HHS Public Access

Author manuscript

Can J Cardiol. Author manuscript; available in PMC 2021 May 01.

Published in final edited form as:

Can J Cardiol. 2020 May ; 36(5): 635–647. doi:10.1016/j.cjca.2020.01.013.

Inflammation in Hypertension

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Abstract

For more than 50 years, evidence has accumulated that inflammation contributes to the pathogenesis of hypertension. Immune cells have been observed in vessels and kidneys of hypertensive humans. Biomarkers of inflammation, including high sensitivity C-reactive protein, various cytokines and products of the complement pathway are elevated in humans with hypertension. Emerging evidence suggests that hypertension is accompanied and indeed initiated by activation of complement, the inflammasome and by a change in the phenotype of circulating immune cells, particularly myeloid cells. High dimensional transcriptomic analyses are providing insight into new subclasses of immune cells that are likely injurious in hypertension. These inflammatory events are interdependent and there is ultimately engagement of the adaptive immune system through mechanisms involving oxidative stress, modification of endogenous proteins and alterations in antigen processing and presentation. These observations suggest new therapeutic opportunities to reduce end-organ damage in hypertension might be employed and guided by levels of inflammatory biomarkers.

Brief summary

Hypertension is accompanied by a systemic inflammatory response, characterized by activation of complement, myeloid cells, inflammasome activation and vascular cell perturbations. These promote renal and vascular dysfunction, worsening blood pressure elevation and leading to end organ damage. Recent observations regarding these mechanisms of inflammation have suggested numerous therapeutic opportunities to reduce hypertension-related morbidity and mortality.

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Disclosures:

The authors have no conflict of interests.

Introduction:

Inflammation is the immediate, non-specific response to invading organisms, foreign bodies, necrotic cells, irritants or neoplastic cells. This innate immune response involves a coordinated action of immune cells, the vessel wall and chemical/humoral mediators. Vascular responses include increased permeability and changes in endothelial properties that promote rolling, adherence, and diapedesis of various immune cells. Clinically, these acute events lead to the classic findings of rubor (redness), tubor (swelling), dolor (pain) and calor (heat).

In response to experimental insults like the subcutaneous air pouch or injections of carrageenan, zymosyn or dextran there is an influx of neutrophils and monocytes within hours.[1–3] Monocytes can differentiate into inflammatory macrophages, monocyte derived dendritic cells or can reemerge as activated monocytes.[4] Resident macrophages in peripheral tissues can also respond to inflammatory stimuli, proliferate and likely play a role in resolution of inflammation.[5] Immune cells and stomal cells at the site of inflammation release antibacterial proteins and peptides, prostaglandins, reactive oxygen species, nitric oxide (NO), complement and clotting factors. Such mediators kill invading organisms in a non-specific fashion, assist in wound healing and compartmentalize the inflammatory process. Innate immune cells also release matrix metalloproteinases that break down matrix, allow cell migration and help clear necrotic tissue. Infiltrating and resident immune cells also sense danger associated molecular patterns (danger signals or DAMPs) released by the invading organism or from damaged cells of the host. Such signals include ligands for Toll-like receptors, such as bacterial coat lipopeptides, double stranded RNA, flagellar proteins and immune complexes. Inflammatory macrophages, dendritic cells and activated monocytes also phagocytose invading organisms and necrotic cells and process foreign or modified self-proteins to peptides that are then presented on their surface in the context of major histocompatibility complexes (MHC). These antigen presenting cells can either transmigrate to secondary lymphoid organs to activate T cells or can activate resident T cells locally. In this fashion, inflammatory innate immune responses bridge to adaptive immunity. Thus, while inflammation is generally considered an innate immune response, adaptive immunity is often eventually engaged and there is interaction between these two broad arms of the immune system. A latter phase, often associated with resolution of inflammation, is tissue fibrosis, which is mediated by factors like tissue growth factor β and other cytokines released from immune cells and by local parenchymal and stromal cells.

Traditionally, these events were considered localized and self-limited, however it is now clear that inflammation can transition to a chronic phase and that there are forms of sterile (non-infectious) inflammation that are systemic. In contrast to the profoundly beneficial effects of acute inflammation that occurs in response to a localized insult, persistent systemic inflammation can be deleterious, leading to progressive tissue injury, organ dysfunction and fibrosis. In the past 15 years, an expanding literature has implicated virtually all aspects of inflammation in the genesis of hypertension and its associated organ damage. In this review, we will highlight some of the major observations made regarding these factors and attempt to synthesize how these not only worsen blood pressure elevation but also lead to its long-term deleterious effects of this disease. Recent reviews have

summarized the role of adaptive immunity in hypertension, including T cells, B cells and their derived cytokines in hypertension, and we will therefore not consider adaptive immunity in depth, except to point out obvious links to innate, inflammatory responses.[6–9]

Reactive oxygen species and inflammation in hypertension:

Several factors in the hypertensive milieu, including angiotensin (ang) II, increased sodium, catecholamines and altered mechanical forces enhance the cellular production of ROS.[10] A major enzyme complex involved in this response is the NADPH oxidase, however the mitochondria also produce excess ROS in hypertension, and there are feedforward mechanisms engaged whereby ROS from the NADPH oxidase can stimulate radical formation in the mitochondria.[11] Uncoupled nitric oxide synthase and xanthine oxidase have also been implicated in the ROS formed in hypertension.[12] These sources are activated in endothelial cells, vascular smooth muscle cells, neuronal cells and renal tubular cells and contribute to vasoconstriction, increased endothelial adhesiveness, increased sympathetic outflow and renal tubular sodium transport. In addition, infiltrating macrophages can amplify local ROS levels. A major effect of ROS is the promotion of inflammation, in part by activating redox sensitive transcription factors. In particular NFκB activation is potently stimulated by increased cellular levels of ROS, which in turn activates transcription of several of the factors discussed elsewhere in this review. Superoxide reacts with NO in a diffusion limited fashion, forming the potent oxidant peroxynitrite. This reaction also reduces the bioavailable levels of NO which normally inhibits NFκB via several mechanisms.[13–15] This topic has been reviewed in depth recently.[10]

Vascular events contributing to inflammation in hypertension:

As mentioned in the introduction, inflammation involves a coordinated interaction between the vessel wall, particularly the endothelium, and circulating immune cells. An early event is rolling of leukocytes on the endothelium, mediated by the interaction of vascular selectins, including E-selectin and P-selectin, with leukocyte glycoprotein ligands like P-selectin glycoprotein ligand-1 (PSGL-1) and E-selectin ligand-1 (ESL-1). This is followed by interaction of cell adhesion molecules (CAMs) including the intracellular adhesion molecules (ICAMs) 1–5 and the vascular cell adhesion molecule 1 (VCAM-1) with leukocyte integrins including the lymphocyte function-associated antigen 1 (LFA-1) and the very late antigen 4 (VLA-4). CAMs are produced not only by endothelial cells, but also by pericytes and vascular smooth muscle cells. The interaction of selectins and CAMs with their ligand is often accompanied by diverse intracellular signaling events in both the vascular cell and the leukocyte. A summary of these events is provided in Figure 1.

Chemokines are a subset of cytokines that avidly attract leukocytes. There are 4 classes of chemokines, including the CC chemokines that have two adjacent cysteines near their amino terminus, the CXC chemokines that have two cysteines separated by one amino acid at the amino terminus, the C chemokines that have one cysteine at the amino terminus and the CX3C chemokine fractalkine have three amino acids between the two amino-terminal cysteines. Chemokines signal through their binding to 7 transmembrane spanning receptors and also interact with endothelial glycosaminoglycans. It has been proposed that “microgradients” of chemokines within the glycosaminoglycans can help direct trafficking

of immune cells to the vessel wall.[16] Recent in-depth reviews of leukocyte adhesion and trafficking have elucidated the current knowledge of these events.[17–20]

Several factors governing leukocyte adhesion and trafficking seem to be affected by hypertension and likely play a role in this disease. Liu et al showed that ang II-induced hypertension was associated with an increase in vascular ICAM-1 expression, and that this was attenuated by inhibiting the NADPH oxidase.[21] Recently, Lang et al reported that an ICAM-1 neutralizing antibody markedly reduced hypertension, improved vascular function, reduced vascular hypertrophy and attenuated vascular inflammation in mice infused with ang II.[22] We have found that hypertensive stretch markedly stimulates the expression of ICAM-1 by human endothelial cells, and the concomitant binding of human monocytes to these cells.[23]

The endothelial expression of VCAM-1 is stimulated by ROS and altered mechanical forces and is inhibited by NO.[24] Given that oxidative stress is increased, and NO bioavailability is decreased in hypertension, it would seem logical that VCAM-1 expression by endothelial cells might be increased. Indeed, correlations between blood pressure and circulating levels of VCAM-1 have been reported in humans.[25, 26] To our knowledge, the role of VCAM-1 in systemic hypertension has not been elucidated experimentally. This might in part be because embryonic deletion VCAM-1 is lethal, however blocking antibodies against VCAM-1 are available and could be used in such studies.[20] The ligand for VCAM-1, VLA4, exists on multiple cells including T cells, B cells and monocytes in an inactive state (Figure 1), and upon activation, undergoes a conformational change that promotes its interaction with VCAM-1.[27] This interaction not only enhances immune cell binding to the endothelium, but also signals production of cytokines like IL-1β and IL-6.[28] Blockade of the VCAM-1 ligand VLA4 with monoclonal antibodies reduced atherosclerosis in ApoE-deficient mice.[29] The anti-VLA4 monoclonal antibody Natalizumab is currently used in humans for treatment of multiple sclerosis and Crohn's disease.

