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REVIEW

IL-1β and IL-18: inflammatory markers or mediators of hypertension?

S M Krishnan[1], C G Sobey[1,2], E Latz[3,4,5], A Mansell[6] and G R Drummond[1,2]

[1]*Department of Pharmacology, Monash University, Clayton, Vic, Australia,* [2]*Department of Surgery, Monash Medical Centre, Southern Clinical School, Monash University, Clayton, Vic, Australia,* [3]*Institute of Innate Immunity, University Hospital, University of Bonn, Bonn, Germany,* [4]*Department of Infectious Diseases and Immunology, University of Massachusetts Medical School, Worcester, MA, USA,* [5]*German Center for Neurodegenerative Diseases, Bonn, Germany, and* [6]*Centre for Innate Immunity and Infectious Diseases, MIMR-PHI Institute of Medical Research, Clayton, Vic, Australia*

Correspondence
A/Professor Grant R Drummond, Vascular Biology and Immunopharmacology Group, Department of Pharmacology, Monash University, Building 13E, Wellington Road, Clayton, Vic. 3800, Australia. E-mail: grant.drummond@monash.edu

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Chronic inflammation in the kidneys and vascular wall is a major contributor to hypertension. However, the stimuli and cellular mechanisms responsible for such inflammatory responses remain poorly defined. Inflammasomes are crucial initiators of sterile inflammation in other diseases such as rheumatoid arthritis and gout. These pattern recognition receptors detect host-derived danger-associated molecular patterns (DAMPs), such as microcrystals and reactive oxygen species, and respond by inducing activation of caspase-1. Caspase-1 then processes the cytokines pro-IL-1β and pro-IL-18 into their active forms thus triggering inflammation. While IL-1β and IL-18 are known to be elevated in hypertensive patients, no studies have examined whether this occurs downstream of inflammasome activation or whether inhibition of inflammasome and/or IL-1β/IL-18 signalling prevents hypertension. In this review, we will discuss some known actions of IL-1β and IL-18 on leukocyte and vessel wall function that could potentially underlie a prohypertensive role for these cytokines. We will describe the major classes of inflammasome-activating DAMPs and present evidence that at least some of these are elevated in the setting of hypertension. Finally, we will provide information on drugs that are currently used to inhibit inflammasome/IL-1β/IL-18 signalling and how these might ultimately be used as therapeutic agents for the clinical management of hypertension.

Abbreviations

AP-1, activator protein-1; CRP, C-reactive protein; DAMP, danger-associated molecular pattern; eNOS, endothelial NOS; IL-18BP, IL-18 binding protein; IL-18Rα, IL-18 receptor α chain; IL-1Ra, IL-1 receptor antagonist; IL-1RI, IL-1 receptor type I; IL-1RII, IL-1 receptor type II; NLR, NOD-like receptor; NOX, NADPH oxidase; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor; ROS, reactive oxygen species; Th1, T-helper 1; Th17, T-helper 17; VSMC, vascular smooth muscle cell

Tables of Links

TARGETS	
Catalytic receptors[a]	**Enzymes**[d]
IL-1 receptor	Caspase-1
IL-1 decoy receptor (IL-1RII)	HMG CoA reductase
IL-18 receptor	Endothelial NOS
GPCRs[b]	Inducible NOS
Angiotensin AT_1 receptor	
CCR2	
Ligand-gated ion channels[c]	
P2X7 receptor	

LIGANDS
A-438079
Anakinra
Angiotensin II
Canakinumab
IL-1Ra
IL-18
IL-33
Simvastatin
TNF-α

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 ([a,b,c,d] Alexander *et al.*, 2013a,b,c,d).

Introduction

Hypertension is associated with chronic inflammation in key tissues and organs involved in the regulation of BP such as the kidneys and blood vessels. Renal inflammation results in glomerular injury and impaired sodium urinary excretion, while inflammation in the vasculature can contribute to impaired endothelial function, resistance and stiffening, all of which are key factors involved in the development of hypertension (Ross, 1999; Pauletto and Rattazzi, 2006; Rodriguez-Iturbe *et al.*, 2012). The signalling platforms known as inflammasomes have emerged as crucial initiators of inflammation in response to diverse pathogen- and host-derived danger signals. The primary function of inflammasomes is to activate the cysteine protease, caspase-1, which in turns processes the proinflammatory IL-1 family cytokines IL-1β and IL-18 from their inactive to active forms (Schroder and Tschopp, 2010a). While it is clear that circulating levels of IL-1β and IL-18 are increased in hypertension (Dalekos *et al.*, 1997; Rabkin, 2009), to date, no studies have examined whether this occurs downstream of inflammasome and caspase-1 activation. It is also not known whether inhibition of the production or actions of IL-1β and/or IL-18 reduces renal and vascular inflammation and thereby affords protection in hypertension. This review will highlight the role that IL-1β and IL-18 play as early initiators of inflammation. Furthermore, we will describe what inflammasomes are and present evidence for why they might be considered as important mediators of renal and vascular inflammation in hypertension, and thus potential targets for future antihypertensive therapies.

Renal and vascular inflammation in hypertension

Hypertension is a major risk factor for the two leading causes of death worldwide, ischaemic heart disease and stroke (WHO, 2013). It is widely accepted that chronic overactivation of the renin-angiotensin-aldosterone system is a major contributor to hypertension (Weir and Dzau, 1999). The actions of angiotensin II on AT_1 receptors expressed on resident cells of blood vessels, kidneys and the CNS are responsible for its 'classical' prohypertensive actions, including vasoconstriction, increased vascular superoxide production, enhanced sodium reabsorption and elevated sympathetic activity (Palatini, 2001; Levy, 2004; Probstfield and O'Brien, 2010). However, it has recently been shown that angiotensin II may contribute to renal and vascular inflammation by inducing the activation and accumulation of leukocytes in the kidneys and artery wall respectively (Johnson *et al.*, 1992; Haller *et al.*, 1997; Suzuki *et al.*, 2003; Rodriguez-Iturbe *et al.*, 2004; Guzik *et al.*, 2007).

