Themed Section: Immune Targets in Hypertension

REVIEW ARTICLE

Monocytes as immune targets in arterial hypertension

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The role of myelomonocytic cells appears to be critical for the initiation, progression and manifestation of arterial hypertension. Monocytes can induce vascular inflammation as well as tissue remodelling and (mal)adaptation by secreting chemokines and cytokines, producing ROS, expressing coagulation factors and transforming into macrophages. A multitude of adhesion molecules promote the infiltration and accumulation of monocytes into the kidney, heart, brain and vasculature in hypertension. All these facets offer the possibility to pharmacologically target monocytes and may represent novel therapeutic ways to treat hypertension, attenuate hypertension-associated end organ damage or prevent the development or worsening of high blood pressure.

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Abbreviations
AngII, angiotensin II; CCR, CC chemokine receptor; CVD, cardiovascular disease; ICAM-1, intercellular adhesion molecule-1; MCP-1, monocyte chemoattractant protein 1; NOX, NADPH oxidase; SHRs, spontaneously hypertensive rats; TF, tissue factor; VCAM-1, vascular cell adhesion molecule 1
**Introduction**

Arterial hypertension is currently regarded as the leading risk factor for morbidity and mortality worldwide (Lim *et al*., 2012). In particular, it is the main pathophysiologial and epidemiological driver of heart failure, ischaemic stroke and ischaemic heart disease including acute myocardial infarction, the single most frequent cause of death in the world. The immune system is central in the development and perpetuation of high blood pressure and in hypertension-related end organ damage (Norlander *et al*., 2018). Interestingly, individuals with a constitutive overexpression of inflammasome-related genes, in particular **IL-1β**, have higher blood pressure, vascular stiffness and experience premature death (Furman *et al*., 2017). While there is a myriad of interactions of the immune system with all critical players in blood pressure regulation (CNS, kidney, microvasculature, conductance vessels, heart), the role of myelomonocytic cells is inherent in all of them.

**Role of monocytes in high blood pressure and hypertensive end organ damage**

In the brain, angiotensin II (AngII) signalling mainly through the AngII receptor type 1 (**AT1, receptor**) increases neuronal activity in brain areas such as the rostral ventrolateral medulla or subfornical organ with efferent projections into the periventricular nucleus of the hypothalamus, to the solitary tract and others. This results in increased systemic sympathetic outflow, thereby inducing, maintaining or amplifying high blood pressure (Ferguson, 2009; de Kloet *et al*., 2015). The microglia representing the tissue resident myelomonocytic cell type in the brain may play a critical role in blood pressure control. Hypertension induces the activation and proliferation of microglia in the brain, an essential feature of neuroinflammation, with concomitant intracerebral up-regulation of **IL-1β**, IL-6 and TNF-α expression as well as ROS formation (Wu *et al*., 2012). Ablation of CD11b+ cells by a diphtheria toxin-mediated approach blocked AngII-driven microgliosis as well as inflammatory cytokine expression and attenuated arterial hypertension (Shen *et al*., 2015). Neuroinflammation is also a hallmark of Alzheimer’s disease and other forms of dementia, significantly associated with hypertension. Intriguingly, it is an early step in hypertension preceding amyloid deposition (Carnevale *et al*., 2012a), making myeloid cells in the brain central in both the development of hypertension and end organ damage (Carnevale *et al*., 2012b).

The kidneys are the major site of renin release, blood volume control and electrolyte homeostasis and are central to the development of hypertension (Goldblatt, 1947). They are inflamed in chronic hypertension (Wilson, 1963), leading to hypertensive kidney disease (McMaster *et al*., 2015). However, renal inflammation may also precede development of hypertension (Rodriguez-Iturbe *et al*., 2004), and the infusion of AngII leads to a persistent accumulation of myelomonocyte populations in the renal medulla and cortex (Ozawa *et al*., 2007). For example, Ly6C+ monocytes and macrophages infiltrating the kidneys promote sodium reabsorption via the NKCC2 co-transporter in the nephron, which can be alleviated by blockade of **IL-1 receptor 1** (Zhang *et al*., 2016).

