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The Mosaic Theory Revisited: Common Molecular Mechanisms Coordinating Diverse Organ and Cellular Events in Hypertension

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Abstract

Over 60 years ago, Dr. Irvine Page proposed the Mosaic Theory of hypertension, which states that many factors, including genetics, environment, adaptive, neural, mechanical and hormonal perturbations interdigitate to raise blood pressure. In the past two decades, it has become clear that common molecular and cellular events in various organs underlie many features of the Mosaic Theory. Two of these are the production of reactive oxygen species (ROS) and inflammation. These factors increase neuronal firing in specific brain centers, increase sympathetic outflow, alter vascular tone and morphology and promote sodium retention in the kidney. Moreover, factors such as genetics and environment contribute to oxidant generation and inflammation. Other common cellular signals, including calcium signaling and endoplasmic reticulum stress are similarly perturbed in different cells in hypertension and contribute to components of Dr. Page's theory. Thus, Dr. Page's Mosaic Theory formed a framework for future studies of molecular and cellular signals in the context of hypertension, and has greatly aided our understanding of this complex disease.

Keywords

Oxidant stress; inflammation; superoxide; T cells; macrophages

Introduction

I was extremely honored to receive the Distinguished Scientist Award of the American Society of Hypertension in 2012. This annual award is named for various eminent scientists in the field of hypertension, and it was a particularly rewarding for me to receive this as the Irvine Page Award. Dr. Page was a pioneer in hypertension, an extraordinary scientist and a Lasker award recipient who had a lasting impact in hypertension research and cardiovascular medicine. His contributions included discovery of angiotensin II (which he named angiotenin), serotonin, the description of a neurogenic contribution to renal hypertension, the concept of baroreflex resetting and the Mosaic Theory of hypertension (1). The mosaic theory is worth special consideration.

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The Mosaic Theory, historical aspects and challenges

Before entering medicine, Dr. Page was trained in mathematics and chemistry. He was interested in mathematical models and thus sought to apply these to the problem of hypertension. Today, we refer to this approach as “systems biology”, but Dr. Page applied these principles to develop the concept of the Mosaic Theory many years before this term was popular. In the 1940s, as now, there was ongoing debate regarding the etiology of hypertension, with various investigators advocating renal, neural and hormonal causes. Dr. Page had contributed to each of these fields, and ultimately concluded that it was overly simplistic to assign all hypertension to any one cause. In his writings, he mentioned the term “mosaic” on several occasions but his first proposal of the Mosaic Theory seems to have been in 1949 (2). He wrote, “Even the simplest hypertension is a mosaic in which many mechanisms are to a greater or lesser extent involved. Elevated blood pressure is the resultant of multiple forces acting on the variety of tissues which compose the circulatory apparatus. Is it then to be supposed that this is any simple problem the solution of which will be found in the elucidation of but one of these forces?” Thus his Mosaic Theory proposed that the etiology of most cases of human hypertension, and indeed experimental hypertension, is multifactorial, and that genetic, environmental, anatomic, adaptive, neural, endocrine, humoral and hemodynamic “forces” interdigitate to cause hypertension (Figure 1) (3). Dr. Page likened this interaction to the phase rule of Josiah Willard Gibbs, which states that the state of a system is equal to its number of phases and the mass of each phase (4). It should be noted that the factors in figure 1 are derived from his 1949 manuscript (2), but this octagonal figure did not appear in that manuscript. Over subsequent years, several variations of this figure appeared in his and others’ writing, but the general concept has remained similar to that presented in figure 1.

The Mosaic Theory has continued to be challenged by evidence that hypertension is predominantly caused by perturbations of one organ. Of special note, the renowned physiologist Arthur Guyton advocated that hypertension is predominantly due to alterations of renal function (5). Dr. Guyton and co-workers developed the concept that all hypertension involves a shift in the renal function or pressure natriuresis curve, which leads to sodium retention and ultimately blood pressure elevation. Of interest, however, Dr. Guyton pointed out that extrarenal factors such as increased sympathetic tone, alterations of circulating hormones such as aldosterone, vasopressin or atrial natriuretic peptide, or changes in levels of electrolytes could shift the renal function curve. Several of these, including neuronal alterations, hormones and dietary intake of salt (environment) are components of the Mosaic Theory. Thus, Dr. Guyton’s elegantly proposed renal mechanisms for hypertension encompassed many features of the Mosaic Theory.

