UNIVERSIDADE FEDERAL DE MINAS GERAIS

INSTITUTO DE CIÊNCIAS BIOLÓGICAS

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS BIOLÓGICAS

FISIOLOGIA E FARMACOLOGIA

EFEITOS DA DELEÇÃO GENÉTICA DOS GENES QUE CODIFICAM A ECA2 E O RECEPTOR MAS NA EVOLUÇÃO DA GRAVIDEZ EM CAMUNDONGOS

RENATA LÚCIA VIEIRA PIMENTEL

BELO HORIZONTE – MINAS GERAIS

DEZEMBRO, 2010

RENATA LÚCIA VIEIRA PIMENTEL

EFEITOS DA DELEÇÃO GENÉTICA DOS GENES QUE CODIFICAM A ECA2 E O RECEPTOR MAS NA EVOLUÇÃO DA GRAVIDEZ EM CAMUNDONGOS

Tese apresentada ao Programa de Pós-Graduação em Fisiologia e Farmacologia do Instituto de Ciências Biológicas da Universidade Federal de Minas Gerais como requisito à obtenção do título de Doutor em Ciências, área de concentração Fisiologia.

ORIENTADOR: PROF. DR. ROBSON AUGUSTO S. SANTOS

BELO HORIZONTE – MINAS GERAIS

DEZEMBRO, 2010

DEDICATÓRIAS

À Deus,
Por me proporcionar tantas oportunidades de crescimento pessoal e profissional, iluminando sempre o meu caminho.

Aos meus pais,
Com simplicidade, honestidade, perseverança e muito amor, me ensinaram que obstáculos sempre aparecerão em nosso caminho, mas que, quando se tem fé, dignidade, persistência e dedicação, nada é impossível. São meus maiores exemplos de vida, meu porto seguro! Se hoje estou chegando a algum lugar, devo isso à abdicação de vocês a muitos prazeres da vida, sempre em prol da educação, união e felicidade dos filhos. Essa conquista é nossa!

Ao meu marido Wendel,
Pessoa fundamental nessa caminhada. Apoiou-me sempre, independentemente das dificuldades ou da distância. Amor, cumplicidade, incentivo, compreensão pelas ausências, paciência pela espera e presença nas alegrias e nos momentos mais difíceis. Meu amor, essa conquista também é sua!

Aos meus irmãos Diogo e Amanda (in memorian),
A família é o alicerce da vida! Nada teria sentido se não pudéssemos contar com a amizade mais verdadeira que existe, aquela de sangue, de um irmão, incondicional, que não se escolhe e que nunca se perde.

Aos meus sogros, cunhados (as), sobrinhos e Letícia, minha afilhada,
Pela presença e torcida para que eu pudesse chegar ao fim dessa caminhada. O incentivo e apoio da família fortalecem a tomada de decisões e alivia o peso dos obstáculos.

AGRADECIMENTOS

Ao meu orientador, Prof. Dr. Robson Santos, meu querido chefe. Agradeço a confiança depositada em mim e a oportunidade dada há tanto tempo atrás, que me possibilitou verdadeiro crescimento pessoal e profissional. Foi um bonito caminho trilhado: no início, apenas uma parceria, mas que se transformou em grande amizade. Foram nove anos de muita história para contar e de muito aprendizado a divulgar. Jamais esquecerei!

Aos professores Dr. Michael Bader e Dr[a].Natália Alenina pela oportunidade de vivenciar a pesquisa em Berlin e acrescentar novos achados em nosso estudo e ao Dr. Mihail Todiras pelo auxílio com os experimentos de Telemetria;

À Prof[a]. Maria José, pela agradável companhia e por estar sempre disponível para ajudar;

À grande amiga Betinha Velloso, pela participação sempre presente neste caminho percorrido, com conversas, discussões sobre a Pré-Eclâmpsia e sobre a vida, amiga nas horas difíceis e também nos momentos de muitas risadas;

À querida amiga Jana, minha quase irmã! Que me ajudou a ser forte quando a saudade apertava em Berlin, que sempre trouxe palavras doces e animadoras, fazendo parecer fácil o que antes era impossível. Amiga para todas as horas, seja nos inúmeros experimentos ou mesmo nos momentos de lazer e de irmos às compras. Dupla infalível!

Ao Wendel, que com carinho e dedicação enriqueceu este trabalho com as diversas análises de Telemetria;

Ao Marcos Melo e Roberto Queiroga pela contribuição com os experimentos de Doppler e Vaso Isolado;

Às amigas Soninha, Aline e Marilene, pelos vários momentos de descontração e conversas agradáveis;

Aos amigos Zezé e Ilma, pela amizade, dedicação e empenho em ajudar, sempre com alegria e palavras cativantes;

Aos professores e colegas do Laboratório de Hipertensão, pelos maravilhosos anos de convivência e amizade;

