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Applying nanomedicine in maladaptive inflammation and angiogenesis

Amr Alaarg[a,b,c], **Carlos Pérez-Medina**[a], **Josbert M. Metselaar**[b,d], **Matthias Nahrendorf**[e], **Zahi A. Fayad**[a], **Gert Storm**[b,c], and **Willem J. M. Mulder**[a,f,*]

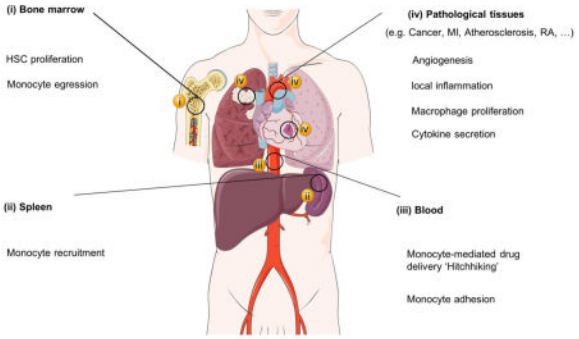
[a]Translational and Molecular Imaging Institute, Icahn School of Medicine at Mount Sinai, New York, USA [b]Department of Biomaterials Science and Technology, MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands [c]Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht, The Netherlands [d]Institute for Experimental Molecular Imaging, University Clinic and Helmholtz Institute for Biomedical Engineering, Aachen, Germany [e]Center for Systems Biology, Massachusetts General Hospital and Harvard Medical School, Boston, USA [f]Department of Medical Biochemistry, Academic Medical Center, Amsterdam, The Netherlands

Abstract

Inflammation and angiogenesis drive the development and progression of multiple devastating diseases such as atherosclerosis, cancer, rheumatoid arthritis, and inflammatory bowel disease. Though these diseases have very different phenotypic consequences, they possess several common pathophysiological features in which monocyte recruitment, macrophage polarization, and enhanced vascular permeability play critical roles. Thus, developing rational targeting strategies tailored to the different stages of the journey of monocytes, from bone marrow to local lesions, and their extravasation from the vasculature in diseased tissues will advance nanomedicine. The integration of *in vivo* imaging uniquely allows studying nanoparticle kinetics, accumulation, clearance, and biological activity, at levels ranging from subcellular to an entire organism, and will shed light on the fate of intravenously administered nanomedicines. We anticipate that convergence of nanomedicines, biomedical engineering, and life sciences will help to advance clinically relevant therapeutics and diagnostic agents for patients with chronic inflammatory diseases.

Graphical abstract

*Corresponding author at: Translational and Molecular Imaging Institute, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1234, New York, NY 10029, USA, willem.mulder@mssm.edu (Willem Mulder).



Keywords

Monocytes; Macrophages; Chronic inflammation; Immunomodulation; Atherosclerosis; Cancer; Angiogenesis; Nanomedicine; Molecular imaging; Targeted drug delivery

1. Introduction

Inflammation is a key underlying process in several disorders, including cancer, cardiovascular diseases, rheumatoid arthritis, and inflammatory bowel disease (IBD). The aforementioned maladies are leading causes of morbidity and mortality worldwide and impose a substantial socioeconomic burden[1,2]. Although new therapeutics are being developed, the incidence of complications remains high under the current standard of care[3,4]. This is in part because conventional therapies are not specific to the diseased tissue, and therefore cause considerable off-target adverse effects[5]. Equally important, disease heterogeneity is not taken into account. Current diagnostic approaches do not allow identification of those patients who would benefit the most from a given therapy or those who would likely suffer from complications[6–8]. Additionally, therapeutic strategies are often disease-specific, disregarding the common denominator: inflammation. Seemingly diverse, the abovementioned diseases possess common pathophysiological features driven – or aggravated– by inflammation, including leukocytosis, tissue remodeling, local cell proliferation and angiogenesis[9–11].

Extensive research of different pathophysiological processes has unveiled the role of multiple immune cells in diseased tissues that drive the development and progression of inflammatory disorders. One of the most effector cells in inflammatory lesions is a monocyte-derived macrophage, which is a key component of innate immunity[12–16]. Monocytes and macrophages not only contribute to the local inflammatory milieu of chronic inflammatory diseases but also modulate endothelial permeability and recruitment of supplementary immune cells, thereby driving disease progression[17,18]. Elucidating and understanding macrophage dynamics over the course of inflammatory disease progression offer unique opportunities for designing more specific and efficacious diagnostic and therapeutic agents. For example, our increased knowledge of the inflammatory process has yielded powerful immunotherapies[19], including anti-tumor necrosis factor alpha (TNF-α) antibodies[20], interleukin 6 (IL-6) inhibitors[21], and bifunctional antibodies[22], which modulate the immune response to achieve remission of chronic inflammation.

Simultaneously, nanomedicine –defined as “the application of nanotechnology for treatment, diagnosis, monitoring, and control of biological systems” [23]– has experienced unprecedented growth in the past decade. In addition to improving the therapeutic index of drugs, monocyte/macrophage-targeted nanomedicine can be implemented as a cell-specific drug delivery strategy to pharmacologically modulate inflammation. Such ‘immunomodulatory nanoplatforms’ can also be adopted for diagnostic and imaging purposes, not only at the level of local inflammatory lesions and organs involved in monocytosis but also to visualize macrophage dynamics systemically[24,25].

This review discusses the interplay between advances in nanomedicine and our understanding of chronic inflammatory disorders. This vantage point allows exploiting the commonalities of monocyte/macrophage dynamics across diseases for targeted therapy and diagnosis. We will highlight how nanomedicine can be applied at the inflammatory process’ different stages, in progressing disease. In addition, we will share our perspective on inflammation-oriented nanomedicine design and how it will facilitate developing improved therapies and diagnostic tools for patients. Although this review focuses on monocytes and macrophages as key effector cells in chronic inflammation and most prone to take up nanomedicines, other immune cells, such as T and B cells, have vital roles in complex paracrine signaling between macrophages and other cells in the inflammatory lesions, discussed in detail in other reviews [26–29].

2. Inflammation and angiogenesis in disease

Inflammation is a vital protective process in host defense against infections and injuries, which ultimately –through a resolution process– restores homeostatic conditions in the affected tissue [30]. However, persistent unresolved inflammation can contribute to the initiation and progression of several chronic diseases, including cancer[27], atherosclerosis[31], rheumatoid arthritis[29], and IBD [32]. The inflammatory response consists of interplay between innate and adaptive immunity[33,34]. This cross-talk modifies the function of other cells, such as epithelial cells (e.g. endothelial cells) and mesenchymal cells (e.g. smooth muscle cells) over time, leading to different disease stages[35,36]. Macrophages are key players that intercommunicate with adaptive immune T and B cells, and also directly affect the inflammatory milieu through secretion of inflammatory mediators[10,37]. Inflammatory macrophages differentiate from lesion infiltrating monocytes and express a set of pattern recognition receptors (e.g. Toll-like receptors and scavenger receptors) that can sense pathogen-associated molecular patterns (PAMPs) and endogenous tissue damage-associated molecular patterns (DAMPs)[38]. Engagement of these receptors results in activation of nuclear factor-kappa B (NF-κB), and production of proinflammatory cytokines, reactive oxygen and nitrogen species, and other mediators that can intensify the inflammatory response[39,40]. Moreover, due to elevated metabolic activity, inflamed tissues are notoriously hypoxic, activating macrophages, fibroblasts, and endothelial cells to produce hypoxia-inducible factors (HIFs) [41–43] and vascular endothelial growth factor (VEGF). Note that VEGF was originally denoted vascular permeability factor (VPF). Chronic exposure to HIF 1 and 2, VEGF, and inflammatory cytokines results in degradation of endothelial cell adherens junctions, dissolution of the basement membrane, and dramatic destabilization of existing microvessels[44–46].

Moreover, these factors facilitate endothelial cells' proliferation and migration, inducing the growth of new blood vessels from existing ones, a process known as angiogenesis.. Angiogenesis and chronic inflammation, long treated as two distinct processes, are thus codependent [47–49]. In the next sections, we will provide an overview of the involvement of monocytes and macrophages in the pathogenesis of several chronic inflammatory diseases, and discuss the common aberrant endothelial function and pathological angiogenesis, which are affected by the local inflammatory milieu.