For more than 45 years, monocytes have been known to infiltrate the vasculature in arterial hypertension and promote proliferation of connective tissue (Olsen, 1971). Remodelling of the (micro)vasculature is the key step in the increase in systemic vascular resistance, a hallmark feature of arterial hypertension (Folkow *et al*., 1973). The vascular accumulation of monocytes has been widely accepted as a key primary step in atherogenesis, occurring early on in the pathogenesis of the disease (Cybulsky and Gimbrone Jr, 1991). Research has always been centred on monocytes, meaning bone marrow derived circulating cells that represent putative future macrophages infiltrating various organs and tissues. This view traditionally omits the resident macrophages. The role of resident macrophages and that of infiltrating myelomonocytic cells in hypertension is unclear. However, it is well known that yolk sac macrophages express more **MerTK** genes (encoding for the proto-oncogene tyrosine-protein kinase MER) than CC chemokine receptor 2 (**CCR2**) genes and are early organ resident macrophages, in contrast to bone marrow derived monocytes, that are myelomonocytic cells (Schulz *et al*., 2012). In principle, yolk sac-derived macrophages, fetal liver monocytes and bone marrow derived monocytes have the same capacity to populate empty niches and develop into phenotypically ‘identical’ tissue macrophages (van de Laar *et al*., 2016) in the same vein, some new evidence suggests that cardiac and arterial resident macrophages, which express MerTK, play a protective role by removing apoptotic cells and suppressing vascular inflammation, whereas infiltrating CD11b+Ly6+ monocytes play a pathophysiological role in the heart and blood vessels, for instance in the setting of atherosclerosis (Cai *et al*., 2017; DeBerge *et al*., 2017). These data point towards the long-established dichotomy into pro-inflammatory (Ly6Chi) and reparative (Ly6Chi) monocytes and classically activated ‘M1’ macrophages versus reparative ‘M2’ macrophages (Geissmann *et al*., 2003; Moore and Tabas, 2011). While the protective role of M2-like macrophages has been shown in experimental models of atherosclerosis, their role in modulating vascular injury or blood pressure in arterial hypertension remains less clear. A recent review focused on the role of macrophage polarization in hypertension, trying to shed some light on the obscure mechanisms and incomplete concepts (Harwani, 2018). For instance, the group of Grant Drummond has demonstrated that continued exposure to AngII infusion in vivo induces an increase in the population of CD206+4F4/80+ macrophages in the vasculature, paralleled by increased aortic expression of arginase-1 and Fc receptor-like S scavenger receptor mRNA, compatible with an expansion of the M2 like macrophage population (Moore *et al*., 2015). In that paper, the exact role of these cells remained unclear; nevertheless, antagonization of CCR2 (see below) reduced both the abundance of this population and reduced blood pressure. To the contrary, Ndisang and Mishra (2013) have demonstrated that pharmacological intervention to increase the abundance of this population and reduced blood pressure. However, it is well known that more advanced atherosclerotic lesions contain a functionally active renin-angiotensin-system, facilitating continuous recruitment of monocytes to the plaque and possibly contributing to plaque instability and rupture.
application of mechanical strain also increased MCP-1 expression, underlining a fundamental role of this chemokine for chemotaxis in high blood pressure (Capers et al., 1997a). Ishibashi and co-workers showed the critical role of the MCP-1 receptor CCR2 on monocytes in arterial hypertension. Blocking the receptor by an antagonizing antibody prevented vascular inflammation and remodelling (Ishibashi et al., 2004). Blocking the MCP-1/CCR-2 axis and other CC chemokine pathways (CCR1, CCR5) prevented AngII-induced monocyte adhesion to the microvasculature (Mateo et al., 2006). Likewise, antagonizing CXC chemokine receptors like CXCR2 also reduces MCP-1, RANTES (ligand to CCR1 and S) and MIP1a (CCL3) levels, thereby attenuating AngII-induced monocyte adhesion in vitro (human umbilical arterial cells) and in vivo (splanchnic circulation) (Abu Nabah et al., 2007).