RESUMO

INTRODUÇÃO: A gravidez é caracterizada por um aumento em muitos dos diferentes componentes do sistema renina-angiotensina (SRA) circulante. Durante a gravidez normal, as gestantes são normotensas graças a uma atividade aumentada do SRA. Este perfil pode ser devido, pelo menos em parte, a uma aumentada atividade do eixo ECA2 / Ang-(1-7) / MAS, o braço vasodilatador do SRA. Entretanto, não se sabe ainda se a deficiência nesse eixo vasodilatador seria uma conseqüência ou um fator contribuinte no desenvolvimento de alterações que ocorrem na gravidez.
OBJETIVO: O objetivo deste trabalho foi avaliar o efeito da deleção genética do receptor MAS ou da ECA2 no comportamento do SRA e nas alterações hemodinâmicas presentes na evolução da gravidez em camundongos.
MATERIAIS E MÉTODOS: Para avaliar diretamente essa possibilidade, alterações fenotípicas induzidas pela deficiência da ECA2 ou do MAS em camundongos C57Bl/6 e FVB/N foram determinadas na gravidez. Para isso utilizamos fêmeas C57Bl/6 ECA2$^{-/-}$, C57Bl/6 MAS $^{-/-}$, FVB/N MAS $^{-/-}$ e fêmeas controles WT, entre 12 e 20 semanas de vida, para acasalamento com machos de mesmo background e modificação genética. A pressão arterial foi mensurada por sistema de telemetria, antes e durante a gravidez, bem como até 3 dias após o parto. A função endotelial foi examinada usando a preparação de vaso isolado. O peso dos fetos e da placenta, bem como as expressões gênica placentária para componentes do SRA e protéica placentária para o receptor de VEGF foram avaliados. Também foi analisada a hemodinâmica da artéria umbilical no 19º dia gestacional, por meio de ultrassonografia, além da função renal e dos níveis circulantes de citocinas.
RESULTADOS: As fêmeas FVB/N KO MAS apresentaram uma elevação tempo-dependente da pressão arterial durante a gestação; tendência a aumentado índice de resistividade das artérias umbilicais; restrição de crescimento fetal; proteinúria; oligúria; aumento de citocinas circulantes e disfunção endotelial, características essas similares a algumas das manifestações clínicas encontradas no desenvolvimento de Pré-Eclâmpsia. Concomitantemente a esse achado, a deficiência do MAS em camundongos no background genético C57Bl/6 provocou, a princípio, níveis pressóricos normais, que se mantiveram até o final da gestação, embora sem a presença de proteinúria. No entanto, ao final da gravidez essas fêmeas apresentaram um pico pressórico, com marcante proteinúria, oligúria, aumento de citocinas circulantes, bem como disfunção endotelial e restrição de crescimento fetal, demonstrando que as conseqüências da deleção do MAS, na gravidez, é background dependente. Ainda em relação ao eixo vasodilatador do SRA, a deleção da ECA2 causou, nas fêmeas, aumentados níveis pressóricos antes da gravidez. Esse fenótipo foi mantido durante todo o período gestacional, associado, ainda, com marcante excreção fracional protéica e restrição de crescimento fetal, caracterizando alguns dos sintomas clínicos verificados no quadro de mulheres que desenvolvem a Pré-Eclâmpsia sobreposta à hipertensão arterial crônica.
CONCLUSÃO: A deleção genética de componentes do eixo vasodilatador do SRA causou ajustes hemodinâmicos alterados durante a gravidez, caracterizados, principalmente, por elevação da pressão arterial no final da gestação e restrição de crescimento fetal em camundongos. Estes dados suportam um importante papel do eixo ECA2 / Ang-(1-7) / MAS no desenvolvimento fetal e no ajuste hemodinâmico durante a gestação, sugerindo que esse eixo possa ser um importante alvo terapêutico para o tratamento de alterações existentes durante o período gestacional.

ABSTRACT

BACKGROUND: Pregnancy is characterized by an increase in many of the different components of the circulating renin-angiotensin system (RAS). During normal gestation, pregnant woman are normotensive because there is an increased activity of RAS. This could be due, at least in part, to the increased activity of the ACE2/Ang-(1-7)/Mas axis, the vasodilator arm of the RAS. However, it is not clear if the deficiency in this vasodilator axis is a consequence or contributing factor in the development of abnormalities in pregnancy.
AIM: The aim of this study was to evaluate the effect of genetic deletion of MAS receptor or ACE2 in the RAS activity and in the hemodynamic changes present in the evolution of pregnancy in mice.
MATERIALS AND METHODS: To directly investigate this possibility the phenotypic alterations induced by ACE2 or MAS deficiency in C57Bl/6 and FVB/N were determined in pregnant mice. Twelve - twenty weeks old C57Bl/6 $ACE2^{-/-}$, C57Bl/6 $MAS^{-/-}$, FVB/N $MAS^{-/-}$, and WT female mice were used for mating with males of similar background and genetic modification. Blood pressure was measured, by telemetry, before, during the pregnancy and until 3 days after delivery. The endothelial function was examined using isolated vessel preparations. The pups and placenta weight were assessed, as well as placental gene expression for RAS components and protein expression for VEGF- receptor. We also analyzed the hemodynamic of umbilical artery, on 19^{th} pregnancy day, by ultrasound, as well as a renal function and a cytokine circulating levels.
RESULTS: The female mice FVB/N MAS KO presented an increased, time-dependent, in the blood pressure levels, during the pregnancy; tendency to increased umbilical arteries resistivity index, fetal growth restriction, proteinuria, oliguria, increase in cytokines and endothelial dysfunction similar to some of the clinical manifestations found in the development of preeclampsia. Concomitantly with this finding, the deficiency in the MAS KO mice, in the genetic background C57Bl/6, resulted in the normal blood pressure levels, in the beginning, which remained until the end of pregnancy, although without the presence of proteinuria. However, in late pregnancy these females showed a pressure peak, with marked proteinuria, oliguria, increased cytokines, endothelial dysfunction, as well as a fetal growth restriction, demonstrating that the consequences of the MAS deletion, in pregnancy, is background dependent. In addition in the vasodilator axis of the RAS, the ACE2 deletion caused, in females, increased blood pressure before pregnancy. This phenotype was kept throughout the gestational period, associated, also, with striking fractional excretion of protein and fetal growth restriction, featuring some of the clinical symptoms observed in the context of women who develop preeclampsia superimposed on the chronic arterial hypertension.
CONCLUSION: The genetic deletion of the RAS-vasodilatatory axis components leads to abnormal hemodynamic adjustment during pregnancy, mainly characterized by elevated blood pressure in late pregnancy and fetal growth restriction in mice. These data support an important role of the ACE2 / Ang-(1-7) / Mas axis in the fetal development and hemodynamic adjustment during pregnancy, suggesting that this axis may be an important therapeutic target for the treatment of existing changes during pregnancy.

"A literatura deve ser realmente o lugar onde podem surgir novas idéias que repensem o mundo." (Salman Rushdie)

REFERÊNCIAS BIBLIOGRÁFICAS

1. REFERÊNCIAS BIBLIOGRÁFICAS

Adamson SL, Lu Y, Whiteley KJ, Holmyard D, Hemberger M, Pfarrer C, Cross JC. Interactions between trophoblast cells and the maternal and fetal circulation in the mouse placenta. **Dev Biol** 250: 358–373, 2002.

Alexander BT, Bennett WA, Khalil RA, Granger JP. Preeclampsia: linking placental ischemia with cardiovascular-renal dysfunction. **News Physiol Sci** 16: 282 – 286, 2001.

Alexander BT. Placental insufficiency leads to development of hypertension in growth-restricted offspring. **Hypertension** 41: 457 – 462, 2003.

Alexander de Groot CJM, Taylor RN. New insights into the etiology of pre-eclampsia. **Ann Med** 25: 243-249, 1993.

Almeida AP, Frábregas BC, Madureira MM, Santos RJ, Campagnole-Santos MJ, Santos RA. Angiotensin-(1-7) potentiates the coronary vasodilatatory effect of bradykinin in the isolated rat heart. **Braz J Med Biol Res** 33: 709 – 13, 2000.

Andreatta-van Leyen S, Romero MF, Khosla MC, Douglas JG. Modulation of phospholipase A2 activity and sodium transport by angiotensin-(1–7). **Kidney Int** 44: 932 - 6, 1993.

Anton L, Merrill DC, Neves LA, Stovall K, Gallagher PE, Diz DI, Moorefield C, Gruver C, Ferrario CM, Brosnihan KB. Activation of local chorionic villi angiotensin II levels but not angiotensin (1-7) in preeclampsia. **Hypertension** 51: 1066 – 1072, 2008.