In reflecting further on the Mosaic Theory, studies performed in the past two decades have begun to elucidate the interactions proposed in this theory at molecular and cellular levels. These local events coordinate the actions of several organs, including the brain, the vasculature and the kidney, to raise blood pressure. I have been fortunate to have a role in some of this research, and would like to reflect on how my work and similar findings from many colleagues have added to and validated Dr. Page’s Mosaic Theory.

The role of oxidative stress and reactive oxygen species in the Mosaic Theory

One example is that oxidative stress is both upstream and downstream of the factors included in the Mosaic Theory. My contribution to this began with experiments I performed with Donald Heistad and Mark Armstrong in the 1980s. We were among the first to discover that experimental atherosclerosis impaired endothelium-dependent vasodilatation, and that

lowering cholesterol would correct this (6, 7). When it was discovered that endothelium-dependent vasodilatation was mediated by nitric oxide (NO), we immediately adapted chemiluminescence to measure NO and its oxidation products, and made the exciting discovery that diet-induced hypercholesterolemia did not reduce vascular NO, but led to its oxidation to inactive nitrite and nitrate (8). We subsequently showed that this was due to an increase in vascular, and specifically endothelial superoxide production (9). Ultimately, our experiments showed that many pathological states increased vascular superoxide production, including hypercholesterolemia, hypertension, diabetes and aging (10). A major question was how do non-phagocytic cells make superoxide and other reactive oxygen species (ROS). My colleague Kathy Griendling and her co-workers showed that vascular smooth muscle cells possess an NADH/NADPH oxidase and that this could be stimulated by angiotensin II (11). We subsequently showed that angiotensin II could activate the NADPH oxidase *in vivo* and that production of ROS was in part responsible for the hypertension and vascular smooth muscle hypertrophy caused by angiotensin II (12, 13). At the time we began these studies, most scientists believed that superoxide production was a unique property of phagocytic cells such as granulocytes, monocytes and macrophages. The idea that non-phagocytic cells could produce superoxide was new, and at first not widely accepted. This field was greatly aided by the discovery that the catalytic component of the NADPH oxidase or gp91^{phox}, was a member of a larger family of 5 such enzymes, subsequently termed the Nox proteins (14). The modes of activation, rate of ROS production and type of ROS produced vary from one Nox to the other. Most importantly, these enzymes have very different cellular distribution, and thus when activated can differentially affect processes such as cell migration, growth, gene transcription and apoptosis. Some of these are normal cellular functions, and should not be viewed as uniformly deleterious.

We also found several instances where ROS from the Nox enzymes activated other enzymes to produce superoxide. As an example, our studies showed that ROS from the NADPH oxidase could oxidize tetrahydrobiopterin, a co-factor for the NO synthases (15). When this happens, the NO synthases become “uncoupled” so that they produce superoxide rather than NO. More recently we found that there is interplay between the NADPH oxidase and the mitochondria, such that ROS from one can activate the other (16, 17). Novel ROS scavengers targeted to the mitochondria have proven effective in lowering blood pressure in experimental models (17, 18). Based on studies such as these, we proposed a paradigm in which small amounts of ROS, or “kindling” radicals produced by the NADPH oxidase, can activate other enzymes, in other parts of the cell, to produce larger quantities of radicals, or “bonfire” radicals (19).

Figure 2 illustrates several mechanisms by which oxidant stress interplays with the factors in the Mosaic Theory, and I will highlight some of these below:

Genetic

Polymorphisms of pro-oxidant and antioxidant enzymes co-segregate with blood pressure (20, 21).

Environmental

Pollutants (22), emotional stress (23), and dietary intake have both pro- and anti-oxidant effects.

Anatomic and adaptive

Vascular smooth muscle hypertrophy, vascular stiffening and rarefaction are driven by oxidative stress (24).

Neural

Nox enzymes in the brain affect neuronal firing and ultimately sympathetic outflow. In the subfornical organ of the brain, Nox 2 and Nox 4 increase neuronal firing and differently modulate water intake and sympathetic outflow (25). Oxidative stress affects baroreflex function (26).

Humoral and endocrine

Angiotensin II, aldosterone and catecholamines activate the NADPH oxidases and other ROS generating enzymes (27). ROS in the CNS increase sympathetic outflow, which can activate renin release.