Chronic low-grade inflammation appears to play an important role in the pathogenesis of hypertension. In hypertensive patients and in animal models, there is increased activity of the prototypic transcription factor, NF-κB (Ruiz-Ortega *et al.*, 2001; Zhou *et al.*, 2010a), which leads to increased tissue and/or circulating levels of proinflammatory mediators including the acute phase protein, C-reactive protein (CRP) (Bautista, 2003), adhesion molecules including intercellular adhesion molecule 1 and vascular cell adhesion molecule 1, chemokines, such as CCL2 (MCP-1) and CCL5 (RANTES) (Mervaala *et al.*, 1999; Dorfmuller *et al.*, 2003; Boulbou *et al.*, 2005; Madej *et al.*, 2005; Chan *et al.*, 2012), and proinflammatory cytokines such as IL-6, TNF-α (Gu *et al.*, 2006; Zhang *et al.*, 2012) and, of direct relevance to the current review, IL-1β and IL-18 (Dalekos *et al.*, 1997; Rabkin, 2009). Furthermore, numerous studies have shown that by blocking the actions of several of the above mediators either by genetic deletion or pharmacological inhibition, it is possible to reduce disease parameters in hypertension. For example, mice lacking IL-6 display a blunted increase in systolic BP and a reduction in renal damage and fibrosis compared with wild-type mice following induction of hypertension by acute stress or the infusion of angiotensin II (Lee *et al.*, 2004; 2006; Zhang *et al.*, 2012). Chemokine recep-

tor antagonists prevent the accumulation of immune cells in target tissues by blocking chemokine-dependent chemotaxis of these cells. A selective antagonist of the chemokine receptor CCR2 was shown to reduce macrophage infiltration into the aorta, and consequently to reduce systolic BP in deoxycorticosterone acetate/salt-treated mice (Chan *et al.*, 2012). Similar protective actions have been reported following inhibition of TNF-α and NF-κB in various experimental models of hypertension (Muller *et al.*, 2000; Zhou *et al.*, 2010a; Sriramula *et al.*, 2013; Wang *et al.*, 2013).

IL-1β and IL-18 are elevated in hypertension and are potential mediators of renal and vascular inflammation

IL-1β and IL-18 are members of the proinflammatory IL-1 cytokine superfamily (Dinarello, 2002). The major cellular sources of IL-1β and IL-18 are monocytes and macrophages (Kahlenberg and Dubyak, 2004; Dinarello *et al.*, 2013), however other cell types, such as vascular endothelial cells and renal tubular epithelial cells, may also generate these cytokines under certain conditions (Ala *et al.*, 1992; Dewberry *et al.*, 2000; Striz *et al.*, 2005). The proinflammatory actions of IL-1β and IL-18 are achieved by stimulation of their specific cell surface receptors, namely the IL-1 type 1 receptor (IL-1RI) and the IL-18 receptor α chain (IL-18Rα) respectively (Dinarello, 2002). These receptors are found on several leukocyte subsets relevant to renal and vascular inflammation in hypertension. These include immune cells, such as lymphocytes, monocytes and macrophages, constitutive cell types of the vessel wall, such as vascular endothelial cells and vascular smooth muscle cells (VSMCs), as well as cells in the kidney such as renal endothelial cells and tubular epithelial cells (Nakamura *et al.*, 2000; Gerdes *et al.*, 2002; Miyauchi *et al.*, 2009). Both receptors are members of the immunoglobulin superfamily and display remarkable similarities in terms of their amino acid sequences, overall architecture and the signal transduction mechanisms they utilize (O'Neill, 2002; Sims, 2002).

The binding of IL-1β and IL-18 to their receptors causes the recruitment of distinct yet highly homologous accessory proteins, which facilitate high-affinity binding between the ligand-receptor complex. For the IL-1β/IL-1RI complex, the relevant accessory protein is termed IL-1RAcP, whereas that for the IL-18/IL-18Rα complex is IL-18Rβ (Figure 1) (Sims, 2002; Arend *et al.*, 2008). The binding of accessory proteins to IL-1RI and IL-18R also initiates the recruitment of several adapter molecules to the cytoplasmic domains of the receptors. Such adapter molecules include myeloid differentiation factor 88, IL-1R-associated kinase and TNF receptor-associated factor 6 (Figure 1) (Thomassen *et al.*, 1998; Arend *et al.*, 2008). These in turn activate signal transduction pathways involving the kinases, JNK and p38 MAPK, as well as transcription factors such as NF-κB and activator protein-1 (AP-1) (Thomassen *et al.*, 1998; Arend *et al.*, 2008) which are renowned for inducing a proinflammatory gene expression profile in various cell types.

IL-33 is a more recently identified member of the IL-1 family (Arend *et al.*, 2008). In contrast to IL-1β and IL-18, it is the uncleaved form of IL-33 that is active. Moreover, IL-33 triggers an anti-inflammatory type 2 immune response when it binds to its receptor, ST2, which results in the release of cytokines such as IL-5 and IL-13 (Pei *et al.*, 2014). While recent studies have suggested a possible protective role of IL-33/ST2 signalling in other cardiovascular diseases such as heart failure and atherosclerosis (Miller and Liew, 2011; Januzzi, 2013), to date no studies have investigated the role of IL-33 in hypertension.

It is important to note that the actions of IL-1β and IL-18 in a given tissue are governed not only by their concentrations within that tissue and the expression profile of their respective receptors, but also by the presence of several inhibitor molecules that exist for each cytokine (Figure 1). For IL-1β, these include the decoy receptor, IL-1R type II (IL-1RII), which is similar in structure to the extracellular domain of the IL-1RI, however, it has a very short cytoplasmic tail and thus lacks the ability to stimulate intracellular transduction mechanisms (Dinarello, 1996; Schroder and Tschopp, 2010a). Furthermore the IL-1 receptor antagonist (IL-1Ra) is another endogenous inhibitor of IL-1β. IL-1Ra occurs in two forms, one that is secreted from circulating leukocytes and another that is retained intracellularly, especially in monocytes and epithelial cells (Arend *et al.*, 1998). Similarly, there exists an endogenous antagonist of IL-18 known as the IL-18 binding protein (IL-18BP). IL-18BP is constitutively secreted and binds to IL-18 with high affinity (400 pM), thereby neutralizing the actions of this cytokine (Dinarello *et al.*, 2013). The experimental and clinical use of these inhibitors in inflammatory disease models are discussed in further detail later in this review.