As mentioned above, chemokines and their receptors play major roles in leukocyte trafficking in inflammation. Their role in hypertension been reviewed in depth recently.[30] As discussed in this review, the two studied most are CCR2 and CCR5. Circulating levels of the ligand for CCR2, CCL2 (also referred to as monocyte chemoattractant protein MCP-1) are increased in humans with hypertension.[31] Several studies have shown that inhibition of the CCR2/MCP-1 interaction reduces macrophage infiltration and end-organ damage in experimental models of hypertension. Ishibashi et al showed that while chronic ang II infusion caused a similar blood pressure increase in wild-type and $CCR2^{-/-}$ mice, the latter were protected against aortic thickening and inflammation.[32] Similarly Liao et al showed that $CCR2^{-/-}$ mice, while developing similar degrees of hypertension as wild-type mice, were protected against renal infiltration of macrophages and were remarkably protected against the development of albuminuria, renal collagen deposition, glomerular injury and oxidative kidney injury during ang II infusion.[33] Elmarkby et al showed that the CCR2 antagonist RS102895 reduced renal ICAM1, NFκB activation, TNFα levels and attenuated renal collagen deposition and albuminuria in rats infused with ang II.[34] This agent also reduced renal atrophy and macrophage infiltration in a murine model of renal artery stenosis.[35] In this case, CCR2 blockade significantly lowered blood pressure by about 15 mmHg

compared to mice not receiving this agent. The same group recently showed that mice lacking the ligand for CCR2, CCL2 or RANTES, also exhibited reduced renal infiltration of macrophages and attenuated renal atrophy compared to wild-type mice, despite similar degrees of hypertension.[36] Chan et al demonstrated that the CCR2 antagonist INCB3344 lowered blood pressure in mice following the onset of DOCA-salt hypertension and attenuated aortic macrophage infiltration in these animals.[37] This study was unique in that it used a pharmacologic agent to reverse established hypertension and vascular inflammation. These studies of CCR2/MCP-1 blockade or deletion are somewhat confusing, because some show a decrease in blood pressure while other don't. These differences might be due to variations in the models or methods of blood pressure measurement.

Our group has studied the role of RANTES or CCL5 in hypertension, where it seems to have a predominant role in regulation of T cell infiltration, particularly in the perivascular adipose tissue.[38] The receptors for this ligand include CCR1, CCR3 and CCR5. We showed that mice lacking RANTES had a significant reduction of IFNγ-producing T cells and developed less vascular dysfunction in response to ang II infusion, despite achieving similar degrees of hypertension. Pharmacological inhibition of RANTES with the synthetic peptide metRANTES achieved a similar effect as observed in the knockout mice. In humans we observed an inverse correlation between plasma RANTES levels and flow-mediated dilatation or endothelial injury as evidenced by circulating von Willebrand factor. These data suggest that CCL5 likely promotes T cell and to a lesser extent macrophage homing to perivascular tissues where these cells release cytokines like IFNγ that produce vascular dysfunction and injury.

In general, CCR5 is expressed on activated T cells in coordination with other events, like shedding of CD62L and CCR7, leading to mobilization of these cells from secondary lymphoid organs. In contrast, CCR7 directs immune cell homing to secondary lymphoid organs. This is true for both T cells and for antigen presenting cells, like dendritic cells. In the case of antigen presenting cells, homing to secondary lymphoid organs allows these cells to interact with T cells in lymph nodes and the spleen, where conditions are optimal for T cell activation. We have shown that hypertension is associated with accumulation of splenic dendritic cells that produce copious amounts of IL-6, IL-23 and IL-1β, compatible with such a homing event in hypertension.[39] Interestingly, in mice lacking CCR7, we find the accumulation of such activated dendritic cells in the spleen of ang II infused mice is attenuated, but find these dendritic cells remain in the kidney, where they locally activate T cells.[40]

Effector T cells, macrophages, natural killer cells and platelets express CX3CR and home to sites where the CX3C fractalkine (CXCL3) is expressed. Mice lacking CX3CR1 develop reduced fibrosis as compared to wild-type mice when subjected to DOCA-salt hypertension.[41] This is associated with reduced collagen deposition, reduced TGFβ expression and fewer monocyte/macrophages infiltrating the kidneys, but minimal change in blood pressure.

Related to the function of vascular adhesion molecules and chemokines is the expression and function of matrix metalloproteinases. These degrade matrix, allowing migration of immune cells. Barhoumi et al recently showed that genetic deletion of MMP2 in mice

completely prevents the elevation of blood pressure caused by ang II infusion.[42] This was associated with a preservation of endothelium-dependent vasodilatation and inhibition of vascular remodeling in the MMP2$^{-/-}$ mice. MMP2 deletion also markedly reduced vascular VCAM1 and MCP1 levels in the aorta and inhibited the accumulation of both monocyte/macrophages and T cells induced by ang II infusion.

Inflammasome activation and hypertension:

Inflammasomes are multicomponent cytoplasmic complexes that promote cleavage of precursor to active forms of IL-1α,β, IL-18 and IL-37. An in-depth discussion of the various subtype components of inflammasomes is beyond the scope of this review, but has been covered in depth elsewhere.[43] Briefly, the canonical, NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome assembles in response to diverse signals, including danger and pathogen associated molecular patterns, bacterial toxins, urate and cholesterol crystals and acute phase reactants (Figure 2). This involves caspase-1 recruitment to the caspase activation and recruiting (CARD) domain of an adaptor termed ASC where caspase 1 dimerizes and becomes capable of cleaving pro-IL-1β or pro-IL-18 to their active forms. Non-canonical inflammasomes utilize caspases 4, 5 and 11. Their products vary depending on cell type, such that myeloid cells predominantly produce IL-1β while epithelial cells, endothelial cells and fibroblasts release IL-1α. The ultimate synthesis of these mature cytokines thus involves a priming step, in which pro-IL-1β and pro-IL-18 and components of the inflammasome are transcribed, often in response to NFκB activation, and a triggering phase that requires inflammasome assembly and ultimate cleavage of these pro-cytokines to their mature forms.

Several studies have implicated the inflammasome and its products in hypertension. Serum levels of IL-1β have been reported to be elevated in humans with essential hypertension compared to subjects who had familial hypercholesterolemia without hypertension.[44] Monocytes of hypertensive individuals release increased levels of IL-1β in response to ex vivo stimulation with angiotensin II or LPS.[45] Alexander et al performed unbiased mRNA sequencing of monocytes from normotensive and hypertensive humans and found that 21 of 60 upregulated genes in hypertension were related to the IL-1β pathway.[46] In particular, the IL-18 receptor associated protein (IL18RAP) gene expression in monocytes correlated with mean arterial pressure in both normotensive and hypertensive individuals. In a separate cohort, the Minority Health Genomics and Translational Research Bio-Repository Database; IL-18RAP was also significantly correlated with blood pressure.

Krishnian et al showed that DOCA-salt hypertension in mice is associated with increased renal mRNA levels of ASC, NLRP3, pro-caspase 1 and pro-IL-1β. These investigators further showed that ASC-deficient mice develop blunted hypertension, had fewer renal macrophages and developed less renal fibrosis compared to wild-type mice in response to the DOCA-salt challenge. Likewise, a pharmacological inflammasome inhibitor, MCC950, reduced hypertension in wild-type mice.[47]

As mentioned above, uric acid crystals can activate the canonical inflammasome, and elevated uric acid levels have been implicated in hypertension. Recently, Zambom et al have shown that lowering uric acid levels with allopurinol prevents inflammasome activation and

lowers blood pressure in a model of hypertension caused by NO inhibition and high salt feeding in rats.[48] These investigators also showed that NFκB inhibition reduced blood pressure and protected against renal injury, supporting the concept that transcriptional priming of the inflammasome is also likely active in hypertension.