2.1 Cancer

Cancer is a multifaceted malady in which cells are no longer completely responsive to the signals that regulate cellular differentiation, growth, proliferation, and death. As a result, these cancerous cells accumulate within the tissue, causing local damage and inflammation[27]. Rudolf Virchow established the first link between cancer and inflammation in the 19th century when he observed the infiltration of leukocytes in neoplastic tissues[50]. In the last twenty years, our understanding of carcinogenesis and the tumor microenvironment has supported Virchow's hypothesis, substantiating the role of inflammation in the initiation, promotion, and metastatic progression of cancer[51,52]. Moreover, increasing epidemiological evidence suggests that several chronic inflammatory diseases (e.g. IBD and hepatitis), associated or not with infectious agents, predispose individuals to several types of cancer[51,53]. Tumor-associated macrophages (TAMs) are the most abundant immune cells in the tumor microenvironment[54]. They are derived from circulating inflammatory monocytes, which are preferentially attracted to lesions by tumor-derived chemotactic factors, like C-C motif chemokine ligand 2 (CCL-2; also known as monocyte chemoattractant protein 1, MCP-1)[55]. TAM density is positively correlated with the levels of tumor-derived CCL-2, and usually associated with poor prognosis in various types of cancer[56–58]. The protumorigenic activities of TAMs can be appreciated in cancer initiation, tumor cell invasion and migration, and metastasis [59]. Inflammatory macrophages are key producers of reactive nitrogen and oxygen species that can generate oncogenic mutations and lead to tumor initiation[60]. These reactive species also cause activation of epithelial cells and the consequent recruitment of more monocytes[61]. In addition to the initiation phase, most invasive tumors demonstrate collective intravasation, in which groups of tumor cells invades the blood vessels while maintaining cell-cell contacts [62,63]. Tumor cell intravasation is shown to occur upon physical contact with macrophages, which induces RhoA GTPase activity in tumor cells, regulates actin cytoskeleton, and triggers the formation of invadopodia [64,65]. The combined effect of improved RhoA GTPase activity and proteolytic enzymes (e.g. MMPs), secreted by TAMs and cancer-associated fibroblasts (CAFs), enables tumor cells to degrade and break through matrix barriers in the course of tumor cell transendothelial migration [66–68]. Moreover, the paracrine signaling between tumor cells and stromal cells (e.g. CAFs and TAMs), through epidermal growth factor (EGF) and colony stimulating factor-1 (CSF-1), can activate tumor cell growth, and enhance migration and extravasation [69,70].. In most tumors, malignant switch and tumor propagation require an adequate supply of oxygen and nutrients, and an effective way to remove waste products, which is achieved through the development of a dense vessel network that connects the tumor to host circulation. Tumor vasculature development, also known as the angiogenic switch, is profoundly dependent on TAMs and

other stromal cells (e.g. endothelial cells, smooth muscle cells, fibroblasts), which secrete several angiogenic growth factors and proteinases, including VEGFs [71,72] and matrix metalloproteinases[73]. The developed tumor vasculature is usually chaotic and leaky (i.e. with large inter-endothelial cell fenestrations), facilitating tumor cell intravasation and metastatic dissemination [74]. These migrating cells establish themselves at metastatic niches where they recruit monocytes and macrophages, mainly via CCL-2. Metastasis-associated macrophages (MAMs) secrete another chemokine, CCL-3, which affects MAM retention and interaction with tumor cells, enhancing metastatic seeding and growth[57].

2.2 Atherosclerotic cardiovascular diseases

Atherosclerosis is a chronic inflammatory disease of the large- and medium-sized arteries[37]. Although atherosclerotic cardiovascular diseases are as old as ancient Egyptian mummies[75], they remain the leading cause of mortality worldwide, accounting for most deaths among non-communicable diseases. According to the World Health Organization, 17.7 million deaths per year, an estimated 31% of all deaths worldwide, can be attributed to atherosclerotic diseases[76]. Due to recent advances in immunology, the inflammatory component of atherosclerosis is now more appreciated, and the disease is no longer thought to be only due to aberrant lipid deposition. Inflammation plays a prominent role at different stages of atherosclerosis and contributes to its complications[40,77]. At early stages, risk factors such as smoking, hypertension, and elevated levels of apolipoprotein B-containing lipoproteins can induce, partially via activating NF-κB, focal expression of endothelial adhesion molecules, including vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecules (ICAMs)[78,79]. The focal expression of these adhesion molecules in areas that are prone to develop atherosclerotic lesions (e.g. aortic root and arches) facilitates the binding and adherence of circulating immune cells, such as monocytes. Once adhered, monocytes transmigrate to the subendothelial space and mature into resident macrophages under the influence of a complex mix of vascular wall-derived chemokines, such as macrophage colony-stimulating factor (M-CSF)[80]. The accumulation of lipoproteins, calcium, and immune cells within the vessel wall leads to the development of focal lesions, known as atherosclerotic plaques. This buildup is mainly affected by plaque-resident macrophages, which secrete apoB-lipoprotein binding proteoglycans increasing apoB retention in the subendothelial space[81]. Moreover, macrophages produce reactive oxygen and nitrogen species inducing lipoprotein modifications, mainly through peroxidation. These modifications fuel further inflammatory processes that result in recruitment of more monocytes into the arterial *intima*[82]. Additionally, macrophages engulf the native and modified lipoproteins leading to the formation of foam cells, which further amplify lipoprotein oxidation, uptake, retention, and modification through expression of scavenger receptors, such as type A scavenger receptor (SRA) and a member of the type B family, namely CD36[83,84]. These receptors can also cooperate with toll-like receptors and promote inflammasome activation and secretion of proinflammatory cytokines in response to modified lipoproteins [85,86]. Moreover, macrophages secrete proteolytic enzymes, including MMPs, which may contribute to atherosclerotic plaque remodeling and instability[87]. Similar to tumor angiogenesis, atherosclerotic plaques also undergo neovascularization under the influence of macrophage-derived angiogenic factors[88]. Neovascularization contributes to advanced plaques instability by facilitating the infiltration

of additional inflammatory immune cells and/or acting as a source of intraplaque hemorrhage[89,90]. Furthermore, perturbed lipid efflux may increase macrophage cell death in advanced stages, aggravating the inflammatory burden and decreasing plaque stability[91].

2.3 Rheumatoid arthritis

Rheumatoid arthritis (RA) is an immune-mediated, chronic inflammatory disease that primarily affects synovial membranes, cartilages, and bones[29]. The prevalence of the disease is around 1% globally and usually associated with progressive disability, severe morbidity and systemic complications, such as accelerated atherosclerosis[92]. The cause of RA is unknown[93]. However, the increasing understanding of RA pathophysiology underscores the role of immune cells in the initiation and progression of the disease[94]. The cross-talk between immune cells and skeletal systems, the two key components of RA osteoimmunology, results in the production of autoantibodies, infiltration of immune cells into the affected joints, and ultimately joint destruction[95]. Macrophages are key effectors in these processes, as evidenced by their abundance in the synovial lining and the strong correlation between macrophage number and the extent of joint destruction[96,97]. The crosstalk between macrophages and T cells plays a crucial role in disease initiation. Macrophages activate naïve T cells, likely by acting as antigen presenting cells and/or through T cell-monocyte/macrophage interaction[98,99]. Once activated, naïve T cells enter a proliferative state and secrete cytokines, including interferon-gamma (IFN-γ) and IL-17, which further skew macrophages towards an inflammatory state[100]. Immunohistological studies of isolated synovium have shown that activated macrophages are the main producers of proinflammatory cytokines, including IL-1, IL-6, and TNF-α[101,102]. These cytokines trigger synovial fibroblast activation, leading to hypertrophied synovium (also called pannus) which is a tumor-like tissue that invades and destroys the local articular tissue[102,103]. Furthermore, macrophage-derived granulocyte-macrophage colony stimulating factor (GM-CSF) and other cytokines stimulate the maturation of innate immune cells, their efflux from bone marrow, and their migration into the synovium[104]. In addition to the inflammatory component, RA progression is usually associated with pathophysiological angiogenesis. The infiltration of immune cells and the highly inflammatory milieu results in local hypoxia, secretion of HIFs and growth factors (mainly by macrophages and fibroblasts), increased vascular permeability, and formation of new blood vessels to supply nutrients and oxygen [105,106]. Such a complex microenvironment of proinflammatory cytokines and immune cells stimulate osteoclasts –multinucleated cells of the monocytic lineage– to degrade bone matrix and solubilize bone calcium, leading to inflammation-driven bone erosion in advanced stages[107,108].