IL-1 family cytokines are considered to be 'early-response' cytokines. This means that they are released in the earliest stage of an immune response and act as a trigger for a subsequent cascade of proinflammatory cytokines. IL-1β stimulates the release of IL-6 and IL-17a, while IL-18 promotes the production of IFN-γ, IL-2 and IL-12 (Labow *et al.*, 1997; Dinarello, 2002; Cahill and Rogers, 2008; Mills *et al.*, 2013). These downstream cytokines are associated with highly proinflammatory T-helper 1 (Th1)- and T-helper 17 (Th17)-type immune responses and there is evidence to suggest that Th1 and Th17 cells play a major role in hypertension (Shao *et al.*, 2003; Platten *et al.*, 2009; Madhur *et al.*, 2010). In addition to these well-described actions on immune cells, IL-1β and IL-18 have also been shown to have direct effects on the vascular wall that might be consistent with a prohypertensive role. For example, large and resistance-like rat arteries that had undergone *ex vivo* incubation with IL-1β displayed impaired endothelium-dependent relaxation responses to ACh compared with vessels that were incubated with vehicle (Loughrey *et al.*, 2003; Jimenez-Altayo *et al.*, 2006). This effect appeared to be due to increased vascular reactive oxygen species (ROS) production, as IL-1β-treated vessels expressed higher levels of the pro-oxidant enzymes, inducible NOS and xanthine oxidase, and generated more superoxide than controls (Briones *et al.*, 2005; Jimenez-Altayo *et al.*, 2006). Moreover, treatment of the vessels with superoxide dismutase partially reversed the impaired relaxation response to ACh (Jimenez-Altayo *et al.*, 2006). In a separate study on

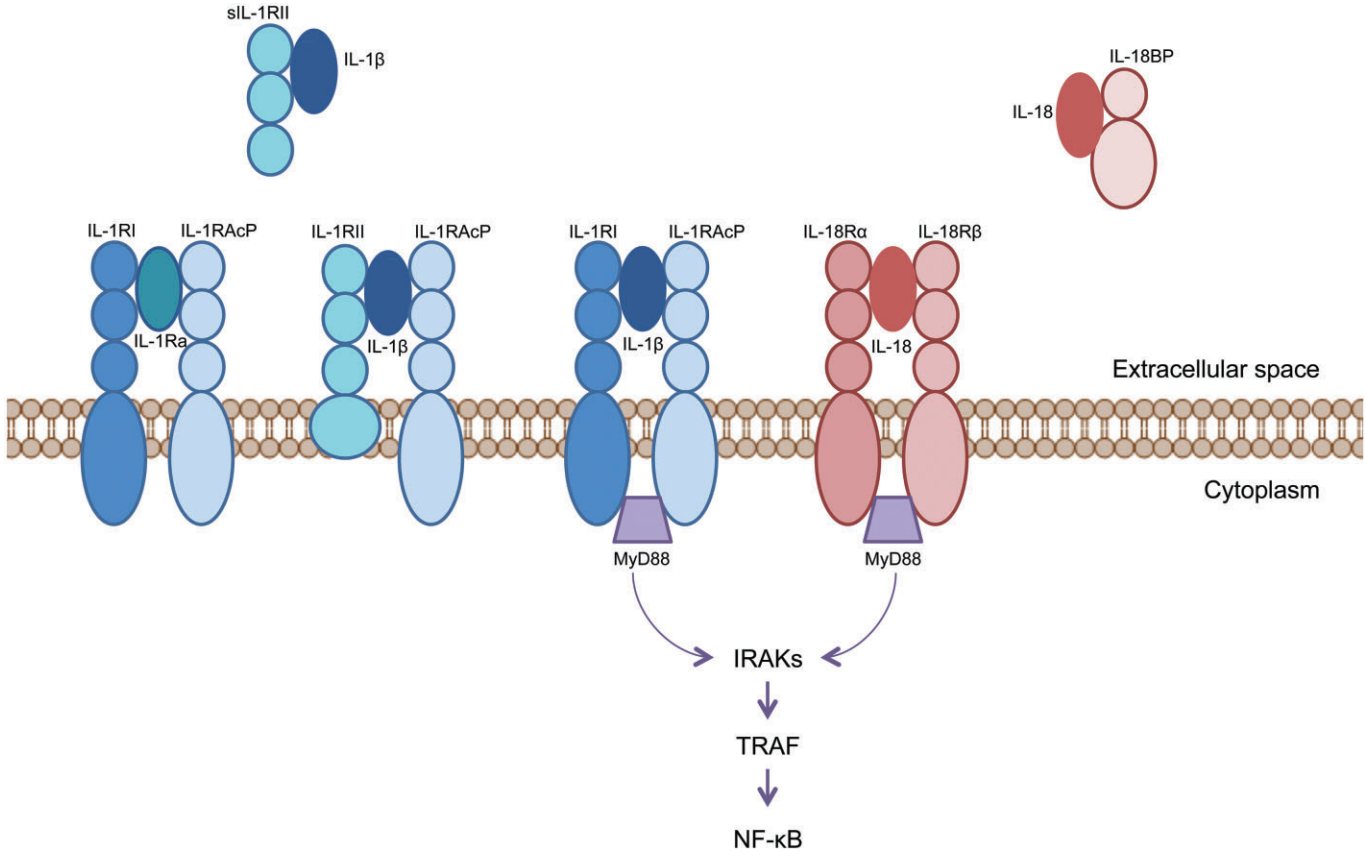

Figure 1

Signalling pathway and endogenous antagonists of IL-1β and IL-18. Binding of IL-1β to IL-1R1 and IL-18 to IL-18Rα is facilitated by the accessory proteins IL-1RAcP and IL-18Rβ, respectively, resulting in recruitment of the adapter proteins myeloid differentiation factor 88 (MyD88), IL-1 receptor-associated kinase (IRAK) and TNF receptor-associated factor (TRAF), which then causes NF-κB activation. Endogenous inhibitory molecules also exist for both cytokines. For IL-1β, these include an IL-1R antagonist (IL-1Ra), which competes with the IL-1RI for IL-1β binding, as well as a second IL-1β receptor, IL-1RII. The membrane-bound form of IL-1RII receptor contains a short cytosolic signalling domain whereas the soluble form of IL-1RII contains only the extracellular portion of the receptor. Thus, while they bind IL-1β, they fail to support the activation of intracellular signal transduction pathways. Similarly, the actions of IL-18 are negatively regulated by a binding protein known as IL-18BP.

isolated aortas from spontaneously hypertensive rats, IL-1β directly evoked contractile responses and augmented those to the α_1-adrenoceptor agonist, phenylephrine (Dorrance, 2007). Together with the IL-1β-mediated impairment of endothelium-dependent vasodilatation, such increases in contractile activity could conceivably contribute to increased total peripheral vascular resistance, which is a major determinant of BP.

