcification formation in one animal. In contrast to the findings in the healthy rabbits, the PCL-RGD functionalization had no beneficial impact anymore in the diabetic rats [146] (Fig. 4D). The authors hypothesized that the apparent lack of performance in the diabetic rats was partially due to the detrimental effect of diabetes on endothelial reformation, which was delayed in the diabetic animals [146]. Other studies have reported on a diabetes-associated decreased fibrinolytic activity, resulting in increased risk for thrombus formation in vascular grafts when compared to non-diabetic animals [148,253]. Chow et al. reported on increased stiffening of collagen (from decellularized porcine aortic roots) and elastin scaffolds (from decellularized porcine carotid arteries) after 1 month of subcutaneous implantation in diabetic rats, when compared to non-diabetic rats [230]. The authors postulated this to be due to cross-link formation induced by the diabetic environment with accumulation of AGEs and lipid peroxidation products, as well as increased $CD68^+$ macrophage infiltration. In a follow-up study, they reported on the failure of the M1 to M2 macrophage phenotypic switch in elastin scaffolds in diabetic rats, in contrast to non-diabetic rats [147]. The authors hypothesized that these findings are probably due to the presence of permanent hyperglycaemic and oxidative stress and the decreased activity of endogenous antioxidants in the diabetic rats. This could partially be rescued by preseeding with adipose tissue-derived stem cells onto the graft, which are known to exert immunomodulatory properties [147].

3.2.4.2. Dyslipidemia and obesity. Atherosclerosis can be considered one of the most common vascular pathologies globally and is often the underlying cause of stent placement or a coronary bypass procedure [231,254]. Two of the most important risk factors of atherosclerosis are obesity and dyslipidemia, predominantly hyperlipidemia, which implies an increase in total phospholipid fatty acid serum levels, including saturated fatty acids (i.e. palmitic acid, stearic acid, lauric acid, and myristic acid) [234,255]. Saturated fatty acid intake has been correlated with an increase in total circulating cholesterol levels, as well as low-density lipoprotein cholesterol (LDL) specifically, the main lipoprotein associated with atherosclerosis development [256]. Hypercholesterolemia can be inherited as a genetic disorder (familial hypercholesterolemia) which causes LDL levels to be very high, increasing the risk to develop atherosclerosis early in life [257].

Dyslipidemia, for example characterized by elevated levels of low over high density lipoprotein cholesterol (LDL-C/HDL-C), have been shown to be predictive for incidences of major adverse cardiac events, like stent thrombosis, after PCI [258]. The impact of obesity remains debatable [259], although the highest body mass index (BMI) quartiles were associated with poorer arteriovenous

fistula maturity (BMI $\geq$ 35) [260] and early complications (i.e. infections) after coronary artery bypass grafting surgery (BMI $\geq$ 40) [261]. Although obesity constitutes a variety of systemic alterations, generally including dyslipidemia, it was described that these alterations reprogram macrophage-biomaterial interactions. Boersema et al. reported on an *in vitro* study in which the response of human monocyte-derived macrophages isolated from obese donors to a variety of biomaterials was compared to that of healthy age- and sex-matched individuals [262]. Their findings were that the responses were biomaterial-specific and that macrophages from obese patients generally responded in a more pro-inflammatory fashion (in terms of surface marker expression and cytokine secretion) when compared to the cells of lean subjects, even when isolated from their diseased environment and placed into an idealized *in vitro* setting.

In order to prolong graft patency in atherogenic environments and induce homeostasis, few attempts have been made to create grafts with immunomodulatory properties, as proposed for *in situ* tissue engineering. Illustrative is the study of Wei et al. who demonstrated that the incorporation of mesenchymal stem cell-derived extracellular vesicles in a heparinized PCL vascular graft contributed to a M2 macrophage subtype, enhanced endothelialisation and reduced thrombosis and calcification in an atherogenic environment [263] (Fig. 4C). It is further noted that alternative lipids, like poly unsaturated fatty acids and high density lipoprotein (HDL) can be used for their anti-inflammatory properties. Galetti et al. already acclaimed in 1989 the benefit of a polyunsaturated fatty acid-rich diet on reendothelialization, neo-tissue formation and long-term graft patency of biodegradable polyurethane infrarenal aortic grafts implanted in pigs [236]. Similar observations were made for HDL that proved to have anti-inflammatory, anti-oxidative, anti-apoptotic and endothelial regenerative properties [264,265] ultimately resulting in advanced wound healing [238] and attenuated vein graft atherosclerosis. These findings further propose that cells that are exposed to pro-atherogenic stimuli modify the regenerative response and might require extra stimuli to induce long-term graft patency in *in situ* tissue engineering cardiovascular implants.

3.2.4.3. Chronic kidney disease and vascular access grafts. One important target application for *in situ* tissue engineering is the vascular access graft for renal dialysis. There is a rise in prevalence and incidence of CKD and end-stage kidney disease (ESKD) as a consequence of the increasing life expectancy of the general population in combination with high prevalence of risk factors, such as obesity [225,226]. Although regional differences exist worldwide, CKD occurs approximately twice as much in diabetics when compared to age- and sex-matched non-diabetics [266]. Patients who are at the most advanced stage of CKD (stage 5), known as ESKD patients, require renal replacement therapy (dialysis or kidney transplantation). Globally, the number of people receiving renal replacement therapy is expected to increase from approximately 2.5 million patients at present to 5.4 million patients by 2030 [267]. Hemodialysis treatment is the most widely used renal replacement therapy (70–90%), which implies that these patients require the creation of a vascular access [268]. This vascular access is often a fistula, graft or tunneled catheter, and allows the patients' bloodstream to be connected to the hemodialysis device [269]. Successful long-term haemodialysis relies on a functional vascular access, and is therefore often called the 'Achilles heel of hemodialysis therapy' [270]. Unfortunately, high rates of venous stenosis caused by intimal hyperplasia formation, result in vascular access dysfunction, if the vascular access was able to mature in the first place [271–273]. The exact underlying mechanism of the pathobiology of vascular access dysfunction remain a topic of debate. CKD and ESKD patients show increased vessel thickness and calcification, which is suggested to be caused by increased SMC proliferation induced by the increased oxidative and proinflammatory environment with increased levels of AGEs and ROS [274]. When assessing tissue segments from stenosed lesions of the arteriovenous fistulae and polytetrafluoroethylene (PTFE) grafts from human patients, it appeared that the venous segment stenosis mainly consists of myofibroblasts with a few contractile SMCs. In the PTFE grafts, the intragraft cells were mainly macrophages [275]. As arteriovenous fistula creation is not always possible in CKD patients and non-degradable grafts occlude, one of the proposed solutions is the development of tissue engineering strategies [270]. Recently, a phase 2 clinical trial by the Niklason group showed successful implantation of bioengineered human acellular vessels, which recellularized and remodelled into functional endogenous tissue that could be used as vascular access in ESKD patients [276].

