Published in final edited form as:
Adv Exp Med Biol. 2012 ; 758: 1–5. doi:10.1007/978-94-007-4584-1_1.

The Role of Hypoxia-Inducible Factors in Oxygen Sensing by the Carotid Body

Gregg L. Semenza and
Vascular Program, Institute for Cell Engineering; Departments of Pediatrics, Medicine, Oncology, and Radiation, Oncology; and McKusick-Nathans Institute of Genetic Medicine, The Johns Hopkins University, School of Medicine, Broadway Research Building, Suite 671, 733 N. Broadway, Baltimore, MD 21205, USA

Nanduri R. Prabhakar
Institute for Integrative Physiology and Center for Systems Biology of O2 Sensing, Biological Sciences Division, University of Chicago, 5841 S Maryland Ave, MC 5068 Room N-711, Chicago, IL 60637, USA

Gregg L. Semenza: gsemenza@jhmi.edu; Nanduri R. Prabhakar: nprabhak@medicine.bsd.uchicago.edu

Abstract

Chronic intermittent hypoxia (IH) associated with sleep-disordered breathing is an important cause of hypertension, which results from carotid body-mediated activation of the sympathetic nervous system. IH triggers increased levels of reactive oxygen species (ROS) in the carotid body, which induce increased synthesis and stability of hypoxia-inducible factor 1α (HIF-1α) and calpain-dependent degradation of HIF-2α. HIF-1 activates transcription of the *Nox2* gene, encoding NADPH oxidase 2, which generates superoxide. Loss of HIF-2 activity leads to decreased transcription of the *Sod2* gene, encoding manganese superoxide dismutase, which converts superoxide to hydrogen peroxide. Thus, IH disrupts the balance between HIF-1-dependent pro-oxidant and HIF-2-dependent anti-oxidant activities, and this loss of redox homeostasis underlies the pathogenesis of autonomic morbidities associated with IH.

Keywords

Cardiorespiratory homeostasis; Obstructive sleep apnea; Oxidative stress; Oxygen homeostasis

Hypoxia-inducible factor 1 (HIF-1) is a transcriptional activator that functions as a master regulator of oxygen homeostasis in all metazoan species (Semenza 2009, 2010). HIF-1 is a heterodimeric protein that is composed of an O_2-regulated HIF-1α subunit and a constitutively expressed HIF-1β subunit (Wang and Semenza 1995; Wang et al. 1995). Proline and asparagine residues in HIF-1α are hydroxylated under aerobic conditions (Kaelin and Ratcliffe 2008), which provides a mechanism for the decreased HIF-1α protein stability and transactivation function that are observed in well-oxygenated, as compared to hypoxic cells (Jiang et al. 1997). Database searches for homologs of HIF-1α led to the discovery of HIF-2α (Ema et al. 1997; Flamme et al. 1997; Hogenesch et al. 1997; Tian et al. 1997), which is also subject to O_2-dependent regulation and heterodimerization with HIF-1β (Wiesener et al. 1998). Whereas HIF-1α is expressed by most nucleated cells of all

Correspondence to: Gregg L. Semenza, gsemenza@jhmi.edu.

metazoan species, HIF-2α is present only in the vertebrate lineage and is only expressed in a restricted number of cell types (Loenarz et al. 2011).

Homozygosity for a null (knockout) allele at the *Hif1a* locus encoding HIF-1α results in embryonic lethality at midgestation with defects in erythrocytosis, vascularization, and cardiogenesis (Iyer et al. 1998; Ryan et al. 1998; Yoon et al. 2006), demonstrating that all three components of the circulatory system are dependent upon HIF-1 for normal development. Mice that are heterozygous for the knockout allele develop normally but have impaired responses to hypoxic and ischemic stimuli (Yu et al. 1999; Shimoda et al. 2001, 2006; Cai et al. 2003, 2008; Li et al. 2006; Bosch-Marce et al. 2007; Whitman et al. 2008; Feinman et al. 2010; Zhang et al. 2010; Kannan et al. 2011; Keswani et al. 2011)

Perhaps the most remarkable phenotype of $Hif1a^{+/-}$ mice was the demonstration that the carotid bodies (CBs) of these mice do not sense/respond to hypoxia, despite the fact that they are histologically normal, including glomus cell morphometry, and respond appropriately to other stimuli such as hypercarbia and cyanide (Kline et al. 2002; Peng et al. 2006). In contrast to the failure of the CBs from these mice to sense hypoxia, $Hif1a^{+/-}$ mice manifest normal ventilatory responses to a hypoxic challenge, indicating that other chemosensors compensate for the loss of CB function *in vivo*. However, hypoxic ventilatory acclimatization responses are defective in $Hif1a^{+/-}$ mice, suggesting that this is a CB-specific function (Kline et al. 2002; Peng et al. 2006).