Both IL-1α and IL-1β signal through the type 1 IL-1 receptor (IL1R1). Zhang et al provided evidence that activation of this receptor promotes blood pressure elevation during ang II infusion. Mice lacking IL1R1 developed blunted hypertension in response to ang II. Anakinra, an inhibitory IL1R1 antibody, similarly reduced ang II induced blood pressure elevation. These investigators provided evidence that IL-1R1 activation prevents maturation of intrarenal macrophages that elaborate NO, and that this loss of NO signaling promotes renal sodium reuptake.[49] Related to these studies, the recent Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) showed that treatment with an IL-1β neutralizing monoclonal antibody reduced cardiovascular event rates in subjects with prior myocardial infarction and elevated high sensitivity C reactive protein.[50] Canakinumab had no effect on blood pressure, although a trend was apparent for this agent to have its greatest benefit on death and adverse cardiovascular events among those in the highest quintile of blood pressure.

Complement activation and hypertension:

The complement system is an ancient component of innate immunity composed of more than 50 soluble factors produced by somatic (particularly hepatic) cells and immune cells.[51] Complement activation occurs by a classical pathway, a lectin-initiated pathway and an alternate pathway. These are briefly summarized in Figure 3. The classical pathway is initiated when the recognition molecule C1q is bound to cell surface bound IgM, IgG or C reactive protein. This ultimately leads to formation of C3-convertase C4b2a. The lectin-initiated pathway is activated upon binding of pattern recognition receptors like mannose-binding lectin, collectins, and the ficolins by structures on pathogens, similarly leading to C3-convertase formation. The alternate complement pathway is unique because it is constitutively active, due to a thioester bond within C3 that is continuously hydrolyzed by plasma water.[52] Its activity is limited by complement-regulatory proteins which preferentially recognize and are inhibited by self-cell surfaces and are less inhibited by foreign surfaces.[53] All three of these pathways yield active products including C3a and C5a that bind to receptors on cells or enter the circulation to mediate systemic inflammation. Cellular receptors for complement signal intracellular events and/or cell killing. C5a has pleiotropic effects on immune cells, including enhancement of adhesion molecule expression, chemotaxis, degranulation, phagocytosis, and oxidative burst and modulation of cytokine production.[54] C5a signaling upregulates activating Fc receptors and down-regulates inhibitory Fc receptors on cell surfaces. These events promote antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis.[55] Activation of complement receptors on platelets promotes leukocyte/platelet aggregation, and is involved in disorders including heparin-induced thrombocytopenia, paroxysmal nocturnal hemoglobinuria and sepsis.[56]

There is substantial epidemiological evidence that complement is involved in hypertension. Engstrom et al followed men for 15 years and found that both C3 and C4 levels were elevated in those with hypertension at baseline.[57] They further showed that among those without hypertension at baseline the incidence of new hypertension and the change in both systolic and diastolic pressure over the follow-up was proportional to the initial levels of C3, but not C4. Volcik et al investigated the Complement Factor H (CFH) Y402H polymorphism in the ARIC cohort. CFH is a component of the alternate pathway, and variations of protein could affect its ability to suppress complement activation. In this large biethnic population, the risk for incident CHD and ischemic stroke was increased in whites carrying the 402H allele, and this association seemed to be dependent upon hypertension status.[58] Magen et al extensively evaluated patients with resistant arterial hypertension, controlled arterial hypertension and normotensive controls and found that those with resistant hypertension had elevated levels of C3 and high sensitivity C reactive protein.[59] They also found a striking relationship between plasma C3 levels and systolic pressure.

Experimental studies have implicated several components of the complement pathway in the pathogenesis of hypertension. Ruan et al showed that C3 expression is increased in the perivascular adipose tissue of rats with DOCA-salt hypertension and that it promotes migration and differentiation of adventitial fibroblasts to myofibroblasts.[60] A subsequent study from this group showed that C3 expression was predominant in macrophages in the perivascular adipose tissue, and that it mediates polarization of macrophages to an inflammatory phenotype that produces iNOS, IL-6 and TNFα. The authors also showed that C3 activates C5 which in turn seems to mediate vascular hypertrophy and fibrosis.[61]

T regulatory cells (Tregs) are a unique subset of T cells that inhibit activation of other T cells and exert anti-inflammatory effect. Previous studies have shown that T regs modulate blood pressure and/or prevent end organ damage in several experimental models of hypertension.[62–65] Chen et al showed that ang II can stimulate expression of C3R and C5R in Tregs and that infusion of ang II markedly reduced T regs in the kidneys of wild type mice, but not in mice lacking the C3 and C5 receptors (C3R and C5R).[66] These double knockout mice also developed blunted hypertension and accumulated fewer $CD4^+$ and $CD8^+$ T cells in the kidney. C3R and C5R deficiency was also associated with a reduction in renal fibrosis, superoxide production and glomerular injury. These elegant experiments illustrated how complement receptors can modulate adaptive immunity in hypertension by affecting the activity of T regulatory cells.

Complement activation occurs in normal pregnancy, likely to aid in clearance of fetoplacental material, fetal DNA and immune complexes.[67] In hypertensive disorders of pregnancy, complement activation is excessive, and genetic polymorphisms of complement proteins seem to predispose to pre-eclampsia.[68, 69] Regal et al found that soluble Complement Receptor 1 (sCR1), an inhibitor of complement activation, attenuated hypertension in a placental ischemia model of pre-eclampsia.[70] The precise roles of complement activation in pregnancy associated hypertension require further investigation.

Antigen presenting cells in hypertension:

Professional antigen presenting cells include dendritic cells, macrophages and B cells. These cells process foreign proteins and modified self-proteins to peptides that are presented on the cell surface in the context of major histocompatibility complexes (MHC), where they are recognized by T cells that possess a T cell receptor specific for the peptide/MHC. This process also involves other ligand receptor interactions between the T cells and antigen presenting cells including co-stimulatory molecules like CD28 with the B7 ligands and CD27 with CD70 (Figure 4). We have shown that both of these interactions are important in hypertension.[71, 72] The CD27/CD70 interaction seems particularly important for formation of memory T cells in hypertension. T cells primed by this “immunological synapse” proliferate, alter their surface molecules and begin to produce powerful cytokines that have profound impact on adjacent cells. Our group showed that dendritic cells acquire enhanced ability to produce cytokines and drive T cell proliferation in hypertension, and that adoptive transfer of dendritic cells from a hypertensive mouse could prime hypertension in a recipient mouse.[39] In this and other studies, we have found that self-proteins are modified by isolevuglandins (isoLGs, otherwise referred to as isketals or gamma ketoaldehydes).[40, 73] These are oxidation products of fatty acids like arachidonic acid that rapidly form covalent bonds with protein lysines. These modified proteins seem to act as neo-antigens and scavengers of these lower blood pressure and reduce end-organ damage in several experimental models of hypertension (Figure 5).

Macrophages can also act as antigen presenting cells. De Ciuceis et al showed that mice lacking macrophage colony stimulating factor (m-CSF) have blunted hypertension and are protected against alterations of vascular remodeling and vascular dysfunction in response to ang II.[74] The authors demonstrated a reduction in vascular infiltration of macrophages in these mice, however the protection against hypertension could have been due to a lack of other cells in these animals, as m-CSF is required for production of monoblasts, promonocytes, monocytes, macrophages, and osteoclasts from hematopoeitic lineages.[75]

Finally, B cells also efficiently present antigen, particularly to helper $CD4^+$ T cells. This not only stimulates T cells, but also primes B cells to alter the class and quantity of antibody production. We previously found that B cell adoptive transfer did not affect hypertension in lymphocyte deficient RAG-$1^{-/-}$ mice.[76] However Chan et al have used several approaches to suggest that B cells indeed play a role.[77] Additional studies of how B cells contribute are warranted, but one potential mechanism is via antigen presentation.

Myeloid cells in hypertension:

Circulating myeloid cells include monocytes, neutrophils, basophils, eosinophils, erythrocytes and platelets. Of these, the most studied in hypertension are monocytes and monocyte-derived cells. Circulating monocytes represent a heterogenous and pleiotropic subset of leukocytes that arise from hematopoietic stem cells, which give rise to a cell known as the common myeloid precursors (CMPs). CMPs were traditionally thought to sequentially yield granulocyte-monocyte precursors (GMP) and monocyte dendritic cell precursors (MDP).[78] Recently Yanzez et al have shown that in mice there is likely a divergence after CMPs (Figure 6), yielding parallel pathways for GMPs and MDPs.[79] Based

on transcriptomic analysis, monocytes derived from GMPs are “neutrophil-like” while those from MDPs express genes common to dendritic cells and macrophages. In the mouse, monocytes have been characterized as “classical”, and “patrolling” based on expression of Ly6C. Yanez et al showed that both GMP and MDP cells can give rise to Ly6C hi and low cells. GMPs also gave rise to classical neutrophils, while MDPs seem to be a predominant source of monocyte-derived dendritic cells.