Monocyte derived cytokine production in arterial hypertension

IL-6 is a pro-inflammatory cytokine that can be produced by myelomonocytic cells. It is one of the few cytokines for which an independent association with arterial hypertension has been demonstrated. In epidemiological studies, it was identified to be an independent risk factor for hypertension in apparently healthy individuals (Bautista et al., 2005). IL-6 may also serve as a biomarker for elevated blood pressure, since it was shown to be significantly elevated in patients with hypertension compared to normotensive controls (Chamarthi et al., 2011). In experimental research, knockout of IL-6 protected mice from developing high blood pressure in response to AngII and high salt. This was paralleled by partial protection from kidney injury, as assessed by albuminuria (Lee et al., 2006). Pharmacological inhibition of IL-6 by a neutralizing antibody was able to lower blood pressure and preserve kidney function in salt-sensitive Dahl rats. Interestingly, this nephroprotection was associated with reduced numbers of monocytes infiltrating the kidney and a decreased abundance of renal macrophages (Hashmat et al., 2016). This suggests that intervening in the IL-6 signalling pathways may be an elegant way to attenuate end organ damage in hypertension by blocking activation of myelomonocytic cells.

IL-12 is secreted by activated monocytes and macrophages, typically when exposed to IFN-γ. In addition, it can also be active as a membrane bound form (Fan et al., 1996). In the setting of AngII-induced hypertension, it was shown that IFN-γ derived from NK1.1⁺ NK cells stimulates monocytes to form IL-12, which in turn augments the formation of IFN-γ by NK cells (Kossmann et al., 2013), a classical function of this cytokine (D’Andrea et al., 1992). This mutual activation depends on the transcription factor T-box expressed in T-cells (T-bet), which is critical not only for IFN-γ transcription in lymphoid cells like T-cells and NK cells but also for IL-12 formation by myelomonocytes (Soderquest et al., 2011). The abundance of T-bet is highest in lymphoid cells such as T-cells and NK cells. Based on the data of Kossmann et al., targeting of T-bet specifically in monocytes to block IL-12 synthesis or in T-cells and NK cells to block IFN-γ formation could offer a possible approach to attenuate vascular inflammation in hypertension.

Monocyte chemotaxis in arterial hypertension

In 1997, Capers et al. showed that monocyte chemotactic protein 1 (MCP-1; also known as CCL2) mRNA expression is increased in the aorta of AngII as well as noradrenaline-infused rats that could be reversed by co-administration of a diuretic. Supporting experiments in rat isolated aortic smooth muscle cells showed that...
Monocyte vascular rolling, adhesion, infiltration and accumulation in arterial hypertension

AngII induced the adhesion and binding of monocytes, but not neutrophils, to human and rabbit aortic endothelial cells. This was completely dependent on AT₁ receptor-mediated signal transduction. Interestingly, in this cell culture system, adhesion was independent of the up-regulation of endothelial vascular cell adhesion molecule 1 (VCAM-1) or intercellular adhesion molecule-1 (ICAM-1) (Kim et al., 1996). Later, Pueyo and co-workers convincingly showed that AngII does indeed induce VCAM-1 mRNA expression in endothelial cells in an AT₁ receptor-dependent manner, which was NF-κB- and ROS-dependent (Pueyo et al., 2000). In vivo models of arterial hypertension later provided strong evidence that adhesion molecules are necessary for attracting monocytes in arterial hypertension. For example, Tummala et al. showed that AngII induced the expression of VCAM-1 not only in rat cultured aortic smooth muscle cells but also in the vasculature of AngII-infused rats. This expression was AT₁ receptor-dependent, and proteasome inhibitors were able to block the NF-κB related transactivation of VCAM-1 expression (Tummala et al., 1999).