The CB is also known to sense and respond to intermittent hypoxia (IH) (Prabhakar et al. 2005). Patients with sleep-disordered breathing (also known as sleep apnea) are subjected to chronic IH, which leads to increased sympathetic nerve activity, hypertension, and its sequelae (Somers et al. 1995; Nieto et al. 2000; Peppard et al. 2000; Shahar et al. 2001). Exposure of rodents to IH for several weeks results in activation of the sympathetic nervous system, leading to elevated plasma catecholamine levels and systemic hypertension (Fletcher et al. 1992; Bao et al. 1997; Lesske et al. 1997; Kumar et al. 2006; Dick et al. 2007; Prabhakar et al. 2007a). Remarkably, $Hif1a^{+/-}$ mice are completely protected from the elevation of blood pressure and plasma catecholamines that are observed in wild type mice littermates after 10 days of IH (consisting of 15 s of hypoxia, followed by 5 min of normoxia, nine episodes per hour for 8 h per day) (Peng et al. 2006).

IH results in the generation of reactive oxygen species (ROS) in the CB, as reflected in the levels of thiobarbituric acid-reactive substances, and treatment of wild-type mice with the free radical scavenger MnTMPyP blocks the development of IH-induced hypertension (Prabhakar et al. 2007b). The induction of HIF-1α that is observed in the brains of mice exposed to IH is also blocked by radical scavengers, indicating that increased ROS levels are required for HIF-1 activation in response to IH (Peng et al. 2006). When $Hif1a^{+/-}$ mice are subjected to IH, increased levels of ROS are not detected in the brain, indicating that HIF-1 activation is required for increased ROS in response to IH. These results suggested a feed-forward mechanism, in which the increased generation of ROS induces HIF-1 activity, which in turn leads to increased ROS generation. Studies in PC12 rat pheochromocytoma cells revealed a complex signal transduction pathway by which IH stimulates HIF-1α protein synthesis, stabilization, and transactivation involving: NADPH oxidase; Ca^{2+} signaling via phospholipase Cγ, protein kinase C, and CaM kinase; prolyl hydroxylases; and mTOR (Yuan et al. 2005, 2008). A critical role for NADPH oxidase in mediating IH-induced oxidative damage has also been demonstrated in mice (Zhan et al. 2005; Peng et al. 2009; Khan et al. 2011).

Recent studies indicate that the transactivation of the *Nox2* gene, which encodes NADPH oxidase 2, is critical for the increase in ROS associated with chronic IH (Yuan et al. 2011).

Induction of Nox2 mRNA expression was demonstrated in the CB, cerebral cortex, and brainstem, but not in the cerebellum, of wild-type mice, whereas Nox2 mRNA expression was not induced in any of these tissues in *Hif1a*$^{+/-}$ mice (Yuan et al. 2011). Analysis of the cerebellar tissues from wild-type mice exposed to IH revealed no activation (by phosphorylation) of phospholipase Cγ or mTOR and no induction of HIF-1α protein, indicating that the IH-induced feed-forward mechanism, which is active in CB, cortex, and brainstem, is not active in the cerebellum (Yuan et al. 2011). Further studies are required to determine whether the response to IH is localized to specific regions of the cortex and brainstem.

Whereas HIF-1α is expressed at low levels in the CB under normoxic conditions and is dramatically induced by IH, HIF-2α is expressed at high levels in the CB under normoxic condition and its levels are dramatically decreased in response to IH, due to calpain-dependent protein degradation (Nanduri et al. 2009). The decreased HIF-2α levels were associated with decreased expression of the *Sod2* gene, which encodes superoxide dismutase 2, the enzyme that converts mitochondrial superoxide to hydrogen peroxide. Remarkably, systemic treatment of IH-exposed rats with the calpain inhibitor ALLM blocked HIF-2α degradation, restored SOD2 activity, and prevented oxidative stress and hypertension (Nanduri et al. 2009).