2.4 Inflammatory bowel disease

Inflammatory bowel disease (IBD), which includes Crohn’s disease (CD) and ulcerative colitis (UC), are chronic, relapsing inflammatory diseases of the gastrointestinal (GI) tract[109]. In these diseases, inflammation impairs the ability of the affected GI to function properly, resulting in persistent diarrhea, abdominal pain, cramping, and rectal bleeding. As most chronic inflammatory diseases, genetic predispositions, environmental triggers, and immune cells contribute to IBD pathogenesis and progression[109,110]. Under normal

physiological conditions, the main function of intestinal immune cells is to maintain the integrity of the epithelial barrier along the GI tract against external stimuli –e.g. food and the microflora– without eliciting a strong inflammatory reaction[111]. Intestinal macrophages, strategically located in the intestinal *lamina propria*, represent the largest macrophage population in the body[112]. During an IBD flare, this tolerance is lost either by a change in the microflora or a defect in the immune response to the existing flora[113,114]. Such a change leads to imbalance in the number of T cells and recruitment of blood monocyte and their differentiation into activated macrophages, which are phenotypically different from resident macrophages[115]. The activated macrophages secrete proinflammatory cytokines, including IL-23 and TNF-α [116,117]. In addition to their inflammatory actions, these cytokines modulates epithelial cell growth, T cell activity, intestinal and vascular permeability, and the production of reactive oxygen species[118,119]. The active phase of IBD is usually accompanied by increased microvascular density and permeability, which facilitate the infiltration of more proinflammatory immune cells[120]. Ultimately, these inflammation-driven changes lead to barrier dysfunction, tissue damage, and fibrosis[121,122].

3. Applying nanomedicine in inflammation dynamics

There are strong associations and comorbidities between different types of chronic inflammatory disorders[123–125]. Also, striking similarities in the dynamics of the aforementioned diseases and other chronic inflammatory disorders exist. The diseases are usually initiated by a persistent local tissue insult or injury that activates the (extra) medullar hematopoiesis and attracts inflammatory monocytes to the lesions. Infiltrating monocytes and lesion-associated macrophages affect other cells in the microenvironment and induce pathological angiogenesis and local tissue remodeling. Such holistic understanding of chronic inflammation dynamics offers opportunities to develop therapeutics and diagnostic agents that can be applied to multiple diseases. Employing nanomedicines in chronic inflammatory diseases can advance, revive, and repurpose efficacious therapeutics and diagnostic agents. Nanomaterials are highly tunable and can be designed to exhibit different sizes, shapes, and surface chemistry, which can be exploited to modulate nanoparticles' *in vivo* behavior (e.g. circulation kinetics, cell uptake, and tissue penetration)[126]. Moreover, nanoparticles can be used as carriers for different therapeutic cargos such as small molecule drugs (hydrophilic and hydrophobic) [127], peptides[128], and nucleic acids[129]. Nanoparticles can also be used to solubilize poorly water-soluble compounds that are intended for parental use[130]. Additionally, nanomedicine\approaches may lead to a drug's improved therapeutic index through increasing the on-target efficacy, while reducing the off-target toxicity [131]. As diagnostic probes, nanoparticles are highly amenable and can be labeled for optical, magnetic resonance imaging (MRI), computed tomography (CT) and nuclear imaging approaches[24,132,133]. In addition, due to the high phagocytic activities of monocytes and macrophages, nanoparticles are suitable for imaging not only inflammatory lesions, but also the dynamics of inflammatory cells in disease [24,134].. Thus, applying nanomedicine at the different stages of monocyte/macrophage dynamics can foster our understanding of inflammation and can be used to modulate these processes. An overview of these processes that can be tackled by nanomedicine on a systemic level is

depicted in Fig. 1. In subsequent sections, we will zoom in on the exploitation of nanomedicine and the processes that monocytes and macrophages modulate during chronic inflammation in their corresponding compartments. In this context, we will share lessons learned and challenges faced, followed by our outlook on the future.

3.1 Bone marrow activation

Under homeostatic conditions, the bone marrow contains self-renewing, quiescent hematopoietic stem cells (HSCs), which maintain the blood levels of monocytes and other immune cells within normal physiological values. However, chronic inflammatory diseases are associated with elevated systemic levels of proinflammatory cytokines, such as IL-1, IL-6, and TNF-α [142–144], and TLR agonists, like heat-shock proteins, and saturated and unsaturated fatty acids[145]. Furthermore, stress, which results in increased sympathetic activity and release of noradrenaline, is often associated with chronic inflammatory diseases [146–148]. Such biochemical changes can lead to HSC proliferation and overproduction of inflammatory monocytes, which ultimately accumulate in lesions[146,149]. The mobilization/egression of inflammatory monocytes from the bone marrow is enhanced by the CCL-2/CCR-2 interaction and the increased permeability of blood vessels in the bone marrow[150]. Moreover, bone marrow components and inflammation contribute to the local angiogenic processes. A classic example is bone marrow angiogenesis in patients with multiple myeloma[151] and breast cancer [152]. Metastatic breast cancer and myeloma plasma cells induce activation of inflammatory cells, including macrophages, to secrete angiogenic factors such as VEGF, fibroblast growth factor-2, and granulocyte macrophage-colony stimulating factor[153], which activate endothelial cells and accelerate angiogenesis in the bone marrow. Moreover, bone marrow macrophages, under the influence of fibroblast- and plasma cells- secreted factors, can acquire endothelial cell markers and transform into cells that are functionally and phenotypically similar to bone marrow endothelial cells [154]. Thus, they participate in the development of the bone marrow microvascular system (i.e. vasculogenic mimicry). Bone marrow also is the main source of endothelial progenitor cells (EPCs) and other myeloid cells which contribute to the angiogenic processes at distant inflammatory lesions[155].

Nanomedicine’s application at different stages of bone marrow activation holds promise for the diagnosis and treatment of inflammatory diseases (Fig. 2). Nanoparticle delivery of antiinflammatory drugs (e.g. corticosteroids)[156] or CCR-2 siRNA [135] can modulate the bone marrow response to circulating proinflammatory cytokines. The enhanced permeability of bone marrow blood vessels and the increased nanoparticle uptake by activated macrophages can facilitate their accumulation and retention[157–159]. Nanoparticles, including liposomes and reconstituted high-density lipoprotein (rHDL), have been shown to accumulate in the bone marrow of animals with inflammatory conditions, such as osteomyelitis[160] and atherosclerosis[161], to a greater extent than in non-diseased counterparts. Moreover, nanoparticle accumulation in the bone marrow can be further enhanced through active targeting. For example, conjugation of bisphosphonates (or alendronate) to poly(lactic-co-glycolic acid) (PLGA) polymeric nanoparticles increases their affinity to hydroxyapatite, a major mineral component of the bone[162,163]. Alternatively, incorporation of certain synthetic substances has been shown to relatively reduce

nanoparticle accumulation in the liver while, concomitantly, increase their accumulation in the bone. Two of such materials are the hydrophilic non-ionic surfactant poloxamer 407 and the anionic amphiphilic lipid L-glutamic acid *N*-(3-carboxy-1-oxopropyl)-1,5-dihexadecyl ester which have been used as integral components of bone marrow-targeted nanospheres[164] and liposomes[141], respectively. The use of bone marrow-targeted nanomedicines can improve the therapeutic efficacy of small molecules, such as bortezomib in myeloma[162]. Tackling the hyper-proliferative state and/or the egression of HSCs and inflammatory monocytes has been shown to be an upstream approach for managing inflammatory diseases[135]. In addition, combining bone marrow-targeted nanomedicines with molecular imaging can be used to assess the effect of this therapeutic approach on bone marrow activation. For instance, the proliferation of bone marrow macrophages and HSCs can be quantified noninvasively with molecular imaging using ^{18}F-3'-fluoro-3'-deoxythymidine (^{18}F-FLT) positron emission tomography–computed tomography (PET/CT) [165–167]. Furthermore, their activation can be evaluated by ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT[168].