ICAM-1 is induced by AngII in vivo, at least in part in an NADPH oxidase dependent manner (Liu et al., 2003). In coronary vessels, however, AngII had only small effects on the expression of VCAM-1 and ICAM-1; here, it preferentially increased the expression of the adhesion molecule E selectin (Grafe et al., 1997). In the rat mesentery, which represents a classical microvasculature, P-selectin was induced by AngII both via the AT₁ as well as the AT₂ receptor (Piqueras et al., 2000). Another important ligand on monocytes promoting endothelial adhesion is Mac-1 (also known as integrin α₅β₂ or CD11b/CD18). It can bind to ICAM-1 on endothelial cells (Diamond et al., 1990) but also to fibrinogen and junctional adhesion molecule-3. In addition, it engages with the glycoprotein Ibα on platelets to form monocyte-platelet-conjugates (Simon et al., 2000) and is an essential feature in vascular injury (Wang et al., 2005). In stroke-prone SHRs, administration of an AT₁ receptor blocker reduced leukocyte expression of Mac-1, implying an AngII-dependent induction of this integrin in arterial hypertension (Takemori et al., 2000).

By using intravital epifluorescence video microscopy, it was revealed that leukocyte rolling and adhesion to the endothelium of both low flow regions of the circulation like arterioles and mesenterics (Piqueras et al., 2000) as well as high flow arterial beds (carotid artery) is a characteristic event in vascular inflammation in AngII-induced arterial hypertension. By using transgenic mice with conditional expression of yellow fluorescent protein under the transcriptional control of the gene lysozyme M, which is specific for neutrophils, monocytes and macrophages (Gordon et al., 1974; Clausen et al., 1999), Lagrange and co-workers showed that almost all of these rolling and adhering leukocytes are of myeloid origin (Lagrange et al., 2018). Importantly, this vascular inflammation can be modified by anti-inflammatory interventions or modulations of anti-inflammatory systems. A constitutive lack of the anti-inflammatory and antioxidative enzyme haem oxygenase 1 (HO-1) not only increased the susceptibility of mice to develop endothelial dysfunction and high blood pressure in response to AngII but also increased leukocyte rolling (Wenzel et al., 2015). This was linked to an augmented vascular accumulation of Cd11b⁺Ly6Cѳ monocytes and Cd11b⁺F4/80⁺ macrophages. Inversely, germ-free mice with an attenuated capacity to mount a classical type 1 immune response show significantly less monocyte rolling and adhesion to the endothelium in response to AngII than conventionally reared controls (Karbach et al., 2016). Consequently, these mice do not develop arterial hypertension, endothelial dysfunction and vascular accumulation of Cd11b⁺Ly6Cѳ and Cd11b⁺F4/80⁺ cells. When VCAM-1 and its counterpart receptor on leukocytes, the very late antigen 4, are experimentally blocked by antagonizing antibodies in AngII-infused mice, monocyte rolling and adhesion to the endothelium are effectively blocked in vivo. The same was true for blocking Mac-1, suggesting that the ICAM-1/Mac-1 axis may also be critical for monocyte adhesion in hypertension (Kossmann et al., 2017).

In order to allow infiltration of leukocytes into the vascular wall or the perivascular space, the biochemical activity of proteases is needed. These enzymes cleave components of the endothelial barrier, the basal membrane and the extracellular matrix, such as elastin and collagen. In atherosclerotic lesions, enigmatic for vascular remodelling, high expression and activity of elastases, collagenases and gelatinases have been detected. Among the proteolytic enzymes, MMPs, serine proteases and cysteine proteases (such as lysosomal cathepsin S and K) have received the highest attention (Liu et al., 2004). The role of proteases as prerequisite to allow leukocyte infiltration in arterial hypertension is less well understood. Our data on platelet-localized vascular thrombin amplification in arterial hypertension in the absence of overt clotting suggest an involvement of protease-activated receptor signalling in vascular inflammation induced by AngII (Kossmann et al., 2017). In a mouse model of acute aortic dissection induced by AngII, MMP-9 was significantly up-regulated in the diseased aorta. Pharmacological inhibition of MMP-9 as well as genetic deficiency of MMP-9 largely protected from acute aortic dissection. Both dissection and MMP-9 activity were reduced by depleting Gr-1⁺ cells (comprising both neutrophils and Ly6Cѳ monocytes) with a monoclonal antibody (Kurihara et al., 2012). Similarly, monocytes of thrombospondin-1-deficient mice had reduced migratory capacity and endothelial adhesion in response to AngII, and thrombospondin-1⁻/⁻ mice were largely protected from AngII-induced aortic aneurysm, in part explained by the lack of thrombospondin-1-mediated proteolytic damage in the vessel wall (Liu et al., 2015).