Based on the striking results obtained from *Hif1a*$^{+/-}$ mice, CBs from *Hif2a*$^{+/-}$ mice were analyzed. Whereas CBs from *Hif1a*$^{+/-}$ mice did not respond to hypoxia (Kline et al. 2002), CBs from *Hif2a*$^{+/-}$ mice manifested augmented sinus nerve activity in response to hypoxia, whereas responses to hypercarbia or cyanide were normal, as was CB histology including glomus cell morphometry (Peng et al. 2011). *Hif2a*$^{+/-}$ mice manifested an augmented hypoxic ventilatory response and instability of breathing. *Hif2a*$^{+/-}$ mice were also found to be hypertensive with elevated plasma norepinephrine levels even under normoxic conditions (Peng et al. 2011). Expression of Sod2 mRNA was significantly reduced in the CB of *Hif2a*$^{+/-}$ mice. Remarkably, treatment of *Hif2a*$^{+/-}$ mice with the superoxide scavenger MnTMPyP normalized the CB response to hypoxia, normalized the hypoxic ventilatory response and blood pressure, and corrected the abnormalities of breathing (Peng et al. 2011). Taken together, the increased oxidative stress associated with IH (as well as all of its downstream sequelae) results both from increased HIF-1 → Nox2 signaling and decreased HIF-2 → Sod2 signaling in response to IH. Thus, an imbalance between pro-oxidant and anti-oxidant activities underlies the pathogenesis of autonomic morbidities associated with IH. More broadly, these results suggest that the functional antagonism between HIF-1 and HIF-2 may play a fundamental role in redox regulation and the maintenance of cardiorespiratory homeostasis.

Acknowledgments

Research from authors' laboratories was supported by contracts/grants HHS-N268201000032C, PO1-HL65608, P20-GM78494, RO1-HL55338, U54-CA143868 (G.L.S.) and HL-76537, HL-90554, and HL-86493 (N.R.P) from the National Institutes of Health.

References

Bao G, Metreveli N, Li R, Taylor A, Fletcher EC. Blood pressure response to chronic episodic hypoxia: role of the sympathetic nervous system. J Appl Physiol. 1997; 83:95–101. [PubMed: 9216950]

Bosch-Marcé M, Okuyama H, Wesley JB, Sarkar K, Kimura H, Liu YV, Zhang H, Strazza M, Rey S, Savino L, Zhou YF, McDonald KR, Na Y, Vandiver S, Rabi A, Shaked Y, Kerbel R, LaVallee T, Semenza GL. Effects of aging and HIF-1 activity on angiogenic cell mobilization and recovery of perfusion following limb ischemia. Circ Res. 2007; 101:1310–1318. [PubMed: 17932327]

Cai Z, Manalo DJ, Wei G, Rodriguez ER, Fox-Talbot K, Lu H, Zweier JL, Semenza GL. Hearts from rodents exposed to intermittent hypoxia or erythropoietin are protected against ischemia-reperfusion injury. Circulation. 2003; 108:79–85. [PubMed: 12796124]

Cai Z, Zhong H, Bosch-Marce M, Fox-Talbot K, Wang L, Wei C, Trush MA, Semenza GL. Complete loss of ischaemic preconditioning-induced cardioprotection in mice with partial deficiency of HIF-1α. Cardiovasc Res. 2008; 77:463–470. [PubMed: 18006459]

Dick TE, Hsieh YH, Wang N, Prabhakar NR. Acute intermittent hypoxia increases both phrenic and sympathetic nerve activities in the rat. Exp Physiol. 2007; 92:87–97. [PubMed: 17138622]

Ema M, Taya S, Yokotani N, Sogawa K, Matsuda Y, Fujii-Kuriyama Y. A novel bHLH-PAS factor with close sequence similarity to hypoxia-inducible factor 1α regulates the VEGF expression and is potentially involved in lung and vascular development. Proc Natl Acad Sci U S A. 1997; 94:4273–4278. [PubMed: 9113979]