Although no studies have examined the effects of IL-18 on vascular tone, this cytokine has been shown in several studies to promote the proliferation and migration of VSMCs (Chandrasekar *et al.*, 2006; Valente *et al.*, 2012); processes that are critical to the vascular remodelling associated with and contributing to hypertension. Again these effects appeared to result from increases in NADPH oxidase (NOX)-derived ROS production and the subsequent activation of NF-κB- and AP-1-dependent signalling pathways (Valente *et al.*, 2012). Furthermore, the proliferative response of cultured VSMCs to angiotensin II was blocked following siRNA-mediated knockdown of IL-18 (Valente *et al.*, 2012), indicating that IL-18 may be a crucial intermediate in the pathway by which angiotensin II promotes vascular remodelling. The actions of IL-1β and/or IL-18 in mediating inflammation associated with hypertension are summarized in Figure 2.

As mentioned, there is evidence that circulating and vascular levels of IL-1β and IL-18 are elevated in hypertension. For instance, patients with essential hypertension had higher serum levels of IL-1β than normotensive controls (Dalekos *et al.*, 1997). Furthermore, monocytes isolated from peripheral blood of hypertensive individuals generated higher amounts of IL-1β in response to *ex vivo* stimulation with either angiotensin II or LPS than monocytes from normotensive controls (Dörffel *et al.*, 1999; Li *et al.*, 2005). These findings not only suggest that monocytes from hypertensive individuals are primed for the production of IL-1β, but they also indicate that angiotensin II may directly act on monocytes to initiate the production and/or release of the cytokine. Consistent with this latter concept, angiotensin AT_1 receptor antagonists inhibited IL-1β production by monocytes taken from hypertensive individuals, either when administered to patients *in vivo* or when pre-incubated *ex vivo* with cells fol-

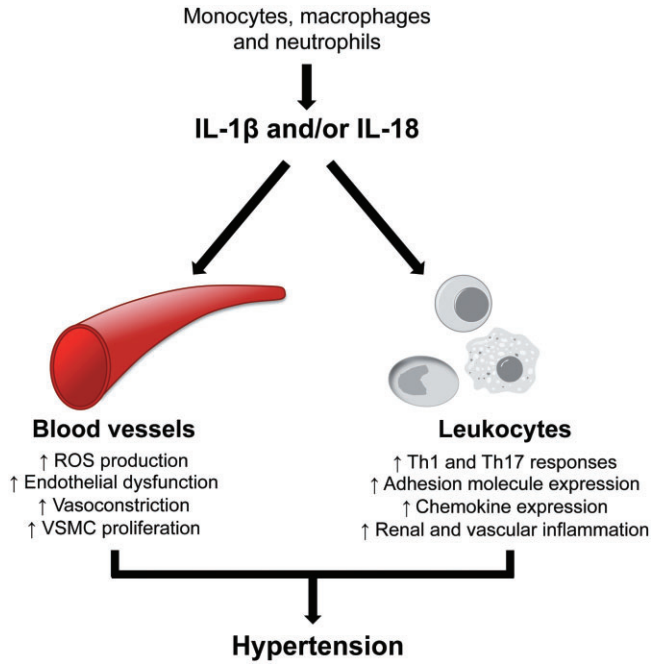

Figure 2

Actions of IL-1β and/or IL-18 in mediating hypertension. IL-1β and IL-18 are mainly secreted by monocytes, macrophages and neutrophils. These proinflammatory cytokines can act on immune cells such as macrophages, dendritic cells and neutrophils as well as non-immune cell types, including vascular endothelial and smooth muscle cells, to induce inflammation and other prohypertensive effects.

lowing their isolation (Dörffel *et al.*, 1999; Li *et al.*, 2005). Given that monocytes accumulate in the vessel wall and interstitium of the kidneys during hypertension (Haller *et al.*, 1997; Boos and Lip, 2006), these cells could represent a significant source of vascular and renal IL-1β. There is also evidence of enhanced responsiveness to IL-1β in hypertension. Specifically, *ex vivo* treatment with IL-1β caused a greater vasoconstrictive response in aortas from hypertensive rats compared with normotensive rats, and this involved activation of COX (Dorrance, 2007). Whether this increased vascular responsiveness was due to up-regulation of IL-1R1 or downstream signalling elements remains to be determined. Finally, levels of IL-1Ra were found to be elevated in patients with essential hypertension compared with normotensive individuals (Peeters *et al.*, 2001), and this might be indicative of a compensatory response to offset elevated concentrations of IL-1β.

Regarding IL-18, a meta-analysis investigating the association between IL-18 and hypertension identified a significant positive correlation between BP and circulating IL-18 levels (Rabkin, 2009). IL-18 levels are also positively correlated with intima-media thickness of the carotid artery (Yamagami *et al.*, 2005), which is a downstream consequence of hypertension and a marker of future cardiovascular risk in patients (Van Bortel, 2005). Taken together, the points raised earlier highlight the role of IL-1 family cytokines as early mediators of inflammation and as potential contributors to the pathogenesis of hypertension.

Release of IL-1β and IL-18 occurs as a consequence of caspase-1 and 'inflammasome' activation

Caspases are cysteine proteases that are best known for their role in regulating apoptosis. However, it is now known that the primary function of some members of the caspase family is to regulate inflammation (Wolf and Green, 1999). Collectively, these proinflammatory caspases are termed group I caspases (Martinon and Tschopp, 2007). Of the 13 mammalian caspases identified, five are thought to regulate inflammation (caspases 1, 4 and 5 in humans and caspases 1, 11 and 12 in mice) (Martinon and Tschopp, 2004; 2007), with caspase-1 being the best characterized proinflammatory caspase in humans and mice. The major role of caspase-1 in inflammation is to catalyze the intracellular processing of the proinflammatory cytokines, pro-IL-1β (31 kDa) and pro-IL-18 (24 kDa) into their mature and biologically active forms, IL-1β (17.5 kDa) and IL-18 (18 kDa) respectively (Dinarello, 2002). This step is essential as it allows the cytokines to be released from the cytosol into the extracellular space where they can act in a paracrine fashion on receptors on neighbouring cells to exert their proinflammatory influence. There is some evidence that IL-1β can be activated independently of caspase-1 by neutrophil-derived serine proteases such as elastase, cathepsin G and proteinase 3. However, these pathways are likely to play a role in the maturation of the cytokine only in disease conditions associated with an increase in neutrophil infiltration (Guma *et al.*, 2009).

