Published in final edited form as:

J Hypertens. 2012 January ; 30(1): 42–45. doi:10.1097/HJH.0b013e32834ee23c.

Essential Hypertension: Perspectives and future directions

Songcang Chen, MD

Diabetes Center, University of California at San Francisco, San Francisco, CA 94143-0540

Essential hypertension (EH) is characterized by chronic elevation of blood pressure (BP) due to an unknown etiology. It affects nearly 95% of hypertensive patients [1]. Genetic causes account for about half of EH (see below). In the US, more than 65 million adults have EH [2]. Since EH is usually asymptomatic and requires lifelong treatment; as a result, only 70% of these people become aware that they have elevated BP, only 59% are being treated, and only 34% have well controlled BP [2]. Sustained high BP due to undiagnosed, untreated or suboptimally treated hypertension leads to target organ damage.

Epidemiological data indicate that EH is a major modifiable risk factor for coronary heart disease, stroke, congestive heart failure and renal failure [2]. Since its pathogenesis is left unclear, treatment of EH remains largely empiric, with physicians selecting one or several different kinds of antihypertensive medicines until BP is adequately controlled. Because of the high prevalence of EH, the inability to make treatment specifically directed at the underlying etiology, and the need for lifelong treatment and follow-up, the care of patients with EH has become one of the largest expenses in the American health care budget.

In the past several decades, a wide variety of physiological studies have established that many signaling pathways affect short-term BP regulation [3]. These include the renin-angiotensin II(AII)-aldosterone system, sympathetic nerve-adrenergic receptor system, a series of genes participating in control of renal salt handling [4], endothelin (ET) and its A receptor (ETA) signaling in vascular smooth muscle (VSM) cells, pathways which all result in vasoconstriction, and factors produced by vessel endothelial cells that cause vasodilation (e.g. nitric oxide) (Figure 1). While the effect of these systems has been established for short-term BP regulation, determining which of these pathways contributes to EH as primary alterations or secondary responses has proven difficult. However, study of monogenic forms of EH has consistently shown that genetic hypertension originally derives from variations of genes involved in renal salt handling [3, 4]. Activation of any one of these pathways leads to resistance arterial remodeling and increased vascular tone, resulting in high BP. Once elevated vascular tone is established, it cannot be returned to the original normal point, even though available anti-hypertensive drugs alone or in combination can effectively and temporarily reverse the vascular tone to normal. The critical issue to be elucidated in the

Address correspondence to: Songcang Chen, M.D., Diabetes Center UCSF, 1119 HSW 513 Parnassus Ave, San Francisco, CA 94143-0540, Tel (415) 476-2729, FAX (415) 564-5813, schen@diabetes.ucsf.edu.

The author has no conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

next decade is what common downstream gene activation in these signaling pathways triggers irreversible vascular remodeling, to cause a new set point for vascular tone. If a target gene responsible for the final common pathway converging from these different signaling systems is identified, a novel antihypertensive medicine against this gene activity could permanently alter vascular remodeling and reverse elevated vascular tone to normal. Such a therapy could replace lifelong treatment, which not only brings about a huge expense in health care, but also can cause lack of adherence and compliance to the medical regimen, leading to inadequate blood pressure control.

Another important issue is what factors cause EH. With advances from molecular biology, it is well accepted that EH is an age-dependent, complex common trait resulting from the interaction of environmental, epigenetic and genetic determinants (Figure 1). However, the pathogenesis of EH is largely not understood despite intense efforts.

Environment and EH

A variety of environmental factors, such as smoking, socioeconomic status, stress, high salt diets, obesity and vitamin D deficiency, have been shown to play roles in the pathogenesis of EH. These factors cause EH through epigenetic and genetic interaction, or by the induction of specific gene expression. While the exact mechanisms by which environmental factors cause EH are not clear, recent research has provided exciting clues shedding light on the mechanisms of salt and vitamin D deficiency-induced hypertension. Wirth A et al [5] showed that G12-G13-leukemia associated Rho guanine nucleotide exchange factor signaling in VSM cells mediates salt-induced hypertension. Several human studies have demonstrated that vitamin D deficiency in some populations leads to EH [6, 7]. Further studies have shown that vitamin D receptor (VDR) knockout [8] and 1- α -hydroxylase knockout [9] mice develop hypertension accompanied by elevated renin gene expression, which was confirmed in the kidney tissue of our VDR total knockout mice [10]. We also showed that vitamin D inhibited AII- or ET-induced cell proliferation and the key cell cycle determinant Cdc25A expression in VSM cells [11, 12], as well as activated natriuretic peptide receptor A expression in VSM cells, and inner medullary collecting duct cells in vitro and in vivo [13, 14]. It remains unclear so far whether these alterations in gene expression are involved in vitamin D deficiency-induced hypertension, but the results are suggestive. Continued efforts are needed to elucidate the complex interaction among genes, the physiological, and the environmental factors which occur in EH, and identify how these factors trigger the development of EH through alteration of gene expression. Understanding gene and environmental interaction may allow more rational introduction of environmental interventions in an attempt to prevent future occurrence of the disease in at-risk people.