Vascular

ROS promote vasoconstriction, enhance vascular smooth muscle hypertrophy and induce endothelial apoptosis (24, 26, 28).

In most of the above cases, there is good experimental evidence to support a role of ROS, however some are more speculative but logical. The fascinating conclusion however is that the production of small, short lived molecules like ROS induce myriad events in various organs that are included in Dr. Page's Mosaic Theory and ultimately promote blood pressure elevation and end-organ damage.

The role of inflammation in components of the Mosaic Theory

In addition oxidative stress, a related pathological process in hypertension is inflammation. In any condition where oxidative stress occurs, inflammation often follows and there is substantial interplay between the two (19). Oxidant events signal expression of adhesion molecules and chemokines on the surface of endothelial cells, promoting entry of inflammatory cells into the vessel and adjacent tissues. ROS modulate polarization of T cells, altering their production of cytokines. ROS also influence antigen presentation by dendritic cells and have been proposed to cause self-proteins to become antigenic via oxidative modification. Once inflammatory cells enter target tissues, they become sources of ROS, leading to a feed-forward amplification of oxidant stress.

Studies from as early as the 1960s suggested that there is an immune component to hypertension. In these early studies, investigators found that thymectomy and splenectomy could prevent hypertension in experimental models (29), that athymic mice were protected from hypertension (30), and that splenocytes from rats with DOCA-salt hypertension would cause hypertension in the recipient animal (31). Based on these considerations, we elected to extend our studies of oxidant stress to the role of inflammation in hypertension several years ago. We found that RAG-1^{-/-} mice, which lack both B and T lymphocytes, are protected against various forms of experimental hypertension, including that caused by angiotensin II, DOCA-salt, norepinephrine or emotional stress (32-34). Adoptive transfer of T cells restores hypertension in these various models. We subsequently showed that Abatacept, which prevents T cell co-stimulation, prevents and reverses angiotensin II and DOCA-salt induced hypertension in mice (35).

As in the case of oxidative stress, there is evidence that inflammation is either upstream or downstream of all of the factors described in Dr. Page's Mosaic Theory. Some examples include:

Genetic

Polymorphisms of cytokines, including TNF α , TGF β and interleukin-6 are associated with human hypertension (36-38).

Environmental

Factors such as stress, diet and pollutants can activate immune cells (39-41). Experimental stress raises blood pressure in a T cell dependent fashion (34).

Anatomic and Adaptive

Vascular hypertrophy in hypertension is in part mediated by inflammatory cytokines. Mice lacking T cells or interleukin-17 are protected against these vascular changes (32, 42). Atherosclerosis, a chronic inflammatory disease, is a common cause of renal artery stenosis.

Neural

Lesions of the anteroventral 3rd ventricle (AV3V) region prevent T cell activation and accumulation of perivascular inflammatory cells. Activation of the central nervous system by deletion of an antioxidant enzyme promotes T cell activation and vascular inflammation (33, 43). There is abnormal cholinergic activation of inflammatory cells in genetically hypertensive rats (44). Hypothalamic inflammation promotes hypertension (45).

Humoral and Endocrine

T cells, macrophage and dendritic cell functions are affected by the hypothalamic-pituitary axis (46), angiotensin II, aldosterone (47), leptin (48), and catecholamines (33).

Hemodynamic

Shear stress and vascular stretch affect expression of adhesion molecules and chemokines and promote immune cell adherence and entry into the vessel wall (49, 50).

The integrated action of the above events is an accumulation of inflammatory cells in the kidney and the vasculature. In the vasculature this is predominantly in the perivascular adipose tissue and in the kidney, these cells accumulate in the perivascular regions and adjacent to glomeruli. Our studies and those of others suggest that hypertension promotes macrophages and T cells to release cytokines that promote vasoconstriction, vascular remodeling and sodium retention leading to both blood pressure elevation and end-organ damage. Again, these cellular events are either upstream or downstream of each factor in the Mosaic Theory.