3.2 Monocyte mobilization and recruitment

In the course of chronic inflammation, recruitment and trafficking of inflammatory monocytes are driven by a gradient of circulating chemokines. Although bone marrow is the major source of blood monocytes, extramedullar hematopoiesis (i.e. outside the bone marrow), especially in the spleen, is also driven by inflammation[170,171] (Fig. 3). After fetal development, splenic hematopoiesis remains dormant, and the spleen acts as a reservoir seeded with HSCs mobilized from the bone marrow. However, these spleen-resident HSCs are highly responsive, and they regain their proliferative capacity upon exposure to hormonal and inflammatory cues[170,172,173]. For example, inflammatory conditions, such as atherosclerosis-triggered ischemic events, can activate splenic hematopoiesis and result in overproduction and deployment of splenic inflammatory monocytes into the circulation[172]. Hence, imaging splenic activity in such pathological conditions, for example by ^{18}F-FDG-PET, can be useful to monitor therapeutic response and has been shown to serve as a good predictor of future complications by Tawakol and colleagues[174]. The accelerated hematopoiesis and rapid egress of inflammatory monocytes from splenic niches rely in part on CCL-2/CCR-2 interaction and angiotensin II (Ang II)-Ang type I and II receptors[14,175,176]. Applying nanomedicine to target splenic inflammatory monocytes is compelling due to the high accumulation of systemically administered nanoparticles in the spleen[177]. Leuschner *et al.* have used CCR-2 siRNA-loaded nanoparticles to selectively knock down the expression of CCR-2 in splenic inflammatory monocytes without affecting the patrolling, non-inflammatory subset[135]. Such a treatment led to a monocyte reduction in lesions and was shown a viable therapeutic approach in multiple conditions such as acute myocardial infarction (AMI), pancreatic islet transplantation, and cancer[135]. Similarly, irbesartan-loaded PLGA nanoparticles have been used to block Ang II type 1 receptor, inhibiting the recruitment of inflammatory monocytes and reducing infarct size in a myocardial ischemia-reperfusion (IR) injury model[178].

Noninvasive monitoring of the journey of inflammatory monocytes through the circulation could provide insights into their homing, tissue adhesion, and tissue penetration

characteristics. Such understanding would not only allow evaluating disease progression and response to treatment but could also help to design immunomodulatory therapeutics which have monocyte-like features to increase their tissue/lesion penetration. Several imaging techniques combined with or without nanomedicines have been used to monitor monocytes on the move. For example, intravital microscopy (IVM) can be used to detect fluorescent cells (e.g. GFP^+ monocytes) in live organisms and to study their behavior in the circulation, in hematopoietic tissues, and in healthy and diseased tissues with a single-cell resolution[175,181–183]. Moreover, the exclusive uptake of certain fluorescently labeled nanoparticles, such as single-walled carbon nanotube (SWNT), by inflammatory monocytes allows studying both nanoparticle and monocyte trafficking in tumor models using IVM[179]. Alternatively, monocyte dynamics can be studied in deeper tissues with excellent spatial resolution using magnetic resonance imaging (MRI). Contrast MRI uses exogenous cell labels, such as superparamagnetic iron oxide (SPIOs) nanoparticles or Fluorine-19 (^{19}F)-based perfluorocarbon (PFC) nanoemulsions[184]. Iron oxide nanoparticles have already been used to image monocyte dynamics in a rodent model of glioblastoma[185] and in patients with myocardial infarction[186]. Alternatively, ^{19}F-MRI allows direct detection and imaging of labeled cells for unambiguous identification and quantification unlike iron oxide-based MRI [187]. Therefore, the detected signal can be derived directly from the injected PFC nanoemulsion engulfed by monocytes, for example after myocardial infarction[188].

Nuclear imaging with PET or single-photon-emission-computed-tomography (SPECT), which are highly sensitive and quantitative methods, could be another method to evaluate monocyte trafficking *in vivo*. SPECT with Technetium-99m tagged autologous monocytes – radiolabeled *ex vivo* and reinjected in the same patients– has been used to visualize the continuous migration of monocytes into the inflamed synovial tissue of RA patients[189]. The same approach has been used to monitor monocyte recruitment in live atherosclerotic apolipoprotein E knockout ($Apoe^{-/-}$) mice for up to 7 days with Indium-111 (^{111}In)-tagged monocytes and micro-SPECT/CT [180]. Moreover, the use of Zirconium-89 (^{89}Zr)-feraheme nanoparticles, which are specifically taken up by blood monocytes, can enable studying monocyte dynamics by PET[190].

The homing features of circulating monocytes can be exploited to advance targeted therapeutics and diagnostic agents in inflammatory diseases. Such an approach has been realized by designing monocyte-mimicking nanoparticles as drug delivery systems to prolong their circulation times and achieve specific tissue targeting. Nanoporous silicon nanoparticles coated with leukocyte membranes possess cell-like functions and exert their targeting through receptor-ligand interaction, evading opsonization and clearance by the immune system[191]. In a similar approach, Cao *et al.* have prepared camouflaged liposomes with isolated macrophage membranes, which homed to lung metastasis and improved the delivery of an anti-cancer drug[192]. Furthermore, incorporating lipid and protein components extracted from leukocytes into a liposomal formulation has been shown to improve their targeting to inflamed vasculature, enabling selective and effective delivery of dexamethasone[193].

An alternative approach is hitchhiking/backpacking with monocytes, which can be achieved by designing polymeric nanoparticles that strongly attach to the surface of monocytes[194]. These cellular backpacks were shown to evade monocyte phagocytosis (due to size, disk-like shape, and flexibility) without affecting monocytes' ability to target inflamed tissues *in vivo*[195,196].

The interactions between circulating inflammatory monocytes and the adhesion molecules expressed on the activated endothelium are inherently linked to lesion inflammation, and, therefore, also represent a potential therapeutic target. Knocking down multiple cell adhesion molecules using targeted delivery of siRNA-loaded nanoparticles has been shown to decrease monocyte recruitment in atherosclerotic plaques and ischemic myocardium, thereby reducing inflammation of infarcted myocardium and improving recovery after ischemia in mice [197]. Additionally, targeting adhesion molecules, like VCAM-1, P-selectin, or ICAM-1, with nanoparticles can be used for molecular imaging of the activated endothelium in atherosclerosis[198,199], cancer[200], and arthritis[201]. For example, echogenic nanoparticles can be applied for molecular ultrasound imaging of vascular markers in inflammatory lesions. Lee *et al.* demonstrated a positive correlation between *in vivo* ultrasound imaging of VEGF receptor-2 (VEGFR-2)-targeted microbubbles and the VEGFR-2 expression on endothelial cells of breast cancer tumors[202]. Furthermore, echogenic immunoliposomes targeting ICAM-1, VCAM-1, and tissue factor have been applied for atherosclerosis imaging [203].

3.3 Enhanced microvascular permeability

Local macrophage activity and lesion growth (e.g. tumors, atherosclerotic plaque, or RA pannus) drive the generation of blood vessels to meet the increased demand for oxygen and nutrients. Angiogenic neovessels in chronic inflammation are phenotypically heterogeneous and characterized by excessive branching, chaotic patterns and enhanced permeability to macromolecules and nanomedicines[45]. Therefore, applying nanomedicine to target the processes governing angiogenesis is an attractive approach to delivering therapeutic and imaging agents[204]. The formation of neovessels is intricately controlled by angiogenic factors, including VEGFs and VEGFRs (Fig. 4). Inhibition of angiogenesis using polymeric nanoparticles loaded with angiogenesis inhibitors such as the fumagillin analog TNP-470 has been shown to 1) suppress tumor growth in melanoma [205], Lewis lung carcinoma[205], and ovarian cancer mouse models[206]; 2) reduce plaque angiogenesis and inhibit advanced atherosclerosis in $Apoe^{-/-}$ mice[207,208]; and 3) suppress arthritis and protect from bone destruction in mice[209]. Alternatively, inhibiting the secretion of proinflammatory cytokines and proteases, which affect the proliferation and migration behavior of the preexisting endothelial cells, can be a complementary strategy to direct anti-angiogenic therapies. For example, liposomal delivery of anti-inflammatory compounds such as glucocorticoids has been shown to suppress tumor growth in mice, partially through inhibition of tumor angiogenesis[210].

Angiogenic neovessels are also characterized by overexpression of certain receptors like $\alpha v\beta 3$ integrin adhesion receptors compared to quiescent vessels[214–217]. Attaching ligands (e.g. antibodies, nanobodies, and peptides) to the nanoparticles can allow better

distribution in the vascular bed of the lesion and increase their internalization by target endothelial cells[218,219]. For example, αvβ3 integrin-targeted delivery of an anti-angiogenic gene has been shown to selectively increase apoptosis of tumor endothelial cells, which subsequently led to tumor cell apoptosis and regression of primary and metastatic tumors[220]. Additionally, αvβ3 integrin-targeted ligands and nanoparticles have been used to image angiogenesis in cancer[221–223], atherosclerosis[224,225], and arthritis[226], using different imaging modalities such as ultrasound, MRI, PET, and SPECT. These αvβ3-targeted imaging strategies can also be used to monitor the therapeutic response[207,208].