Caspases are themselves synthesized as zymogens and must be cleaved in order to be activated. This is achieved by the multi-protein enzyme complexes known as inflammasomes (Petrilli *et al.*, 2007; Schroder and Tschopp, 2010a). Inflammasomes are comprised of upstream NOD-like receptors (NLRs), which are part of the pattern recognition receptor (PRR) superfamily (Lamkanfi and Dixit, 2014). PRRs are known to play an integral role in the innate immune response (Gordon, 2002; Kanneganti *et al.*, 2007). NLRs are auto-activated when they detect 'pathogen-associated molecular patterns' (PAMPs) such as conserved motifs on microbes such as LPS and flagellin (Jha and Ting, 2009). Furthermore, host-derived stress signals otherwise known as danger-associated molecular patterns (DAMPs) have also been shown to induce activation of NLRs. DAMPs that have been shown to activate NLRs include ROS such as superoxide and hydrogen peroxide (Davis and Ting, 2010; Latz, 2010; Zhou *et al.*, 2010b), high concentrations of extracellular ATP (Mariathasan *et al.*, 2006), hyaluronan, which is released from the extracellular matrix in response to injury (Yamasaki *et al.*, 2009), β amyloid, the major peptide present in amyloid plaques characteristic of Alzheimer's disease (Halle *et al.*, 2008) and crystalline substances such as uric acid (Martinon *et al.*, 2006), cholesterol (Duewell *et al.*, 2010) and silica (Hornung *et al.*, 2008), which are thought to mediate the chronic inflammatory responses in gout, atherosclerosis and silicosis respectively.

While several NLRs have been identified, information on functional significance is only available for a few of these receptors. This includes the NLRP3-, NLRP1- and IPAF-containing inflammasomes, all of which respond to a diverse

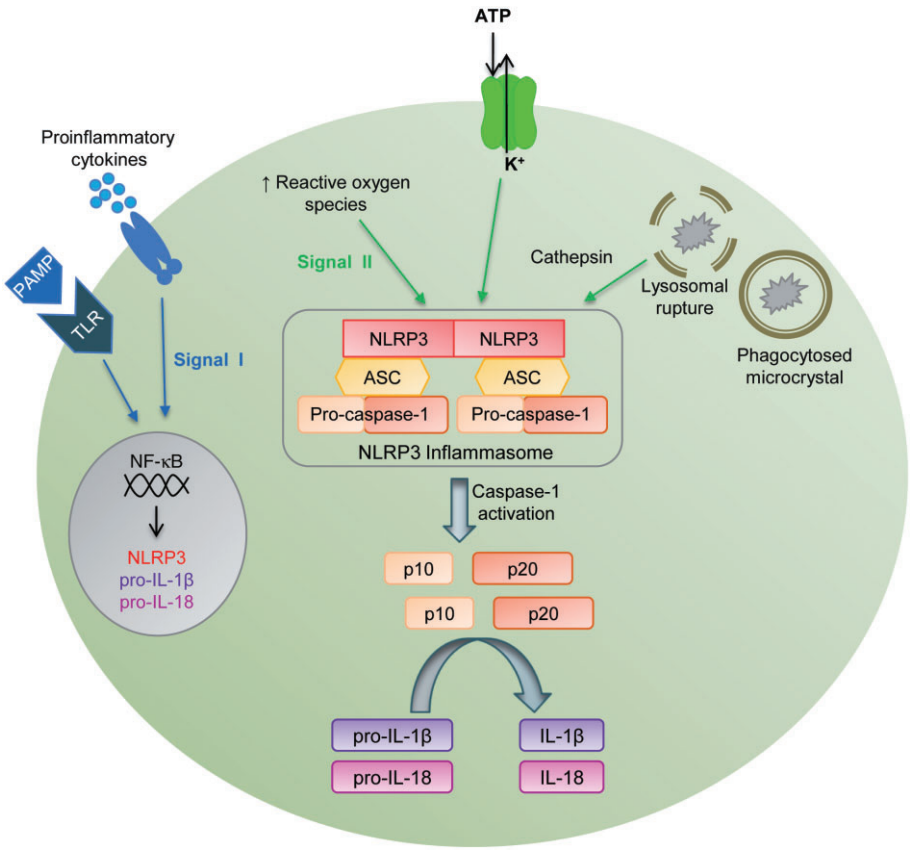

Figure 3

Schematic representation of activators and effectors of the NLRP3 inflammasome. The NLRP3 inflammasome consists of the pattern recognition receptor, NLRP3, the adaptor protein, ASC, and pro-caspase-1. Activation of the NLRP3 inflammasome occurs in two steps. Signal I occurs downstream of Toll-like receptors (TLR) and receptors for cytokines such as TNF, and involves NF-κB-mediated up-regulation of NLRP3, pro-IL-1β and pro-IL-18 gene expression. Signal II occurs when danger-associated molecular patterns (DAMPs) including ATP, microcrystals and ROS, all of which have been shown to be elevated in hypertension, are detected by NLRP3. This leads to oligomerization of NLRP3 subunits and recruitment of ASC and pro-caspase-1. Pro-caspase-1 then undergoes autocleavage into two subunits p10 and p20, which heterodimerize to form the fully active caspase-1. Caspase-1 then processes pro-IL-1β and pro-IL-18 into their active, proinflammatory forms.

range of stimuli (Schroder *et al.*, 2010b). To date, the NLRP3-containing inflammasome (also known as NALP3) is the best characterized and the isoform that is reported to link inflammation to several metabolic diseases, including diabetes and atherosclerosis (De Nardo and Latz, 2011; Wen *et al.*, 2012; Lu and Kakkar, 2014). There are three basic subunits that make up the NLRP3 inflammasome: (i) the NLRP3 protein, which consists of the basic NLR structure [leucine-rich repeats at the C-terminus, a central nucleotide-binding and oligomerization domain (NACHT) and a pyrin-domain at the N-terminus]; (ii) ASC, a heterodimeric adapter protein also consisting of a pyrin domain as well as a caspase activation and recruitment domain (CARD); and (iii) pro-caspase-1 (Jha and Ting, 2009; Schroder *et al.*, 2010b).