4. Influence of patient-specific microenvironmental factors at the cellular level

As described in Section 3, the combination of various systemic factors defines the patient-specific immunological state and regenerative capacity (Fig. 5A). In order to distil the underlying biological mechanisms, the following section will address the influence of these defining microenvironmental factors at the cellular level (Fig. 5B), with a focus on the key cellular players that govern biomaterial resorption and tissue formation: macrophages and tissue producing cells within the extracellular matrix (ECM) (Fig. 5C). We will describe the influence of (sex) hormones (Section 4.1), the effect of a shift in redox balance/oxidative stress as observed in aging (Section 4.2), the effects of metabolic systemic disturbances: hyperglycaemia (Section 4.3.1) and fatty acids/palmitate (Section 4.3.2), the influence of uremic conditions as a result of kidney failure (Section 4.4), and variability in hemodynamic loads as an effect of e.g. stiffening or dilation of the vessel wall, narrowing of the vessels, or elevated blood pressure (Section 4.5).

4.1. Sex hormones

Female sex hormones, such as estrogen and progesterone, and male sex hormones, especially testosterone, are well known to differ between males and females and impose numerous differences in development between the sexes. Moreover, the temporal changes in concentrations of sex hormones are highly variable between males and females, which makes that sex-specific differences between patients should always be studied in correlation with patient age. During reproductive years in females, levels of estrogens are generally high, however variable throughout the menstrual cycle (e.g. Estradiol: 210–740 pmol/L) [277,278]. After menopause, estrogen levels decline rapidly and remain low throughout life (e.g. Estradiol > 15 pmol/L) [279]. In males, testosterone levels rise during puberty and slowly and steadily decline with aging [280]. Estrogen, and specifically its most potent isoform 17β-Estradiol (E2), has been suggested to be at least in part responsible for the cardioprotective effect in pre-menopausal females, who exhibit a reduced incidence of CVD compared to age-matched males [213]. In addition, in young women who had an ovariectomy, prevalence of coronary artery disease was greater compared to women with intact ovaries [281].

On a more fundamental level, sex hormones have direct effects on both macrophages and VSMCs, as well as ECM remodeling as a result of that. Ovariectomized (OVX) animal models are widely used to study the effect of sex hormones on cardiovascular pathologies. Using an OVX mouse model, Liu et al. recently found estrogen to be directly responsible for reducing vascular stiffening through inhibition of

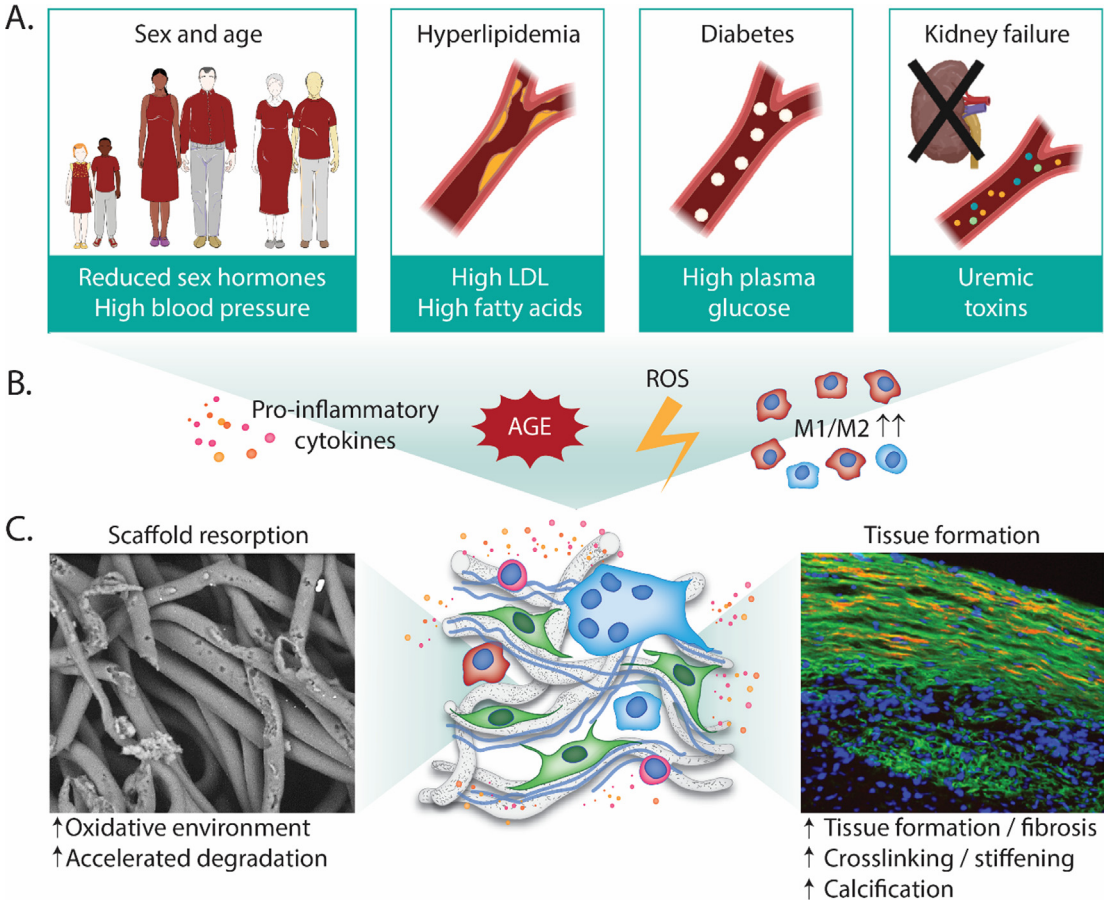

Fig. 5. Overview of patient characteristics possibly influencing immune-driven regeneration. Patient characteristics including sex, age, hyperlipidemia, diabetes and kidney failure change systemic conditions such as sex hormones, blood pressure, LDL, fatty acids, plasma glucose, and uremic toxins, respectively (A). Systemic decreases and increases in these factors contribute to a local graft environment rich in pro-inflammatory cytokines, AGE, ROS and pro-inflammatory macrophages (B), which can affect the scaffold resorption and tissue formation, during the immune-driven regenerative response (C). Images adapted from [32,65] and Servier medical art (https://smart.servier.com).

macrophage secretion of elastase (MMP-12) [282]. Estrogen has been reported to decrease neointima hyperplasia and improve re-endothelialisation after coronary artery stenting in pigs [283]. Bowling et al. demonstrated that estrogen reduced the pro-inflammatory response of bone marrow derived-macrophages and VSMCs after arterial injury in an OVX mouse model [284].