3.4 The proinflammatory milieu and local cell proliferation

Tackling the adhesion of circulating monocytes to the lesion vasculature can yield favorable therapeutic outcomes in chronic inflammatory diseases as mentioned before. However, once monocytes adhere, they infiltrate into the lesions and differentiate into macrophages, which possess an inflammatory phenotype and secrete large amounts of proteases, inflammatory cytokines, reactive radicals, and auto- and paracrine signaling molecules [227–229]. These “flaring” molecules drive lesion remodeling, invasiveness (and metastasis in the case of cancer), and can induce a phenotypical change in preexisting macrophages and other cells[230–232]. Thus, preventing macrophage activation and dampening local inflammation by using nanomedicines to deliver anti-inflammatory drugs can induce a favorable phenotype[233]. Glucocorticoids are potent anti-inflammatory drugs, which, however, generally come with severe side effects upon prolonged use[234]. Alternatively, glucocorticoid nanomedicines have been shown to silence local inflammation and halt the progression of several chronic inflammatorydiseases, including atherosclerosis[235], cancer[236], and RA[212,237] while minimizing side effects. Another approach is to activate inflammation-resolution pathways through delivering proresolving mediators to lesions (e.g. annexin A1 and resolvin D1). Such an approach can result not only in anti-inflammatory effects but also in tissue repair and restoration of homeostatic conditions[238]. Nanoparticle delivery of an annexin A1-mimicking peptide to atherosclerotic lesions results in a marked improvement in key advanced plaque features, including an increase in the protective collagen layer, a decrease in protease activity, suppression of oxidative stress, and reduced plaque necrosis[239].

Although monocyte recruitment is a key process driving the settlement of lesion-associated macrophages, the expansion of the macrophage population can also be driven by local proliferation[240–243]. Tackling monocyte recruitment alone may not be sufficient to reduce local inflammation, especially in advanced stages[244–246]. Consequently, restricting the expansion of the macrophage population can reduce the burden of local inflammation. For example, depletion of TAMs using clodronate liposomes slows down tumor growth *in vivo* and increases the efficacy of other anti-cancer drugs[247,248]. Additionally, clodronate liposomes have been used to deplete synovial macrophages, which resulted in reduced inflammation and prevented joint destruction[249,250]. Furthermore, simvastatin reconstituted HDL nanoparticles have been applied to reduce atherosclerotic plaque inflammation[213] by inhibiting local macrophage proliferation[251] in $Apoe^{-/-}$ mice with advanced atherosclerotic plaques. Methotrexate, a folate inhibitor with anti-proliferative activities, conjugated to dendrimer nanoparticles has been shown to reduce

arthritis-induced inflammatory parameters such as ankle swelling, paw volume, cartilage damage, and bone resorption in a rat model of collagen-induced arthritis[252]. The same group has also demonstrated that methotrexate nanoparticles improve the therapeutic response in an animal model of human epithelial cancer[253]. Of note, low-dose of methotrexate is currently being studied in the Cardiovascular Inflammation Reduction Trial (CIRT) to test if it can reduce vascular inflammation and decrease rates of myocardial infarction, stroke, and cardiovascular death (Clinical Trial Identifier: NCT01594333).

The increased macrophage activity drives changes in the inflammatory milieu, which include elevated protease activity, abnormal glucose metabolism, and decreased pH [227,254,255]. Such changes can be exploited to develop “smart” probes and nanomedicines that are responsive to the changes inherent to inflammatory lesions. An attractive approach is to design nanomedicines with bioactive domains that can be activated by the increased activity of proteases like caspases, MMPs, and proteinases[256–259]. For example, Boeneman *et al.* have developed caspase 3-sensitive quantum dot-fluorescent protein nanoparticles[260]. Similarly, cathepsin B-sensitive fluorogenic chitosan nanoparticles have been used to discriminate metastases *in vivo* in three metastatic mouse models[261]. Also, Ferber *et al.* have adopted a nanotheranostic approach by developing two cathepsin B-sensitive N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer-based systems for noninvasive imaging of breast cancer progression and drug release[262]. MMP-sensitive dual ^{64}Cu-labeled fluorescent chitosan nanoparticles have also been used to visualize tumors *in vivo* by PET and near-infrared fluorescence imaging[263]. Moreover, active targeting of MMP sensitive dendrimer nanoparticles designed for dual MRI/optical imaging improves MRI-guided clinical staging, presurgical planning, and intraoperative fluorescence-guided surgery[264]. In addition to the biochemical changes, lesion-associated macrophages overexpress certain receptors such as major histocompatibility complex class II (Class II MHC) and surface integrin CD11b, which can also be exploited for imaging purposes[265]. Rashidian *et al.* have developed nanobodies labeled with ^{18}F targeting MHC II^{+} and CD11b^{+} cells, which allow specific, noninvasive imaging of immune responses by PET/CT, showing higher specificity over the clinically used ^{18}F-FDG PET/CT[266]. Alternatively, we have developed ^{89}Zr-labeled rHDL to image TAM by PET[136] specifically.

4. Lessons, challenges, and perspectives

Chronic inflammatory diseases and associated angiogenesis share common pathophysiological features in which monocytes and macrophages are key effector cells. Understanding and exploiting monocyte dynamics and functions can lead to the development of improved therapeutic and diagnostic agents that are clinically useful in multiple diseases and disease settings. Nanomedicines can be engineered, developed, and customized in numerous ways to tackle the different features of maladaptive inflammation and angiogenesis, for therapeutic and diagnostics endeavors. Additionally, due to monocytes and macrophages’ high uptake capacity, nanomedicines can also enable us to study these cells’ dynamics in disease and decipher different pathophysiological features.. Therefore, it stands out as a promising approach to modulate monocyte/macrophage function and to also visualize and quantitate their dynamics. However, to broaden our exploitation of

nanomedicine and reinvigorate clinical translation, several challenges and opportunities need to be taken into consideration:

- First, the application of nanomedicine, especially for drug delivery, needs to be rigorously assessed. Traditionally, nanomedicine's main application was improving a drug's therapeutic index by increasing the concentration in the target tissue, while simultaneously minimizing the off-site effects. Today, the community is concerned about the small quantities of injected nanomaterial that reaches target lesions (e.g. tumor) in patients, and if nanomedicines provide real benefits [267–269]. These debates are mainly fueled by limited clinical experience with nanomedicines and undermine a rational discourse.
- Second, research groups are often inclined to apply their nanomedicine in a single disease, such as cancer, overlooking the potential application in other diseases. A holistic understanding of the pathophysiological processes in chronic inflammation would allow repurposing, reviving and reapplying nanomedicines across a range of maladies without the need to create novel nanomedicines. Patient/disease-centric approaches for applying nanomedicines are more valuable than material-based approaches[270,271].
- Additionally, we have witnessed an expansion in the development of new materials for nanomedicine, but these are rarely fully evaluated under biologically relevant conditions. Implementing screening procedures to evaluate new and preexisting nanomaterials with regards to their compatibility with different drugs, their biological behavior and tissue/cell specificity and their toxicity profile is the key to developing clinically relevant nanotherapeutics and diagnostic agents[272–274].
- Applying nanomedicines in maladaptive inflammation and angiogenesis can be more challenging due to the inherent heterogeneity of the disease and the dynamic changes in lesion phenotype over time. Furthermore, heterogeneity and plasticity are hallmarks of monocytes and macrophages[59,275]. Growing evidence demonstrates the need to liberate our research from the dichotomous concept of macrophage activation: classical vs. alternative, i.e. M1 and M2, respectively [276,277]. These facts have implications on how nanomedicines can be best applied. Firstly, lesion heterogeneity can be manifested in the remarkable heterogeneity of the enhanced permeability and retention (EPR) effect, which impacts nanomedicine accumulation and, hence, their efficacy. Implementation of screening methods to identify patients who can benefit from nanomedicine should be a key factor for further developments [278]. Secondly, developing nanomedicines based on the M1/M2 macrophage paradigm is a shorthand approach that will probably not lead to clinically viable products. Understanding the function, dynamics, and memory of monocytes and macrophages, in their systemic and local milieu, is a rather more enabling and clinically relevant strategy.

Given the impact of chronic inflammatory diseases, successful translation of nanomedicines into the clinic can be socioeconomically rewarding, yet challenging. Convergence of

nanomedicine, life and physical sciences, bioinformatics, bioengineering, and pharma perspectives can help to reduce development costs, close the gap between preclinical research and clinical translation, and ultimately bring more efficacious nanomedicines to patients (Fig. 5).