In humans, circulating monocytes are characterized by different surface markers than those for mice, specifically based on their surface expression of the toll-like receptor 4 (TLR4) co-receptor CD14 and the FcγIII receptor CD16 (Figure 7).[80] When monocytes are first released from the bone marrow, they display high levels of CD14 and little or no CD16 ($CD14^{++}CD16^{-}$) on their cell surface. These “classical monocytes” circulate for approximately one day before either dying, transmigrating or transforming into another cell type.[81] Non-classical monocytes, characterized by high levels of CD16 and low levels of CD14 or $CD14^{low}CD16^{++}$, are known to expand in inflammatory states. Upon stimulation, these $CD14^{low}CD16^{++}$ cells exhibit increased production of TNFα.[82] From 5 to 10% of circulating monocytes express both CD14 and CD16, and are referred to as intermediate monocytes.[83,84] These cells also expand in inflammatory states such as rheumatoid arthritis, psoriasis and peripheral artery disease.[85];[86];[87];[88] Recent deuterium labeling studies indicate that intermediate and non-classical monocytes arise sequentially from the CD14 population.[81]

It is now very clear that monocytes and monocyte-derived cells play a critical role in hypertension. In a seminal study, Wenzel et al used a diptheria toxin based strategy to deplete monocytes and granulocytes from mice and found this prevented the rise in blood pressure and reduced the vascular dysfunction and the increase in vascular superoxide production caused by chronic ang II infusion.[89] Adoptive transfer of monocytes restored these abnormalities, while adoptive transfer of granulocytes did not. In a subsequent study, this group also showed that monocytes produce cytokines like IL-12 that activate Natural Killer cells and that these contribute to endothelial dysfunction in ang II-induced hypertension.[90]

Evolving concepts regarding myeloid cells and pathogenesis of disease:

In prior years, it was thought that the transmigration of monocytes across the endothelium invariably led to transformation of these cells to either an inflammatory macrophage or a monocyte-derived dendritic cell and monocytes served as the major, if not the only source of these tissue-residing cells. This concept has been modified by two major observations. First, it is now clear that populations of specialized macrophages reside in peripheral tissues that have developed in the yolk sac rather than from blood born monocytes.[91] These specialized cells include tissue resident macrophages, Kupfer cells in the liver, skin and mucosal Langerhans cells and microglial cells in the brain.[5] Resident macrophages are capable of self-renewal,[92] and are involved tissue homeostasis and resolution of inflammation. A second important observation is that monocytes can enter and re-emerge from the interstitium of tissues without transformation to another cell type, and in fact peripheral tissues contain untransformed monocytes.[4] Depending on the environment encountered in

the interstitium, these re-emerging monocytes can acquire enhanced capacity to express MHC II and to present antigen to T cells. Thus, the transmigration of monocytes across the endothelium does not invariably lead to their transformation to a macrophage or dendritic cell, and indeed many monocytes reside in tissue and can re-emerge and migrate to lymph nodes with minimal differentiation. Figure 1 depicts such cells.

These considerations do not negate the fact that monocytes differentiate to macrophages or dendritic cells in vivo. Indeed, monocyte transmigration and transformation clearly occur at sites of inflammation and is mediated by the state of the vascular endothelium. As an example, Randolph et al showed that endothelial cells activated by lipopolysaccharide or zymosyn can promote the differentiation of monocytes to either macrophages and dendritic cells.[93] The issue of the precise identity of inflammatory myeloid cells is also complicated by the fact that recent high dimensional transcriptomic analysis shows that these cells substantially overlap, and that there is a gradient of gene and surface maker expression among cells types and substantial interindividual variation.[94–96] Complicating this issue further is the realization that small subsets of myeloid/monocytic cells may have very unique, pro-inflammatory characteristics. As an example, Villani et al have identified a unique subset of circulating dendritic cells that express the tyrosine kinase Axl and Siglec 6, which they termed AS cells.[94] These cells produce large amounts of IL-6, IL-1β and TNFα and are capable of potently driving T cells proliferation. While AS cells represent about 0.1% of all circulating myeloid cells, they could be major drivers of immune activation, because one antigen presenting cells can activate 10s to 100s of T cells. Thus, small subsets of cells, not previously recognized by conventional methodology, could have major impact on inflammation and immune activation in a disease like hypertension. Taken together, it is apparent that “pigeon-holing” cells into one named type or another can be misleading and overlook unique rare cells that might be important. We would therefore urge a more open consideration of cell subtypes in various pathologies beyond simple traditional assignment as macrophages, dendritic cells or monocytes.

Vascular-immune cell cross talk and hypertension:

An important question in understanding the genesis of inflammation in hypertension is how immune cells are activated. Consistent with the concept established by Randolph et al,[93] accumulating evidence suggests that signals from the vessel play an important role. We previously showed that mice with excessive ROS production in vascular smooth muscle cells develop dendritic cell activation. This was accompanied by an increase in vascular Nox1 and a 2-fold increase in vascular hydrogen peroxide and superoxide. We found these animals develop aortic fibrosis and stiffening over time and that this is accompanied by an increase in the accumulation of isoLG-modified proteins in dendritic cells and the perivascular infiltration of T cells.[73] We have also established that increased sympathetic outflow in hypertension stimulates endothelial superoxide production, which in turn promotes the presence of isoLG-adducts in dendritic cells.[97] These studies are compatible with the concept that ROS generated in vessels either diffuse to adjacent myeloid cells where they oxidize lipids to form isoLGs or that isoLG modified proteins are released from vascular cells and phagocytosed by antigen presenting cells. Additional studies are required to elucidate these possibilities.

This interplay of vascular and immune cells likely occurs in humans. We recently showed that human endothelial cells undergoing “hypertensive” 10% stretch, vs normotensive 5% stretch caused a dramatic change in the phenotype of co-cultured human monocytes, as characterized by a marked increase in the percent of CD14++/CD16+ cells, corresponding to an intermediate monocyte phenotype.[23] We also found that humans with hypertension had a marked redistribution of their circulating monocytes to this intermediate phenotype. These transformed cells markedly increased mRNA expression for the cytokines IL-6, IL-1β, TNFα and IL-23 and could potently stimulate proliferation of T cells from the same human subject. Human monocytes exposed to endothelial cells undergoing hypertensive cyclical stretch also acquired the surface marker CD209, previously thought to represent transformation to a monocyte-derived dendritic cell, but they did not display changes in morphology as expected of conventional dendritic cells. In this study, we showed that hydrogen peroxide and IL-6 released from the endothelium, together with a loss of endothelial NO caused by hypertensive cyclical stretch mediated these responses in adjacent monocytes, in large part via signal transducer and transactivator (STAT)-3 signaling (Figure 8).

Summary:

As apparent in this review, it has become clear that inflammation contributes not only to blood pressure elevation, but also to the end organ damage that accompanies this disease. In many experimental studies, interventions that alleviate inflammation, such as knock out of a gene or pharmacological inhibition of an inflammatory mediator markedly reduces renal and vascular damage or alleviates effects of hypertension on the central nervous system, while having only modest, and in some cases no effects on blood pressure. These observations indicate that a major component of end-organ damage in hypertension is mediated by local inflammation which in turn might be independent of the level of blood pressure. Infiltrating immune cells release powerful mediators including cytokines, matrix metalloproteinases, reactive oxygen species and promote complement fixation, which in turn diffuse to adjacent parenchymal cells and cause dysfunction and damage. The resolution phase of inflammation invariably entails deposition of collagen and fibrosis, which leads to replacement of parenchymal cells and permanent changes in organ composition. Fibrosis, remodeling and vascular rarefaction are prominent examples of such long-lasting changes that occur in vessels, the heart and the kidney in hypertension.

A major related question is whether inflammation is the consequence or cause of hypertension. Based on several experimental studies, it seems that both are likely true. Factors such as ang II, excess salt and increased sympathetic outflow have direct vasoconstrictor and renal effects that cause modest elevations of blood pressure, which in turn lead to signals such as those described by Loperena et al.[23] The subsequent inflammatory responses perturb vascular and renal function and further raise blood pressure. It is also likely that sustained inflammation leads to permanent changes in renal and vascular function, such as fibrosis and cell death that are not reversable, and therefore interventions that are effective in short-term experimental studies might not lower blood pressure in humans where hypertension has been sustained for many years. In this way, there is likely a disconnect between the level of blood pressure and the underlying inflammatory process.

This is important because interventions like monoclonal antibody treatment and small molecules are available that might help resolve inflammation in hypertensive humans, but simple measures of blood pressure might not effectively guide such therapy. Efforts to detect ongoing inflammation, perhaps via one or a combination of biomarkers, by high dimensional transcriptome or protein analysis of circulating cells, or via imaging techniques might prove useful and help guide therapy in a patient-specific manner in hypertension and related cardiovascular diseases.

Acknowledgments

Funding Sources:

This work was supported by the National Institutes of Health Grants R35HL140016 and Program Project Grant P01HL129941 to D.G.H. and American Heart Association Scientist Development Grant 17SDG33670829 to L.X.