Taken together, pharmacological interventions to block rolling, adhesion and vascular infiltration of monocytes could be a promising way to limit immune-mediated vascular injury in hypertension (Figure 1).

Coagulation factors, monocytes and hypertension

While the role of coagulation factors in the propagation of vascular inflammation has been appreciated for many years, its role in hypertension has only recently gained more attention. Tissue factor (TF) kicks off the coagulation cascade in the classical scheme of extrinsic coagulation (‘tissue factor
In the vasculature, it is exposed to the plasma upon vessel injury and complexes with factor (F) VII to form the prothrombinase complex, leading to FX activation and ultimately thrombin formation (Figure 2). Interestingly, TF is expressed not only by endothelial cells or vascular smooth muscle cells but also by neutrophils and monocytes. Currently, monocytes are regarded as the prime source of TF expression and activity in venous thrombosis and atherosclerosis. Upon stimulation via the ADP/P2X7 axis, macrophages produce inflammasome-dependent endosomal ROS, form filipodia, transport TF to the extracellular surface and shed TF-rich, procoagulant microparticles (Rothmeier et al., 2015). Deletion of TF specifically in LysM-positive immune cells prevents the initiation of deep vein thrombosis in mouse models (von Bruhl et al., 2012; Subramaniam et al., 2017). AngII has been shown to increase TF mRNA and protein expression in vascular smooth muscle cells (Taubman et al., 1993). We have found increased mRNA expression of TF in monocytes isolated from mice infused with AngII (unpublished data). Blocking TF activity with the antibody 21E10 prevented both AngII-induced vascular dysfunction in mice as well as the rolling and adhesion of leukocytes to the endothelium of the carotid (Kossmann et al., 2017). This indicates a causative role for TF in contributing to arterial hypertension, at least in part through the induction of thrombin (FIIa). Heterotypic thrombin generation within the vessel wall was shown to be increased in SHRs and could be blocked by an ACE inhibitor. Smooth muscle cells isolated from SHRs were more sensitive to thrombin-induced proliferation than SMCs from control rats (Ait Aissa et al., 2015). Additionally, the expression of thrombin receptors (PARs) has been shown to be up-regulated in the vessel wall of AngII-infused rats, which was mediated by AT1 receptors and lead to increased susceptibility to thrombin-induced vasoconstriction (Capers et al., 1997b). Thrombin itself is a strong inducer of MCP-1 in vascular cells and may thereby increase monocytes adhesion to the endothelium (Wenzel et al., 1995). As early as 1993, it was shown that in the presence of AngII, thrombin-induced platelet aggregation was significantly higher in patients with uncontrolled hypertension than in treated hypertensives and control individuals (Touyz and Schiffrin, 1993). Blocking FIIa activity by the direct thrombin inhibitor hirudin prevented endothelial leukocyte rolling and adhesion and improved vascular dysfunction in AngII-induced hypertension. Similar to antagonizing TF activity, it attenuated vascular ROS formation and markers of vascular inflammation (Kossmann et al., 2017). Interestingly, the TF-mediated thrombin activity appears to be propagated by an amplification loop via the coagulation factor FXI in hypertension. That pathway was proposed earlier in coagulation research (Gailani and Broze Jr, 1991) and can be
exploited therapeutically to perform safe thromboprophylaxis (Buller et al., 2015). Blocking FXI synthesis prevented localized thrombin generation in platelets and lowered pro-inflammatory platelet-monocyte complexes, the vascular accumulation of myeloid cells, ROS formation in the vessel wall and ultimately dampened the blood pressure increase in models of hypertension (Kossmann et al., 2017). This unexpected role of FXI in mediating myeloid cell driven inflammation and vascular damage in hypertension needs to be addressed by further research. Besides driving thrombin generation on platelets, the protease function of FXIa could also contribute to non-canonical signalling pathways that directly affect inflammatory damage. For instance, the pro-inflammatory role of FXI could also relate to its novel function in the cleavage of prochemerin (Ge et al., 2018), which might be involved in hypertension-induced vascular inflammation as well.