August P, Mueller FB, Sealy JE, Edersheim TG. Role of renin-angiotensin system in blood pressure regulation in pregnancy. **Lancet** 345: 896 - 897, 1995.

Averill DB, Diz DI. Angiotensin peptides and the baroreflex control of sympathetic outflow: pathways and mechanisms of the medulla oblongata. **Brain Res Bull** 51(2): 119 - 28,1999.

Bader M, Paul M, Fernandez-Alfonso M, Kaling M, Ganten D. A molecular Biology and Biochemistry of the Renin- Angiotensin System. In: **Textbook of Hypertension** Swales JD, ed. Oxford : Blackwell Scientific Publications, 1994.

Benyo DF, Smarason A, Redman CW, Sims C, Conrad KP. Expression of inflamatory cytokines in placentas from women with preeclampsia. **J Clin Invest** 86: 2505 – 2512, 2001.

Bohlender J, Ganten D, Luft FC. Rats transgenic for human renin and human angiotensinogen as a model for gestational hypertension. **J Am Soc Nephrol** 11: 2056 - 2061, 2000.

Bolte AC, Geijn HP, Dekker GA. Pathophysiology of preeclampsia and the role of serotonin. **European Journal of Obstetrics Gynecology and Reproductive Biology** 95: 12 - 21, 2001.

Bardford M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. **Anal Biochem** 72: 248-254, 1976.

Brosnihan KB, Santos RAS, Block CH, Schiavone MT, Welches MT, Welches WR, Khosla MC, Greene LJ, Ferrario CM. Biotransformation of angiotensins in the central nervous system . **Therapeutic Research** 9: 184 - 195,1988.

Brosnihan KB, Li P, Ferrario CM. Angiotensin-(1-7) dilates canine coronary arteries through kinins and nitric oxide. **Hypertension** 27: 523 – 8, 1996.

Brosnihan KB, Neves LAA, Joyner J, Averill DB, Chappell MC, Sarao R, Penninger J, Ferrario CM. Enhanced renal imunocytochemical expression of Ang-(1-7) and ACE2 during pregnancy. **Hypertension** 42 (4), part 2, 749-753, 2003.

Brown, MA, Zammit VC, Mitar DM. Extra cellular fluid volumes in pregnancy–induced hypertension. **J Hypertension** 10: 61-68, 1992.

Brown MA, Wang J, Whitworth JA. The renin-angiotensin-aldosterone system in pre-eclampsia. **Clin Exp Hypertens** 19: 713 – 726, 1997.

Butz GM, Davisson RL. Long-term telemetric measurement of cardiovascular parameters in awake mice: a physiological genomics tool. **Physiol Genomics** 5: 89 – 97, 2001.

Cabral ACV, Diniz SS. O Pré Natal. In: **Obstetrícia** Ed. Imprensa Oficial, Minas Gerais, pp. 17-29, 1998.

Campagnole-Santos MJ, Diz DI, Santos RAS, Khosla MC, Brosnihan KB, Ferrario CM. Cardiovascular effects of angiotensin-(1-7) microinjected into the dorsal medulla of rats. **Am J Physiol** 257: 11234 - 11329, 1989.

Campagnole-Santos MJ, Heringer SB, Batista EN, Khosla MC, Santos RAS. Differential barorreceptor reflex modulation by centrally infused angiotensin peptides. **Am J Physiol** 263 (1): R 89 - 94, 1992.

Caniggia I, Grisaru-Gravnosky S, Kuliszewsky M, Post M, Lye SJ. Inhibition of TGF-beta 3 restores the invasive capability of extravillous trophoblasts in preeclamptic pregnancies. **J Clin Invest** 103(12): 1641-50, 1999.

Carter AM. Animal models of human placentation - a review. **Placenta** 28(Suppl A): 41–47, 2007.

Chaiworapongsa T, Romero R, Kim YM, Kim GJ, Kim MR, Espinoza J, Bujold E, Gonçalves L, Gomez R, Edwin S, Mazor M. Plasma soluble vascular endothelial growth factor receptor-1 concentration is elevated prior to the clinical diagnosis of pre-eclampsia. **J Matern Fetal Neonatal Med** 17: 3 – 18, 2005.

Chappell MC, Iyer SN, Diz DI and Ferrario CM. Metabolism of angiotensin-(1-7) by angiotensin-converting enzyme . **Hypertension** 31: 362 - 367, 1998.

Clapp JF III, Capeless E. Cardiovascular function before, during, and after the first and subsequent pregnancies. **Am J Cardiol** 80: 1469 – 1473, 1997.

Clark SL, Cotton DB, Pivarnik JM, et al. Position change and central hemodynamic profile during normal third-trimester pregnancy and post partum. **Am J Obstet Gynecol** 164: 883 – 887, 1991.

Conrad KP. Animal models of pre-eclampsia: do they exist? **Fetal Med Rev** 2: 67– 88, 1990.

Conrad KP, Benyo DF. Placental cytokines and the pathogenesis of preeclampsia. **Am.J. Reprod Immunol** 37: 240 - 249, 1997.

Corvol P, Michaud A, Soubrier F, Williams TA. Recent advances in knowledge of the structure and function of the angiotensin I converting enzyme. **J Hypertens Suppl** 13: 3 - 10, 1995.

Cox SL, Trendelemburg AU, Starke K. Prejunctional angiotensin receptors involved in facilitation of noradrenaline release in mouse tissues. **Br J Pharmacol** 127(5): 1256 – 62, 1999.

Crackower MA, Sarao R, Oudit GY, Yagil C, Kozieradzki I, Scanga SE, Oliveira-dos-Santos AJ, da Costa J, Zhang L, Pei Y, Scholey J, Ferrario CM, Manoukian AS, Chappell MC, Backx PH, Yagil Y, Penninger JM. Angiotensin-converting enzyme 2 is an essential regulator of heart function. **Nature** 417:822–828, 2002.

Crews JK, Novak J, Granger JP, Khalil RA. Stimulated mechanisms of Ca21 entry into vascular smooth muscle during NO synthesis inhibition in pregnant rats. **Am J Physiol** 276:530 - 538, 1999.

Cunningham FG, Gant NF, Leveno KJ , Gilstrap LC, Hauth JC, Wenstrom KD. Hypertensive disorders in pregnancy . In: **Williams obstetrics**. ed. New York: Mc Graw-Hill. 567 – 618, 2001.

Davisson RL, Hoffmann DS, Butz GM, Aldape G, Schlager G, Merrill DC, Sethi S, Weiss RM, Bates JN. Discovery of a spontaneous genetic mouse model of preeclampsia. **Hypertension** 39: 337 – 342, 2002.