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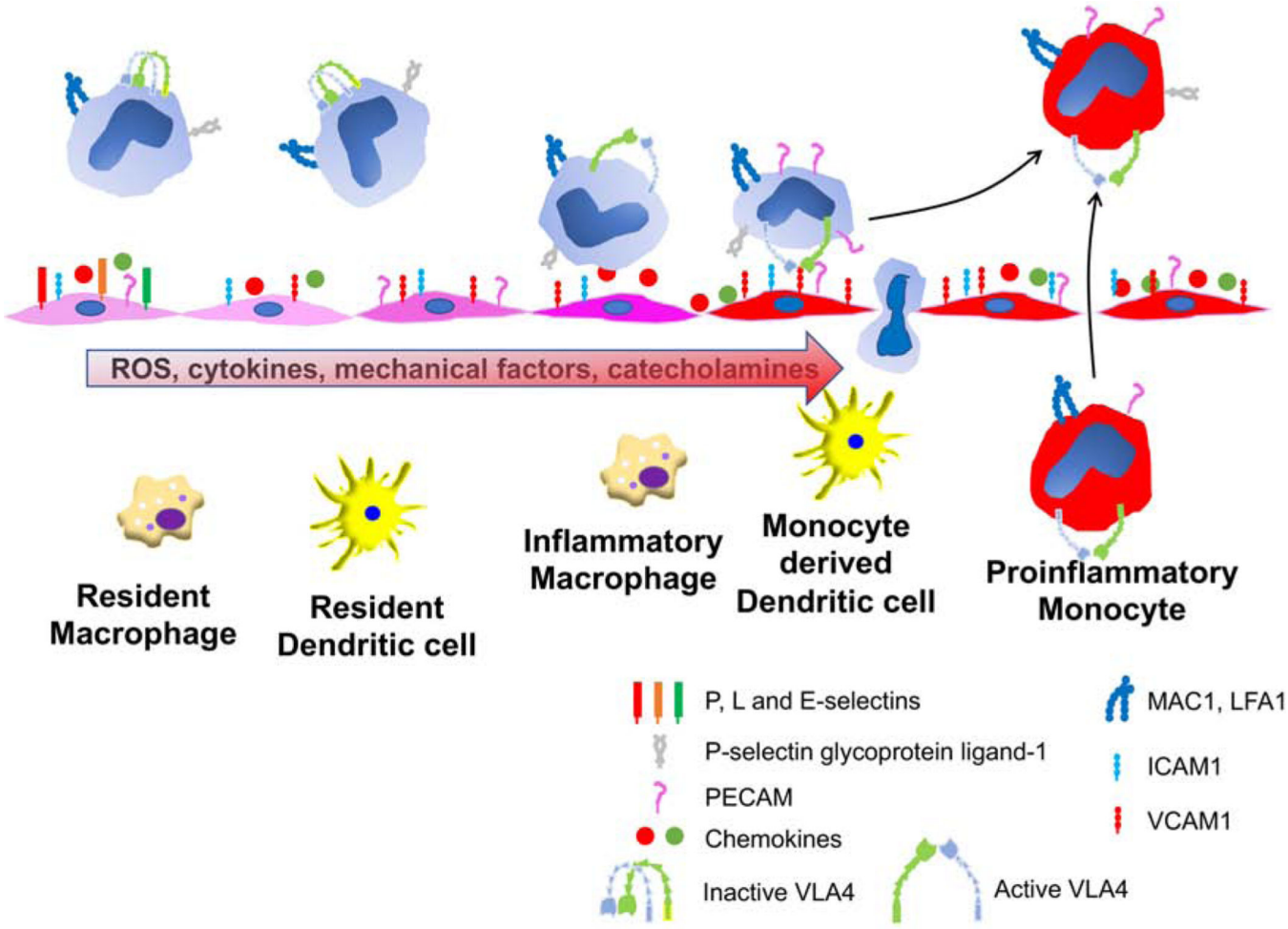

Figure 1:

Endothelial leukocyte interactions. In response to a variety of stimuli, including reactive oxygen species (ROS), inflammatory cytokines, mechanical forces and catecholamines, endothelial cells express increased levels of chemokines, selectins and adhesion molecules, including the intracellular adhesion molecule (ICAM)-1 and the vascular cell adhesion molecule (VCAM)-1. Monocytes possess ligands, including very late antigen 4 (VLA4), the leukocyte functional antigen 4 (LFA4) and the macrophage antigen 1 (Mac1) that bind to these receptors and promote initially rolling, then adhesion and ultimately transmigration. VLA4 undergoes a transformational change that enhances its ability to interact with VCAM-1. Transmigrated monocytes can transform to inflammatory macrophages, monocyte-derived dendritic cells or can exist in a minimally differentiated but activated state and can re-emerge as activated circulating monocytes. Resident macrophages and dendritic cells are also present in the interstitium of tissues and have major roles in tissue repair and immune surveillance.

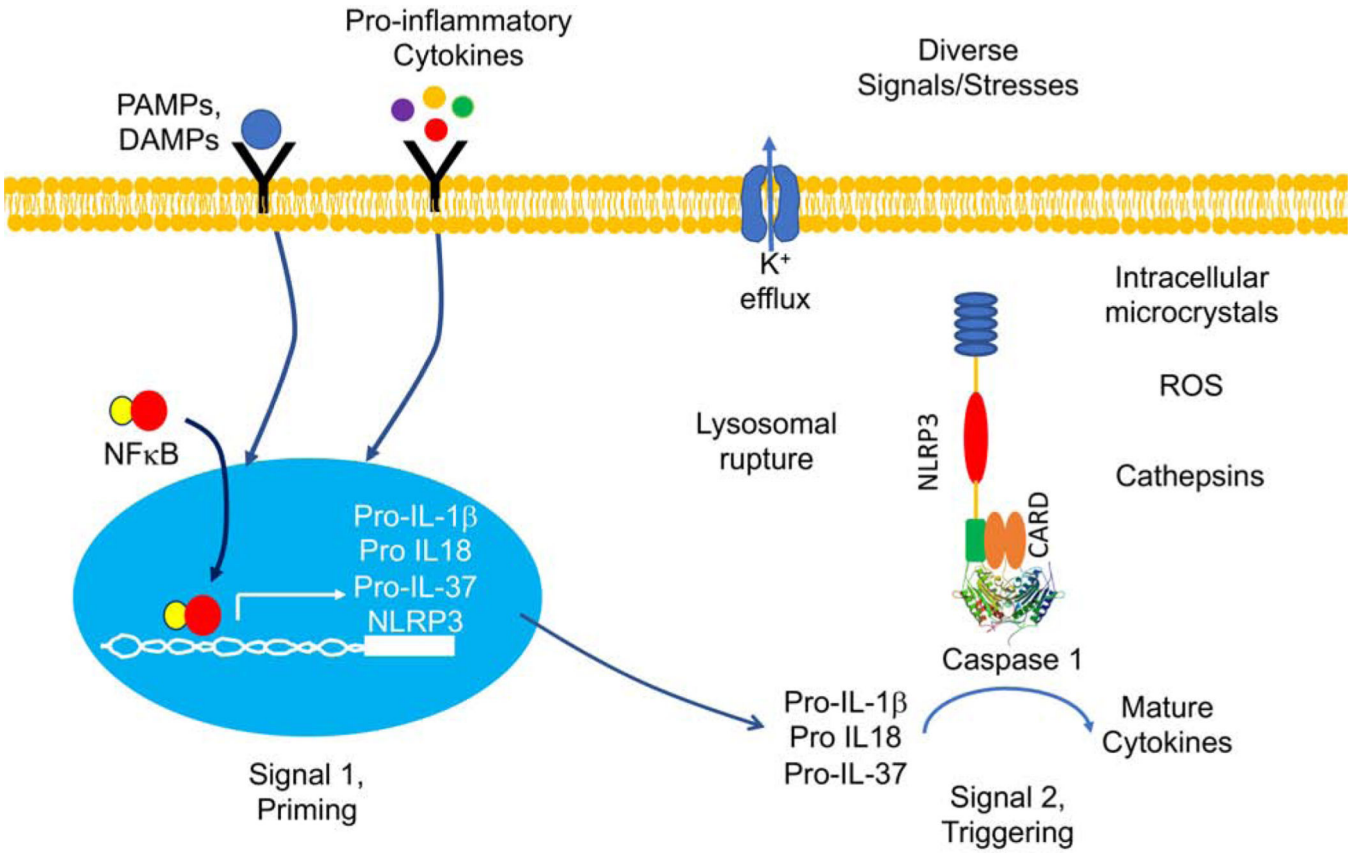

Figure 2:

Canonical inflammasome activation. Danger and pattern recognition pattern (DAMPs and PAMPs) molecules signal via Toll-like receptors to activate transcription of components of the NLRP3 inflammasome and also pro-forms of IL-1, IL-18 and IL-37. Cytokine signaling and these surface signals are transcriptionally mediated by nuclear factor kappa B (NFκB). These initial events are referred to as Signal 1 or priming. Signal 2 requires additional triggering signals, including reactive oxygen species (ROS), intracellular microcrystals, cellular potassium efflux or lysosomal lysis. These lead to inflammasome assembly and recruitment of caspase 1 which in turn cleaves pro-forms to mature IL-1β, IL-18 and IL-37. Caspases 4/5 and 11 are alternatively activated by bacterial surface proteins and can also process these pro-cytokines. Inflammasome components NOD-like receptor family pyrin domain containing 3 (NLRP3) and caspase activation and recruiting (CARD) are depicted.

