DEPARTAMENTO DE FARMACOLOGIA
FACULDADE DE MEDICINA DE RIBEIRÃO PRETO
65 anos (1955-2020)

RFA-5706 Farmacologia Cardiovascular

O Sistema Imune e o Sistema Cardiovascular

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icbufmg

FiS FAR
Pós-graduação UFMG
FISIOLOGIA • FARMACOLOGIA

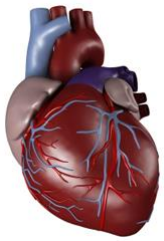
DEPARTAMENTO DE FARMACOLOGIA
ICB | UFMG

LAFACI
Laboratório de Farmacologia Cardiovascular e da Inflamação

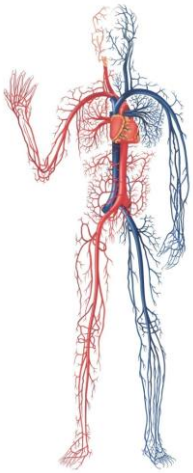
Maio de 2020

Sistema Cardiovascular

Componentes

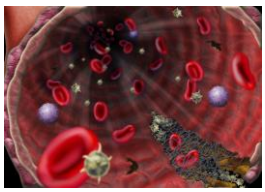


Coração



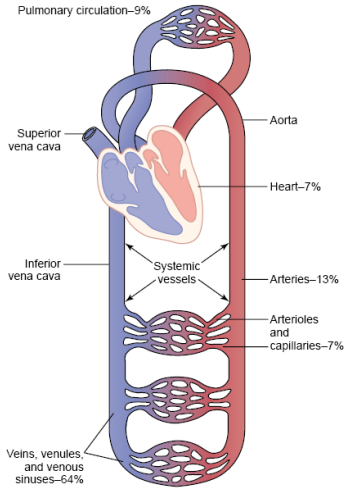
Vasos

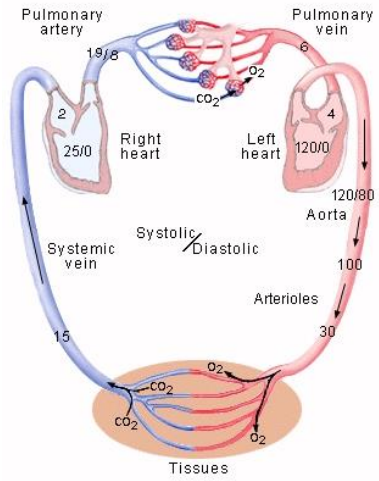
Sangue



Sistema Cardiovascular

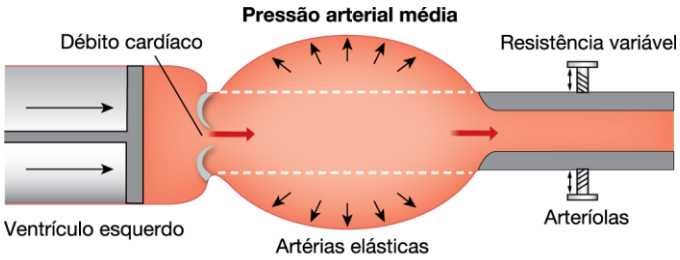
Anatomia: disposição em circuito





Pressão Arterial

Contribuição do DC e da RPV para a pressão arterial

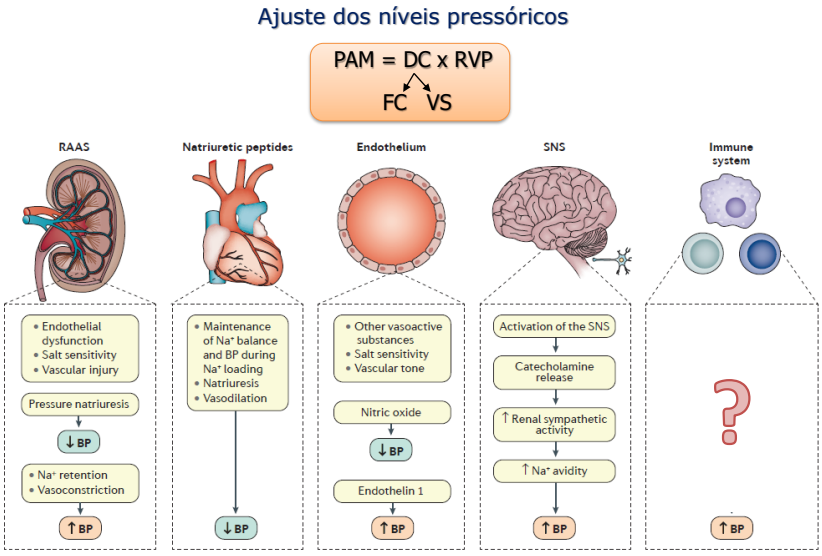


Pressão arterial média ∝ débito cardíaco × resistência

✓ Pressão sistólica: força do coração para bombear o sangue.

✓Pressão diastólica: força resultante da resistência arterial à passagem do sangue.

Pressão Arterial



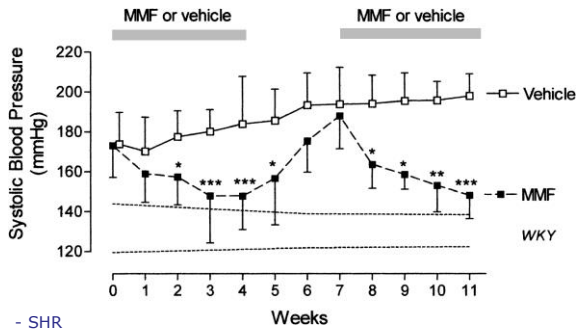
Nature Reviews Disease Primers. 4: 18014 (2018).

Histórico

- Pacientes hipertensos possuem níveis elevados de marcadores inflamatórios circulantes (PCR, citocinas, moléculas de adesão). *Nephrol Dial Transplant* (2006) 21: 850–853