De Gasparo M, Catt KJ, Inagami T, Wright JW, Unger T. International union of pharmacology. XXIII. The angiotensin II receptors. **Pharmacol Rev** 52(3): 415 – 72, 2000.

Dechend R, Viedt C, Muller DN, Ugele B, Brandes RP, Wallukat G, Park JK, Janke J, Barta P, Theuer J, Fiebeler A, Homuth V, Dietz R, Haller H, Kreuzer J, Luft FC. AT1 receptor agonistic antibodies from preeclamptic patients stimulate NADPH oxidase. **Circulation** 107: 1632 – 1639, 2003.

Dechend R, Gratze P, Wallukat G, Shagdarsuren E, Plehm R, Brasen JH, Fiebeler A, Schneider W, Caluwaerts S, Vercruysse L, Pijnenborg R, Luft FC, Muller DN. Agonistic autoantibodies to the AT1 receptor in a transgenic rat model of preeclampsia. **Hypertension** 45: 742 – 746, 2005.

Deddish PA, Marcic B, Jackman HL, Wang HZ, Skidgel RA, Erdos EG. N-domain – specific substrate and C-domain inhibitors of angiotensin converting enzyme . Angiotensin-(1-7) and Keto – ACE. **Hypertension** 31: 912 - 917,1998.

Dellipizzi AM, Hilchey SD, Bell-Quilley CP. Natriuretic action of angiotensin-(1–7). **Br J Pharmacol** 111: 1 - 3, 1994.

Der Sarkissian S, Grobe JL, Yuan L, Narielwala DR, Walter GA, Katovich MJ, Raizada MK. Cardiac overexpression of angiotensin converting enzyme 2 protects the heart from ischemia-induced pathophysiology. **Hypertension** 51(3):712 - 718, 2008.

Díez-Freire C, Vasquez J, Correa MF, Ferrari MF, Yuan L, Silver X, Torres R, Raizada MK. ACE2 gene transfer attenuates hypertension-linked pathophysiological changes in SHR. **Physiol Genomics** 27(1): 12 - 19, 2006.

Dimmeler S, Dernbach E, Zeiher, AM. Phosphorylation of the endothelial nitric oxide synthase at ser-1177 is required for VEGF-induced endothelial cell migration. **FEBS Lett.** 477: 258 – 262, 2000.

Djurovic S, Schjetlein R, Wilsoff F, Haugen G, Husby H, Berg K. Plasma concentration of Lp(a) lipoprotein and TGF-beta 1 are altered in preeclampsia. **Clin Genet** 52: 371 - 376, 1997.

Donoghue M, Hieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R, Breitbart R, Acton S. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin-(1-9). **Circ Res** 87(5): 1 - 9, 2000.

Duvekot JJ, Cheriex EC, Pieters FA, Menheere PP, Peeters LH. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. **Am J Obstet Gynecol** 169: 1382 – 1392, 1993.

Dzau VJ, Pratt RE. Renin angiotensin system: biology, physiology, and pharmacology. In: **The Heart and Cardiovascular System**. New York: Raven Press, 1631 – 1662, 1986.

Dzau VJ, Burt DW, Pratt RE. Molecular biology of the renin angiotensin system. **Am J Physiol** 225: F 563 - F573, 1988.

Eder DJM, M.T. A role for brain angiotensin II in experimental pregnancy-induced hypertension in laboratory rats. **Clin Exp Hyper Preg** 431 – 451, 1988.

Esther CR Jr, Howard TE, Marino EM, Goddard JM, Capecchi MR, Bernstein KE. Mice lacking angiotensin-converting enzyme have low blood pressure, renal pathology, and reduced male fertility. **Lab Invest** 74: 953 - 965,1996.

Faria-Silva R, Duarte FV, Santos RA. Short-term angiotensin(1-7) receptor MAS stimulation improves endothelial function in normotensive rats. **Hypertension** 46: 948 – 52, 2005.

Ferrario CM, Barnes KL, Block CH, Brosnihan KB, Diz DI, Khosla MC and Santos RAS. Pathways of angiotensin formation and function in the brain. **Hypertension** 15 I13 - I19, 1990.

Ferrario CM, Chapell MC, Tallant EA, Brosnihan KB, Diz DI. Counterregulatory actions of angiotensin-(1-7). **Hypertension** 30: 535 – 541, 1997.

Ferrario CM, Chappel MC, Dean RH, Iyer SN. Novel Angiotensin Peptides Regulate Blood Pressure, Endothelial Function, and Natriuresis. **J Am Soc Nephrol** 9:1716 - 1722,1998.

Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI, Gallagher PE. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. **Circulation** 111(20): 2605-10, 2005.

Ferreira AJ, Santos RAS, Almeida AP. Angiotensin-(1-7): Cardioprotetive effect in miocaidical ischemia/reperfusion. **Hypertension** 38: 665 – 668, 2001.

Fraga-Silva RA, Pinheiro SV, Gonçalves AC, Alenina N, Bader M, Santos RA. The antithrombotic effect of angiotensin-(1-7) involves mas-mediated NO release from platelets. **Mol Med** 14(1-2): 28 – 35, 2008.

Fleming I, Fisslthaler B, Dimmeler S, Kemp BE, Busse R. Phosphorylation of Thr(495) regulates Ca(2+)/calmodulin-dependent endothelial nitric oxide synthase activity. **Circ Res** 88: 68 – 75, 2001.

Freeman EJ, Chisolm GM, Ferrario CM, Tallant EA. Angiotensin-(1-7) inhibits vascular smooth muscle cell growth. **Hypertension** 28:104 – 8, 1996.

Funakoshi Y, Ichiki T, Ito K, Takeshita A. Induction of interleukin-6 expression by angiotensin II in rat vascular smooth muscle cells. **Hypertension** 34:118 – 125, 1999.

Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. **Nature** 288: 373 - 376, 1980.

Gadonski G, LaMarca BB, Sullivan E, Bennett W, Chandler D, Granger JP. Hypertension produced by reductions in uterine perfusion in the pregnant rat: role of interleukin 6. **Hypertension** 48: 711 – 716, 2006.

Gallinat S, Busche S, Raizada MK and Sumners C. The angiotensin II type 2 receptor: an enigma with multiple variations. **Am J Physiol Endocrinol Metab** 278: E357 - E374, 2000.

Gant NF, Worley RJ, Everett RB, MacDonald PC. Control of vascular responsiveness during human pregnancy. **Kidney Int** 18(2): 253-8 Review, 1980.

Georgiades P, Ferguson-Smith AC, Burton GJ. Comparative developmental anatomy of the murine and human definitive placentae. **Placenta** 23: 3 - 19, 2002.