Further downstream of the coagulation cascade, Abdalla et al. (2004) showed that the transglutaminase coagulation factor XIII may crosslink the AT1 receptors on monocytes and would, therefore, be required to allow the full activation of monocytes by AngII. This is intriguing, because non-conventional roles for FXIII have also been demonstrated to be important for collagen crosslinking in the process of wound healing and scar formation post myocardial infarction (Nahrendorf et al., 2006).

Altogether, a new area of research is opened up with regard to novel extracellular roles of coagulation factors in hypertension that could also serve as drugable immunotargets (Figure 2). Clinical evidence comes from the recent COMPASS trial. Here, the addition of a very low, non-anticoagulant dose of the FXa inhibitor rivaroxaban to standard therapy with acetylsalicylic acid reduced cardiovascular disease (CVD) events in secondary prevention (Eikelboom et al., 2017). It will be challenging – and potentially rewarding – to explore the possible vasoprotective effects of targeting coagulation factors, in particular with regard to monocytes and hypertension.

**NADPH oxidase in monocytes as putative target**

NADPH oxidase is a core component of the innate immune response and abundantly expressed in mononuclear phagocytes (neutrophil granulocytes, monocytes and macrophages) but also by other immune cells as well as endothelial cells, smooth muscle cells and adventitial cells, like fibroblasts, perivascular adipocytes and pericytes. The multiple roles of NADPH oxidase in CVD and hypertension have been extensively reviewed before. For stringency reasons, we also do not expand on the important other sources of ROS in this review, such as an uncoupled NO synthase, the mitochondrial respiratory chain or xanthin oxidases (Li et al., 2014).

The NADPH oxidase in myelomonocytes deserves specific attention (Cathcart, 2004). Like their counterparts in the myeloid lineage, the neutrophil granulocytes, monocytes contain a phagocyte-type NADPH oxidase with the catalytic subunit gp91phox (nox2) and anchoring unit p22phox, together making the cytochrome b558. To be activated, regulatory subunits need to translocate from the cytosol to the membrane, including the p67phox and the p47phox, together with the small GTPase rac1 (Figure 1). The activation
process in neutrophils is slightly different, with the GTPase rac2 substituting the rac1 (Zhao et al., 2003), priming these innate cells for rapid release of superoxide in the so-called oxidative burst (Leusen et al., 1996), essential for microbial killing and neutrophil extracellular trap formation (Fuchs et al., 2007).