Feinman R, Deitch EA, Watkins AC, Abungu B, Colorado I, Kannan KB, Sheth S, Caputo FJ, Lu Q, Ramanathan M, Attan S, Badami CJ, Doucet D, Barlos D, Bosch-Marcé M, Semenza GL, Xu DZ. HIF-1 mediates pathogenic inflammatory responses to intestinal ischemia reperfusion injury. Am J Physiol Gastrointest Liver Physiol. 2010; 299:G833–G843. [PubMed: 20689059]

Flamme I, Fröhlich T, von Reutern M, Kappel A, Damert A, Risau W. HRF, a putative basic helix-loop-helix-PAS-domain transcription factor is closely related to hypoxia-inducible factor-1α and developmentally expressed in blood vessels. Mech Dev. 1997; 63:51–60. [PubMed: 9178256]

Fletcher EC, Lesske J, Qian W, Miller CC 3rd, Unger T. Repetitive, episodic hypoxia causes diurnal elevation of blood pressure in rats. Hypertension. 1992; 19:555–561. [PubMed: 1592450]

Hogenesch JB, Chan WK, Jackiw VH, Brown RC, Gu YZ, Pray-Grant M, Perdew GH, Brad field CA. Characterization of a subset of the basic-helix-loop-helix-PAS superfamily that interacts with components of the dioxin signaling pathway. J Biol Chem. 1997; 272:8581–8593. [PubMed: 9079689]

Iyer NV, Kotch LE, Agani F, Leung SW, Laughner E, Wenger RH, Gassmann M, Gearhart JD, Lawler AM, Yu AY, Semenza GL. Cellular and developmental control of O_2 homeostasis by hypoxia-inducible factor 1α. Genes Dev. 1998; 12:149–162. [PubMed: 9436976]

Jiang BH, Zheng JZ, Leung SW, Roe R, Semenza GL. Transactivation and inhibitory domains of hypoxia-inducible factor 1α. Modulation of transcriptional activity by oxygen tension. J Biol Chem. 1997; 272:19253–19260. [PubMed: 9235919]

Kaelin WG Jr, Ratcliffe PJ. Oxygen sensing by metazoans: the central role of the HIF hydroxylase pathway. Mol Cell. 2008; 30:393–402. [PubMed: 18498744]

Kannan KB, Colorado I, Reino D, Palange D, Lu Q, Qin X, Watkins A, Caputo FJ, Semenza GL, Deitch EA, Feinman R. Hypoxia-inducible factor plays a gut-injurious role in intestinal ischemia reperfusion injury. Am J Physiol Gastrointest Liver Physiol. 2011; 300:G853–G861. [PubMed: 21183660]

Keswani SC, Bosch-Marcé M, Reed N, Fischer A, Semenza GL, Hoke A. Nitric oxide prevents axonal degeneration by inducing HIF-1-dependent expression of erythropoietin. Proc Natl Acad Sci U S A. 2011; 108:4986–4990. [PubMed: 21383158]

Khan SA, Nanduri J, Yuan G, Kinsman B, Kumar GK, Joseph J, Kalyanaraman B, Prabhakar NR. NADPH oxidase 2 mediates intermittent hypoxia-induced mitochondrial complex I inhibition: relevance to blood pressure changes in rats. Antioxid Redox Signal. 2011; 14:533–542. [PubMed: 20618070]

Kline DD, Peng Y, Manalo DJ, Semenza GL, Prabhakar NR. Defective carotid body function and impaired ventilatory responses to chronic hypoxia in mice partially deficient for hypoxia-inducible factor 1α. Proc Natl Acad Sci U S A. 2002; 99:821–826. [PubMed: 11792862]

Kumar GK, Rai V, Sharma SD, Ramakrishnan DP, Peng YJ, Souvannakitti D, Prabhakar NR. Chronic intermittent hypoxia induces hypoxia-evoked catecholamine efflux in adult rat adrenal medulla via oxidative stress. J Physiol. 2006; 575:229–239. [PubMed: 16777938]

Lesske J, Fletcher EC, Bao G, Unger T. Hypertension caused by chronic intermittent hypoxia–influence of chemoreceptors and sympathetic nervous system. J Hypertens. 1997; 12:1593–1603. [PubMed: 9488210]