Inflammasome activity and production of IL-1β and IL-18 in monocytes and macrophages are tightly regulated via a two-step signal process. *Signal I* involves NF-κB- and/or AP-1-dependent up-regulation of the genes that encode for the various signalling components including NLRP3, pro-caspase-1, pro-IL-1β and pro-IL-18. *Signal II* involves the detection of PAMPS or DAMPs by NLRP3, and this in turn promotes the recruitment of ASC and pro-caspase-1 to the complex (Figure 3). The clustering of pro-caspase-1 at the inflammasome complex initiates its autocleavage into two subunits, p10 (10 kDa) and p20 (20 kDa), which heterodimerize to form the active caspase-1 enzyme (Schroder and Tschopp, 2010a).

Evidence of a role for inflammasome activation in hypertension

The consistent observation that levels of IL-1β and IL-18 are elevated in hypertension (Dalekos *et al.*, 1997; Rabkin, 2009) might be taken as circumstantial evidence that the condition is associated with an increase in inflammasome-dependent caspase-1 activation. However, apart from a single study describing an increase in mRNA expression of pro-caspase-1 in the aorta and renal artery of spontaneously hypertensive rats compared with normotensive Wistar Kyoto rats (Chen *et al.*, 1997), no studies have directly investigated whether

hypertension is associated with inflammasome activation. In a genotype association analysis, Omi *et al.* (2006) showed that the incidence of a specific gain-in-function polymorphism of the NLRP3 gene was significantly higher in hypertensive than normotensive individuals. Furthermore, these authors described a gene–dose relationship whereby homozygotes for the polymorphism displayed higher BPs than heterozygotes (by 3 mmHg), who in turn displayed higher BPs than wild-type individuals (by 2 mmHg) (Omi *et al.*, 2006).

If inflammasome activity is indeed a crucial determinant of hypertension, we are left with the question: what stimuli are responsible for inflammasome activation in the setting of hypertension? While we can presently only speculate on the nature of such stimuli, it is worth noting that hypertension *is* associated with increased levels of certain DAMPs that are often regarded as 'classical' activators of the NLRP3 inflammasome. These stimuli, which include microcrystals, high levels of extracellular ATP and ROS (Schroder and Tschopp, 2010a), are described in the succeeding paragraphs.

Microcrystals

There is a growing body of evidence that microcrystals can induce inflammasome activation, and may be implicated in the pathogenesis of various inflammatory diseases, including atherosclerosis and inflammatory lung diseases (Dostert *et al.*, 2008; Duewell *et al.*, 2010). Microcrystals, which range in size from 0.5 to 3.0 nm, form as a result of high concentrations of relatively insoluble solutes in the circulation and tissues. Microcrystals are detected by phagocytes and engulfed into the phagolysosome within the cell. However, the shard-like structures of many microcrystals rupture the lysosomal membrane, releasing its contents, including cathepsins and other proteolytic enzymes, into the cytosol. These lysosomal enzymes are thought to act as the triggers of inflammasome activation (Schroder *et al.*, 2010b).

Monosodium urate crystals are known to trigger NLRP3 inflammasome activation, and thereby mediate inflammation associated with gout and pseudo-gout (Martinon *et al.*, 2006). Importantly, a high serum level of urate (hyperuricaemia) is considered a risk factor for the development of hypertension (Ward, 1998; Bos *et al.*, 2006). Studies dating back to the 19th century have reported a strong association between hyperuricaemia and hypertension (Haig, 1889; Bos *et al.*, 2006). In support of a causal link between the two conditions, induction of mild hyperuricaemia in rats resulted in a marked increase in BP (Mazzali *et al.*, 2001). Furthermore, clinical trials have shown that allopurinol, a drug used for the treatment of hyperuricaemia and gout, was highly effective at reducing BP in hypertensive adolescents, but less so in older individuals, suggesting that hyperuricaemia may have an especially important role early in the pathogenesis of hypertension (Feig *et al.*, 2008). It remains to be determined whether microcrystal-induced inflammasome activation represents the mechanistic link between hyperuricaemia and elevated BP.

Extracellular ATP

Extracellular ATP acting at the P2X7 receptor is a well-described stimulus for NLRP3 inflammasome activation and there is evidence that this receptor might play a role in hypertension. In general, high levels of extracellular ATP occur as a consequence of cellular damage and a loss of plasma membrane integrity and thereby serve as a danger signal to the immune system (Trautmann, 2009). There is some controversy surrounding how ATP/P2X7 signalling actually leads to inflammasome assembly. The P2X7 receptor is a ligand-gated ion channel and initially it was thought that the K^+ efflux that followed activation of this receptor represented the signal for inflammasome activation (Mariathasan *et al.*, 2006). It has also been suggested that P2X7-dependent activation of inflammasomes may involve the recruitment of the pore-forming protein, pannexin-1, to the plasma membrane, in turn allowing the entry of DAMPs into the cell which are ultimately the stimuli for inflammasome activation (Schroder and Tschopp, 2010a). However, more recently, it was suggested that DAMPs, including microcrystals, are able to directly stimulate the release of endogenous ATP to cause IL-1β production in a P2X7-dependent mechanism (Riteau *et al.*, 2012). Regardless, all of these possibilities involve a central role for the P2X7 receptor in inflammasome activation. In addition, expression of this receptor was elevated in various models of hypertension in rodents, and its deletion (i.e. in P2X7 receptor-knockout mice) is associated with lower BP and less renal fibrosis and inflammation (Vonend *et al.*, 2004; Ji *et al.*, 2012a,b).