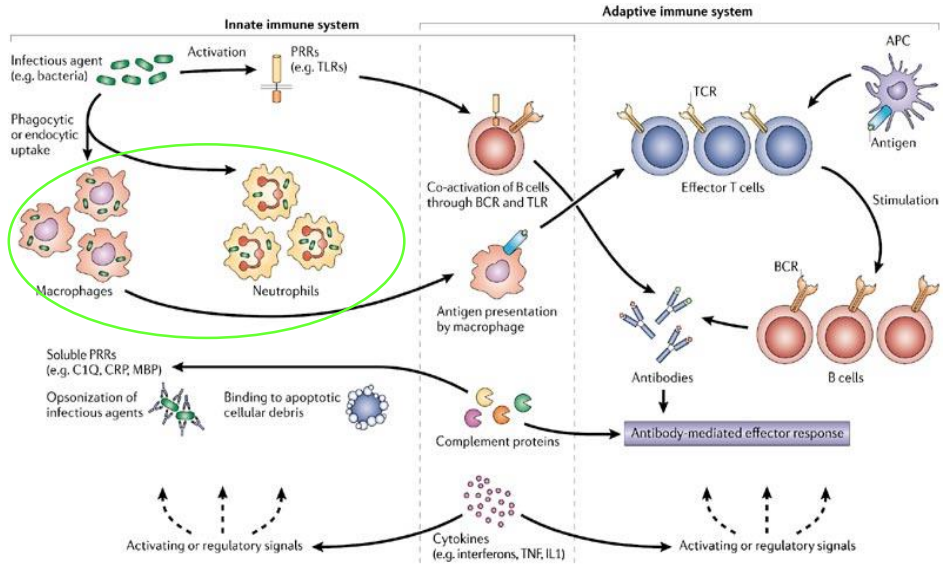
- Pacientes HIV+ imunossuprimidos possuem menor incidência de hipertensão. *AIDS* (2003) 19: 953–960

- Tratamento de ratos hipertensos com imunossupressor reduz a pressão arterial. *Am J Physiol Renal Physiol* 2002;282:F191-F201



- SHR
- Micofenolato de mofetil (MMF), 20mg/Kg V.O.

O Sistema Imune



Nature Reviews Genetics. 2006. 7, 917-928.

Sistema Imune Inato – Resposta Celular

Arteriosclerosis, Thrombosis, and Vascular Biology
Volume 25, Issue 10, 1 October 2005, Pages 2106-2113
https://doi.org/10.1161/01.ATV.0000181743.28028.57

VASCULAR BIOLOGY

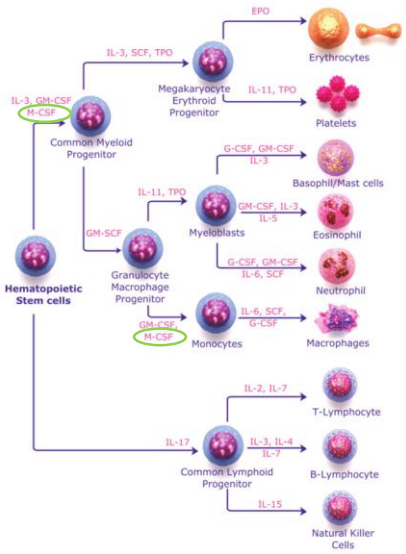
Reduced Vascular Remodeling, Endothelial Dysfunction, and Oxidative Stress in Resistance Arteries of Angiotensin II–Infused Macrophage Colony-Stimulating Factor–Deficient Mice

Evidence for a Role in Inflammation in Angiotensin-Induced Vascular Injury

Carolina De Ciuceis, Farhad Amiri, Pascal Brassard, Dierk H. Endemann, Rhian M. Touyz, and Ernesto L. Schiffrin

Sistema Imune Inato – Resposta Celular

Entendendo o modelo



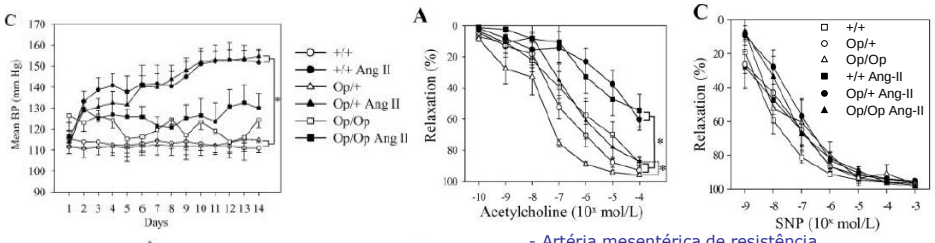
M-CSF: macrophage colony-stimulating fator.

Osteopetrotic (op/op) mice have a severe deficiency of osteoclasts, monocytes, and peritoneal macrophages.

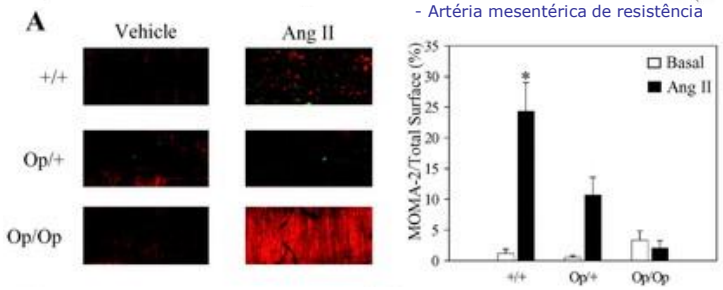
The osteopetrotic phenotype included stunted growth, bone sclerosis, domed skull, and absence of tooth eruption

Sistema Imune Inato – Resposta Celular

- Camundongos Op/Op (deficientes para M-CSF) têm menor PA, proteção à disfunção vascular, infiltrado vascular de Macrof., induzidos por Ang-II (1µg/kg/min, 14 dias, S.c.).



- Artéria mesentérica de resistência



Sistema Imune Inato – Resposta Celular

Circulation
Volume 124, Issue 12, 20 September 2011, Pages 1370-1381
https://doi.org/10.1161/CIRCULATIONAHA.111.034470

American Heart Association.

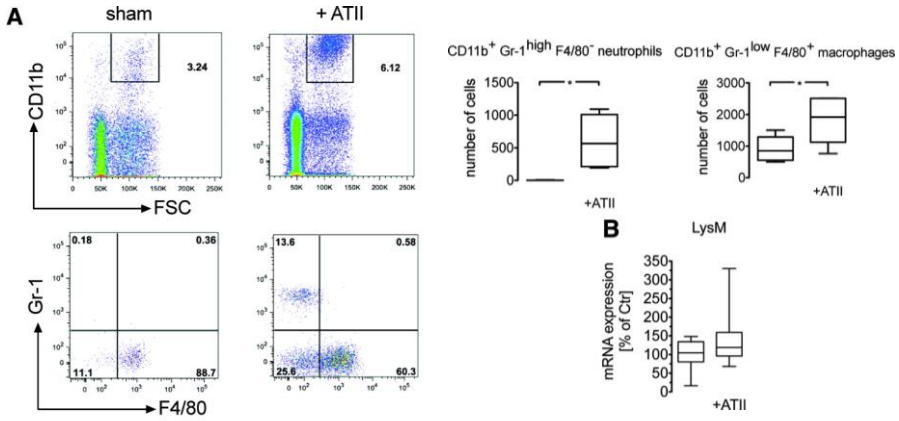
ORIGINAL ARTICLE - VASCULAR MEDICINEVASCULAR MEDICINE