4.1.1. Influence of sex hormones on macrophages

When focusing on the effects of macrophages specifically, *in vitro* studies using human peripheral blood-derived macrophages revealed that estrogen receptors directly influenced polarization through nuclear translocation of nuclear factor-κB (NF-κB) transcription, involved in pro-inflammatory M1 polarization [285] (Fig. 6). After stimulation with pro-inflammatory compounds such as lipopolysaccharide (LPS) and IFN-g, high estrogen levels reduced TNF-a expression, upregulated IL-10 expression, and induced upregulation of CD206 and CD163 marker expression by human macrophages, indicative of an anti-inflammatory phenotype [286,287]. In addition, estrogen stimulation increased migration only for M2 polarized macrophages but not for M1 polarized macrophages [288]. In RAW264.7 macrophages, stimulation with high estrogen levels combined with anti-inflammatory stimuli, led to an upregulation of IL-10, again suggesting estrogen facilitates in the onset of inflammation resolution [289].

4.1.2. Influence of sex hormones on tissue cells and matrix remodeling

In addition to modulating inflammation, estrogen has also been described to have direct effects on VSMC function and tissue remodeling. For example, a phenotype-dependent effect of estrogen was found in *in vitro* cultured rabbit aortic SMC; high levels of estrogen induced prolonged G0 phase before entering cell cycle in contractile SMCs, while in synthetic SMCs estrogen stimulated proliferation [290]. Huang et al. isolated VSMCs from human saphenous and umbilical veins in which E2 stimulation reduced proliferation and migration, however, interestingly, the same concentration of E2 stimulated proliferation in VSMCs isolated from varicose veins [291]. The effect of hormones on tissue deposition by human VSMCs has been studied by Natoli et al. in a 4-week *in vitro* culture [292]. The addition of all sex steroids (i.e. estrogen, progesterone and testosterone) reduced collagen deposition by these cells, with the highest reduction caused by estrogen. In addition, the ratio between elastin and collagen ratio was highest in the estrogen and progesterone groups, when compared to testosterone alone. In terms of tissue remodeling, testosterone was found to increase expression of MMP-3 when compared to estrogen, whereas MMP-2 was not affected by addition of any of the tested sex hormones [292]. Additionally, Grandas et al. showed estrogen to induce membrane type (MT)1-MMP secretion, but unaffecting MMP-2 nor tissue inhibitor of metalloproteinase (TIMP) RNA levels in human VSMCs [293].

Taken together, these data suggest that high (i.e. pre-menopausal) levels of estrogen generally promote M2 macrophage polarization and resolution of inflammation and that estrogen plays a role in maintaining elasticity of cardiovascular tissue by maintaining the elastin/collagen balance. However, estrogen

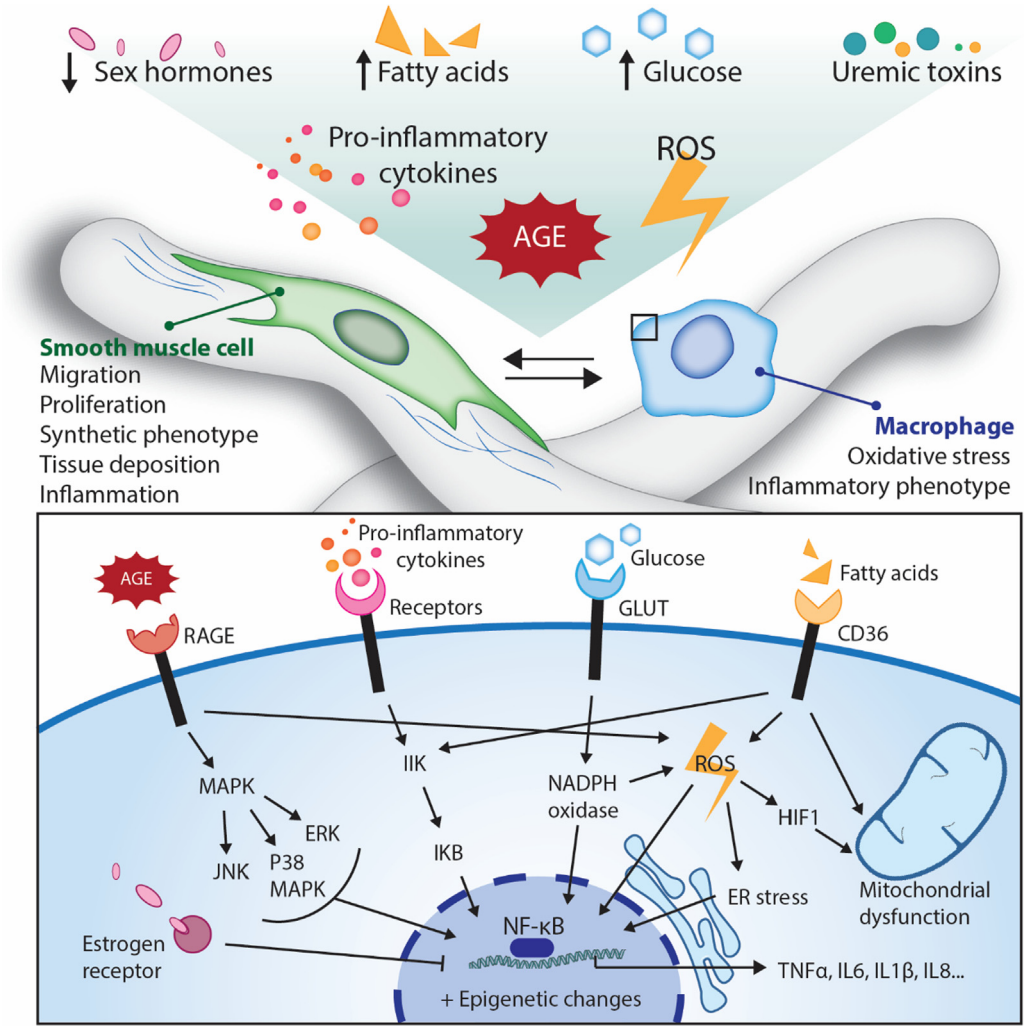

Fig. 6. Schematic overview of the effects of estrogen, fatty acids, glucose, and uremic toxins, and consequently increased systemic pro-inflammatory cytokines, AGE and ROS on smooth muscle cells and macrophages and the intra-cellular pathways involved in these effects. Organelle schematics adapted from Servier Medical Art (https://smart.servier.com).