Li J, Bosch-Marcé M, Nanayakkara A, Savransky V, Fried SK, Semenza GL, Polotsky VY. Altered metabolic responses to intermittent hypoxia in mice with partial deficiency of hypoxia-inducible factor 1α. Physiol Genomics. 2006; 25:450–457. [PubMed: 16507783]

Loenarz C, Coleman ML, Boleininger A, Schierwater B, Holland PW, Ratcliffe PJ, Schofield CJ. The hypoxia-inducible transcription factor pathway regulates oxygen sensing in the simplest animal, Trichoplax adhaerens. EMBO Rep. 2011; 12:63–70. [PubMed: 21109780]

Nanduri J, Wang N, Yuan G, Khan SA, Souvannakitti D, Peng YJ, Kumar GK, Garcia JA, Prabhakar NR. Intermittent hypoxia degrades HIF-2α via calpains resulting in oxidative stress: implications for recurrent apnea-induced morbidities. Proc Natl Acad Sci U S A. 2009; 106:1199–1204. [PubMed: 19147445]

Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG, Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study, Sleep Heart Health Study. JAMA. 2000; 283:1829–1836. [PubMed: 10770144]

Peng Y, Yuan G, Ramakrishnan D, Sharma SD, Bosch-Marcé M, Kumar GK, Semenza GL, Prabhakar NR. Heterozygous HIF-1α deficiency impairs carotid body-mediated systemic responses and reactive oxygen species generation in mice exposed to intermittent hypoxia. J Physiol. 2006; 577:705–716. [PubMed: 16973705]

Peng YJ, Nanduri J, Yuan G, Wang N, Deneris E, Pendyala S, Natarajan V, Kumar GK, Prabhakar NR. NADPH oxidase is required for the sensory plasticity of the carotid body by chronic intermittent hypoxia. J Neurosci. 2009; 29:4903–4910. [PubMed: 19369559]

Peng Y, Nanduri J, Khan SA, Yuan G, Wang N, Kinsman B, Vaddi DR, Kumar GK, Garcia JA, Semenza GL, Prabhakar NR. Hypoxia-inducible factor 2α (HIF-2α) heterozygous-null mice exhibit exaggerated carotid body sensitivity to hypoxia, breathing instability, and hypertension. Proc Natl Acad Sci U S A. 2011; 108:3065–3070. [PubMed: 21288809]

Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep disordered breathing and hypertension. N Engl J Med. 2000; 342:1378–1384. [PubMed: 10805822]

Prabhakar NR, Peng YJ, Jacono FJ, Kumar GK, Dick TE. Cardiovascular alterations by chronic intermittent hypoxia: importance of carotid body chemore flexes. Clin Exp Pharmacol Physiol. 2005; 32:447–449. [PubMed: 15854156]

Prabhakar NR, Dick TE, Nanduri J, Kumar GK. Systemic, cellular and molecular analysis of chemoreflex-mediated sympathoexcitation by chronic intermittent hypoxia. Exp Physiol. 2007a; 92:39–44. [PubMed: 17124274]

Prabhakar NR, Kumar GK, Nanduri J, Semenza GL. ROS signaling in systemic and cellular responses to chronic intermittent hypoxia. Antioxid Redox Signal. 2007b; 9:1397–1403. [PubMed: 17627465]

Ryan HE, Lo J, Johnson RS. HIF-1α is required for solid tumor formation and embryonic vascularization. EMBO J. 1998; 17:3005–3015. [PubMed: 9606183]

Semenza GL. Regulation of oxygen homeostasis by hypoxia-inducible factor 1. Physiology (Bethesda). 2009; 24:97–106. [PubMed: 19364912]

Semenza GL. Oxygen homeostasis. Wiley Interdiscip RevSyst Bio Med. 2010; 2:336–361.

Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Nieto J, O'Connor GT, Boland LL, Schwartz JE, Samet JM. Sleep-disordered breathing and cardiovascular disease. Am J Respir Crit Care Med. 2001; 163:19–25. [PubMed: 11208620]

Shimoda LA, Manalo DJ, Sham JSK, Semenza GL, Sylvester JT. Partial HIF-1α deficiency impairs pulmonary arterial myocyte electrophysiological responses to chronic hypoxia. Am J Physiol. 2001; 281:L202–L208.