Lysozyme M–Positive Monocytes Mediate Angiotensin II–Induced Arterial Hypertension and Vascular Dysfunction

Philip Wenzel, MD*, Maike Knorr, MD*, Sabine Kossmann, MSc, Jan Stratmann, BSc, Michael Hausding, PhD, Swenja Schuhmacher, PhD, Susanne H. Karbach, MD, Melanie Schwenk, MSc, Nir Yogev, PhD, Eberhard Schulz, MD, Matthias Oelze, PhD, Stephan Grabbe, MD, Helmut Jonuleit, PhD, Christian Becker, PhD, Andreas Daiber, PhD, Ari Waisman, PhD, and Thomas Münzel, MD

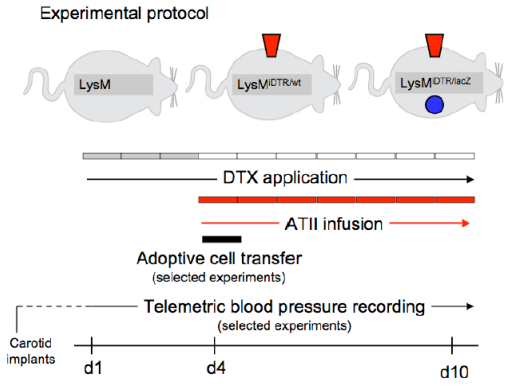
Sistema Imune Inato – Resposta Celular

- Ang-II (1µg/kg/min, 7 dias, S.c.) causa aumento do infiltrado de macrófagos e neutrófilos em artérias aortas de camundongos C57.



Sistema Imune Inato – Resposta Celular

Entendendo o modelo

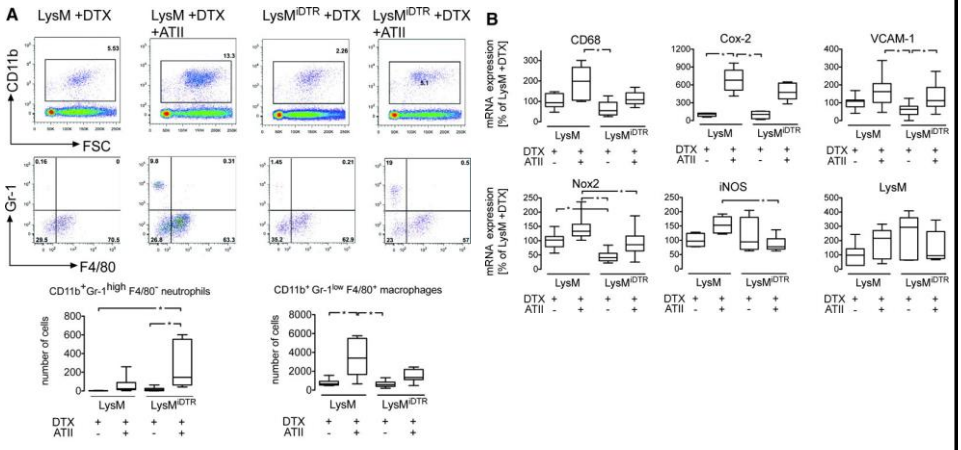


Lysozyme M (Lys M) specifically express in myelomonocytic cells (macrophages, granulocytes).

LysM-Cre-mice were crossed with *cre-inducible diphtheria toxin (DTX) receptor (iDTR) mice* to generate **LysM^{iDTR} mice**, which allow ablation of myelomonocytic cells by low-dose DTX administration.

Sistema Imune Inato – Resposta Celular

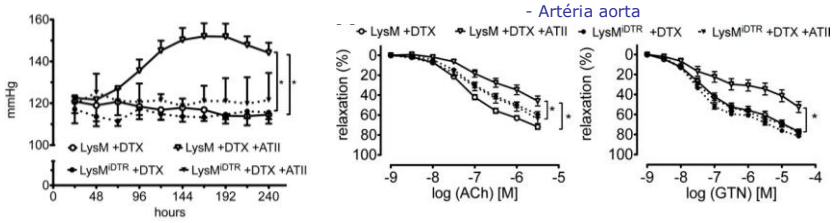
- A depleção de células positivas para lisozima M (LysM) reduz a população de macrófagos e a expressão gênica inflamatória na parede vascular.



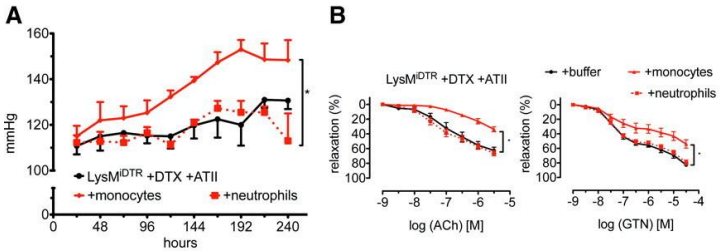
Sistema Imune Inato – Resposta Celular

- A depleção de células positivas para lisozima M (LysM) melhora a função vascular e abole o aumento de pressão arterial.

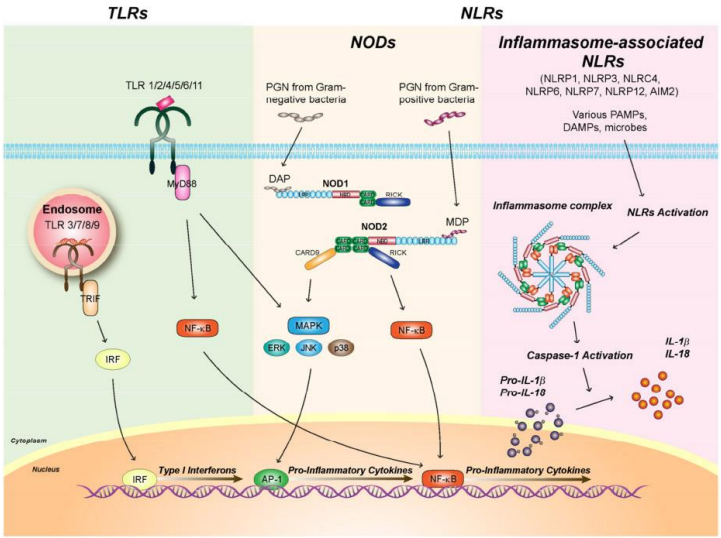
- Artéria aorta



- A reconstituição de *macrófagos* reestabelece o aumento de PA e a disfunção vascular.