In a seminal paper, Rajagopalan et al. showed that the phagocyte-type NADPH oxidase (NOX) in the vasculature produces superoxide in response to AngII. Both NOX-derived ROS formation and endothelial dysfunction could be blocked in vivo by an AT1 receptor blocker in AngII-infused rats (Rajagopalan et al., 1996). Expression of gp91phox, p22phox as well as NOX1 was increased in response to AngII, and concomitantly, endothelial NOS becomes dysfunctional in a ROS-sensitive manner, a process called eNOS uncoupling (Mollnau et al., 2002). This disbalance between superoxide and NO is regarded as the main redox-biochemical mechanism of endothelial dysfunction in hypertension. Pharmacological targeting of the gp91phox by a docking sequence peptide blocking the catalytic activity of the enzyme (gp91ds-tat) prevented AngII-induced infiltration of ED1+ myelomonocytes and attenuated medial hypertrophy in large arteries, independently of blood pressure effects (Liu et al., 2003). The same group has shown that AngII-infused mice treated with the gp91ds-tat, which attenuated NADPH-oxidase-derived superoxide formation, were largely devoid of blood pressure increase (Rey et al., 2001). These data suggest that NADPH oxidase from mononuclear cells might be causally involved in the blood pressure increase in response to AngII. Indeed, when transgenic mice were depleted of monocytes, blunted hypertension could only be re-established by reconstitution with gp91phox competent monocytes, not with monocytes isolated from gp91phox+/− mice (Wenzel et al., 2011). p47phox−/− mice lacking an important regulatory subunit of the phagocyte-type NADPH oxidase had blunted the increase in blood pressure in response to AngII. This was accompanied by a loss of NADPH oxidase-derived superoxide formation, (Landmesser et al., 2001; Liu et al., 2003). Similar findings were obtained in mice deficient in the gp91phox homologue in vascular smooth muscle cells, NOX1. Nox1−/− had normal blood pressure at baseline but a significantly blunted hypertensive response to AngII. This was paralleled by a lack of superoxide formation and preserved NO-dependent vasorelaxation, whereas medial hypertrophy was similar in nox1+/− compared to nox1−/− mice (Matsuno et al., 2005). Interestingly, gp91phox−/− mice had lower blood pressure than their gp91phox+/− counterparts at baseline and a lower blood pressure in response to AngII resulting in a pulse pressure that was not different between the groups (Wang et al., 2001). Importantly, vascular NADPH oxidase-mediated superoxide formation, nitrotyrosine staining and medial hypertrophy were absent in AngII-infused gp91phox−/− mice, similar to the findings obtained with the gp91ds-tat (Rey et al., 2001; Liu et al., 2003) and by depletion of gp91phox competent myelomonocytic cells (Wenzel et al., 2011). In a recent study by Sag et al. using mice with conditional knockout of gp91phox specifically in myelomonocytic cells, the findings of Wang et al. regarding blood pressure response could be corroborated, underpinning a central role for NOX2 inside vascular monocyte/macrophages for blood pressure regulation and vascular tone (Sag et al., 2017). Targeting intrinsic antioxidative pathways inside monocytes has been proven effective as well, at least in the experimental setting. The induction of HO-1 in monocytes suppressed AngII-induced superoxide formation and lowered the expression of CCR2, the receptor for MCP-1, and attenuated the chemotactic response. Administration of downstream products of HO-1, bilirubin and carbon monoxide was equally effective, suggesting the antioxidant properties of HO-1 as a putative immune target on monocytes (Morita et al., 2003).

**Immune modulation as therapeutic target in cardiovascular disease**

The findings of the COMPASS indirectly implicate an involvement of the immune system in the progression of CVD. However, there is a growing body of evidence indicating that an activated immune system might also be targeted by anti-inflammatory therapy (Figure 1). Based on the findings that individuals with elevated high sensitive C-reactive protein levels are at increased risk of CVD events that might benefit from a statin therapy despite normal LDL cholesterol levels (Ridker et al., 1997; Ridker et al., 2008), trials using methotrexate (CIRT trial) or the IL-1β antagonist **canakinumab** (CANTOS trial) have been performed to test the effectiveness of direct anti-inflammatory drugs to lower CVD events and mortality in individuals with a history of coronary artery disease and/or myocardial infarction (Ridker, 2009; Ridker et al., 2017). While results of the CIRT trial are not yet available, the CANTOS trial showed a significant reduction in nonfatal myocardial infarction or stroke and cardiovascular death with canakinumab versus placebo, on top of optimal medical care. Interestingly, the individuals who had the biggest benefit from IL-1β antagonism were those who experienced the biggest drop in hsCRP levels (Ridker et al., 2018). It has to be tested, however, if essential arterial hypertension also can be treated or prevented by an anti-inflammatory strategy. Evidence from patients with autoimmune disease at least suggests that this promise could hold true. In a small single centre study, treatment with the immunosuppressant **mycophenolate mofetil** significantly lowered blood pressure in patients with rheumatoid arthritis or psoriasis who had concomitant arterial hypertension (Herrera et al., 2006). Treating individuals suffering from rheumatoid arthritis with the TNF-α inhibitor, **infliximab**, significantly reduced ambulatory blood pressure (Yoshida et al., 2014). These data have encouraged leading scientist in the field to promote interventional clinical trials to test whether arterial hypertension can specifically be treated by an anti-inflammatory therapy (Leslie, 2018). It remains to be established if myelomonocytic cells qualify as a feasible target for such an approach.