Epigenetics and EH

Epigenetics refers to regulation of gene expression without altering DNA sequence. It occurs by chromatin remodeling through DNA methylation, histone modification, RNA (including microRNA and noncoding RNA)-mediated gene regulation, genomic imprinting, chromosomal inactivation and transposable elements [15]. Epigenetics offers a potential explanation for how environmental factors and aging impact the individual genetic

background to produce variation in the disease. Epigenetic regulation can be a dynamic process or result in heritable changes in gene expression. Emerging studies have shown that epigenetic modification is involved in the development of EH [16]. Recent studies showed methylation of CpG islands in the promoter and first exon of the 11 beta-hydroxysteroid dehydrogenase type 2 (11 β -HSD2) gene leading to decreased transcription and activity of the enzyme [17]. Loss-of-function mutation of this gene leads to salt-sensitive hypertension [18]. Elevated HSD11B2 promoter methylation decreased HSD11B2 activity and was associated with hypertensive patients [19]. Large-scale epigenome-wide human studies are needed to identify the role of methylation mechanisms in EH. In addition, histone modification is also causally linked to EH. With no K (lysine) protein kinase 4 (WNK4), a serine/threonine-protein kinase, regulates renal tubular sodium reabsorption. Patients with loss-of-function mutations in the *WNK4* gene displayed salt-sensitive hypertension [20]. Mu et al [21] recently showed that a high salt diet triggered β -adrenergic-mediated suppression of renal WNK4 gene transcription and the development of salt-sensitive hypertension. They found the underlying molecular mechanism for this downregulation, which involved cAMP-mediated modulation of histone acetylation in the promoter region of the WNK4 gene. The most advanced finding in the epigenetic determination of EH has been made in regards to microRNA (miRNA) modulated BP homeostasis. Endogenous miRNAs regulate gene expression through posttranscriptional or translational repression. The biogenesis of miRNAs involves Dicer, a RNase III endonuclease, which cleaves primary miRNA precursors to mature miRNA [22]. Smooth muscle specific -Dicer knockout mice have systolic BP (SBP) 27.7 mmHg lower than wild-type mice which was accompanied by decreased vessel contractile function [23]. Smooth muscle specific miR-145 and miR143/145 knockout mice also display reduced SBP by about 15–20 mmHg [24, 25]. Conditional deletion of Dicer in the renin cell lineage results in decreased expression of the renin gene accompanied by hypotension [26]. These results suggest that miRNAs are essential for maintaining BP and contractile function in resistance vessels. Improved understanding of the dynamics miRNA expression, the effect of miRNA on the expression of BP regulating genes, and interplay with genetic variation in miRNA binding sites may elucidate part of the pathogenesis of EH.

Genetics and EH

The heritability of hypertension (genetic hypertension) is typically estimated from family and twin studies to be in the range of 30% to 70% [27, 28], with multiple contributory genes and gene-gene interactions. EH occurs in all human populations; the genetic variation responsible for this disease should be preserved widely among diverse human populations, and the frequency of such variation should be relatively high. As mentioned above, currently patients with EH need lifelong treatment which is largely empiric. Thus, determining which common variation might play an important role in the disease will lead to the generation of novel therapeutic targets. However, genome-wide association studies (GWAS) seeking to identify common genetic determinants for EH have not been fruitful. Four large GWAS groups [29-32] in the world did identify a total of more than 30 common loci associated with hypertension. Some of these loci contain genes previously known or suspected to be involved in BP regulation, and some loci exist among diverse human populations. All single

nucleotide polymorphisms (SNPs) reached the threshold of genome-wide significance ($p < 5 \times 10^{-8}$). However, their effect sizes were much smaller (about 1 mmHg) than anticipated and the collective effect of BP loci only explained a small fraction (about 1%) of BP heritability. Notwithstanding the fact that these common loci identified by GWAS for hypertension might be useful for some population-specific candidate gene studies and improve our understanding of the underlying pathophysiology of EH, it is clear that no common gene variation contributed a substantial effect on hypertension, suggesting that the genetic architecture of BP regulation in the population is unlikely to be shaped by commonly occurring genetic variation in a diverse set of BP-influencing genes.