ROS

It is clear that ROS and NF-κB play important roles in priming of the inflammasome (i.e. Signal I) to cause transcriptional up-regulation of NLRP3, pro-IL-1β and pro-IL-18 (Bauernfeind *et al.*, 2009; 2011). However, the role of ROS in NLRP3 and caspase-1 activation (i.e. Signal II) still remains controversial. On the one hand, high levels of ROS have been shown to oxidatively modify caspase-1 protein resulting in a reduction in its catalytic activity (Meissner *et al.*, 2008). Conversely, various DAMPs that are known to activate the NLRP3 inflammasome induce the production of ROS (Cruz *et al.*, 2007; Dostert *et al.*, 2008; Tschopp and Schroder, 2010). Furthermore, several studies have shown that inhibition of ROS can prevent ATP- and microcrystal-induced inflammasome activation (Dostert *et al.*, 2008; Liao *et al.*, 2013; Kojima *et al.*, 2014) and it has thus been proposed that ROS (rather than microcrystals and extracellular ATP) are the actual triggers for assembly of the NLRP3 inflammasome (Schroder and Tschopp, 2010a).

It is well established that hypertensive stimuli, such as angiotensin II, aldosterone and endothelin-1, increase the expression and activity of a family of enzymes called NOX in both immune and non-immune cell types (Drummond *et al.*, 2011; Touyz and Briones, 2011). NOX enzymes are considered primary sources of ROS and play key roles in physiological redox signalling and in the host-defense response to invading pathogens (Drummond *et al.*, 2011). However, in the setting of hypertension, elevated NOX expression may lead to excessive ROS production, which can in turn result in oxidative modifications to other enzymes including endothelial NOS (eNOS), xanthine dehydrogenase and the subunits of the mitochondrial electron transport chain (Touyz and Schiffrin, 2004; Touyz and Briones, 2011). Such modifications uncouple these enzymes from their normal catalytic function and render them as additional enzymatic sources of ROS. In

summary, hypertension is associated with elevated ROS production by a range of enzymic sources. Furthermore, inhibition of ROS production reduces BP and renal and vascular dysfunction in hypertension (Touyz and Schiffrin, 2004; Chan *et al.*, 2007; Araujo and Wilcox, 2014). Thus, it will be interesting to determine the role of ROS-dependent inflammasome priming and activation in the pathogenesis of hypertension.

Therapeutic opportunities

The data discussed above provide evidence for an association between hypertension and inflammasome and/or caspase-1-dependent IL-1β/IL-18 production. However, it remains to be established conclusively whether there exists a causal relationship between inflammasome activation and vascular and renal inflammation. Testing for such an association will involve studies examining the effects of strategies that either inhibit inflammasome activation, or block the actions of IL-1β and IL-18, on renal and vascular inflammation and other disease parameters in experimental models of hypertension. Transgenic mice with selective deficiencies in various components of the inflammasome/IL-1 signalling cascade are available and could be readily used to examine the role of this system in hypertension. Several studies have demonstrated that mice with deficiencies in either caspase-1, IL-1β, IL-1R or IL-18 have a dampened immune response and an impaired ability to produce cytokines such as IL-6, TNF and/or IFN-γ, and that this is associated with protection against chronic inflammatory diseases such as arthritis, atherosclerosis and inflammatory bowel disease (Siegmund *et al.*, 2001; Dinarello, 2002; Chamberlain *et al.*, 2009; Joosten *et al.*, 2009; Duewell *et al.*, 2010). However, to our knowledge, the only study to have utilized such transgenic models for the study of hypertension is that by Chamberlain *et al.* (2009). In this study, it was shown that deficiency of the IL-1R in atherosclerosis-prone apolipoprotein E knockout mice (i.e. IL-1R$^{-/-}$/ApoE$^{-/-}$ double knockouts) was associated with a blunted hypertensive response to high fat diet-feeding compared with the ApoE$^{-/-}$ single knockout strain, as well as reductions in vascular oxidative stress and endothelial dysfunction (Chamberlain *et al.*, 2009). Further studies like this are expected to provide the necessary proof-of-concept that the inflammasome and its cytokine products are promising targets for future antihypertensive therapies. The following section will review the broad classes of pharmacological agents that have been identified as inhibitors of inflammasome-dependent signalling and which could therefore represent future therapeutic agents for the treatment of hypertension.

Inhibitors of IL-1β signalling

The IL-1Ra is an endogenous antagonist that specifically inhibits the actions of IL-1α and IL-1β, but not IL-18 (Dinarello, 2002). Anakinra is a recombinantly synthesized IL-1Ra consisting of the same structure as endogenous human IL-1Ra except for an additional methionine residue at the N-terminus to confer stability (Muller *et al.*, 2000). It is currently used for the clinical treatment of the autoinflammatory disease, rheumatoid arthritis (Mertens and Singh, 2009). Despite its short half-life and poor oral bioavailability (it must be administered subcutaneously), anakinra has been shown in clinical trials to be effective at reducing monocyte infiltration and inflammation in the synovial joints of patients with rheumatoid arthritis (Fleischmann *et al.*, 2004).

Canakinumab is a high-affinity human monoclonal antibody against IL-1β (Kuemmerle-Deschner and Haug, 2013). It has a longer plasma half-life and more favourable safety profile than anakinra and is currently approved for clinical use in the treatment of cryopyrin-associated periodic syndrome – a rare inflammatory condition caused by a mutation in the NLRP3 gene (Kuemmerle-Deschner and Haug, 2013). In a Phase IIb trial on men and women with well-controlled diabetes and a high cardiovascular risk profile, canakinumab treatment for 4 months was shown to reduce circulating markers of inflammation including CRP, IL-6 and fibrinogen, without altering plasma lipid profiles (Ridker *et al.*, 2012). Based on these promising findings, canakinumab was taken into a large multinational Phase III clinical trial [Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)], to investigate its effects on recurrent cardiovascular events such as myocardial infarction and stroke in patients with coronary artery disease and elevated levels of high-sensitivity CRP (Ridker *et al.*, 2011). Results from this study are expected to be released in 2017 and it will be interesting to see what effects (if any) canakinumab treatment has on BP in these high risk patients.

Caspase-1 inhibitors

Caspase-1 has been a prime target for several inflammatory diseases including arthritis and inflammatory bowel disease (Randle *et al.*, 2001). Because caspase-1 inhibition should block the production of both IL-1β and IL-18, it is reasonable to expect that inhibitors of this enzyme will be more efficacious than IL-1R antagonists at reducing inflammation. However, it is also conceivable that caspase-1 inhibitors might have more off-target effects than drugs that selectively target either IL-1β or IL-18 alone.