Gilbert JS, Babcock SA, Granger JP. Hypertension produced by reduced uterine perfusion in pregnant rats is associated with increased soluble fms-like tyrosine kinase-1 expression. **Hypertension** 50: 1142 – 1147, 2007.

Granger JP, Alexander BT, Llinas MT, Bennett WA, Khalil RA. Pathophysiology of hypertension during preeclampsia linking placental ischemia with endothelial dysfunction. **Hypertension** 38: 718 -722, 2001.

Greer IA, Lyall F, Pereira T, Boswell F, Macara LM. Increased concentrations of cytokines interleukin-6 and interleukin-1 receptor antagonist in plasma of women with preeclampsia: a mechanism for endothelial dysfunction? **Obstet Gynecol** 84: 937 – 940, 1994.

Griendling KK, Murphy TJ, Alexander RW. Molecular biology of the renin-angiotensin system. **Circulation** 87:1816 - 1828, 1993.

Gross V, Tank J, Obst M, Plehm R, Blumer KJ, Diedrich A, Jordan J, Luft FC. Autonomic nervous system and blood pressure regulation in RGS2–deficient mice. **Am J Physiol Regul Integr Comp Physiol** 288: R1134 - R1142, 2005.

Gurley SB, Allred A, Le TH, Griffith R, Mao L, Philip N, Haystead TA, Donoghue M, Breitbart RE, Acton SL, Rockman HA, Coffman TM. Altered blood pressure responses and normal cardiac phenotype in ACE2-null mice. **J Clin Invest** 116(8): 2218 - 25, 2006.

Guzin K, Tomruk S, Tuncay YA et al. The relation of increased uterine artery blood flow resistance and impaired trophoblast invasion in preeclamptic pregnancies. **Arch Gynecol Obstet** 272: 283 – 8, 2005.

Hall DR, Odendaal HJ, Steyn DW, Grové D. Expectant management of early onset, severe pre-eclampsia: maternal outcome. **BJOG** 107(10): 1252 - 7, 2000.

Hall JE. Control of sodium excretion by angiotensin II: intrarenal mechanisms and blood pressure regulation. **Am. J. Physiol** 250: R960 - R972,1986.

Hartner A, Cordasic N, Klanke B, Veelken R, Hilgers KF. Strain differences in the development of hypertension and glomerular lesions induced by deoxycorticosterone acetate salt in mice. **Nephrol Dial Transplant** 18: 1999 – 2004, 2003.

Hertig A, Berkane N, Lefevre G, Toumi K, Marti HP, Capeau J, Uzan S, Rondeau E. Maternal serum sFlt1 concentration is an early and reliable predictive marker of preeclampsia. **Clin Chem** 50: 1702 – 1703, 2004.

Hinojosa-Laborde C, Craig T, Zheng W, Ji H, Haywood JR, Sandberg K. Ovariectomy augments hypertension in aging female Dahl salt-sensitive rats. **Hypertension** 44: 405 - 409, 2004.

Hung TH, Skepper JN, Charnock-Jones DS, Burton GJ. Hypoxiareoxygenation: a potent inducer of apoptotic changes in the human placenta and possible etiological factor in preeclampsia. **Circ Res** 90: 1274 – 1281, 2002.

Iwai M; Horiuchi M. Devil and Angel in the renin-angiotensin system: ACE-angiotensin II-AT1 receptor axis *vs.* ACE2-angiotensin-(1-7)-MAS receptor axis. **Hypertension Res** 32(7): 533 – 536, 2009.

Jauniaux E, Poston L, Burton GJ: Placental-related diseases of pregnancy: Involvement of oxidative stress and implications in human evolution. **Hum Reprod Update** 12**:** 747 – 755, 2006.

Jaramillo, H.N. Liver angiotensinogen synthesis and release during captopril treatment in sodium-depleted rats. **Endocrinology** 120:1384 - 1390, 1987.

Joyner J, Neves LA, Granger JP, Alexander BT, Merrill DC, Chappell MC, Ferrario CM, Davis WP, Brosnihan KB. Temporal-spatial expression of ANG-(1-7) and angiotensin-converting enzyme 2 in the kidney of normal and hypertensive pregnant rats. **Am J Physiol Regul Integr Comp Physiol** 293: 169 - 177, 2007.

Joyner J, Neves LA, Stovall K, Ferrario CM, Brosnihan KB. Angiotensin-(1-7) serves as an aquaretic by increasing water intake and diuresis in association with downregulation of aquaporin-1 during pregnancy in rats. **Am J Physiol Regul Integr Comp Physiol** 294: 1073 – 1080, 2008.

Kaplan NM. Hypertension with pregnancy and the pill. **Clinical Hypertension** ed Williams & Wilkins, 323-344, 1998.

Khalil RA, Crews JK, Novak J, Kassab S, Granger JP. Enhanced vascular reactivity during inhibition of nitric oxide synthesis in pregnant rats. **Hypertension** 31:1065–1069, 1998.

Khan F, Belch JJ, MacLeod M, Mires G. Changes in endothelial function precede the clinical disease in women in whom preeclampsia develops. **Hypertension** 46: 1123 – 1128, 2005.

Koga K, Osuga Y, Yoshino O, Hirota Y, Ruimeng X, Hirata T, Takeda S, Yano T, Tsutsumi O, Taketani Y. Elevated serum soluble vascular endothelial growth factor receptor 1 (sVEGFR-1) levels in women with preeclampsia. **J Clin Endocrinol Metab** 88: 2348 – 51, 2003.

Krege JH, John SW, Langenbach LL, Hodgin JB, Hagaman JR, Bachman ES, Jennette JC, O'Brien DA, Smithies O. Male-female differences in fertility and blood pressure in ACE-deficient mice. **Nature** 375: 146 - 148, 1995.

Laemmli U.K. Cleavage of structural proteins during the assembly of the head of bacteriophage T4. **Nature** 227:680-685, 1970.

LaMarca BD, Ryan MJ, Gilbert JS, Murphy SR, Granger JP. Inflammatory cytokines in the pathophysiology of hypertension during preeclampsia. **Curr Hypertens Rep** 9(6): 480-5, 2007.

Langer, B. Plasma active renin, angiotensin I, and angiotensin II during pregnancy and in preeclampsia. New York: **Obst Gynecol** 196, 196 - 202, 1998.

Lee DL, Sturgis LC, Labazi H, Osborne JB Jr, Fleming C, Pollock JS, Manhiani M, Imig JD, Brands MW. Angiotensin II hypertension is attenuated in interleukin-6 knockout mice. **Am J Physiol Heart Circ Physiol** 290: 935 – 940, 2006.