receptor expression, and thus the effect of estrogen, is very heterogenous and varies e.g. with cell type, sex, age, estrogen levels, and even location in vasculature [294–297] (Supplementary Table S2). Next to these direct effects, estrogen is also known to have a regulatory, and in high concentrations favourable, function on other factors that influence wound healing and cardiovascular remodeling, such as oxidative stress, lipid balance and blood pressure [214–218]. Although estrogen has been thoroughly investigated, it is hypothesized that the observed effects after menopause are not solely the effect of declining estrogen levels, but rather due to a shift in the estrogen-androgen balance. High serum testosterone levels are thought to be immune suppressive, as it was shown that testosterone directly inhibits TLR4 receptor expression in macrophages in a mice model [298]. Moreover, using systematic data analysis, a high serum level of testosterone was correlated to inhibition of inflammatory cytokine expression such as TNF-a, IL-6 and IL-1 as well as inhibition of adipose tissue formation. A low serum level of testosterone, however, was associated with higher inflammatory marker expression [299].

4.2. Redox balance/oxidative stress

Oxidative stress is a redox imbalance with high presence of ROS and reactive nitrogen species (RNS). In healthy individuals, such an imbalance can locally occur as response to a foreign body or biomaterial, where macrophages produce high levels of hydrogen peroxide in an oxidative burst reaction, which causes DNA damage and apoptosis. Upon resolution, reductive enzymatic processes normally re-establish the local redox balance. However, with advanced age, a chronic redox imbalance can occur as a result of a weakened anti-oxidant defense and increased production of ROS/RNS. This imbalance with increased ROS activates pro-inflammatory signalling pathways, including NF-κB, contributing to a chronic inflammatory environment as found in elderly [300,301] (Fig. 6).

4.2.1. Influence of oxidative stress on macrophages

In vitro studies have shown that oxidative stress can affect immune cell functionality. For example, Bauer et al. showed that human peripheral blood-derived monocytes are very sensitive to ROS-induced apoptosis due to lower repair mechanisms after DNA damage. However, after stimulation with granulocyte–macrophage colony stimulating factor (GM-CSF) to induce monocyte-to-macrophage differentiation, the differentiated macrophages became more ROS-resistant [302]. In addition, hydrogen peroxide stimulation upregulated a-SMA in human peripheral blood-derived monocytes, as well as fibronectin in macrophages, suggesting a possible role of oxidative stress in

monocyte-to-myofibroblast *trans*-differentiation [303]. Moreover, ROS stimulation promoted pro-inflammatory gene expression through histone acetylation via activation of NF-κB and Activator Protein 1 (AP1) transcription factors in alveolar macrophages [304].

4.2.2. Influence of oxidative stress on tissue cells and matrix remodeling

Next to immune cells, oxidative stress is also influential on endothelial and VSMCs behaviour. For example, vascular balloon injury caused abnormal endothelial nitric oxide synthase (eNOS) localization in aged rats compared to young rats [305]. After percutaneous coronary intervention, oxidative stress is increased via cytoplasmic NADPH oxidase 2 (Nox2), eNOS uncoupling and mitochondrial dysfunction. As a consequence, endothelial dysfunction, VSMCs proliferation, migration and hypertrophy follow, ultimately leading to restenosis [306]. Interestingly, male and female VSMCs react differently to oxidative stress; aortic VSMCs isolated from male rats produced more ROS and underwent apoptosis easier after oxidative stress induction compared to VSMCs isolated from female rats [307]. Additionally, *in vitro* male VSMCs exhibited a stronger response to nitric oxide (NO), with stronger inhibition of proliferation, migration and neointima hyperplasia. Whereas *in vivo* in female rats, more neointima hyperplasia was found [308].

In addition to these effects on macrophages and VSMCs, ROS also targets biomolecules, such as lipid peroxidation and protein oxidation, as well as a biomaterial itself. The degradable polymers used for *in situ* cardiovascular tissue engineering, are often susceptible to oxidative degradation, usually via macrophage production of ROS [65,103]. Consequently, it is conceivable that chronic oxidative stress as present for example in elderly and diabetic patients, might alter the degradation kinetics of a biomaterial. Several studies on *in situ* tissue engineering of vascular grafts have reported on the targeting of the redox balance, for example via Resveratrol- or NO-eluting grafts [309–311], which may prove a high-potential strategy to stimulate functional vascular tissue regeneration, even in compromised conditions of redox disbalance.

4.3. Metabolic disorders

Overall, both hyperglycemic environments as well as lipid products like saturated fatty acids, exacerbate inflammation and activate pro-inflammatory cellular signaling pathways, despite the absence of infection or tissue damage [234,312–315] (Fig. 6). Although this is an oversimplification, several studies suggest that the two main metabolic pathways of macrophages, namely (1) glucose uptake via the glucose transporter (e.g. GLUT1) and (2) fatty acid uptake via fatty acid transporter (e.g. CD36), are also reflecting the macrophage polarization state. In this viewpoint, M1 macrophages mainly use aerobic glycolysis as a quick energy source, whilst the more regenerative M2 macrophages rely on the sustained energy supply of fatty acid oxidation [316–318].

4.3.1. Hyperglycaemia

Blood sugar levels in the body are tightly regulated by the rate of glucose synthesis by the liver and glucose uptake by peripheral tissues. Healthy fasting blood glucose levels are kept below 100 mg/dL (<5.6 mmol/L) [319]. In type-II diabetes, fasting blood glucose of >126 mg/dL (>7 mmol/L) are called hyperglycaemic and are toxic for both macro- and microvascular systems, and therefore sometimes referred to as glucotoxicity [320]. Hyperglycaemia is thought to be the initiator of vascular tissue damage. In diabetes patients, the hyperglycaemia-induced damage is hypothesised to be caused via either repeated acute changes in cellular metabolism and/or through glycation of proteins in the circulation combined with AGE accumulation on ECM proteins. When AGEs react with its receptor (RAGE), oxidative stress and pro-inflammatory signalling pathways are induced (Fig. 6), which eventually result in the vascular damage [319].