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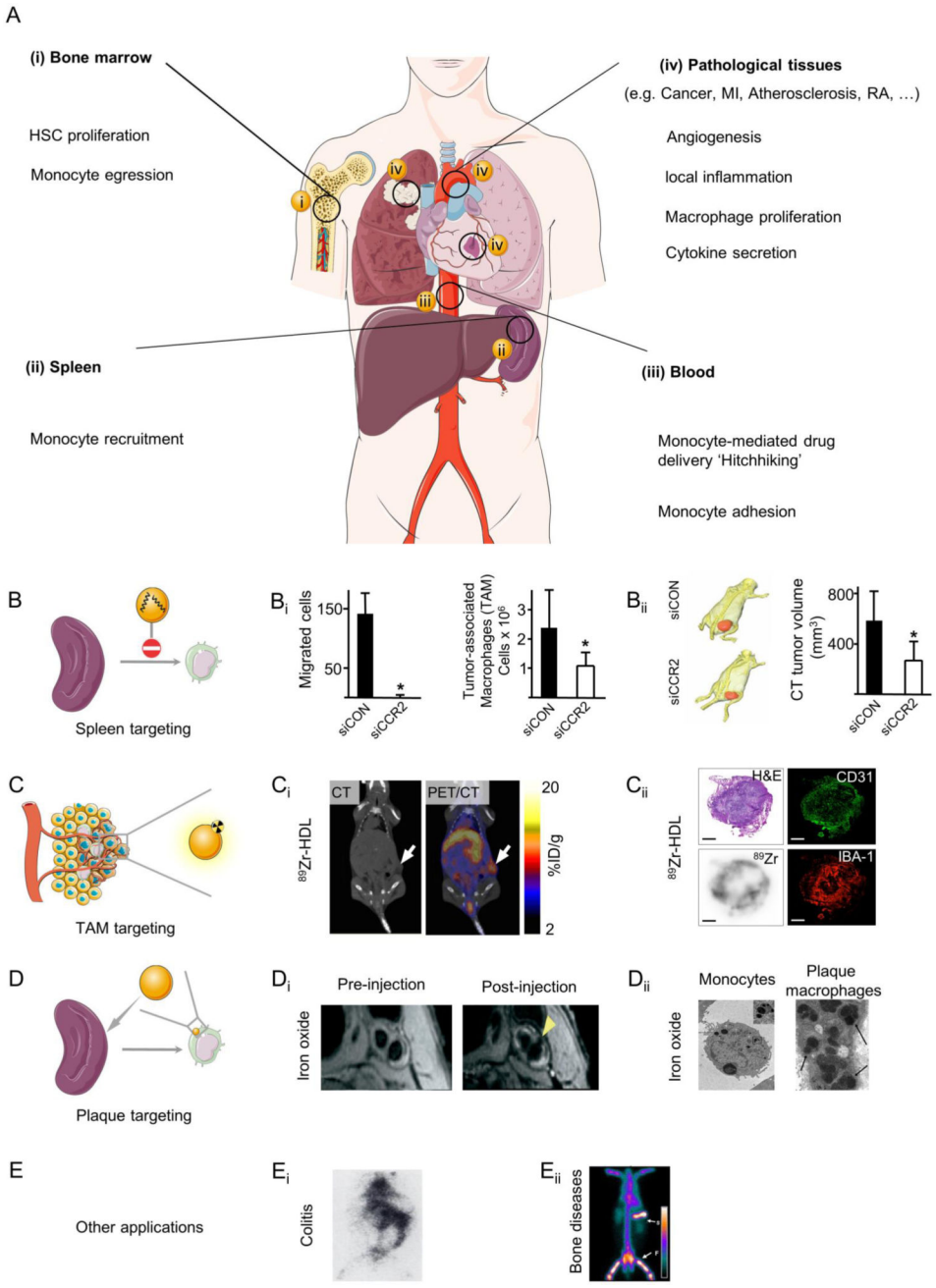

Fig. 1. Applying nanomedicine along the journey of monocytes in inflammatory disorders

(A) Several processes that contribute to monocyte/macrophage dynamics in maladaptive inflammation and angiogenesis can be exploited for imaging and therapeutic purposes at the systems level. In A (i) and (ii), tackling hematopoietic stem cell (HSC) proliferation and monocyte migration from the bone marrow and spleen by nanomedicines can be an upstream approach to control inflammation. In A (iii), trafficking of inflammatory monocytes in the circulation and their adhesion to activated endothelial cells can be exploited for cell-mediated therapies and diagnosis. A (iv) Applying nanomedicines at the lesion level can be realized by tackling the enhanced vascular permeability, local

macrophage proliferation and activity, and the secretion of proteases or cytokines. Examples of nanomedicines targeting (B) the spleen, (C) tumor-associated macrophages, (D) monocyte migration, and (E) other diseased tissues. Graphs and images in B_i and B_{ii} are adapted, with permission, from [135]. PET/CT in C_i and histological images in C_{ii} are reproduced, with permission, from[136]. MRI images in D_i were adapted, with permission, from [137] while histological images in D_{ii} are adapted, with permission, from [138] (left) and [139] (right). Scintigraphic images of rabbits in E_i and E_{ii} are reproduced, with permission, from [140] and [141], respectively. MI: myocardial infarction, RA: rheumatoid arthritis, TAM: tumor-associated macrophages.