Conclusions

In retrospect, it is amazing to realize that much of the current research in hypertension has addressed various factors in the Mosaic Theory at basic levels. As such, Dr. Page's Mosaic Theory provided a framework for us to study the various hypertension "forces" at a molecular and cellular levels. A paradigm has arisen based on this work in which that common molecular events occur in diverse sites, including the brain, the kidney and the vasculature. The response to these signals vary depending on the target tissue, from increased neuronal firing in the central nervous system, to vasoconstriction and vascular remodeling in peripheral vessels to sodium reabsorption in the distal renal tubule. This discussion has focused on oxidant stress and inflammation, but there are clearly others, including altered calcium signaling and endoplasmic reticulum (ER) stress, which are important. It has been a challenge and an honor to contribute to this field of research, to

contribute to our understanding of this complex disease and especially to receive the Irvine Page Award in 2012.

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LITERATURE CITED

1. Frohlich ED, Dustan HP, Bumpus FM, Irvine H. Page: 1901-1991. The celebration of a leader. *Hypertension*. 1991; 18:443-5. [PubMed: 1916989]
2. Page IH. Pathogenesis of arterial hypertension. *J Am Med Assoc*. 1949; 140:451-8. [PubMed: 18129851]
3. Page IH. The mosaic theory of arterial hypertension--its interpretation. *Perspect Biol Med*. 1967; 10:325-33. [PubMed: 6034593]
4. Page IH. Arterial hypertension in retrospect. *Circ Res*. 1974; 34:133-42. [PubMed: 4359468]
5. Guyton AC. Renal function curve--a key to understanding the pathogenesis of hypertension. *Hypertension*. 1987; 10:1-6. [PubMed: 3596763]
6. Freiman PC, Mitchell GG, Heistad DD, Armstrong ML, Harrison DG. Atherosclerosis impairs endothelium-dependent vascular relaxation to acetylcholine and thrombin in primates. *Circ Res*. 1986; 58:783-9. [PubMed: 3087655]
7. Harrison DG, Armstrong ML, Freiman PC, Heistad DD. Restoration of endothelium-dependent relaxation by dietary treatment of atherosclerosis. *J Clin Invest*. 1987; 80:1808-11. [PubMed: 3680531]
8. Minor RL Jr, Myers PR, Guerra R Jr, Bates JN, Harrison DG. Diet-induced atherosclerosis increases the release of nitrogen oxides from rabbit aorta. *J Clin Invest*. 1990; 86:2109-16. [PubMed: 2254462]
9. Ohara Y, Peterson TE, Harrison DG. Hypercholesterolemia increases endothelial superoxide anion production. *J Clin Invest*. 1993; 91:2546-51. [PubMed: 8390482]
10. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. *Circ Res*. 2000; 87:840-4. [PubMed: 11073878]
11. Griendling KK, Minieri CA, Ollerenshaw JD, Alexander RW. Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. *Circ Res*. 1994; 74:1141-8. [PubMed: 8187280]
12. Rajagopalan S, Kurz S, Munzel T, Tarpey M, Freeman BA, Griendling KK, et al. Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. *J Clin Invest*. 1996; 97:1916-23. [PubMed: 8621776]
13. Laursen JB, Rajagopalan S, Galis Z, Tarpey M, Freeman BA, Harrison DG. Role of superoxide in angiotensin II-induced but not catecholamine-induced hypertension. *Circulation*. 1997; 95:588-93. [PubMed: 9024144]
14. Suh YA, Arnold RS, Lassegue B, Shi J, Xu X, Sorescu D, et al. Cell transformation by the superoxide-generating oxidase Mox1. *Nature*. 1999; 401:79-82. [PubMed: 10485709]
15. Landmesser U, Dikalov S, Price SR, McCann L, Fukui T, Holland SM, et al. Oxidation of tetrahydrobiopterin leads to uncoupling of endothelial cell nitric oxide synthase in hypertension. *J Clin Invest*. 2003; 111:1201-9. [PubMed: 12697739]
16. Doughan AK, Harrison DG, Dikalov SI. Molecular mechanisms of angiotensin II-mediated mitochondrial dysfunction: linking mitochondrial oxidative damage and vascular endothelial dysfunction. *Circ Res*. 2008; 102:488-96. [PubMed: 18096818]