**Anti-inflammatory effects of established antihypertensive drugs: monocytes as targets**

While the concept of a specific anti-inflammatory therapy for hypertension is only developing, there is already a lot of evidence that established antihypertensive drugs also have anti-inflammatory properties (Figure 1). This includes inhibitory actions on myelomonocytic cells. For example, angiotensin-converting enzyme (ACE) inhibition has been shown to
prevent arterial NF-κB activation, MCP-1 expression and macrophage infiltration in a rabbit model of early accelerated atherosclerosis (Hernandez-Presa et al., 1997). More specifically, Napoleone et al. (2000) demonstrated that ACE inhibitors may down-regulate TF synthesis in monocytes. Expression of the essential receptor for MCP-1 on monocytes, CCR2, was blunted by AT1 receptor blockers in hypertensive mice (Ishibashi et al., 2004), and AT1 receptor blockade reduces vascular TF in AngII-induced cardiac vasculopathy (Muller et al., 2000a). In a groundbreaking paper, Clozel and co-workers (1991) demonstrated that the extent of subendothelial monocyte and macrophage accumulation paralleled the extent of endothelial dysfunction in SHRs and that both were attenuated by treating the animals with ACE inhibitors.

The finding that monocytes could represent a treatable target in arterial hypertension in humans was made 20 years ago. Monocytes isolated from hypertensive patients secreted significantly higher levels of IL-1β in response to AngII than monocytes isolated from controls. IL-1β levels correlated significantly with blood pressure level. Likewise, IL-1β as well as IL-6 and TNF-α levels secreted by monocytes were higher in those exposed to LPS, revealing their inflammatory phenotype in hypertension (Dorffel et al., 1999). AngII induces the migration of isolated human monocytes, a process that involves pro-inflammatory ERK1/2, Src and p38 MAPK-dependent pathways and that can be abolished by AT1 receptor blockade (Kintscher et al., 2001). High dose treatment of patients afflicted by metabolic syndrome with the AT1 receptor blocker telmisartan induced PPAR-γ target genes in monocytes, such as CD36 (Bahr et al., 2011). Interestingly, the AT1 receptor blocker losartan given to high risk patients with terminal renal failure significantly reduced the number of CD14+CD16+ inflammatory monocytes compared to controls (Merino et al., 2012). These findings suggest that guideline recommended anti-hypertensive drugs directly affect monocyte phenotype and behaviour. This implies that pharmacological targeting of myelomonocytic cells could contribute to improve treatment of humans with arterial hypertension that may even be additive to currently used medication.

**Conclusion**

Monocytes play a key role in the inflammatory continuum of arterial hypertension. Their molecular and cellular (inter)actions are multifaceted and can potentially be exploited for pharmacotherapy of high blood pressure. Promising targets are (i) cytokines such as IL-1β, IL-6, IL-12 or IFN-γ that either are released by or act upon myelomonocytic cells; (ii) chemokine signalling such as the enigmatic MCP-1/CCR2 axis to block monocyte recruitment and down the line also adhesion and infiltration into the vasculature and (iii) phagocyte type NADPH oxidase or antioxidant enzymes to interfere with the ROS formation of myelomonocytic cells. Excitingly, pleiotropic effects of thrombin inhibition or other novel anti-thrombotic regimens may also contribute to the anti-inflammatory therapy of hypertension. Altogether, lowering the inflammatory burden imposed on the organism by inflammatory myelomonocytic cells may help to lower the global burden of disease imposed on mankind by arterial hypertension.

**Nomenclature of targets and ligands**

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018) and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander et al., 2017a,b,c,d).

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**Conflict of interest**

The author declares no conflicts of interest.

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