4.3.1.1. Advanced glycation end products. AGEs are formed when plasma glucose irreversibly cross-links to proteins and lipids, resulting in matrix stiffening [231]. As the formation of AGEs is spontaneous and slow, mainly long-lived proteins with exposed lysine residues are affected, which makes especially the arterial proteins collagen and elastin susceptible to AGE formation. Besides the long half-lives of the proteins, the second determinant of spontaneous AGE formation is the glucose concentration. Hence, the diabetes-associated hyperglycaemic environment increases the change of the spontaneous AGE formation to occur. AGE products can crosslink or form protein adducts on collagen or elastin fibers, and accumulate over the course of months or years to ultimately lead to the irreversible, highly stable crosslinked collagen and elastin, and a stiff vascular wall [321]. The stiffening is further enhanced by the inhibiting effect of high glucose on MMPs, which leads to impaired matrix remodeling and consequent fibrosis and calcification [51]. AGEs can also react with the specific receptor RAGE, which results in oxidative stress and pro-inflammatory signalling causing endothelial dysfunction, stiffening and microvascular complications. The mechanism of AGE formation in the context of diabetes is extensively described by Negre-Salvayre et al. [319]. Next to these downstream pathways, the presence of AGEs in ECM facilitates the entrapment of LDL in the ECM of the vessel wall. Besides stiffening and build-up of LDLs, oxidant-induced fragmentation of glucose and lipid molecules results in short-chain reactive compound formation, which in turn can oxidise proteins and form AGEs [228].

4.3.1.2. Influence of hyperglycaemia on macrophages. The chronic tissue inflammation observed in diabetic patients is characterized by increased presence of tissue resident macrophages with an increased production of pro-inflammatory cytokines (e.g. IL-6, IL-8, TNF-a, IL-1b) [312,322,323]. The direct effect of hyperglycaemia on monocytes/macrophages is still a topic of debate [324] (Supplementary Table S3). Overall, it is observed that monocytes and macrophages, either cultured in hyperglycaemic conditions or isolated from diabetic patients, adopt a more pro-inflammatory M1-like phenotype (Fig. 6). Nevertheless, few groups reported enhanced M2 marker expression in response to hyperglycaemia [249] and others observed unchanged M1 levels versus a decrease in M2 macrophages in diabetic patients [325].

Particularly relevant in the context of *in situ* tissue engineering is the observation in diabetic patients that macrophages fail to switch from a pro-inflammatory M1 to a pro-regenerative M2 phenotype. It is thought that this failure is caused by the hyperglycaemic environment, which to a great extent causes oxidative stress, combined with reduced availability of antioxidants [147,326,327] Although the underlying molecular mechanisms remain unclear [323], various studies have been performed to shed light on this failure to switch, especially in the context of diabetic cutaneous wound healing. Some studies suggest that it might be caused by increased levels of TNF-a, hampering the phenotypical switch from an M1 to an M2 phenotype [328]. Besides, the epigenetic methylation also appears to have a large role in the failure to shift from M1 to M2. A study in type-II diabetic mice found promotor hypomethylation for genes typical for M1, while hypermethylation was observation for the M2 related genes. The authors suggest that these epigenetic alterations skew the macrophage phenotype towards M1 [329]. When macrophages were co-cultured with diabetic fibroblasts in a 3D skin model, macrophage polarization was directed towards M1 [330].

4.3.1.3. Influence of hyperglycaemia on tissue cells and matrix remodeling. The vascular cells that directly experience high blood glucose levels and abnormal insulin levels are the endothelial cells. In diabetes, ECs decrease NO secretion and excessively increase the generation of ROS [228]. In contrast to ECs, VSMCs develop an inflammatory phenotype in response to the hyperglycaemic oxidative environment. Increased proliferation and migration of the VSMCs, as well as excessive ECM production have been observed [231,331]. The increased proliferation and migration of VSMCs to the intimal layer seem to be an effect of the upregulation of chemotactic growth factors and cytokines and degradation of elastic lamina [331,332] as a result of high glucose levels. Increased ECM production by VSMCs may eventually lead to vascular calcification [231]. Although diabetic vascular calcification is not completely understood, a key step appears to be osteogenic differentiation of the VSMCs. Vascular calcification is enhanced by the presence of lipid oxidation products [333]. In addition, the AGE-RAGE-axis is further worsening the pathological vascular calcification [228].

4.3.2. Fatty acids/palmitic acid

Although fatty acids are essential components for cellular structure and function [334], as well as an important source of energy, saturated fatty acids overload have been generally shown to stimulate inflammation by impairing cell lipid metabolism and inducing pro-inflammatory signaling pathways [232,234,335,336]. Hyperlipidemia is associated with elevated systemic levels of monocytes [337] that, upon infiltration in the lesional microenvironment, are exposed to a complex accumulation of cytokines and various lipids, lipoproteins and associated metabolites (i.e. lipid products). These stimuli determine macrophage polarization over a broad spectrum of macrophage phenotypes [338–340].

4.3.2.1. Influence of fatty acids on macrophages. In macrophages, uptake of palmitic acid is mainly regulated by CD36 on the cellular membrane [341,342], whereafter it is processed into various metabolites as extensively reviewed by others [343]. In case of saturated fatty acids overload, lipotoxicity occurs, which inhibits cellular organelle functionality (lysosomal dysfunction, endoplasmic reticulum (ER) stress, mitochondrial damage) [344–346] and evokes amongst others TLR signaling, NLR family pyrin domain containing 3 (NLRP3) inflammasome and NF-κB activation [232,233,315,347–350] (Fig. 6). These lipid-induced alterations in macrophage metabolism and pro-inflammatory pathway activation have been associated with foam cell formation [351,352], excess pro-inflammatory cytokines (e.g. TNF-a, IL-1b, IL-6) [343,353–355], chemokines (e.g. IL-8, MCP-1, macrophage inflammatory protein-1β (CCL4) [353,356,357], as well as degrading compound secretion (e.g. MMP-9, ROS) [353,358,359].