17. Dikalova AE, Bikineyeva AT, Budzyn K, Nazarewicz RR, McCann L, Lewis W, et al. Therapeutic targeting of mitochondrial superoxide in hypertension. *Circ Res.* 2010; 107:106–16. [PubMed: 20448215]
18. Schnackenberg CG, Welch WJ, Wilcox CS. Normalization of blood pressure and renal vascular resistance in SHR with a membrane-permeable superoxide dismutase mimetic: role of nitric oxide. *Hypertension.* 1998; 32:59–64. [PubMed: 9674638]
19. Harrison, DG. Oxidative Stress and Vascular Inflammation. In: Hoffman, G.; Weyand, C.; Langford, C.; Goronzy, J., editors. *Inflammatory Diseases of Blood Vessels*. 2nd ed. John Wiley and Sons; Oxford, UK: 2012. p. 94-104.
20. Moreno MU, San Jose G, Orbe J, Paramo JA, Belouqui O, Diez J, et al. Preliminary characterisation of the promoter of the human p22(phox) gene: identification of a new polymorphism associated with hypertension. *FEBS Lett.* 2003; 542:27–31. [PubMed: 12729892]
21. Mansego ML, Solar Gde M, Alonso MP, Martinez F, Saez GT, Escudero JC, et al. Polymorphisms of antioxidant enzymes, blood pressure and risk of hypertension. *J Hypertens.* 2011; 29:492–500. [PubMed: 21178785]
22. Xu Z, Xu X, Zhong M, Hotchkiss IP, Lewandowski RP, Wagner JG, et al. Ambient particulate air pollution induces oxidative stress and alterations of mitochondria and gene expression in brown and white adipose tissues. *Part Fibre Toxicol.* 2011; 8:20. [PubMed: 21745393]
23. D'Angelo G, Loria AS, Pollock DM, Pollock JS. Endothelin activation of reactive oxygen species mediates stress-induced pressor response in Dahl salt-sensitive prehypertensive rats. *Hypertension.* 2010; 56:282–9. [PubMed: 20547970]
24. Harrison DG, Gongora MC. Oxidative stress and hypertension. *Med Clin North Am.* 2009; 93:621–35. [PubMed: 19427495]
25. Peterson JR, Burmeister MA, Tian X, Zhou Y, Guruju MR, Stupinski JA, et al. Genetic silencing of Nox2 and Nox4 reveals differential roles of these NADPH oxidase homologues in the vasopressor and dipsogenic effects of brain angiotensin II. *Hypertension.* 2009; 54:1106–14. [PubMed: 19805637]
26. Li Z, Mao HZ, Abboud FM, Chappleau MW. Oxygen-derived free radicals contribute to baroreceptor dysfunction in atherosclerotic rabbits. *Circ Res.* 1996; 79:802–11. [PubMed: 8831504]
27. Cai H, Griendling KK, Harrison DG. The vascular NAD(P)H oxidases as therapeutic targets in cardiovascular diseases. *Trends Pharmacol Sci.* 2003; 24:471–8. [PubMed: 12967772]
28. Ma X, Zhang HJ, Whiteis CA, Tian X, Davisson RL, Kregel KC, et al. NAD(P)H oxidase-induced oxidative stress in sympathetic ganglia of apolipoprotein E deficient mice. *Auton Neurosci.* 2006; 126-127:285–91. [PubMed: 16584925]
29. Okuda T, Grollman A. Passive transfer of autoimmune induced hypertension in the rat by lymph node cells. *Tex Rep Biol Med.* 1967; 25:257–64. [PubMed: 6040652]
30. Svendsen UG. Influence of neonatal thymectomy on blood pressure and hypertensive vascular disease in rats with renal hypertension. *Acta Pathol Microbiol Scand A.* 1975; 83:199–205. [PubMed: 1096529]
31. Olsen F. Transfer of arterial hypertension by splenic cells from DOCA-salt hypertensive and renal hypertensive rats to normotensive recipients. *Acta Pathol Microbiol Scand C.* 1980; 88:1–5. [PubMed: 7376880]
32. Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S, et al. Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. *J Exp Med.* 2007; 204:2449–60. [PubMed: 17875676]
33. Marvar PJ, Thabet SR, Guzik TJ, Lob HE, McCann LA, Weyand C, et al. Central and peripheral mechanisms of T-lymphocyte activation and vascular inflammation produced by angiotensin II-induced hypertension. *Circ Res.* 2010; 107:263–70. [PubMed: 20558826]
34. Marvar PJ, Vinh A, Thabet S, Lob HE, Geem D, Ressler KJ, et al. T lymphocytes and vascular inflammation contribute to stress-dependent hypertension. *Biol Psychiatry.* 2012; 71:774–82. [PubMed: 22361077]