This raises the more likely possibility that rare variants which are heterogeneous and uncommon may play a greater role in the phenotype of genetic hypertension. Pioneering work from Lifton's group outlined the contours of the role that rare variants played in EH [33]. They resequenced three genes (NCCT, NKCC2 and ROMK) involved in renal tubular salt reabsorption in the Framingham Heart Study population. They identified novel variations in these genes and defined the frequency of such rare variations in this population. These non-synonymous loss-of-function variants were associated with lower BP and with SBP lower (by 5.7 mmHg at age 40 and by 9.0 mmHg at age 60) in the mutation-bearing group [33]. Similarly, Rao F et al [34] resequenced a locus critical for catecholamine storage, chromogranin A, and discovered a low (~3%) frequency functional variant, Gly364Ser, that had a profound effect on autonomic activity as well as risk for HT. These studies clarify the possibility that the risk of hypertension in some fraction of the population can be strongly affected by functional rare variants. While rare variants in a wide range of genes are likely to be the focus of hypertension genetics for the next decade, the detection of the sheer number of potentially culprit rare variants responsible for human EH will be a daunting task due to human genetic diversity and population-specific genetic variation, even though higher-throughput next-generation human exome-wide and genome-wide sequencing will help to find some rare variants. Alternatively, specific hypertensive rat models represent good tools to uncover novel candidate genes and their genetic variations [35, 36]. Once confirmed, these results could translate to human EH studies in some populations.

The article by Chauvet et al [37] in this issue of *J. Hypertension* provides some promising clues to finding novel candidate hypertensive genes. This group previously isolated segments that harbor 5 blood pressure quantitative trait loci (QTL) on rat chromosome 10 by congenic strains made from crosses of inbred hypertensive Dahl salt-sensitive and normotensive Lewis rats [38]. They have confirmed the individual QTL controlling quantitative variation in BP inherited in a monogenic trait [39]. In this paper, they performed a systematic and comprehensive molecular analysis and revealed 8 novel quantitative trait genes in 4 of the 5 QTL that carry non-conserved mutations. They confirmed that all these genes bear structural mutations and have transcriptional activities. These genes consist of the proline rich 11 gene, benzodiazepine receptor associated protein 1, Loc689764, myotubularin related protein 4, protein phosphatase 1E, PP2C domain containing, ring finger protein 43, Loc100363423 and the ATP-binding cassette, subfamily A, member 8a gene. They may be primary causal genes or signaling molecules involved in BP regulation. Most of their functions are unknown, but the work by Chauvet et al is a critical step as a guide for isolating each gene to do further function testing by congenic fine resolution. Once

the function associated with EH is confirmed by gene knockin or gene knockout approaches, these new genes could become signaling molecules in the EH polygenic network, which could be employed as targets for human EH association studies.

In summary, while gene variants causing monogenic hypertension (less than 1% of EH) have been identified, and specific and effective treatment strategies have been developed, most therapy for EH is still empirically based. Since no common gene variants contribute to a large effect size for this common disease, hunting for population or group-specific rare genetic variants responsible for about 50% of EH will be a daunting task. The rat models of genetic hypertension will be very helpful to find novel candidate causal genes and their variants. Progress in understanding the alteration of gene expression mediated by environmental factors leading to EH, and the role of epigenetics in EH will promote elucidation of the pathogenesis of the other 50%. An equally important issue is to identify the common signaling pathway and its target genes activated by different causal factors, which trigger irreversible vascular remodeling and resetting resistance vessel tone in EH. Such breakthrough research in these two fields of EH will dramatically reduce the morbidity and mortality in coronary heart disease, stroke and renal failure caused by this silent killer in the next decade.

Acknowledgments

The study was supported by NIH grant HL096047.