Although the effects of lipid products like saturated fatty acids, on macrophage recruitment and functionality are generally pro-inflammatory, inter-study and inter-lipid product differences in outcomes are reported, suggesting more nuanced mechanisms [347,356,360–363] (Supplementary Table S4). For instance, it was observed by Cullberg et al. that the stimulatory effect of lipids on monocyte recruitment might be lipid product-dependent. In that study they demonstrated that the saturated fatty acid palmitic acid increased MCP-1 mRNA expression in THP-1-derived macrophages, whereas the monounsaturated fatty acid oleic acid and *trans*-fatty acid elaidic acid had no effects [356]. Certain circumstances of hyperlipidemia may even have a dampening effect on inflammatory responses. Illustrative is the condition of hypercholesterolemia, which has been shown to deactivate the macrophage inflammatory response, chaperoned by a reduced nuclear factor erythroid-2 related factor 2 (Nrf2)-mediated oxidative stress response [363]. Moreover, engulfment of various lipid products have been shown to initiate M2 polarization by activating alternative signaling and transcriptional programs, as extensively reviewed by others [364–366]. The underlining mechanisms that link excess lipid loading and macrophage functionality are not well defined.

4.3.2.2. Influence of fatty acids on tissue cells and matrix remodeling. With respect to VSMCs, atherogenic stimuli, like lipid products, are generally assumed to stimulate VSMC migration and proliferation, although also inhibitory effects of palmitic acid on human VSMC migration and proliferation have been observed [367]. Interestingly, Chung et. al. demonstrated an enhanced migratory and proliferative capacity in rat aortic SMCs when exposed to conditioned medium of palmitate (i.e. the ester or salt of palmitic acid) stimulated mouse (RAW 254.7) and human (THP-1) macrophages [368]. In addition, it was observed that lipid stimuli directly and indirectly via macrophage paracrine signaling, reduce contractile marker expression in rat aortic SMCs *in vitro* and *in vivo* [368–373], contributing to the formation of a more synthetic SMC population [373,374]. These synthetic SMCs are known for their enhanced proteolytic activity [369,375–378], secreting amongst others ROS, MMP-2 and MMP-9, and have been shown to deposit ECM, like collagen (e.g. type I and III) [374,379,380], elastin, glycoproteins (e.g. fibronectin and osteopontin) [374,380,381] and various proteoglycans (e.g. versican, decorin and biglyclan) [380], suggesting enhanced tissue deposition and remodeling. However, lipids have also been associated with SMC apoptosis [382], excessive pro-inflammatory compound secretion [383] and pathological healing, characterized by excessive ECM deposition [378] and crosslinking [384], resulting in dysfunctional fibrotic and necrotic tissues.

The consequences of lipids are not limited to stimulating tissue fibrosis but also might affect the calcifying and thrombotic potential, degradability and infection risk of implants downstream. Upon exposure to lipids, calcifying vesicles might be formed that, together with the deposition of calcification-prone matrix and compounds like BMP-2/4 and ROS, create a favorable environment for calcification [385]. Brodeur et al. confirmed this hypothesis, showing that palmitic acid-supplemented calcification medium resulted in increased osteogenic gene expression, ROS secretion and ultimately calcification in rat aortic segments *ex vivo* and VSMCs *in vitro* [386]. In addition, conditions of hyperlipidemia are associated with increased platelet production and excess degrading compound secretion, like ROS, that could enhance the risk of thrombosis and accelerate biomaterial degradation, respectively [103,387].

Cumulatively, it is expected that conditions of hyperlipidemia will result in a distortion of all regenerative phases, contributing to a state of chronic inflammation, aberrant tissue formation and reduced graft patency. With respect to *in situ* tissue engineering in particular, it is expected that conditions of hyperlipidemia might accelerate graft degradation while enhancing the risk of graft calcification and thrombosis. However, lipid-induced implications have not been experimentally investigated for *in situ* tissue engineering cardiovascular grafts specifically, and future research should focus on filling these important knowledge gaps.

4.4. Uremia

Loss of renal function in CKD and ESKD patients leads to the progressive accumulation of electrolytes and metabolic waste products and derangement in body fluid regulation [388]. A well-studied class of metabolic waste products are the so-called uremic toxins, among others. As many of these toxins have some form of biologic activity, their accumulation leads to a variety of complications, which most frequently include immune dysregulation and

cardiovascular disorders. A comprehensive overview of the uremic toxins and their biological effects is given by Vanholder et at [389].

4.4.1. Influence of uremia on macrophages

The retention of the uremic toxins leads to an increased production of pro-inflammatory cytokines and higher levels of oxidative stress. These conditions create a systemic pro-inflammatory milieu which impairs both the innate and adaptive immune systems, which is elaborately described by Betjes [390] (Supplementary Table S5). Uremic toxins underlie the generation of oxidative stress in the form of ROS production and inflammation leading to the formation of AGEs [390]. Similar to the process of aging and progression of diabetes, uremic conditions in CKD and ESKD patients cause the accumulation of AGEs in blood and tissues [391], although the quantities of accumulation of AGEs in renal patients are much higher compared to aging and diabetic patients [392].

4.4.2. Influence of uremia on tissue cells and matrix remodeling

Besides its hampering effect on the immune system, uraemia also causes excessive and adverse vascular remodeling events, including intimal hyperplasia formation and vascular stiffening [393]. At the cellular level, VSMCs play a key role in this pathological remodeling process [393]. Also the increased calcification of cardiovascular tissues in CKD and ESKD patients, is thought to be caused by phenotypic changes in SMCs, leading to calcium and phosphate precipitation in the tunica media and tunica intima [394]. Monroy et al. (2015) hypothesized that uremic conditions in CKD and ESKD would promote differentiation of VSMCs into a pathophysiological phenotype. Serum from both ESKD patients who were on hemodialysis and healthy donors was collected, pooled and mixed with growth medium to culture human aortic SMCs for up to 3 days. Their findings demonstrated that uremic culture conditions had the ability to modify the VSMC phenotype by reducing the contractile marker gene expression and increased proliferation [395].