Lemos VS, Freitas MR, Muller B, Lino YD, Queiroga CE, Côrtes SF. Dioclein, a new nitric oxide and endothelium-dependent vasodilatador flavonoid. **Eur J Pharmacol** 386(1): 41-6, 1999.

Lester JW. Survey of Selected Physiological Properties of Inbred Hypertensive and Hypotensive Mice **(Dissertação de Mestrado)**. Lawrence, Kan: Genetics Program, University of Kansas, 1989.

Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, Schisterman EF, Thadhani R, Sachs BP, Epstein FH, Sibai BM, Sukhatme VP, Karumanchi SA. Circulating angiogenic factors and the risk of preeclampsia. **N Engl J Med** 350: 672 – 683, 2004.

Li H, Meininger CJ, Hawker JR Jr, Haynes TE, Kepka-Lenhart D, Mistry SK, Morris SM Jr, Wu G. Regulatory role of arginase I and II in nitric oxide, polyamine, and proline syntheses in endothelial cells. **Am J Physiol** 280: 75 – 82, 2001.

Lindheimer MD, Davidson JM. Osmoregulation, the secretion of arginine vasopressin and its metabolism during pregnancy. **Eur J Endocrinol** 132:133 - 138, 1995.

Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. **Methods** 25: 402 – 408, 2001.

Lum C, Shesely EG, Potter DL, Beierwaltes WH. Cardiovascular and renal phenotype in mice with one or two renin genes. **Hypertension** 43: 79 – 86, 2004.

Luque M, Martin P, Martell N, Fernandez C, Brosnihan KB, Ferrario CM. Effects of captopril related to increased levels of prostacyclin and angiotensin-(1-7) in essential hypertension. **J Hypertens** 14: 799-805, 1996.

Mabie WC, DiSessa TG, Crocker LG, Sibai BM, Arheart KL. A longitudinal study of cardiac output in normal human pregnancy. **Am J Obstet Gynecol**.170: 849 – 856, 1994.

Machado RD, Ferreira MA, Belo AV, Santos RAS, Andrade S. Vasodilatador effect of angiotensin-(1-7) in mature and sponge-induced neovasculature. **Regul Pept** 107: 105 – 113, 2002.

Many A, Hubel CA, Fisher SJ, Roberts JM, Zhou Y. Invasive cytotrophoblasts manifest evidence of oxidative stress in preeclampsia. **Am J Pathol** 156: 321 – 331, 2000.

Maric C, Sandberg K, Hinojosa-Laborde C. Glomerulosclerosis and tubulointerstitial fibrosis are attenuated with 17beta-estradiol in the aging Dahl salt sensitive rat. **J Am Soc Nephrol** 15: 1546 - 1556, 2004.

Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, Libermann TA, Morgan JP, Sellke FW, Stillman IE, Epstein FH, Sukhatme VP, Karumanchi SA. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. **J Clin Invest** 111: 649 – 658, 2003.

Mckinley MJ, Allen AM, Mathai ML, May C, Mcallen RM, Oldifield BJ, Weisinger RS. Brain angiotensin and body fluid homeostasis. **Jpn J Physiol** 51(3): 281 – 289, 2001.

Melchiorre K, Wormald B, Leslie K, Bhide A, Thilaganathan B. First trimester uterine artery Doppler indices in term and preterm pre-eclampsia. **Ultrasound Obstet Gynecol** 32: 133 – 7, 2008.

Merrill DC, Karoly M, Chen K, Ferrario CM, Brosnihan KB. Angiotensin-(1-7) in normal and preeclamptic pregnancy. **Endocrine** 18: 239 – 245, 2002.

Molnar M, Hertelendy F. NG-Nitro-L-arginine, an inhibitor of nitric oxide synthesis, increases blood pressure in rats and reverses the pregnancy induced refractoriness to vasopressor agents. **Am J Obstet Gynecol** 166:1560 –1567, 1992.

Mu J, Adamson SL. Developmental changes in hemodynamics of uterine artery, utero- and umbilicoplacental, and vitelline circulations in mouse throughout gestation. Am J **Physiol Heart Circ Physiol** 291: 1421 – 1428, 2006.

Nakamura N, Soubrier F, Menard J, Panthier J-J, Rougeon F, Corvol P. Nonproportional changes in plasma renin concentration, renal renin content, and rat renin messanger RNA. **Hypertension** 7: 855 - 859, 1985.

Neves L, William A, Averill DB, Ferrario CM, Walkup M, Brosnihan B. Pregnancy enhances the Ang-(1-7) vasodilator response in mesenteric arteries and increases the

renal concentration and urinary excretion of Ang-(1-7). **Endocrinology** 10: 2003 - 2009, 2003.

Nguyen, G. The (pro)rennin receptor: pathophysiological roles in cardiovascular and renal pathology. **Curr Opin Nephrol Hypertens** 16: 129 - 133, 2007.

Noris M, Todeschini M, Cassis P, Pasta F, Cappellini A, Bonazzola S, Macconi D, Maucci R, Porrati F, Benigni A, Picciolo C, Remuzzi G. L-arginine depletion in preeclampsia orients nitric oxide synthase toward oxidant species. **Hypertension** 43: 614 – 622, 2004.

Noris M; Perico N; Remuzzi G. Mechanisms of disease: Pre-eclampsia. **Nat Clin Pract Nephrol** 1(2):98 – 114, 2005.

Oelkers WKH. Effects of estrogens and progestogens on the renin-aldosterone system and blood pressure. **Steroids**. 61:166 - 171, 1996.

Oparil S. Arthur C. Corcoran Memorial Lecture. Hormones and vasoprotection. **Hypertension** 33: 170 - 176, 1999.

Page NM. The endocrinology of preeclampsia. **Clinical Endocrinology 57**: 413 - 423, 2002.

Paula RD, Lima CV, Khosla MC, Santos RAS. Angiotensin-(1-7) potentiates the hypotensive effect of bradykinin in conscious rats. **Hypertension** 26: 1154 – 1159, 1995.

Peracoli MT, Menegon FT, Borges VT, de Araujo Costa RA, Thomazini-Santos IA, Peracoli JC. Platelet aggregation and TGF-beta(1) plasma levels in pregnant women with preeclampsia. **J Reprod Immunol** 79: 79 – 84, 2008.

Phillips IM. Functions of Angiotensin in the Central Nervous System. **Annu Rev Physiol** 49:413 - 433, 1987.

Phippard AF, Horvath JS. Animal models of preeclampsia. In: Rubin, PC., editor. Handbook of Hypertension. **Hypertension in Pregnancy**. Amsterdam: Elsevier; 10: 168 – 185, 1988.

Podymow T, August P. Uptodate on the use of antihypertensive drugs in pregnancy. **Hypertension** 51: 960 – 9, 2008.