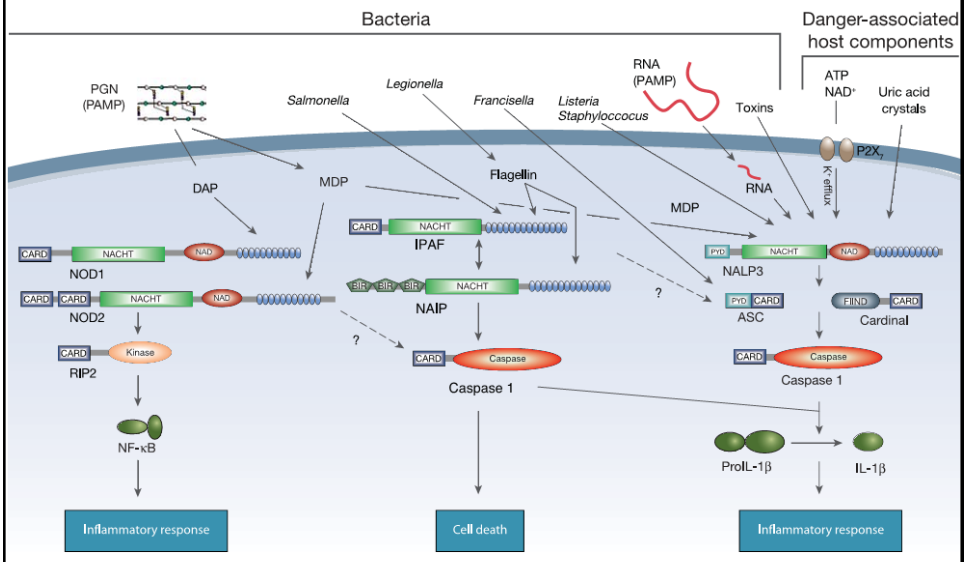


Sistema Imune Inato – Receptores de Reconhecimento de Padrão



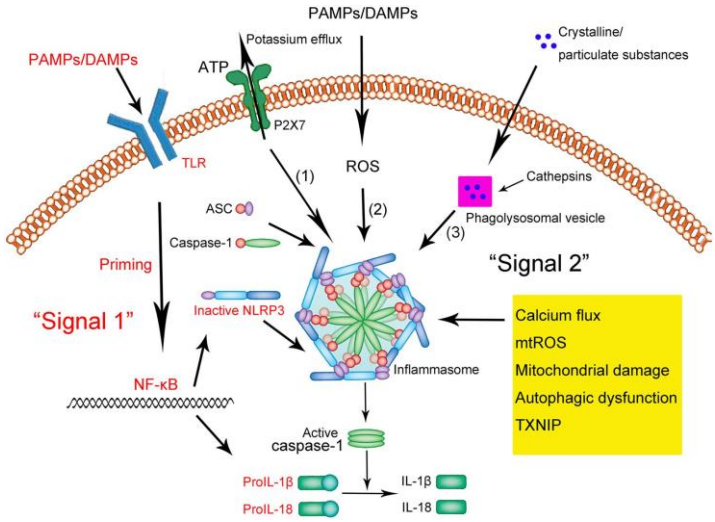
J Bacteriol Virol. 2014 Sep;44(3):215-225.

Sistema Imune Inato – Receptores do Tipo NOD



Nature. 2006; 442:39-44.

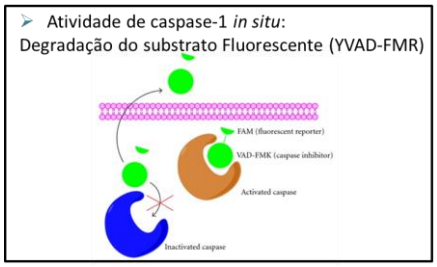
Sistema Imune Inato – Inflamassoma NLRP3

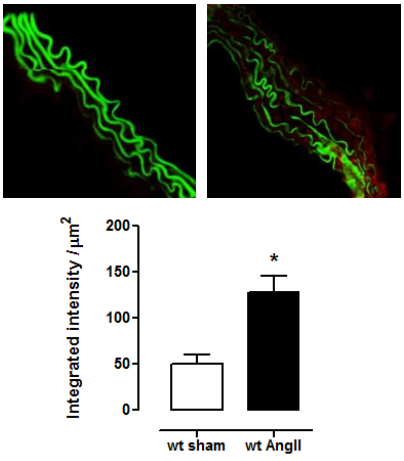


Front. Pharmacol., 05 November 2015

Sistema Imune Inato – Inflamassoma NLRP3

Caspase-1 ativa é aumenta nas aortas de camundongos hipertensos (Ang-II).

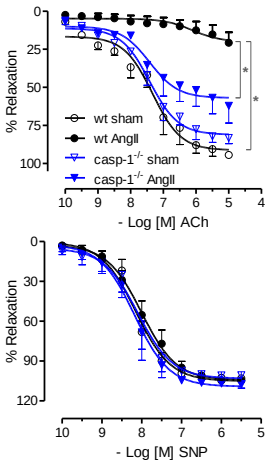


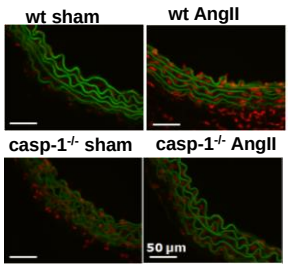


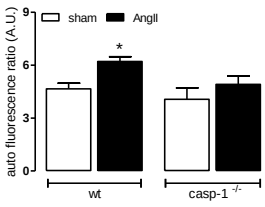
Cau, SB. Unpublished.

Sistema Imune Inato – Inflamassoma NLRP3

Caspase-1 knockout mice are protected from Ang-II–induced endothelial dysfunction.







Cau, SB. Unpublished.

Sistema Imune Inato – Inflamassoma NLRP3

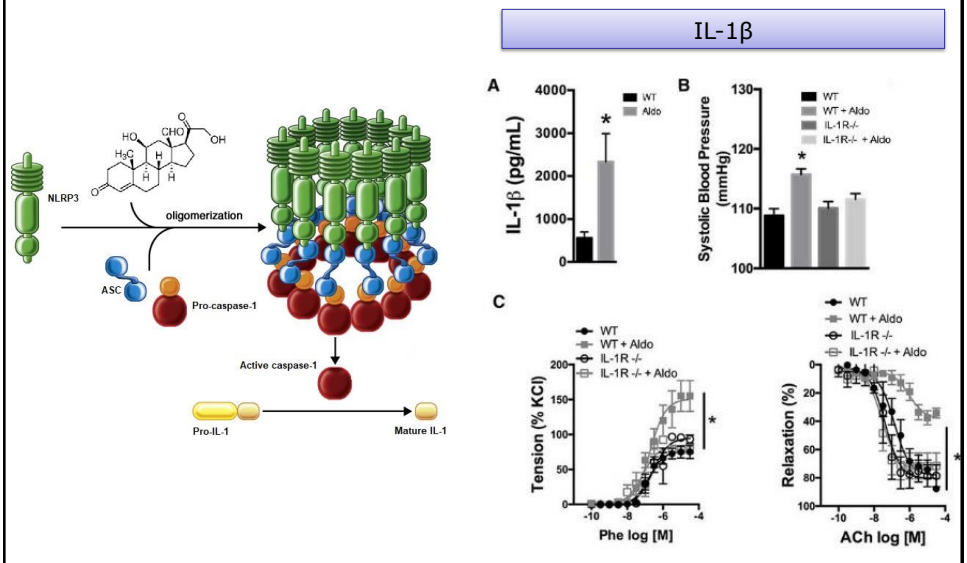
Circulation
Volume 134, Issue 23, 6 December 2016, Pages 1866-1880
https://doi.org/10.1161/CIRCULATIONAHA.116.024369