35. Vinh A, Chen W, Blinder Y, Weiss D, Taylor WR, Goronzy JJ, et al. Inhibition and genetic ablation of the B7/CD28 T-cell costimulation axis prevents experimental hypertension. *Circulation*. 2010; 122:2529–37. [PubMed: 21126972]
36. Xi B, Wang Q, Pan H. Transforming growth factor-beta1 gene +869T/C, but not +915G/C polymorphism is associated with essential hypertension in a Chinese patient cohort. *Mol Biol Rep*. 2012; 39:6107–12. [PubMed: 22209986]
37. Cheung BM, Ong KL, Tso AW, Leung RY, Cherny SS, Sham PC, et al. Relationship of plasma interleukin-6 and its genetic variants with hypertension in Hong Kong Chinese. *Am J Hypertens*. 2011; 24:1331–7. [PubMed: 21833041]
38. Li YY. Tumor necrosis factor-alpha g308alpha gene polymorphism and essential hypertension: a meta-analysis involving 2244 participants. *PLoS One*. 2012; 7:e35408. [PubMed: 22536381]
39. Marvar PJ, Harrison DG. Stress-dependent hypertension and the role of T lymphocytes. *Exp Physiol*. 2012
40. Hlebowicz J, Persson M, Gullberg B, Sonestedt E, Wallstrom P, Drake I, et al. Food patterns, inflammation markers and incidence of cardiovascular disease: the Malmo Diet and Cancer study. *J Intern Med*. 2011; 270:365–76. [PubMed: 21443679]
41. Sun Q, Wang A, Jin X, Natanzon A, Duquaine D, Brook RD, et al. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. *JAMA*. 2005; 294:3003–10. [PubMed: 16414948]
42. Madhur MS, Lob HE, McCann LA, Iwakura Y, Blinder Y, Guzik TJ, et al. Interleukin 17 promotes angiotensin II-induced hypertension and vascular dysfunction. *Hypertension*. 2010; 55:500–7. [PubMed: 20038749]
43. Lob HE, Marvar PJ, Guzik TJ, Sharma S, McCann LA, Weyand C, et al. Induction of hypertension and peripheral inflammation by reduction of extracellular superoxide dismutase in the central nervous system. *Hypertension*. 2010; 55:277–83. [PubMed: 20008675]
44. Harwani SC, Chapleau MW, Legge KL, Ballas ZK, Abboud FM. Neurohormonal Modulation of the Innate Immune System is Pro-inflammatory in the Pre-hypertensive Spontaneously Hypertensive Rat, a Genetic Model of Essential Hypertension. *Circ Res*. 2012
45. Shi P, Diez-Freire C, Jun JY, Qi Y, Katovich MJ, Li Q, et al. Brain microglial cytokines in neurogenic hypertension. *Hypertension*. 2010; 56:297–303. [PubMed: 20547972]
46. Visser JT, De Kloet ER, Nagelkerken L. Altered glucocorticoid regulation of the immune response in the chronic fatigue syndrome. *Ann N Y Acad Sci*. 2000; 917:868–75. [PubMed: 11268418]
47. Luther JM, Gainer JV, Murphey LJ, Yu C, Vaughan DE, Morrow JD, et al. Angiotensin II induces interleukin-6 in humans through a mineralocorticoid receptor-dependent mechanism. *Hypertension*. 2006; 48:1050–7. [PubMed: 17043157]
48. Oral EA, Javor ED, Ding L, Uzel G, Cochran EK, Young JR, et al. Leptin replacement therapy modulates circulating lymphocyte subsets and cytokine responsiveness in severe lipodystrophy. *J Clin Endocrinol Metab*. 2006; 91:621–8. [PubMed: 16317060]
49. Cuhlmann S, Van der Heiden K, Saliba D, Tremoleda JL, Khalil M, Zakkar M, et al. Disturbed blood flow induces RelA expression via c-Jun N-terminal kinase 1: a novel mode of NF-kappaB regulation that promotes arterial inflammation. *Circ Res*. 2011; 108:950–9. [PubMed: 21350211]
50. Harrison DG, Widder J, Grumbach I, Chen W, Weber M, Searles C. Endothelial mechanotransduction, nitric oxide and vascular inflammation. *J Intern Med*. 2006; 259:351–63. [PubMed: 16594903]

Figure 1.

Figure 2.

Figure 3.