Rabelo LA, Xu P, Todiras M, Sampaio WO, Buttgereit J, Bader M, Santos RAS, Alenina N. Ablation of angiotensin-(1-7) receptor MAS in C57/Bl6 mice causes endothelial dysfunction. **J Am Soc Hypertension**, 2(6):418 - 424, 2008.

Redman CW, Sargent IL. Pre-eclampsia, the placenta and the maternal systemic inflammatory response - a review. **Placenta** 24: 21 - 27, 2003.

Roberts JM, Taylor RN, Musci TJ, Rogers GM, Hubel CA, McLaughin MK. Preeclampsia: an endothelial cell disorder. **Am J Obstet Gynecol** 161: 1200 - 1204, 1989.

Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. **Am J Physiol**.256: 1060 -1065, 1989.

Rossant J, Cross JC. Placental development: lessons from mouse mutants. **Nature Reviews Genetics** 2: 538 - 548, 2001.

Saflas AF, Olson DR, Frank AL, Atrash HK, Pokras R. Epidemiology of preeclampsia and eclampsia in the United States. **Am J Obstet Gynecol** 163: 460 - 465, 1990.

Sampaio WO, Nascimento AA, Santos RAS. Systemic and regional hemodynamic effects of angiotensin-(1-7) in rats. **Am J Physiol** 284: 1985 - 1994, 2003.

Santos RAS, Campagnole-Santos MJ. Central and peripheral actions of angiotensin-(1-7). **Brazilian J Med Biol Res** 26:1033 - 1047,1994.

Santos RAS, Simões e Silva AC, Magaldi AJ, Khosla MC, César KR, Passaglio KT, Baracho NCV. Evidence for a physiological role of angiotensin-(1-7) in the control of the hydroelectrolyte balance. **Hypertension** 27: 875 - 884,1996.

Santos RAS, Campagnole-Santos MJ, Andrade SP. Angiotensin-(1-7): an update. **Regulatory Peptides** 91:45 - 62, 2000.

Santos RAS, Fagundes-Moura CR, Simões e Silva AC. Efeitos cardiovasculares e renais do sistema renina-angiotensina. **Rev Br Hipertens** 3: 227 - 236, 2000.

Santos RAS. Interactions between angiotensin-(1-7), kinins and angiotensin II in Kidney and blood vessels. **Hypertension** 38: 660 - 664, 2001.

Santos RA, Simões e Silva AC, Maric C, Silva DM, Machado RP, de Buhr I, Heringer-Walther S, Pinheiro SV, Lopes MT, Bader M, Mendes EP, Lemos VS, Campagnole-Santos MJ, Schultheiss HP, Speth R, Walther T. Angiotensin-(1-7) is an endogenous ligand for the G protein-coupled receptor MAS. **Proc Natl Acad Sci USA** 100: 8258 – 8263, 2003.

Santos RAS, Ferreira AJ, Simões e Silva AC. Recent advances in the angiotensin-converting enyme 2-angiotensin(1-7)-MAS axis. **Exp Physiol** 93(5): 519 - 527, 2008.

Santos SH, Fernandes LR, Mario EG, Ferreira AVM, Porto LCJ, Alvarez-Leite JI, Botion LM, Bader M, Alenina N, Santos RAS. MAS deficiency in FVB/N mice produces marked changes in lipid and glycemic metabolism. **Diabetes**. 57(2): 340 - 7, 2008.

Schiavone MT, Santos RAS, Brosnihan KB, Khosla MC, Ferrario CM. Release of vasopressin from the rat hypothalamo-neurohypophysial system by angiotensin-(1-7) heptapeptide. **Proc Natl Acad Sci,** 4095-4098,1988.

Schindler C, Bramlage P, Kirch W, Ferrario CM. Role of the vasodilator peptide angiotensin-(1-7) in cardiovascular drug therapy. **Vasc Health Risk Manag** 3(1):125 – 37, 2007.

Schlager G, Lester JW, Carrithers JA. Characteristics of the inbred hypertensive mouse strains. **FASEB J** Abstract 3: A1315, 1989.

Shaarawy M, El Meleigy M, Rasheed K. Maternal serum transforming growth factor beta-2 in preeclampsia and eclampsia, a potential biomarker for the assessment of disease severity and fetal outcome. **J Soc Gynecol Invest** 8: 27- 31, 2001.

Shah DM. Role of the renin-angiotensin system in the pathogenesis of preeclampsia. **Am J Physiol Renal Physiol** 288: 614 – 625, 2005.

Sibai BM. Treatment of hypertension in pregnant women. **N Engl J Med** 335: 257-265,1996.

Sibai BM, Dekker G, Kupferminc M. Pre-eclampsia. **Lancet** 365: 785 – 799, 2005.

Sibai BM. Maternal and uteroplacental hemodynamics for the classification and prediction of preeclampsia. **Hypertension** 52(5):805 - 6, 2008.

Sikkema JM, Van Rijn BB, Franx A, Bruinse HW, de Roos R, Stroes ES, van Faassen EE. Placental superoxide is increased in pre-eclampsia. **Placenta** 22(4): 304 - 8, 2001.

Soleymanlou N, Jurisica I, Nevo O, Ietta F, Zhang X, Zamudio S, Post M, Caniggia I: Molecular evidence of placental hypoxia in preeclampsia. **J Clin Endocrinol Metab** 90: 4299 - 4308, 2005.

Tallant EA, Diz DI, Ferrario CM. State-of-the-Art lecture. Antiproliferative actions of angiotensin-(1-7) in vascular smooth muscle. **Hypertension** 34: 950 – 7, 1999.

Takimoto E, Ishida J, Sugiyama F, Horiguchi H, Murakami K, Fukamizu A. Hypertension induced in pregnant mice by placental renin and maternal angiotensinogen. **Science** 274: 995 – 998, 1996.

Taylor RN, Grimwood J, Taylor RS, McMaster MT, Fisher SJ, North RA. Longitudinal serum concentrations of placental growth factor: evidence for abnormal placental angiogenesis in pathologic pregnancies. **Am J Obstet Gynecol** 188: 177 – 182, 2003.

Thadhani R, Ecker JL, Mutter WP, Wolf M, Smirnakis KV, Sukhatme VP, Levine RJ, Karumanchi SA. Insulin resistance and alterations in angiogenesis: additive insults that may lead to preeclampsia. **Hypertension** 43: 988 – 992, 2004.

Theunissen IM, Parer JT. Fluid and electrolytes in pregnancy. **Clin Obstet Gynecol** 37:3-15, 1994.