ORIGINAL RESEARCH ARTICLE

NLRP3 Inflammasome Mediates Aldosterone-Induced Vascular Damage

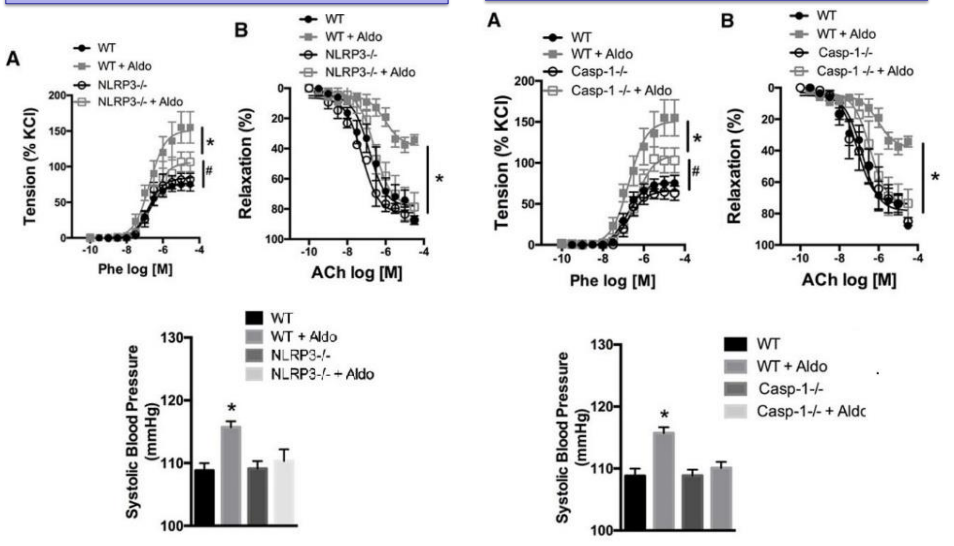
Thiago Bruder-Nascimento, PhD, Nathanne S. Ferreira, MSc, Camila Z. Zanotto, MSc, Fernanda Ramalho, Isabela O. Pequeno, Vania C. Olivon, PhD, Karla B. Neves, PhD, Rheure Alves-Lopes, PhD, Eduardo Campos, Carlos Alberto A. Silva, Rubens Fazan, PhD, Daniela Carlos, PhD, Fabiola L. Mestriner, MSc, Douglas Prado, MSc, Felipe V. Pereira, PhD, Tarcio Braga, PhD, Joao Paulo M. Luiz, MSc, Stefany B. Cau, PhD, Paula C. Elias, MD, Ayrton C. Moreira, MD, PhD, Niels O. Câmara, MD, PhD, Dario S. Zamboni, PhD, Jose Carlos Alves-Filho, PhD, and Rita C. Tostes, PhD

Sistema Imune Inato – Inflamassoma NLRP3



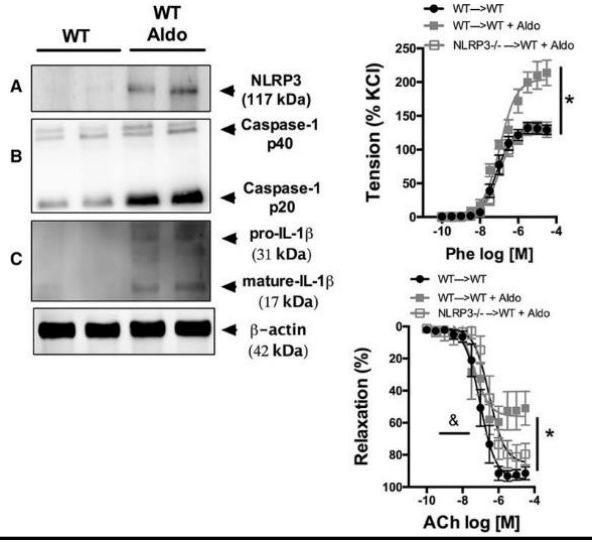
Sistema Imune Inato – Inflamassoma NLRP3

NLPR3 | Caspase 1



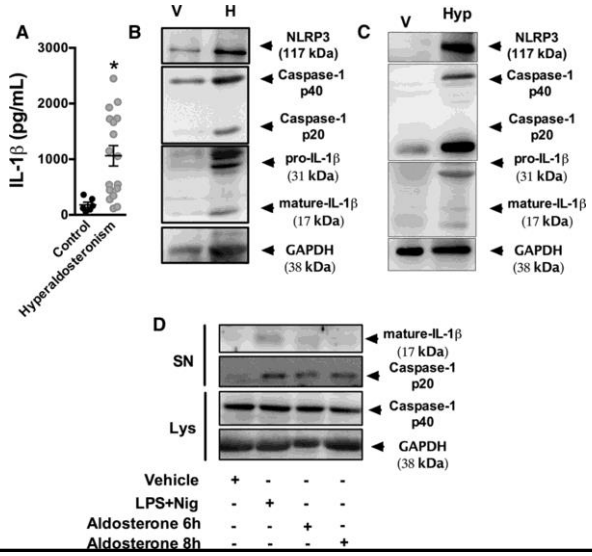
Sistema Imune Inato – Inflamassoma NLRP3

Transferência adotiva de células da medula óssea para animal WT.

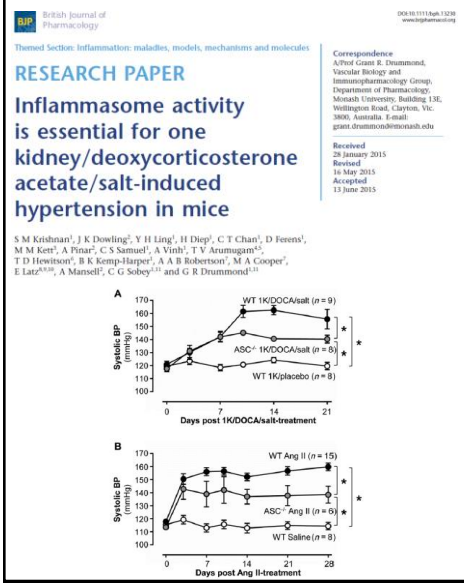


Sistema Imune Inato – Inflamassoma NLRP3

Estudo translacional!