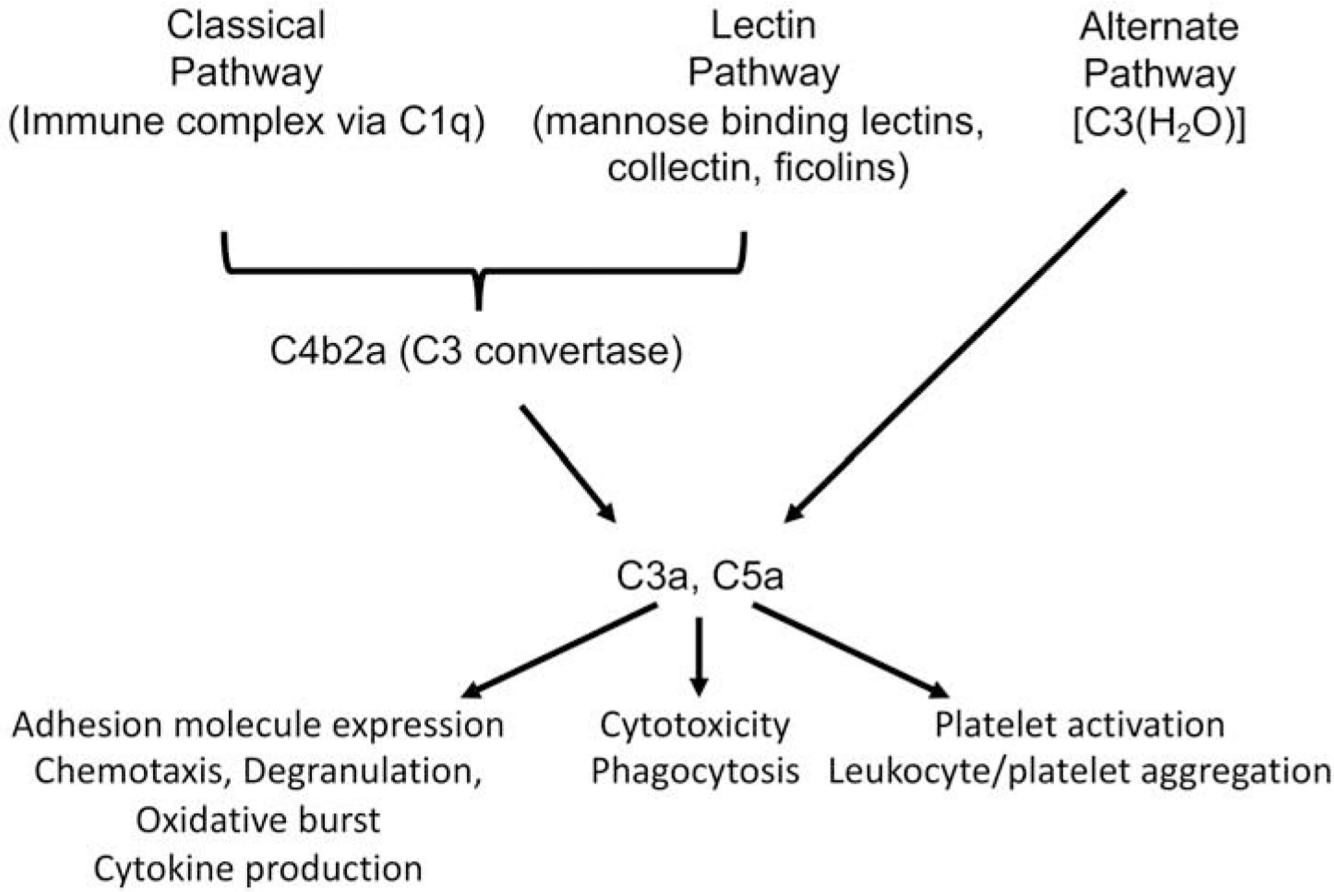

Figure 3:

Simplified depiction of complement pathways. Complement activation can occur via 3 pathways that all lead to formation of C3a and C5a, which in turn act on cellular receptors to mediate among other effects, adhesion molecule expression, oxidative events, cell death and leukocyte platelet aggregation.

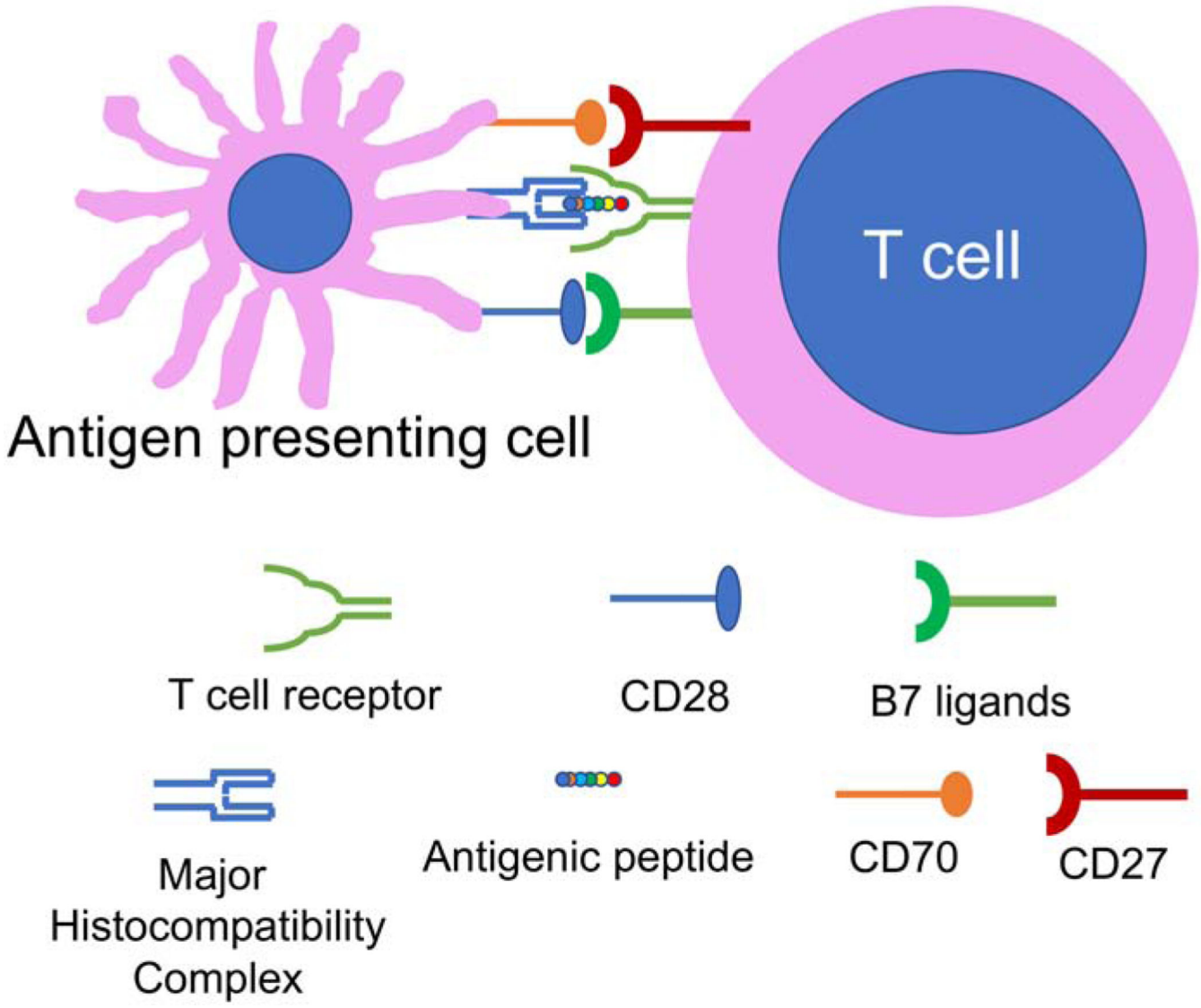

Figure 4:

Summary of the immunological synapse. Antigen presenting cells like dendritic cells, macrophages and B cells process foreign proteins and modified self-proteins to antigenic peptides that are ultimately presented in major histocompatibility complexes. T cells randomly recombine their T cell receptor (TCR) encoding DNA to form TCRs that recognize specific peptide/major histocompatibility complexes. Numerous additional receptors and ligands including CD28/B7 ligands and CD27/CD70 (depicted), programmed death (PD)1/ and programmed death ligand (PDL)1, CD40/CD40L, CD3 and cytotoxic cell lymphocyte antigen (CTLA)4 are present in the microdomain near the TCR to form the immunological synapse and mediate either T cell activation or inhibition. This interaction between antigen presenting cells and T cells represents a transition from innate to adaptive immunity.