Thway TM, Shlykov SG, Day MC, Sanborn BM, Gilstrap LC, Xia Y, Kellems RE. Antibodies from preeclamptic patients stimulate increased intracellular Ca2_ mobilization through angiotensin receptor activation. **Circulation** 110: 1612 – 1619, 2004.

Tigerstedt R, Bergman PG. Niere und Kreislauf. **Arch. Physiol** 8: 223 - 71, 1898.

Tipnis SR, Hooper NM, Hyde R, Karran E, Christie G, Turner A. A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. **J Biol Chem** 275(43): 33238 - 43, 2000.

Tsatsaris V, Goffin F, Munaut C, Brichant JF, Pignon MR, Noel A, Schaaps JP, Cabrol D, Frankenne F, Foidart JM. Overexpression of the soluble vascular endothelial growth factor in preeclamptic patients: pathophysiological consequences. **J Clin Endocrinol Metab** 88: 5555 - 63, 2003.

Unger T. The role of the renin-angiotensin system in the development of cardiovascular disease. **Am J Cardiol** 89: 3 – 9, 2002.

Valdes G, Germain AM, Corthorn J, Berrios C, Foradori AC, Ferrario CM, Brosnihan KB. Urinary vasodilator and vasoconstrictor angiotensins during menstrual cycle, pregnancy, and lactation. **Endocrine** 16:117 – 122, 2001.

Valdes G, Kaufmann P, Corthorn J, Erices R, Brosnihan KB, Joyner-Grantham J. Vasodilator factors in the systemic and local adaptations to pregnancy. **Reprod Biol Endocrinol** 7: 79, 2009.

Valensise H, Vasapollo B, Gadgliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. **Hypertension** 52: 1- 8, 2008.

Vázquez ML, Forte WCN, Tedesco JJA. Quantificação das Populações e Subpopulações de Linfócitos em Gestantes com Pré-eclâmpsia. **RBGO** 26(8): 619 – 624, 2004.

Velloso EP, Vieira R, Cabral AC, Kalapothakis E, Santos RA. Reduced plasma levels of angiotensin-(1-7) and renin activity in preeclamptic patients are associated with the angiotensin I- converting enzyme deletion/deletion genotype. **Braz J Med Biol Res** 40: 583 – 590, 2007.

Velloso EP. Avaliação dos sistemas vasoativos: papel dos autoanticorpos na Preeclâmpsia [Tese]. Belo Horizonte (MG): Universidade Federal de Minas Gerais; 2010.

Venkatesha S, Toporsian M, Lam C, Hanai J, Mammoto T, Kim WM, Bdolah Y, Lim KH, Yuan HT, Libermann TA, Stillman IE, Roberts D, D'Amore PA, Epstein FH, Sellke FW, Romero R, Sukhatme VP, Letarte M, Karumanchi A. Soluble endoglin contributes to the pathogenesis of preeclampsia. **Nature Medicine** 12(6): 642 – 649, 2006.

Verlohren S, Niehoff M, Hering L, Geusens N, Herse F, Tintu AN, Plagemann A, LeNoble F, Pijnenborg R, Muller DN, Luft FC, Dudenhausen JW, Gollasch M, Dechend R. Uterine vascular function in a transgenic preeclampsia rat model. **Hypertension** 51(2): 547 – 53, 2008.

Vickers C, Hales P, Kaushik V, Dick L, Gavin J, Tang J e cols. Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase. **J Biol Chem** 277: 14838 - 14843, 2002.

Vince GS, Starkey PM, Austgulen R, Kwiatkowski D, Redman CW. Interleukin-6, tumour necrosis factor and soluble tumour necrosis factor receptors in women with pre-eclampsia. **Br J Obstet Gynaecol** 102: 20 – 25, 1995.

Wallukat G, Homuth V, Fischer T, Lindschau C, Horstkamp B, Jupner A, Baur E, Nissen E, Vetter K, Neichel D, Dudenhausen JW, Haller H, Luft FC. Patients with preeclampsia develop agonistic autoantibodies against the angiotensin AT1 receptor. **J Clin Invest** 103: 945 – 952, 1999.

Walther T, Balschun D, Voigt JP, Fink H, Zuschratter W, Birchmeier C, Ganten D, Bader M. Sustained long term potentiation and anxiety in mice lacking the MAS protooncogene. **The journal of Biological Chemistry** 273:11867-73, 1998.

Walther T, Wessel N, Kang N, Sander A, Tschöpe C, Malberg H, Bader M, Voss A. Altered heart rate and blood pressure variability in mice lacking the MAS protooncogene. **Braz J Med Biol Res** Jan; 33(1):1-9, 2000.

Wilson M, Morganti AA, Zervoudakis I, Letcher RL, Romney BM, Von Oeyon P, Papera S, Sealey JE, Laragh JH. Blood pressure, the renin-aldosterone system and sex steroids throughout normal pregnancy. **Am J Med** 68:97-104, 1980.

Xia Y, Wen H, Bobst S, Day MC, Kellems RE. Maternal autoantibodies from preeclamptic patients activate angiotensin receptors on human trophoblast cells. **J Soc Gynecol Investig** 10: 82 – 93, 2003.

Xiong X, Mayes D, Demianczuk N, Olson DM, Davidge ST, Newburn-Cook C, Saunders LD. Impact of pregnancy-induced hypertension on fetal growth. **Am J Obstet Gynecol** 180:207 - 13, 1999.

Xu P, Costa-Gonçalves A, Todiras M, Rabelo LA, Sampaio WO, Moura MM, Santos SS, Luft FC, Bader M, Gross V, Alenina N, Santos RAS. Endothelial dysfunction and elevated blood pressure in MAS gene-deleted mice. **Hypertension** 51: 574 - 80, 2008.

Yamamoto K, Ohishi M, Katsuya T, Ito N, Ikushima M, Kaibe M, Tatara Y, Shiota A, Sugano S, Takeda S, Rakugi H, Ogihara T. Deletion of angiotensin-converting enzyme 2 accelerates pressure overload-induced cardiac dysfunction by increasing local angiotensin II. **Hypertension** 47, 718 - 726, 2006.

Young D, Waitches G, Birchmeier C, Fasano O, Wigler M. Isolation and characterization of a new cellular oncogene encoding a protein with multiple potential transmembrane domains. **Cell** 45:711 - 19, 1986.

Zhou Y, McMaster M, Woo K, Janatpour M, Perry J, Karpanen T, Alitalo K, Damsky C, Fisher SJ. Vascular endothelial growth factor ligands and receptors that regulate human cytotrophoblast survival are dysregulated in severe preeclampsia and hemolysis, elevated liver enzymes, and low platelets syndrome. **Am J Pathol** 160:1405 – 23, 2002.

Suporte Financeiro: CNPq, CAPES – PROBRAL, INCT Nanobiofar