4.5. Hemodynamics

Within the cardiovascular environment hemodynamic loads are known to be instrumental for both physiological and pathological remodeling. Differences in hemodynamic loads form an important source of patient-to-patient variability, for example between males and females and young and elderly, as well as differences in loading between implant types. For example, the increase in blood pressure after birth induces maturation of the elastin network in developing heart valves and influences the compliance of vasculature [396,397]. However, hypertension, for example as a result of aging and metabolic syndromes, can cause disruptive remodeling, such as matrix stiffening and micro- and macrovascular dysfunction [398]. The local hemodynamic loads are postulated to be pivotal for the tissue restoration after *in situ* graft implantation [6,399]. Therefore, graft remodeling within implants can differ depending on the hemodynamic location (e.g. arterial versus venous circulation [114]). For example, substantial elastin formation was detected within a tissue-engineered graft when implanted as arterial graft, whereas the elastin content was minimal after implantation of the same graft in the inferior vena cava position [400,401]. Moreover, grafts specifically designed as access graft for kidney dialysis will be exposed to very high shear rates. In addition to implantation side, patient-specific graft mismatch in compliance, size, or geometry, which can cause local changes in the hemodynamic environment, can contribute to local unpredicted maladaptive remodeling and eventually graft failure.

4.5.1. Influence of hemodynamic loads on macrophages

Although relatively little is known about macrophage mechanobiology, it is now well-established that macrophages are mechanosensitive and functionally respond to mechanical loads, including cyclic stretch and shear stress [402–409]. *In vitro* studies have shown that macrophages adapt their phenotype in response to cyclic stretch, both in 2D [410,411] and in 3D [407,408]. In 3D electrospun microfibrous scaffolds, application of high cyclic strain levels (12–15%) induced a pro-inflammatory M1 dominated response in human peripheral blood-derived macrophages, in terms of surface marker expression and cytokine production, whereas moderate strain levels (7–8%) sustained the presence of M2 macrophages [407,408]. Cyclic stretch influences inflammasome in macrophages mechanism [412]. Using a bioreactor to decouple the stretch and shear stress [413,414], our group recently reported that moderate cyclic stretch (4–5%) alone decreased the migration and degradative capacity of THP-1-derived macrophages in 3D scaffolds, whereas physiological shear stress (1 Pa) induced macrophage activation as shown by increased cytokine production, such as MCP-1 [409]. Shear stress also dominantly influences monocyte infiltration in electrospun biomaterials [415,416] and both shear stress and cyclic stretch affect the reciprocal interactions between human peripheral blood-derived mononuclear cells and mesenchymal stromal cells [417].

Apart from modulating inflammation, hemodynamic loads dominantly dictate macrophage-driven tissue formation, mainly by affecting the reciprocal communication between macrophages and (myo)fibroblasts and VSMCs. Using a dynamic *in vitro* co-culture system, Battiston et al. demonstrated that macrophages contribute to matrix production both directly and indirectly by stimulating collagen I and (tropo)elastin production by VSMCs in response to moderate levels of cyclic stretch (7–10%) in 3D polyurethane scaffolds [93]. We recently showed that moderate levels of cyclic strain (4%) enhanced myofibroblast proliferation and matrix deposition in a direct co-culture of human myofibroblasts and monocyte-derived macrophages in electrospun supramolecular elastomeric scaffolds [92]. This stretch-induced progressive matrix deposition was regulated by shear stress through enhanced MMP-1-TIMP-1 mediated collagen remodeling [92].

4.5.2. Influence of hemodynamic loads on tissue cells and matrix remodeling

The influence of mechanical loads on VSMCs is well-established. Mechanical stimuli are known to influence migration, proliferation, differentiation, and apoptosis of VSMCs, which is regulated through many molecular pathways and epigenetic changes (reviewed elsewhere [418]). The cellular response to mechanical stimulation is dependent on loading conditions, such as the level of strain, frequency, and flow velocity and pattern [419]. For example, Gould et al demonstrated that valvular interstitial cells in a 3D collagen gel had distinct responses to equiaxial and anisotropic biaxial strain, with an increasing degree of anisotropy in the strain field resulting in a stronger alignment of the cells and deposited collagen fibers [420]. Numerous *in vitro* studies from the tissue engineering field have reported on the dictative role of mechanical loads on the production and alignment of collagen, glycosaminoglycans and (tropo)elastin in 3D scaffolds [413,421–425].

Interestingly, the cellular response to mechanical loading is not only dependent on the type of loading, but also on the biochemical microenvironment. In healthy mice, transplantation of a vein graft to the arterial position resulted in physiological arterial remodeling, whereas in diabetic mice the VSMCs responded to the arterial pressure system with excessive proliferation and apoptosis resulting in atherosclerotic lesion formation [426]. *In vitro,* culture of VSMCs isolated from diabetic mice revealed subsets that responded differently to mechanical strain when compared to

VSMCs from healthy mice, proposedly through selective mitogen-activated protein kinase (MAPK) activation [427]. In diabetic mice, more ERK-activated cells were present, exhibiting increased proliferation and higher subsets of VSMCs that were more prone to apoptosis. Combining mechanical stretch and AGE stimulation had a synergistic effect on these subsets [426,427].

Taken together, these findings suggest that hemodynamic loads are important immunomodulatory stimuli, with moderate levels of cyclic stretch generally leading to a favourable macrophage secretome to stimulate tissue formation, and with shear stress having a modulating role in this. Excess levels of cyclic stretch, for example due to hypertension, typically promote a pro-inflammatory environment. Interestingly, Motta et al. recently showed that the local phenotypes of inflammatory cells in *in situ* tissue-engineered heart valves are dependent on the local strain distribution over the valve [428]. This is supported by recent in-depth analyses of regenerating resorbable synthetic pulmonary valves by our group, revealing strong spatiotemporal variabilities in inflammation (e.g. in terms of local macrophage phenotypes and MNGC presence) within valves [102]. These findings illustrate the *in vivo* relevance of macrophage mechanobiology and its downstream effect on *in situ* tissue regeneration.

5. Outlook

In situ cardiovascular tissue engineering is becoming a widely studied approach to engineer new blood vessels and heart valves starting from cell-free bioresorbable scaffolds implanted in the bloodstream. While a plethora of materials, material modifications, and processing techniques has been reported to design scaffolds that can harness the inflammatory response of the host who will receive the scaffold, less attention has been paid to patient-specific parameters that influence the host inflammatory response and micro-environment of the new, developing tissue. This touches upon very basic and early questions in the field of regenerative medicine, such as how age or gender affect the human regenerative potential, how genetic predisposition influences neo-tissue development, or even simpler: the predicted variability in tissue outcome in patient populations with similar demographics and disease histories.