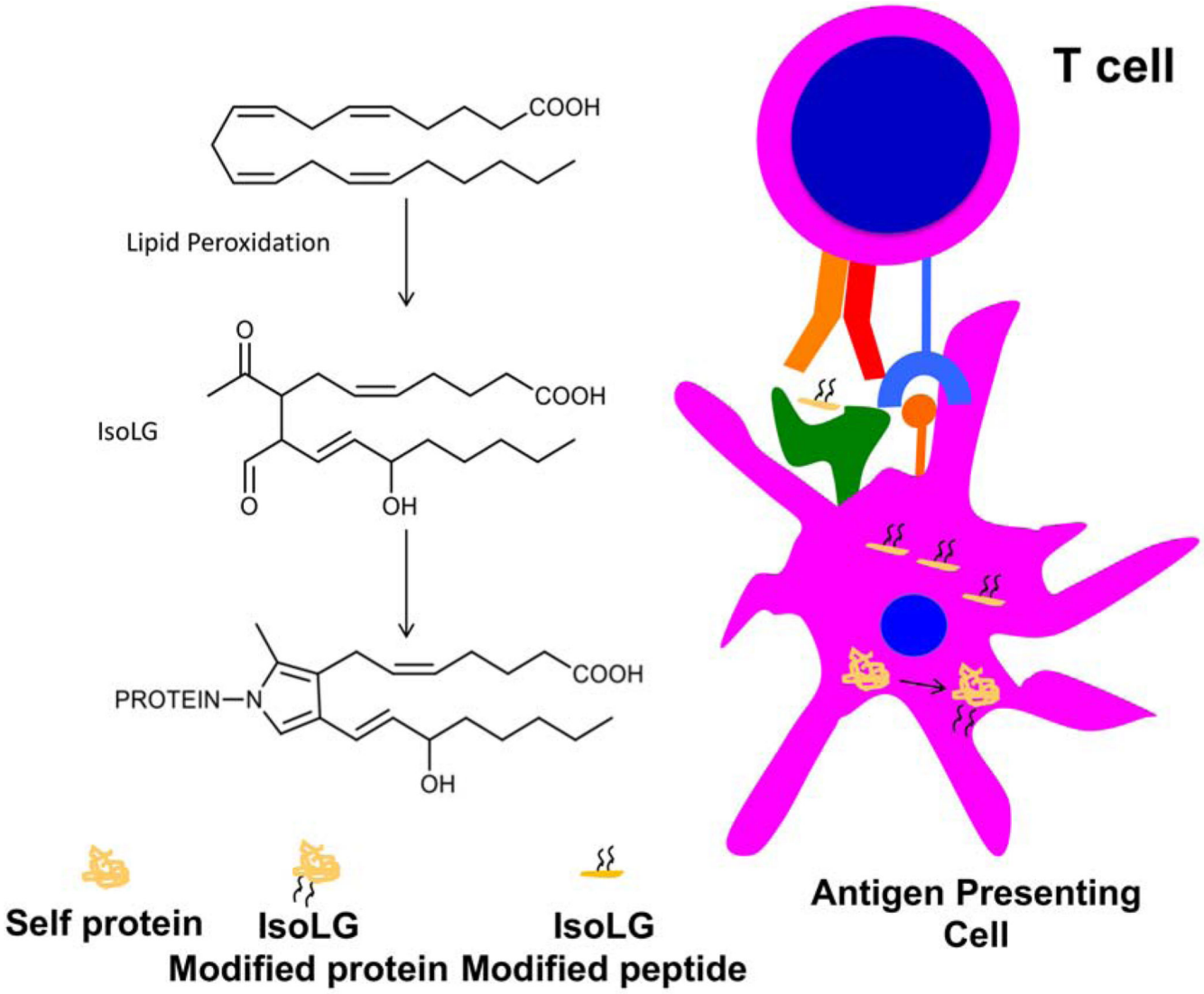

Figure 5:

Isolevuglandin (isoLG) formation as a source of immune activation. In antigen presenting cells oxidation leads to modification of arachidonic acid and similar fatty acids and formation of isoLGs, which are highly reactive and form covalent bonds with lysines on proteins. These modified proteins are processed to peptides and presented in MHCI and MHCII, and ultimately elicit T cell activation and an immune response.

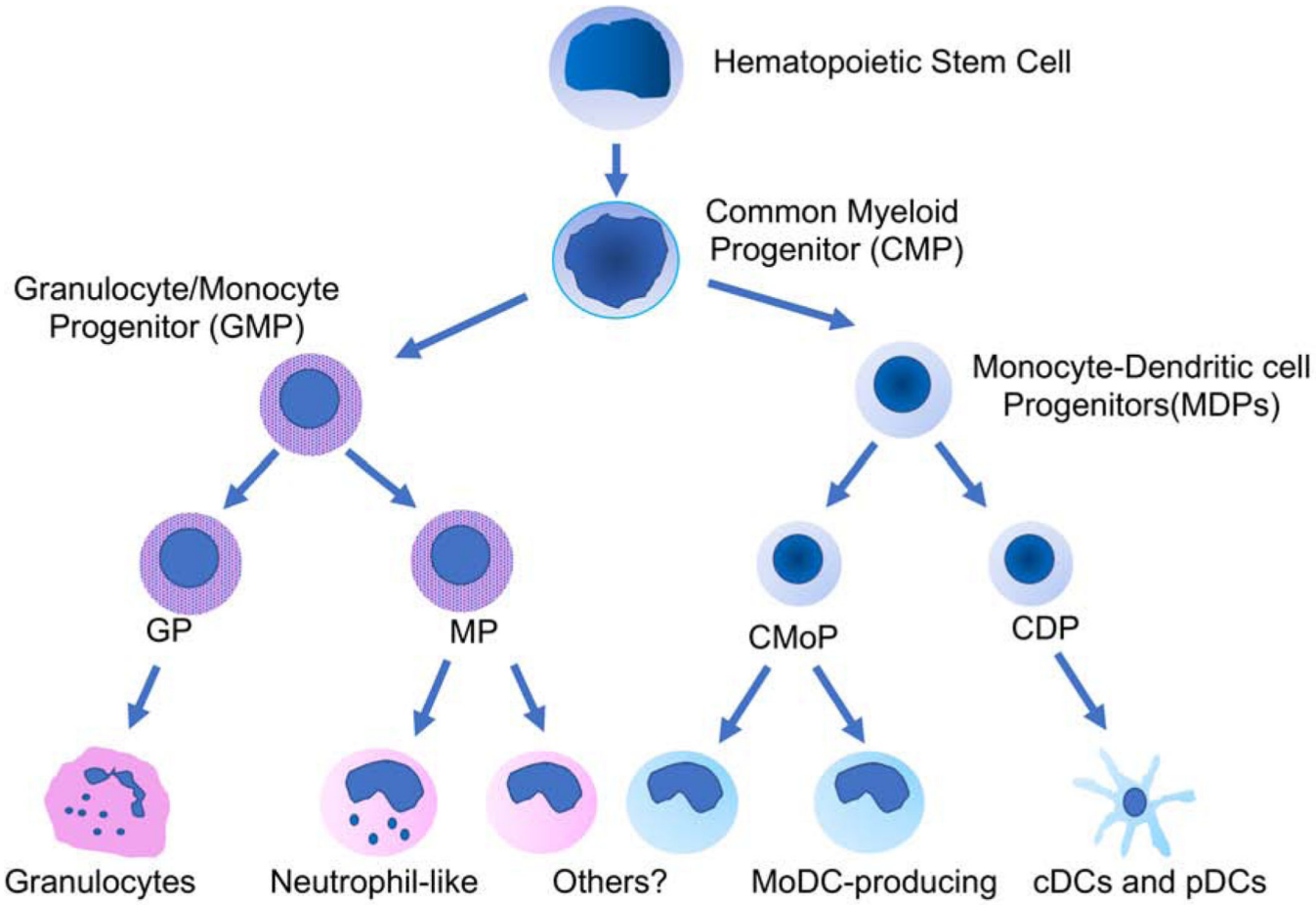

Figure 6:

Formation of monocytes from hematopoietic stem cells via parallel pathways derived from granulocyte/monocyte and monocyte/dendritic cell progenitors. GP – granulocyte precursors, MP – macrophage precursors, CMoP – common monocyte precursors, CDP – common dendritic cell progenitors. Modified from Yanez et al.[79]