Sistema Imune Inato – Inflamassoma NLRP3



British Journal of Pharmacology

Themed Section: Inflammation: maladies, models, mechanisms and molecules

RESEARCH PAPER

Inflammasome activity is essential for one kidney/deoxycorticosterone acetate/salt-induced hypertension in mice

S M Krishnan[1], J K Dowling[2], Y H Ling[1], H Diep[1], C T Chan[1], D Ferens[1], M M Kett[3], A Pinar[2], C S Samuel[1], A Vinh[1], T V Arumugam[4,5], T D Hewitson[6], B K Kemp-Harper[1], A A B Robertson[7], M A Cooper[7], E Latz[8,9,10], A Mansell[2], C G Sobey[2,11] and G R Drummond[1,11]

Correspondence
A/Prof Grant R. Drummond, Vascular Biology and Immunopharmacology Group, Department of Pharmacology, Monash University, Building 13E, Wellington Road, Clayton, Vic. 3800, Australia. E-mail: grant.drummond@monash.edu

Received 28 January 2015
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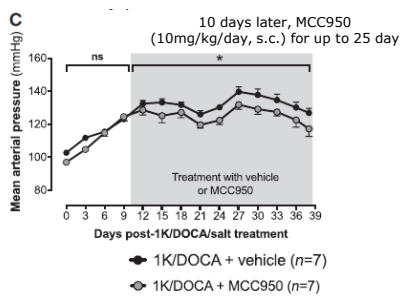
Accepted 13 June 2015

ESC European Society of Cardiology

Cardiovascular Research (2019) 115, 776–787
doi:10.1093/cvr/cvy252

Pharmacological inhibition of the NLRP3 inflammasome reduces blood pressure, renal damage, and dysfunction in salt-sensitive hypertension

Shalini M. Krishnan[†‡], Yeong H. Ling[†‡], Brooke M. Huuskes[2], Dorota M. Ferens[1], Narbada Saini[2], Christopher T. Chan[1], Henry Diep[1,2], Michelle M. Kett[3], Chrishan S. Samuel[1], Barbara K. Kemp-Harper[1], Avril A.B. Robertson[4], Matthew A. Cooper[4], Karlheinz Peter[5], Eicke Latz[6,7,8], Ashley S. Mansell[9], Christopher G. Sobey[1,2], Grant R. Drummond[1,2‡], and Antony Vinh[1,2‡]



Sistema Imune Inato – Receptores do tipo Toll (TLR)

Clinical SCIENCE

www.clinsci.org

Clinical Science (2012) 122, 535–543 (Printed in Great Britain) doi:10.1042/CS20110523 535

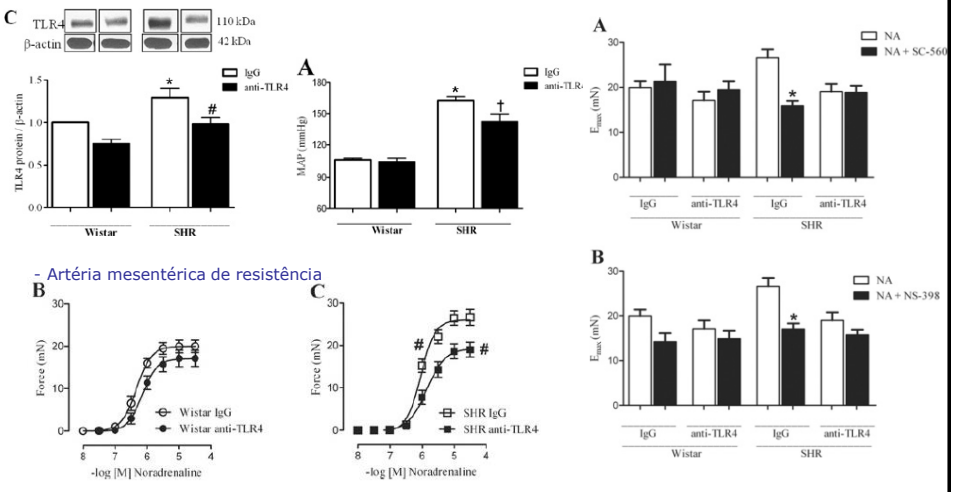
Toll-like receptor 4 contributes to blood pressure regulation and vascular contraction in spontaneously hypertensive rats

Gisele F. BOMFIM*†, Rosangela A. DOS SANTOS*, Maria Aparecida OLIVEIRA*, Fernanda R. GIACHINI†, Eliana H. AKAMINE*, Rita C. TOSTES‡, Zuleica B. FORTES*, R. Clinton WEBB† and Maria Helena C. CARVALHO*

*Department of Pharmacology, University of Sao Paulo, Sao Paulo, SP, Brazil, †Department of Physiology, Georgia Health Sciences University, Augusta, GA, U.S.A., and ‡Department of Pharmacology, School of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, SP, Brazil

Sistema Imune Inato – Receptores do tipo Toll (TLR)

- Anticorpo Anti–TLR-4 reduz a PA e melhora a disfunção vascular de SHR.



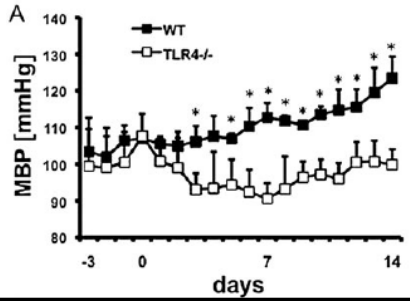
- Artéria mesentérica de resistência

Sistema Imune Inato – Receptores do tipo Toll (TLR)

Cardiovascular Research (2014) **101**, 464–472
doi:10.1093/cvr/cvt265

Damage-associated molecular pattern activated Toll-like receptor 4 signalling modulates blood pressure in L-NAME-induced hypertension

Daniel Sollinger[1†*], Ruth Eißler[2†], Steffen Lorenz[1], Susanne Strand[1], Stefan Chmielewski[2,3], Cristiane Aoqui[2], Christoph Schmaderer[2], Hans Bluyssen[3], Josef Zicha[4], Oliver Witzke[5], Elias Scherer[6], Jens Lutz[1], Uwe Heemann[2], and Marcus Baumann[2]



Sistema Imune Inato – Receptores do tipo Toll (TLR)

Cardiovascular Research (2015) **107**, 119–130
doi:10.1093/cvr/cvv137

Circulating mitochondrial DNA and Toll-like receptor 9 are associated with vascular dysfunction in spontaneously hypertensive rats