Ac-YVAD-cmk and ac-YVAD-CHO are tetrapeptides that specifically and irreversibly inhibit caspase-1. These inhibitors are highly selective for caspase-1 (K_i ~ 1 nM) over other caspase isoforms (K_i = 163 to more than 10 000 nM) (Rabuffetti *et al.*, 2000). Moreover, several studies have shown that ac-YVAD inhibits capsase-1 activity *in vivo*, thereby reducing inflammation in experimental models of spinal cord injury and cerebral haemorrhage (Karaoglan *et al.*, 2008; Suzuki *et al.*, 2009; Wu *et al.*, 2010). Several low MW caspase-1 inhibitors have also been developed and tested in clinical trials for the treatment of inflammatory conditions including rheumatoid arthritis, psoriasis and hepatitis C (Cornelis *et al.*, 2007; MacKenzie *et al.*, 2010). However, each of these trials were terminated either because of toxicity, especially with regard to liver function, or as a result of poor efficacy (MacKenzie *et al.*, 2010). A clinical trial is currently underway to assess the effects of another caspase-1 inhibitor, VX-765, for the treatment of epilepsy (Kaminski *et al.*, 2014). *Post hoc* analysis of data from this trial suggests that VX-765 decreased seizure frequency and that this effect was sustained for >2 weeks after treatment was discontinued (Kaminski

et al., 2014). Epilepsy is a condition that is not classically associated with inflammation. Rather, IL-1β is thought to contribute to epilepsy through directly enhancing NMDA receptor activity via a Src kinase-dependent mechanism (Viviani *et al.*, 2003; Kaminski *et al.*, 2014). It is unclear what effect this action of caspase-1 inhibition would have in terms of treatment of hypertension. On one hand, Src kinase activity is enhanced in VSMCs of spontaneously hypertensive rats and is thought to contribute to vascular remodelling associated with hypertension (Touyz *et al.*, 2002). On the other hand, activation of NMDA receptors in the nucleus tractus solitarius (NTS) has been associated with a reduction in BP (Kubo and Kihara, 1988), and thus caspase-1-mediated inhibition of these receptors might be expected to worsen hypertension. Clearly, these issues, as well as those relating to toxicity, need to be resolved before caspase-1 inhibition can be considered as a therapeutic option for the treatment of hypertension.

P2X7 receptor antagonists

The P2X7 receptor is an ATP-gated ion channel that allows the passage of cations such as Na^+, Ca^{2+} and K^+ (Volonté *et al.*, 2012; Alexander *et al.*, 2013). It displays a restricted expression profile found primarily in macrophages, certain lymphocytes and fibroblasts (Carroll *et al.*, 2009). As mentioned, activation of P2X7 receptors is thought to induce inflammasome activation by facilitating K^+ efflux and/or recruitment of the hemi-channel pannexin-1 and subsequent entry of DAMPs into the cell. A-438079 is a competitive reversible inhibitor of the P2X7 receptor that is at least 100-fold more selective for this receptor than other members of the P2 receptor family (Donnelly-Roberts and Jarvis, 2007). Of direct relevance to the present discussion, A-438079, as well as a structurally distinct inhibitor of P2X7 receptors, Brilliant Blue G, were shown to reduce urinary albumin excretion, macrophage infiltration and BP in a rat model of salt-sensitive hypertension (Ji *et al.*, 2012a). These findings highlight the potential of P2X7 receptor antagonists as novel therapies for the treatment of hypertension.

Pleiotropic actions of statins

Statins (3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors) are widely used in the clinic to reduce serum cholesterol levels – and thus cardiovascular risk – in patients with hypercholesterolaemia (Sirtori, 2014). However, in addition to cholesterol lowering, statins display pleiotropic effects that likely contribute to their beneficial effects on the cardiovascular system. Thus, statins have been shown to have modest antihypertensive effects, especially in patients with resistant hypertension (Borghi *et al.*, 2000; Wassmann *et al.*, 2001; Strazzullo *et al.*, 2007; Briasoulis *et al.*, 2013), and the ability to enhance endothelial function (Tsunekawa *et al.*, 2001; de Jongh *et al.*, 2002; Landmesser *et al.*, 2005) and inhibit ROS production (Wassmann *et al.*, 2001; Delbosc *et al.*, 2002). In addition, statins possess anti-inflammatory properties such as reducing circulating levels of proinflammatory cytokines and suppressing adhesion molecule expression on vascular endothelial and smooth muscle cells (Albert *et al.*, 2001; Chung *et al.*, 2002; Rezaie-Majd *et al.*, 2002). In a recent study, it was shown that treatment of bone marrow-derived macrophages from mice with statins interfered with the processing of pro-IL-1β (Davaro *et al.*, 2014). Specifically, statin treatment was associated with the formation of a 28 kDa intermediate form of IL-1β, which came at the expense of production of the mature 17 kDa form. The partly processed form of IL-1β failed to induce IL-6 production in HEK 293T cells, indicating that it had no intrinsic agonistic activity. Furthermore, pretreatment of cells with the 28 kDa variant blocked the ability of mature IL-1β to stimulate cytokine production in the same assay, suggesting that it may be a novel IL-1RI antagonist. While these findings need to be confirmed *in vivo* in humans, it is tempting to speculate that inhibition of IL-1β processing may explain at least some of the pleiotropic actions of statins in reducing cardiovascular risk.

Conclusion

In summary, there is a growing body of evidence to suggest that hypertension is associated with elevated production of the IL-1 family cytokines, IL-1β and IL-18. At this stage, it is not known whether elevated levels of IL-1β and IL-18 are causes or mere consequences of chronically elevated BP and/or its disease sequelae such as vascular remodelling, atherosclerosis and renal dysfunction. It also remains to be determined whether inflammasome activation is involved and, if so, which stimuli are responsible. Several drugs that are currently in clinical use or undergoing trials for the treatment of other inflammatory disorders act by targeting different components of the inflammasome/IL-1 signalling pathway. Therefore, a better understanding of the activation mechanisms and role of inflammasome-derived IL-1 family cytokines in hypertension has a high potential to improve the way we manage the condition in the clinic.

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Conflict of interest

None.

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