References

1. Carretero OA, Oparil S. Essential hypertension. Part I: definition and etiology. *Circulation*. 2000; 101:329–335. [PubMed: 10645931]
2. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003; 42:1206–1252. [PubMed: 14656957]
3. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. *Cell*. 2001; 104:545–556. [PubMed: 11239411]
4. Vehaskari VM. Heritable forms of hypertension. *Pediatr Nephrol*. 2009; 24:1929–1937. [PubMed: 17647025]
5. Wirth A, Benyo Z, Lukasova M, Leutgeb B, Wettschureck N, Gorbey S, et al. G12-G13-LARG-mediated signaling in vascular smooth muscle is required for salt-induced hypertension. *Nat Med*. 2008; 14:64–68. [PubMed: 18084302]
6. Fiscella K, Winters P, Tancredi D, Franks P. Racial disparity in blood pressure: is vitamin D a factor? *J Gen Intern Med*. 2011; 26:1105–1111. [PubMed: 21509604]
7. Pilz S, Tomaschitz A, Ritz E, Pieber TR. Vitamin D status and arterial hypertension: a systematic review. *Nat Rev Cardiol*. 2009; 6:621–630. [PubMed: 19687790]
8. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest*. 2002; 110:229–238. [PubMed: 12122115]
9. Zhou C, Lu F, Cao K, Xu D, Goltzman D, Miao D. Calcium-independent and 1,25(OH)2D3-dependent regulation of the renin-angiotensin system in 1alpha-hydroxylase knockout mice. *Kidney Int*. 2008; 74:170–179. [PubMed: 18385669]
10. Chen S, Law CS, Grigsby CL, Olsen K, Hong TT, Zhang Y, et al. Cardiomyocyte-specific deletion of the vitamin d receptor gene results in cardiac hypertrophy. *Circulation*. 2011; 124:1838–1847. [PubMed: 21947295]

11. Chen S, Law CS, Gardner DG. Vitamin D-dependent suppression of endothelin-induced vascular smooth muscle cell proliferation through inhibition of CDK2 activity. *J Steroid Biochem Mol Biol.* 2010; 118:135–141. [PubMed: 19961935]
12. Chen S, Law CS, Grigsby CL, Olsen K, Gardner DG. A role for the cell cycle phosphatase Cdc25a in vitamin D-dependent inhibition of adult rat vascular smooth muscle cell proliferation. *J Steroid Biochem Mol Biol.* 2010; 122:326–332. [PubMed: 20813185]
13. Chen S, Ni XP, Humphreys MH, Gardner DG. 1,25 dihydroxyvitamin d amplifies type a natriuretic peptide receptor expression and activity in target cells. *J Am Soc Nephrol.* 2005; 16:329–339. [PubMed: 15590756]
14. Chen S, Olsen K, Grigsby C, Gardner DG. Vitamin D activates type A natriuretic peptide receptor gene transcription in inner medullary collecting duct cells. *Kidney Int.* 2007; 72:300–306. [PubMed: 17440494]
15. Dwivedi RS, Herman JG, McCaffrey TA, Raj DS. Beyond genetics: epigenetic code in chronic kidney disease. *Kidney Int.* 2011; 79:23–32. [PubMed: 20881938]
16. Fornage M. Unraveling hypertension: epigenomics comes of age. *Pharmacogenomics.* 2007; 8:125–128. [PubMed: 17286533]
17. Alikhani-Koopaei R, Fouladkou F, Frey FJ, Frey BM. Epigenetic regulation of 11 beta-hydroxysteroid dehydrogenase type 2 expression. *J Clin Invest.* 2004; 114:1146–1157. [PubMed: 15489962]
18. Lovati E, Ferrari P, Dick B, Jostarndt K, Frey BM, Frey FJ, et al. Molecular basis of human salt sensitivity: the role of the 11beta-hydroxysteroid dehydrogenase type 2. *J Clin Endocrinol Metab.* 1999; 84:3745–3749. [PubMed: 10523024]
19. Friso S, Pizzolo F, Choi SW, Guarini P, Castagna A, Ravagnani V, et al. Epigenetic control of 11 beta-hydroxysteroid dehydrogenase 2 gene promoter is related to human hypertension. *Atherosclerosis.* 2008; 199:323–327. [PubMed: 18178212]
20. Wilson FH, Disse-Nicodeme S, Choate KA, Ishikawa K, Nelson-Williams C, Desitter I, et al. Human hypertension caused by mutations in WNK kinases. *Science.* 2001; 293:1107–1112. [PubMed: 11498583]
21. Mu S, Shimosawa T, Ogura S, Wang H, Uetake Y, Kawakami-Mori F, et al. Epigenetic modulation of the renal beta-adrenergic-WNK4 pathway in salt-sensitive hypertension. *Nat Med.* 2011; 17:573–580. [PubMed: 21499270]
22. Kaikkonen MU, Lam MT, Glass CK. Non-coding RNAs as regulators of gene expression and epigenetics. *Cardiovasc Res.* 2011; 90:430–40. [PubMed: 21558279]
23. Albinsson S, Skoura A, Yu J, DiLorenzo A, Fernandez-Hernando C, Offermanns S, et al. Smooth muscle miRNAs are critical for post-natal regulation of blood pressure and vascular function. *PLoS One.* 2011; 6:e18869. 1-11. [PubMed: 21526127]
24. Boettger T, Beetz N, Kostin S, Schneider J, Kruger M, Hein L, et al. Acquisition of the contractile phenotype by murine arterial smooth muscle cells depends on the Mir143/145 gene cluster. *J Clin Invest.* 2009; 119:2634–2647. [PubMed: 19690389]
25. Xin M, Small EM, Sutherland LB, Qi X, McAnally J, Plato CF, et al. MicroRNAs miR-143 and miR-145 modulate cytoskeletal dynamics and responsiveness of smooth muscle cells to injury. *Genes Dev.* 2009; 23:2166–2178. [PubMed: 19720868]
26. Sequeira-Lopez ML, Weatherford ET, Borges GR, Monteagudo MC, Pentz ES, Harfe BD, et al. The microRNA-processing enzyme dicer maintains juxtaglomerular cells. *J Am Soc Nephrol.* 2010; 21:460–467. [PubMed: 20056748]
27. Levy D, DeStefano AL, Larson MG, O'Donnell CJ, Lifton RP, Gavvas H, et al. Evidence for a gene influencing blood pressure on chromosome 17. Genome scan linkage results for longitudinal blood pressure phenotypes in subjects from the framingham heart study. *Hypertension.* 2000; 36:477–483. [PubMed: 11040222]
28. Tobin MD, Raleigh SM, Newhouse S, Braund P, Bodycote C, Ogleby J, et al. Association of WNK1 gene polymorphisms and haplotypes with ambulatory blood pressure in the general population. *Circulation.* 2005; 112:3423–3429. [PubMed: 16301342]

29. Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, Chasman DI, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature*. 2011; 478:103–109. [PubMed: 21909115]
30. Kato N, Takeuchi F, Tabara Y, Kelly TN, Go MJ, Sim X, et al. Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east Asians. *Nat Genet*. 2011; 43:531–538. [PubMed: 21572416]
31. Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, et al. Genome-wide association study of blood pressure and hypertension. *Nat Genet*. 2009; 41:677–687. [PubMed: 19430479]
32. Newton-Cheh C, Larson MG, Vasan RS, Levy D, Bloch KD, Surti A, et al. Association of common variants in NPPA and NPPB with circulating natriuretic peptides and blood pressure. *Nat Genet*. 2009; 41:348–353. [PubMed: 19219041]
33. Ji W, Foo JN, O'Roak BJ, Zhao H, Larson MG, Simon DB, et al. Rare independent mutations in renal salt handling genes contribute to blood pressure variation. *Nat Genet*. 2008; 40:592–599. [PubMed: 18391953]
34. Rao F, Wen G, Gayen JR, Das M, Vaingankar SM, Rana BK, et al. Catecholamine release-inhibitory peptide catestatin (chromogranin A(352-372)): naturally occurring amino acid variant Gly364Ser causes profound changes in human autonomic activity and alters risk for hypertension. *Circulation*. 2007; 115:2271–2281. [PubMed: 17438154]
35. Pravenec M, Kurtz TW. Recent advances in genetics of the spontaneously hypertensive rat. *Curr Hypertens Rep*. 2010; 12:5–9. [PubMed: 20425152]
36. Deng AY. Genetic basis of polygenic hypertension. *Hum Mol Genet*. 2007; 16:R195–R202. [PubMed: 17911162]
37. Chauvet C, Ménard A, Xiao C, Aguila B, Blain M, Roy J, et al. Novel genes as primary triggers for polygenic hypertension. *J Hypertens*. 2011 in press.
38. Chauvet C, Charron S, Menard A, Xiao C, Roy J, Deng AY. Submegabase resolution of epistatically interacting quantitative trait loci for blood pressure applicable for essential hypertension. *J Hypertens*. 2008; 26:893–901. [PubMed: 18398331]
39. Duong C, Charron S, Deng Y, Xiao C, Menard A, Roy J, et al. Individual QTLs controlling quantitative variation in blood pressure inherited in a Mendelian mode. *Heredity*. 2007; 98:165–171. [PubMed: 17119551]

Figure 1.

This diagram depicts those different causal factors with ageing trigger vessel remodeling and permanently increased vascular tone leading to EH through unknown BP signaling molecules. ET: endothelin, ETA: ET receptor A, NO: nitric oxide