Cameron G. McCarthy[1*], Camilla F. Wenceslau[1], Styliani Goulopoulou[2], Safia Ogbi[1], Babak Baban[3], Jennifer C. Sullivan[1], Takayuki Matsumoto[4], and R. Clinton Webb[1]

[1]Department of Physiology, Georgia Regents University, 1120 15th Street, Augusta, GA 30912, USA; [2]Department of Integrative Physiology and Anatomy, and Obstetrics and Gynecology, University of North Texas Health Science Center, Fort Worth, TX, USA; [3]Department of Oral Biology, Georgia Regents University, Augusta, GA, USA; and [4]Department of Physiology and Morphology, Institute of Medicinal Chemistry, Hoshi University, Tokyo, Japan

Received 6 November 2014; revised 6 April 2015; accepted 17 April 2015; online publish-ahead-of-print 24 April 2015

American Journal of Hypertension Advance Access published September 13, 2016

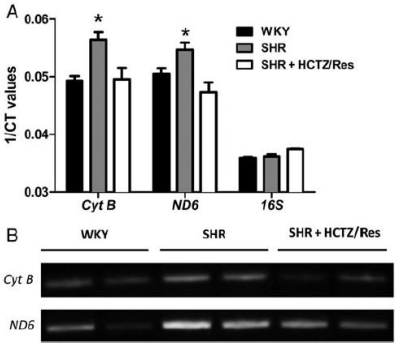
ORIGINAL ARTICLE

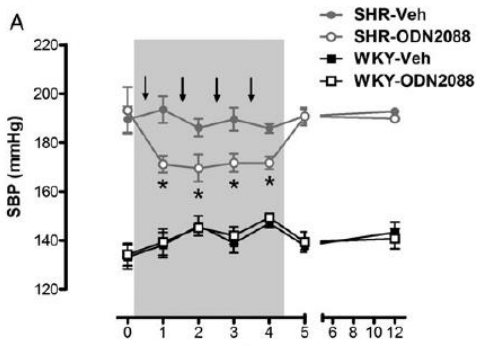
Chloroquine Suppresses the Development of Hypertension in Spontaneously Hypertensive Rats

Cameron G. McCarthy,[1] Camilla F. Wenceslau,[1] Styliani Goulopoulou,[3] Babak Baban,[2] Takayuki Matsumoto,[4] and R. Clinton Webb[1]

Sistema Imune Inato – Receptores do tipo Toll (TLR)

- Ligantes endógenos de TLR-9, DNA mitocondriais, estão aumentados em SHR.
- O tratamento com antagonista TLR-9 (ODN2088) reduz a PA.

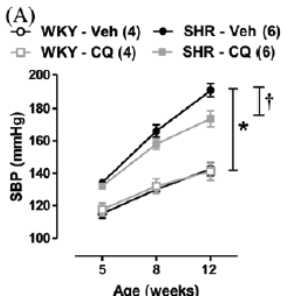


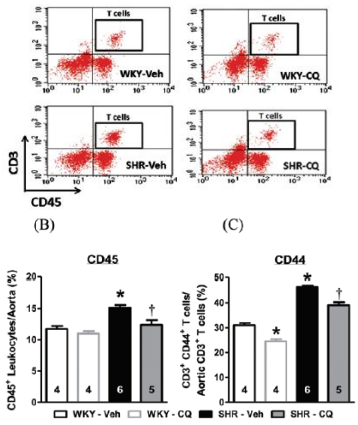


Cardiovasc Res. 2015 Jul 1;107(1):119-30.

Sistema Imune Inato – Receptores do tipo Toll (TLR)

- Cloroquina (agente lisossomotrópico) inibe sinalização por TLR-9 em artérias de resistência *in vitro*, e reduz a PA e o infiltrado de células da imunidade adaptativa *in vivo*.

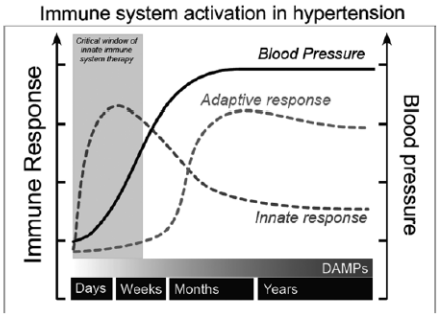


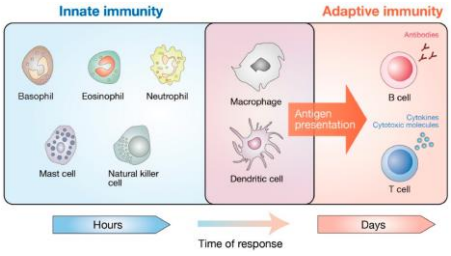


Am J Hypertens. 2017 Feb;30(2):173-181.

Sistema Imune Inato – Receptores do tipo Toll (TLR)

- Modelo hipotético da ativação do sistema imune adaptativa pela resposta inata durante a hipertensão arterial.





Am J Hypertens. 2017 Feb;30(2):173-181.

Cells 2019, *8*(5), 398.

Sistema Imune Inato – Células Dendríticas

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Inhibition and Genetic Ablation of the B7/CD28 T-Cell Costimulation Axis Prevents Experimental Hypertension

Antony Vinh, Wei Chen, Yelena Blinder, Daiana Weiss, W. Robert Taylor, Jörg J. Goronzy, Cornelia M. Weyand, David G. Harrison and Tomasz J. Guzik

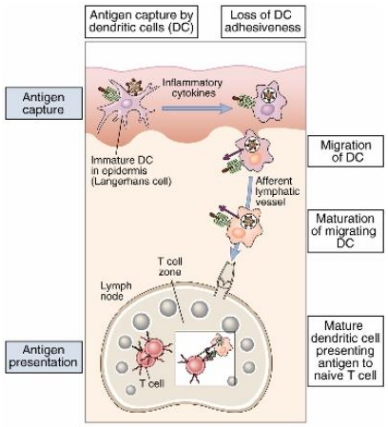
Circulation 2010;122;2529-2537; originally published online Nov 29, 2010;
DOI: 10.1161/CIRCULATIONAHA.109.930446

Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514

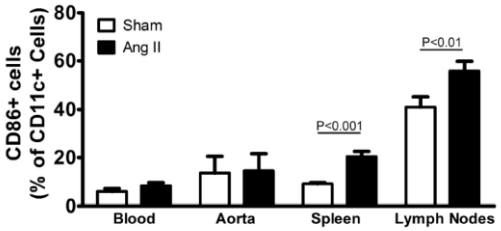
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Sistema Imune Inato – Células Dendríticas

- A expressão de CD 86 por céls. dendríticas (CD11c+) é seletivamente aumentada em órgãos linfóides secundários de cam. hipertensos.