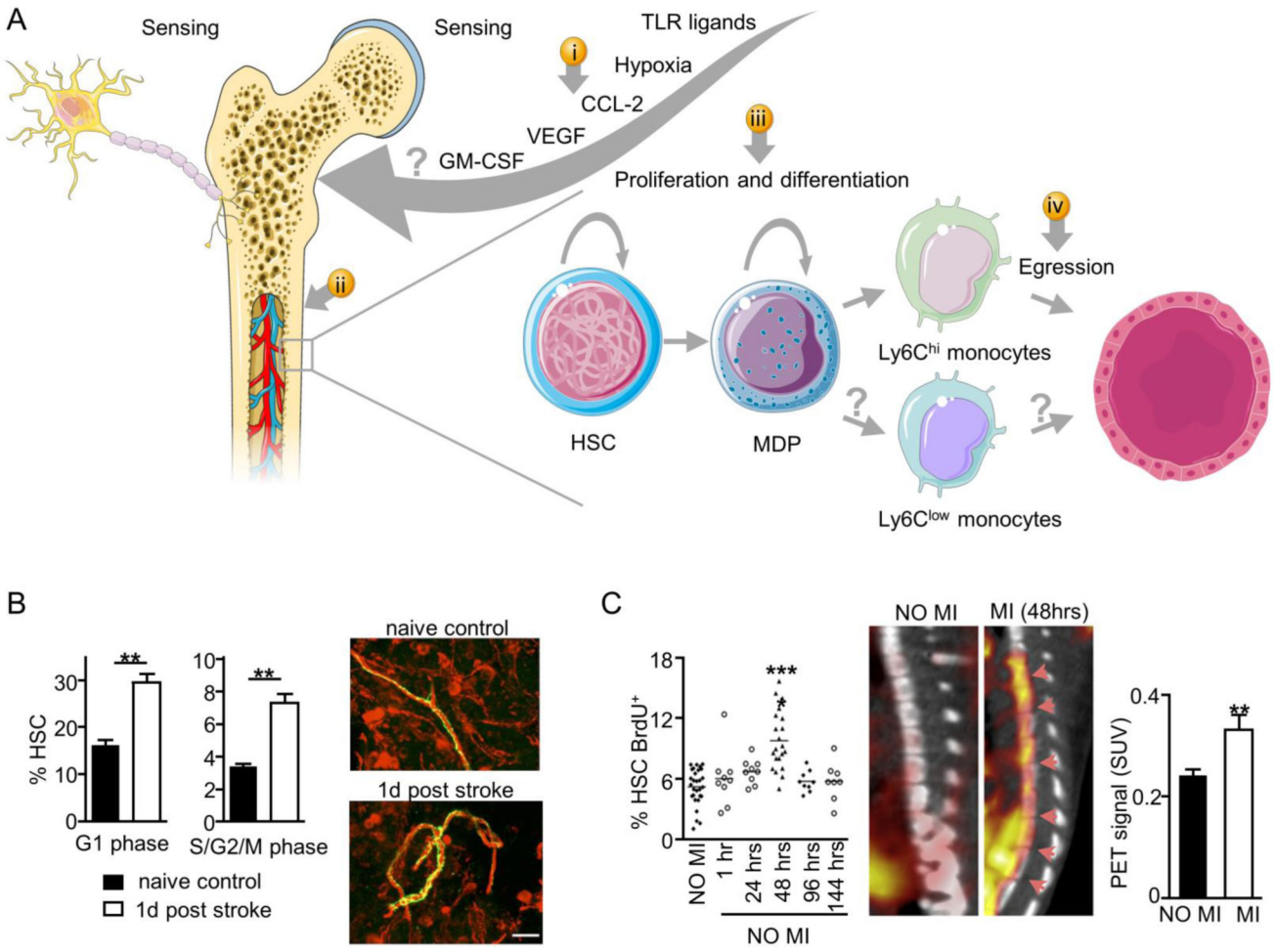

Fig. 2. Bone marrow activation

Inflammatory disorders are characterized by elevated levels of circulating cytokines, growth factors, and damage-associated molecules. The stress and pain associated with the disease increase sympathetic nervous activity. Both biochemical and neuronal changes increase proliferation and migration of both HSCs and inflammatory monocytes (Ly6C^{hi}) from bone marrow niches. (A) Nanomedicine can be used to target different features of bone marrow activation, including (i) circulating bone marrow activators, (ii) bone marrow permeability, (iii) HSC proliferation, and (iv) monocyte egress. Combining nanomedicines with molecular imaging at the medullar level can advance our understanding of disease progress. For example, (B) ischemic stroke increases the sympathetic nervous activity, which regulates the proliferation and cell cycle of HSCs, as shown by immunofluorescence staining of tyrosine hydroxylase rich nerve fibers of the sternal bone marrow. (C) Myocardial infarction (MI) increases HSC proliferation in the bone marrow, a process that can be quantified by BrdU staining, and imaged by ^{18}F-FLT positron emission tomography/computed tomography (PET/CT). Panel B is modified, with permission, from[169]. Panel C is modified, with permission, from [170]. TLR: toll-like receptor, CCL-2: C-C motif chemokine 2, VEGF: vascular endothelial growth factor, GM-CSF: granulocyte-macrophage colony-stimulating

factor, HSC: hematopoietic stem cell, MDP: monocyte and dendritic cell progenitor, SUV: standardized uptake value, BrdU: bromodeoxyuridine.

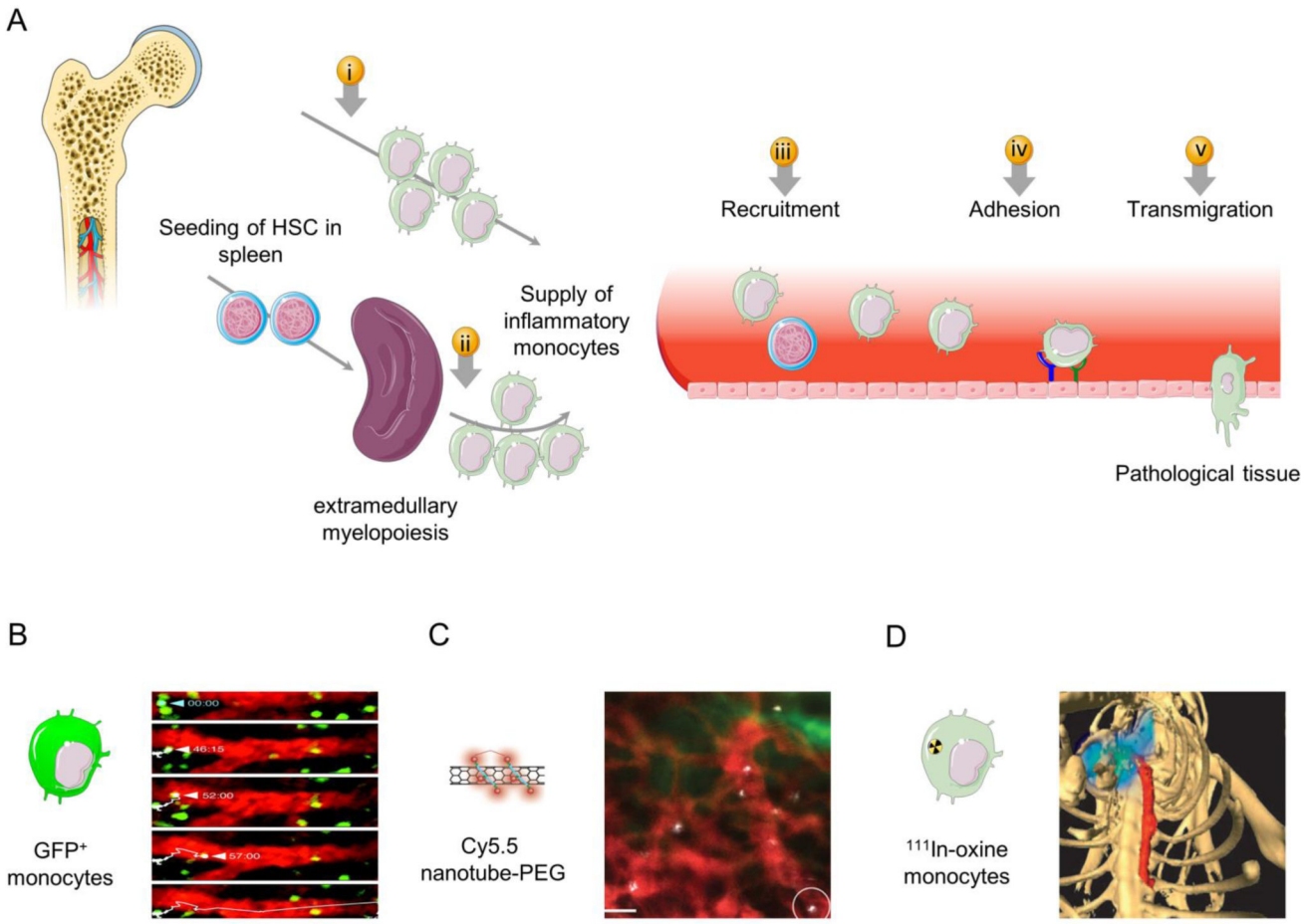

Fig. 3. Monocyte mobilization and recruitment

(A) In response to inflammation, the spleen, in addition to the bone marrow, overproduces monocytes that enter the circulation. The inflammatory monocytes are guided by a gradient of chemokines in their journey to the inflamed lesions. The adhesion and the preferential accumulation of monocytes in lesions are driven by overexpression of certain receptors by the inflamed endothelium, including vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1). Nanomedicines can be exploited for imaging and therapeutic purposes at different stages of the monocyte journey in the circulation, starting from (i) monocyte egress from bone marrow, (ii) monocyte production and release from the spleen, (iii) monocyte trafficking in the blood stream, (iv) adhesion of monocytes to the inflamed endothelium, and (v) monocyte accumulation in the lesions. (B) Ischemic myocardial injury induces rapid deployment of splenic monocytes, which can be imaged by intravital microscopy of green fluorescent protein (GFP^+) monocytes. (C) The preferential uptake of nanoparticles by $Ly6C^{hi}$ monocytes allows studying both monocyte and nanoparticle trafficking in the circulation using intravital microscopy. (D) Labeling monocytes with a radiotracer (e.g. [^{111}Indium] oxyquinoline, ^{111}In-oxine) enables noninvasive tracking and visualization of monocyte accumulation in atherosclerotic plaques and other inflammatory lesions using single photon emission/computed tomography

(SPECT/CT). Panel B is adapted, with permission, from [175]. Panel C is reproduced, with permission, from[179]. Panel D is adapted, with permission, from[180].