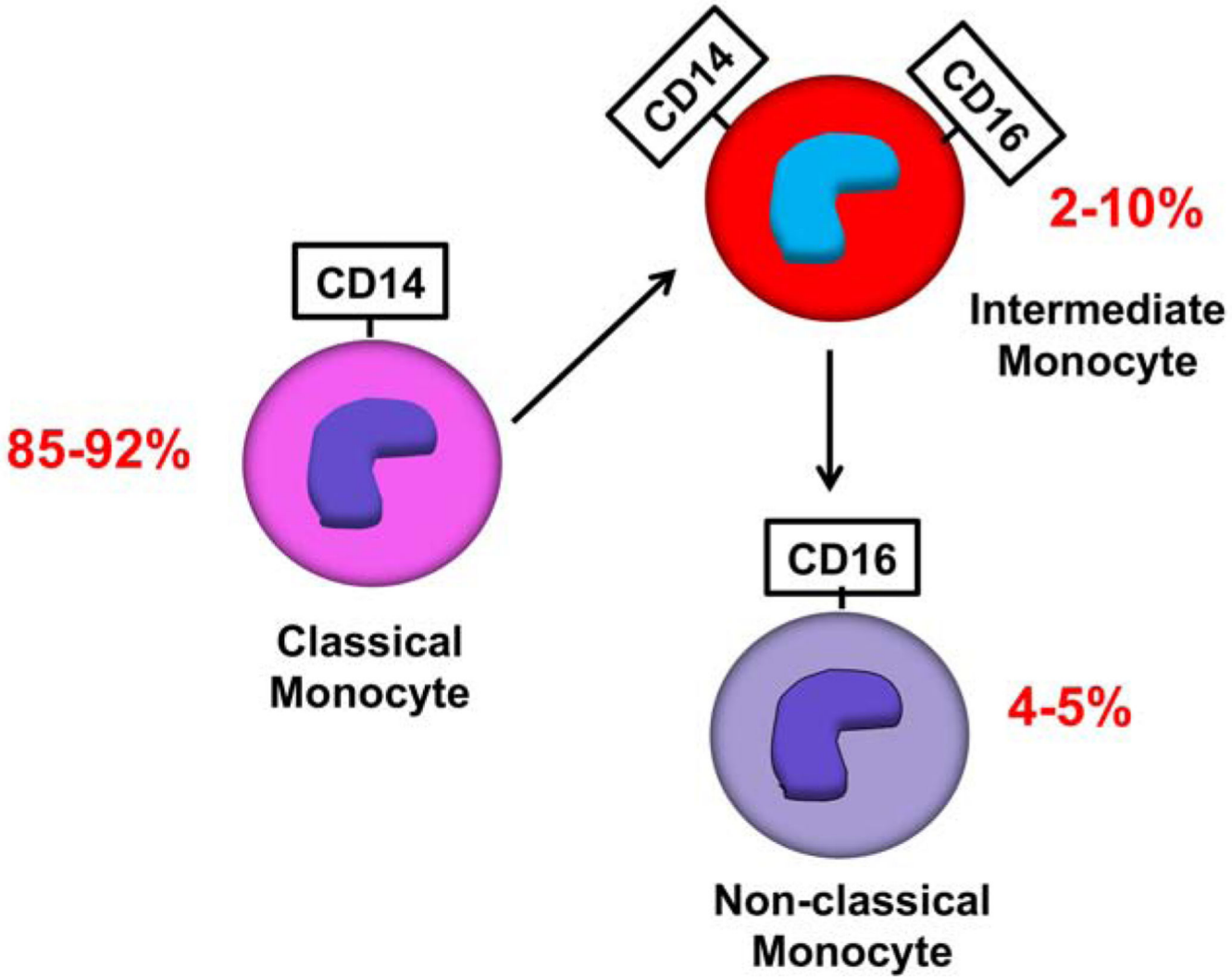

Figure 7:

Evolution of circulating human monocytes. Monocytes released from the bone marrow possess the Toll like co-receptor CD14 and little or no CD16. After about 24 hours in circulation, these cells either die, transmigrate or acquire CD16 to be intermediate monocytes. The cells subsequently exhibit reduced CD14 expression to become non-classical monocytes. Modified from Patel et al.[81]

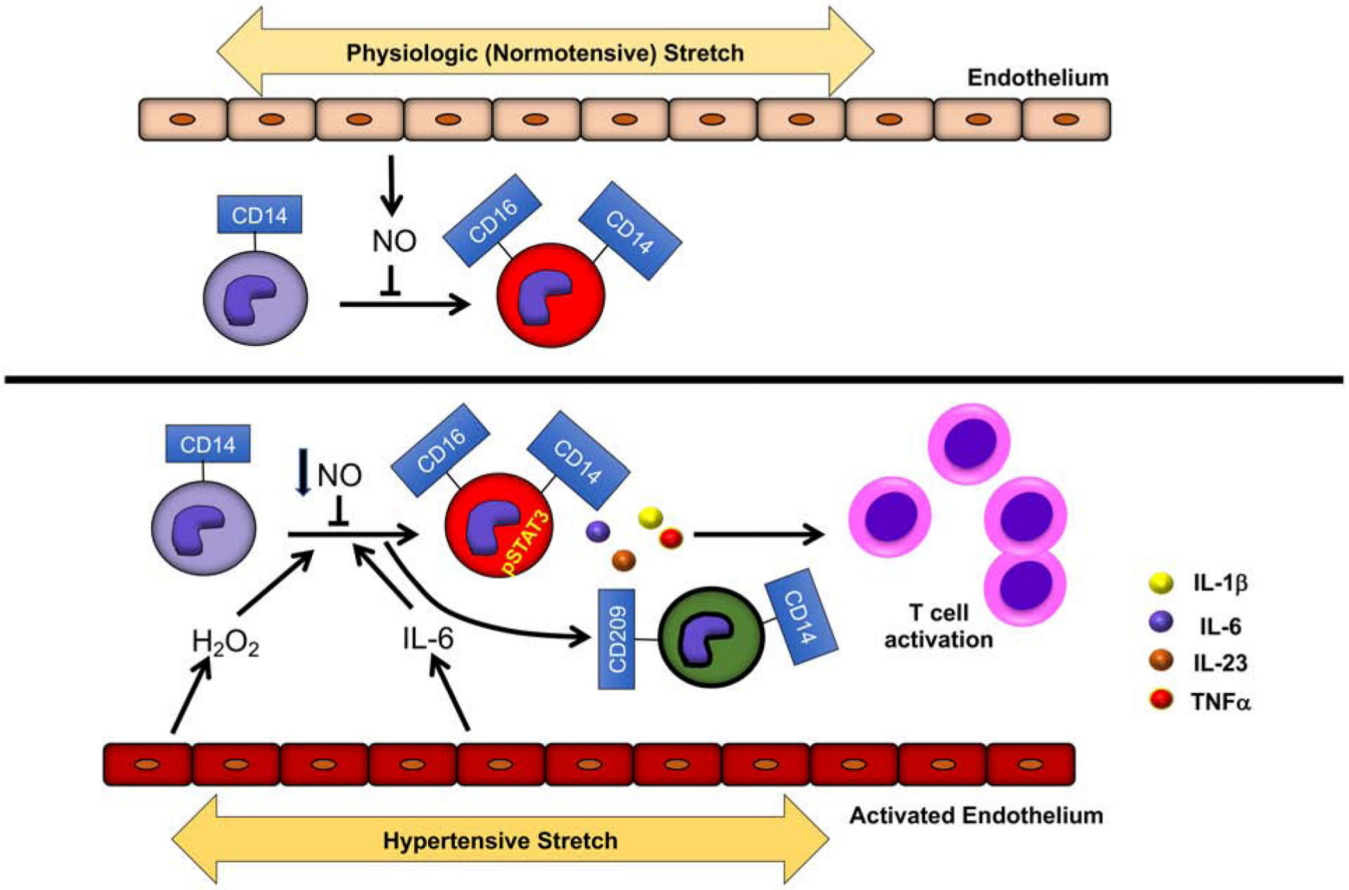

Figure 8:

Impact of endothelial activation by mechanical stretch on monocyte phenotype and function. Under physiological levels of cyclical stretch (upper panel), endothelial cells release nitric oxide (NO) which inhibits signal transducer and activator of transcription (STAT)3 activation and the transformation of classical monocytes to the intermediate phenotype. In the setting of hypertensive stretch (lower panel), there is a loss of endothelium-derived NO, and an increase in release of endothelial hydrogen peroxide (H_2O_2) and IL-6, which promote STAT3 activation and formation of intermediate monocytes and CD209+ cells. These cells produce large amounts of IL-6, IL-23, IL-1β and tumor necrosis factor (TNF) α and potently drive T cell proliferation. Modified from Loperena et al.[23]