Prediction of tissue outcomes would allow for clinical stratification; the identification of patients for whom *in situ* cardiovascular tissue engineering will be beneficial and outperform traditional implants that do not grow and remodel. In that sense, the definition of biomarkers that can forecast the success of *in situ* tissue engineering in a given patient is highly desirable. Considering the reviewed literature herein, such biomarkers might be found for instance in the degree of elastogenesis, which can be tested pre-implantation by culturing tissue samples from patient-derived cells in the presence of the intended scaffold. Alternatively, macrophage surface markers or the production of pro-inflammatory versus anti-inflammatory cytokines in the presence of the scaffold using patient-derived cells can be screened to assess polarization [140,429]. An important observation from the current literature is that macrophage polarization coincides with distinct metabolic and enzymatic profiles that hence can be used to characterize macrophage phenotypes (Section 4.3). As cell metabolism changes with various co-morbidities, the inclusion of immunometabolic biomarkers to assess the outcomes of *in situ* tissue engineering seems logic and important. Likewise, immunometabolic targets can be used if precision scaffold designs are warranted for specific patient groups. In addition, the emerging insights into the concept of 'trained immunity' indicate that innate immune cells are epigenetically primed depending on their immunological history [430]. The chronic inflammation that is associated with metabolic syndromes, such as hyperlipidemia and hyperglycaemia, are at least partly imposed by epigenetic modifications in the macrophages of diabetic patients [431,432]. Diabetic conditions were shown to hamper the epigenetic switch of macrophages into a regenerative phenotype, leading to impaired wound healing [433]. Moreover, Jain and Vogel recently showed that physical cues exerted by the biomaterial environment (i.e. spatial confinement) affected the inflammatory response of macrophage via epigenetic alterations [434]. Together, this suggests that the patient-specific epigenetic signature of innate immune cells, such as monocytes and macrophages, may serve as an effective marker to predict *in vivo* outcome.

For pre-implantation testing, strategies central to the field of patient-specific human disease modelling are of utmost relevance. Here, cells bearing the patient's pathology - often derived from induced pluripotent stem cells - are cultured *in vitro* and subjected to pharmacological and/or environmental stimuli to understand disease mechanisms or to test the cellular response to medication for precision medicine treatments [435]. In analogy to this strategy, patient cells can be cultured into microtissues using miniaturized scaffolds under a variety of (patho)physiological stimuli to understand and predict tissue formation prior to scaffold implantation. Several questions remain as to what extent reductionist *in vitro* models are able to mimic the key aspects of the pathological environment; what can we learn from *in vitro* studies in which healthy human cells are cultured in a simulated diseased environment? To what extent do patient-derived cells maintain their 'diseased' characteristics once they are isolated from their pathological environment? Regarding the latter, the aforementioned epigenetic priming suggests that diseased characteristics are at least partly sustained [436,437]. Orecchioni et al. reported on important differences between *in vitro* polarized macrophages according to often-used protocols and their *in vivo* counterparts [438]. Chen et al. defined the transcriptional profile for various *in vitro* human macrophage activation states and proposed a consensus for their use in relation to *in vivo* human macrophages [439]. The multifaceted nature of interrogating the human patient-specific immune-regenerative response to a biomaterial calls for a holistic approach in which the key elements, such as the biomechanical and biochemical microenvironments, are mimicked in combinatorial engineering systems [92,440,441]. This strategy can be extended with computational modelling to translate the *in vitro* microtissue outcomes to *in vivo* like complex and patient-specific geometries. Nowadays, computational strategies not only allow the prediction of tissue formation and remodeling under hemodynamic loading conditions [442,443], but they can also predict the influence of cell signalling profiles on tissue development [444] and are even increasingly able to foretell successful from aberrant tissue formation [114,399], thereby offering strategies to modify scaffold designs in line with patient-specific tissue environments.

Next to patient-specific characteristics, the surgical intervention as well as post-surgical rehabilitation and medication may influence tissue outcomes independent of scaffold design. For classical, *in vitro* engineered tissues, post-surgical complications have often led to unforeseen maladaptive tissue integration [445]. Other disciplines that might be helpful to forecast the success of *in situ* tissue engineering in individual patients, are the fields of classical replacement surgery and transplant immunology. Host responses to inert implants and transplanted tissues and organs are studied *in vivo* and the knowledge and modulation of immune responses to those (living) implants in diseased subjects [446] might cross-fertilize our sprouting insights in the role of the host in inflammation-driven *in situ* tissue engineering. Thus, collaborating with neighbouring disciplines may help predict and understand the implications of patient variability in tissue outcomes. This is especially important since current *in vivo* outcomes of *in situ* tissue

engineering strategies are mainly obtained from animal studies and pathophysiology and regenerative processes may differ substantially from those in human subjects [101].

It seems obvious to concentrate on patient characteristics when designing scaffold-driven tissue engineering strategies that must fit seamlessly with the inflammatory response and regenerative potential of the patient. Yet, current research efforts are merely - and repeatedly - directed towards how we can modulate or precision engineer our scaffolds to harness the host response, rather than to what extend this is required [447]. The encouraging findings from successful phase-II clinical trials by Niklason et al. suggest that *in situ* cardiovascular tissue engineering is possible, despite the compromised immune system and overall poor health condition[276]. How this translates to resorbable synthetic scaffolds and to other applications remains to be determined. The here reviewed literature does indicate that patient-specific conditions have a strong impact on key aspects of *in situ* cardiovascular tissue engineering, including inflammation, hemodynamic conditions, scaffold resorption, and tissue remodeling capacity. This suggests that a tailored approach may be required in terms of immunomodulatory characteristics, mechanical design, and degradation properties.

On a final note, to bring these patient-specific approaches to biomaterial design reality, some barriers are foreseen. There is a tight balance between the need for customization of the products versus access to these treatments for patients from all socioeconomic backgrounds. The latter is a concern that is shared with almost all emerging biotechnologies [175,448,449]. Consequently, in the development of the *in situ* cardiovascular tissue engineered therapies of tomorrow, all parties (e.g. academic and industry affiliated researchers, hospitals, governments) should share the moral responsibility to prevent socioeconomic inequalities in access to healthcare.

In conclusion, it is evident that *in situ* cardiovascular tissue engineering is at the end of its beginning. With clinical translation within reach, a new stage has arisen for the field in which the patient is placed central stage. This forms an important research directive that calls for leveraging the current knowledge in cardiovascular pathologies, immunology and tissue engineering, and using holistic research methodologies, to push the field of *in situ* cardiovascular tissue engineering towards robust clinical applications.

Declaration of Competing Interest

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

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Appendix A. Supplementary material

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