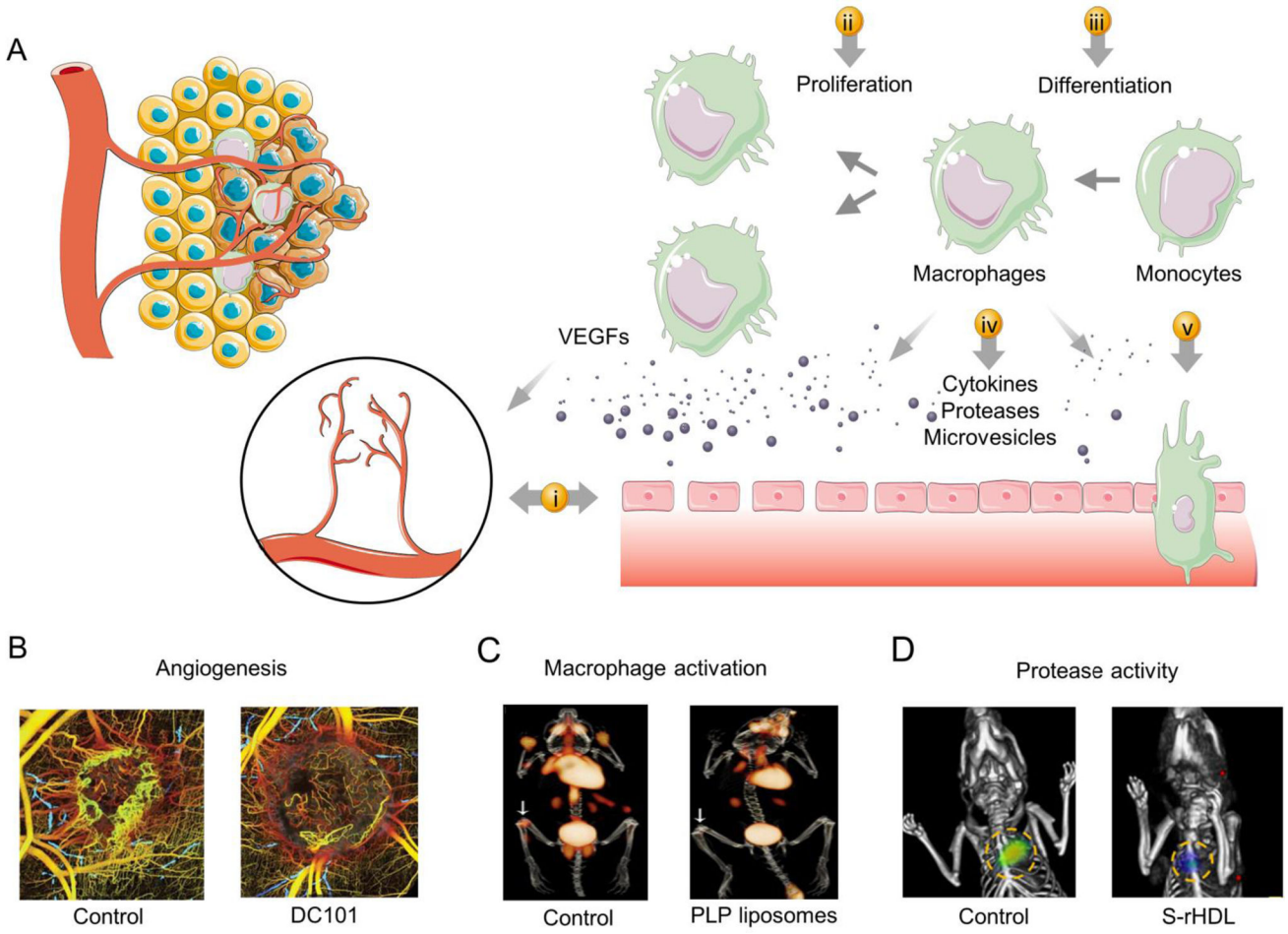

Fig. 4. Enhanced microvascular permeability and local inflammation

(A) Inflammatory monocytes accumulate in inflamed lesions and differentiate into tissue-resident macrophages. A cascade of events ensues such as local macrophage proliferation, the release of proinflammatory cytokines, proteases and cellular vesicles, which can aggravate the inflammatory condition and recruit more inflammatory cells. In addition, the release of vascular endothelial growth factors and other cytokines induce angiogenesis and increase microvascular permeability to macromolecules. Diagnostic and therapeutic nanoparticles can be used to tackle (i) pathological angiogenesis and enhanced permeability, (ii) local cell proliferation, (iii) monocyte differentiation, (iv) cytokine and chemokine release (v) and monocyte infiltration. (B) Cancer-associated angiogenesis and response to anti-angiogenic therapies can be monitored *in vivo* using optical frequency domain imaging. (C) Anti-inflammatory effect of prednisolone phosphate (PLP) liposomes in rheumatoid arthritis can be noninvasively assessed by ^{18}F-FDG PET/CT. (D) Protease activity in response to simvastatin rHDL nanoparticles can be monitored *in vivo* using fluorescence molecular tomography/computed tomography (FMT/CT). Panel B is adapted, with permission, from[211]. Panel C is reproduced, with permission, from[212]. Panel D is adapted, with permission, from[213].

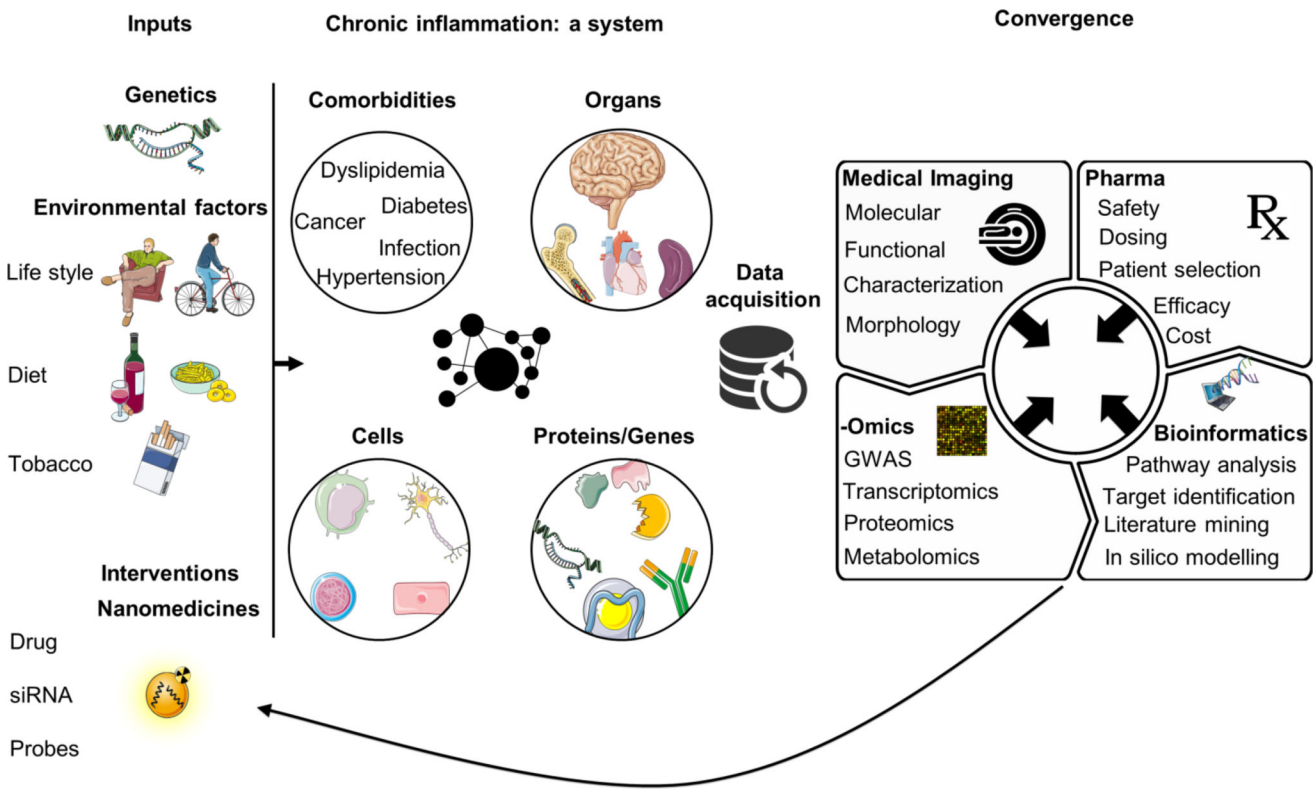

Fig. 5. Considerations for applying and developing nanomedicines for chronic inflammatory diseases

Chronic inflammatory diseases are multifactorial disorders in which genetic background and environmental factors interact and affect different dynamic systems, including genes, signaling pathways, cells, and organs. Nanomedicine should be approached in a holistic way, in which nanodrugs' systemic interactions are investigated, and can be used to visualize and/or modulate multiple processes. Data acquisition and convergence of nanomedicine with the different biomedical fields and big data (e.g. transcriptomics, proteomics, and genomics) can not only contribute to deciphering these complex diseases but also help to predict the efficacy of nanomedicines and to develop clinically relevant products.