Shimoda LA, Fallon M, Pisarcik S, Wang J, Semenza GL. HIF-1 regulates hypoxic induction of NHE1 expression and alkalinization of intracellular pH in pulmonary arterial myocytes. Am J Physiol. 2006; 291:941–949.

Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest. 1995; 96:1897–1904. [PubMed: 7560081]

Tian H, McKnight SL, Russell DW. Endothelial PAS domain protein 1 (EPAS1), a transcription factor selectively expressed in endothelial cells. Genes Dev. 1997; 11:72–82. [PubMed: 9000051]

Wang GL, Semenza GL. Purification and characterization of hypoxia-inducible factor 1. J Biol Chem. 1995; 270:1230–1237. [PubMed: 7836384]

Wang GL, Jiang BH, Rue EA, Semenza GL. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O_2 tension. Proc Natl Acad Sci U S A. 1995; 92:5510–5514. [PubMed: 7539918]

Whitman EM, Pisarcik S, Luke T, Fallon M, Wang J, Sylvester JT, Semenza GL, Shimoda LA. Endothelin-1 mediates hypoxia-induced inhibition of voltage-gated K^+ channel expression in pulmonary arterial myocytes. Am J Physiol. 2008; 294:309–310.

Wiesener MS, Turley H, Allen WE, Willam C, Eckardt KU, Talks KL, Wood SM, Gatter KC, Harris AL, Pugh CW, Ratcliffe PJ, Maxwell PH. Induction of endothelial PAS domain protein-1 by hypoxia: characterization and comparison with hypoxia-inducible factor 1α. Blood. 1998; 92:2260–2268. [PubMed: 9746763]

Yoon D, Pastore YD, Divoky V, Liu E, Mlodnicka AE, Rainey K, Ponka P, Semenza GL, Schumacher A, Prchal JT. HIF-1α deficiency results in dysregulated EPO signaling and iron homeostasis in mouse development. J Biol Chem. 2006; 281:25703–25711. [PubMed: 16787915]

Yu AY, Shimoda LA, Iyer NV, Huso DL, Sun X, McWilliams R, Beaty T, Sham JSK, Wiener CM, Sylvester JT, Semenza GL. Impaired physiological responses to chronic hypoxia in mice partially deficient for hypoxia-inducible factor 1*α*. J Clin Invest. 1999; 103:691–696. [PubMed: 10074486]

Yuan G, Nanduri J, Bhasker RC, Semenza GL, Prabhakar NR. Ca^{2+}/calmodulin kinase-dependent activation of hypoxia-inducible factor 1 transcriptional activity in cells subjected to intermittent hypoxia. J Biol Chem. 2005; 280:4321–4328. [PubMed: 15569687]

Yuan G, Nanduri J, Khan S, Semenza GL, Prabhakar NR. Induction of HIF-1α expression by intermittent hypoxia: involvement of NADPH oxidase, Ca^{2+} signaling, prolyl hydroxylases, and mTOR. J Cell Physiol. 2008; 217:674–685. [PubMed: 18651560]

Yuan G, Khan SA, Luo W, Nanduri J, Semenza GL, Prabhakar NR. Hypoxia-inducible factor 1 mediates increased expression of NADPH oxidase-2 in response to intermittent hypoxia. J Cell Physiol. 2011 2011, Feb 1 Epub ahead of print. 10.1002/jcp.22640

Zhan G, Serrano F, Fenik P, Hsu R, Kong L, Pratico D, Klann E, Veasey SC. NADPH oxidase mediates hypersomnolence and brain oxidative injury in a murine model of sleep apnea. Am J Respir Crit Care Med. 2005; 172:921–929. [PubMed: 15994465]

Zhang X, Liu L, Wei X, Tan YS, Tong L, Chang R, Ghanamah MS, Reinblatt M, Marti GP, Harmon JW, Semenza GL. Impaired angiogenesis and mobilization of circulating angiogenic cells in HIF-1α heterozygous-null mice after burn wounding. Wound Repair Regen. 2010; 18:193–201. [PubMed: 20163569]