Abbas. 5ed.2005.

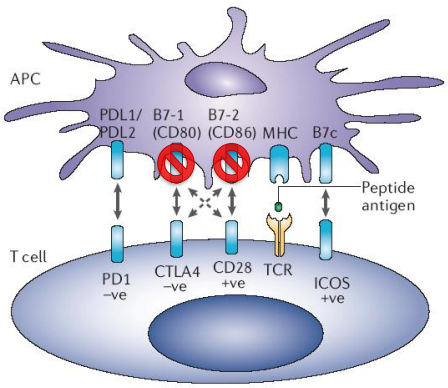


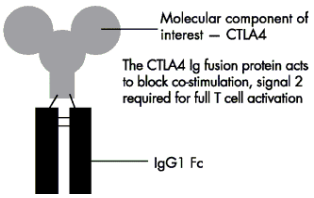
- identificação das **céls. dendríticas** por citometira de fluxo (CD45+, CD11c+, CD80+, CD86+, MHCII+).
- Citometria de Fluxo das céls. dos tecidos (digestão com colagenase).

Circulation 2010. 14;122(24):2529-37.

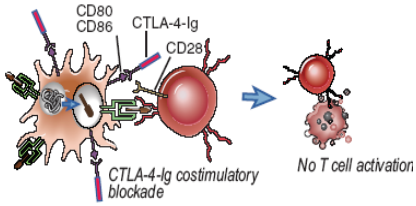
Sistema Imune Inato – Células Dendríticas

Entendendo o modelo





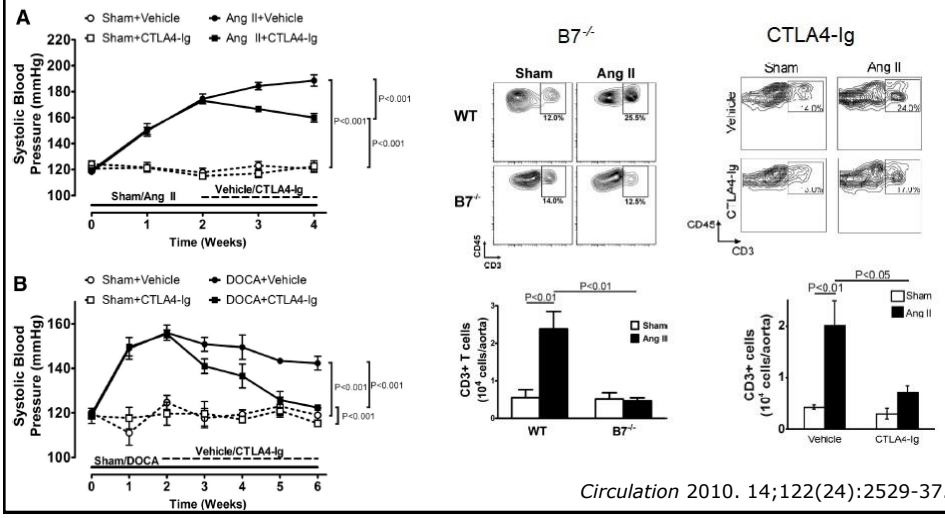
- ***Abatacept (CTAL4-Ig):*** aprovado em 2005 pelo FDA para o tratamento de artrite reumatóide.



Nature Reviews Genetics **7**, 917-928; 2006.

Sistema Imune Inato – Células Dendríticas

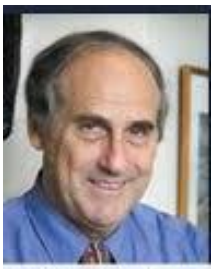
- A inibição da co-estimulação de céls. T reverte a hipertensão e o infiltrado vascular de céls. T.



Circulation 2010. 14;122(24):2529-37.

Sistema Imune Inato

Prêmio Nobel de Medicina e Fisiologia 2011



Ralph M. Steinman

Pela sua descoberta das células dendríticas e do seu papel na imunidade adaptativa.

Bruce A. Beutler — Jules A. Hoffmann

Pelas suas descobertas acerca da ativação da imunidade inata.
(Receptores tipo Toll).

Sistema Imune Adaptativa – Linfócitos (células T e B)

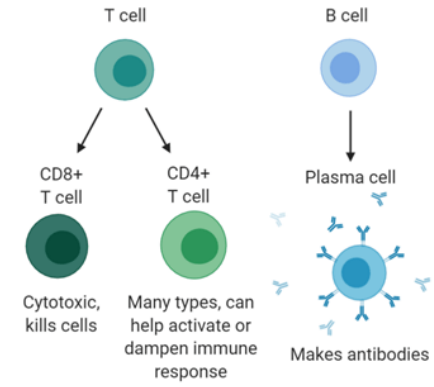


Figure 1: Types of T and B cells

Sistema Imune Adaptativa – Linfócitos T

JEM ARTICLE

Role of the T cell in the genesis of angiotensin II–induced hypertension and vascular dysfunction

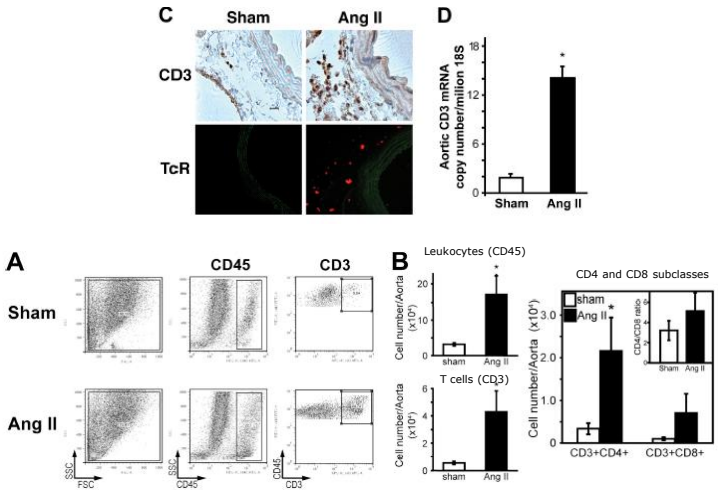
Tomasz J. Guzik,[1,2] Nyssa E. Hoch,[1,2] Kathryn A. Brown,[1,2] Louise A. McCann,[1,2] Ayaz Rahman,[1,2] Sergey Dikalov,[1,2] Jorg Goronzy,[1,2] Cornelia Weyand,[1,2] and David G. Harrison[1,2,3]

[1]Division of Cardiology and [2]Lowance Center for Human Immunology, Department of Medicine, Emory University School of Medicine, Atlanta, GA 30033
[3]Atlanta Veteran Administration Hospital, Atlanta, GA 30033

Nº de citações: 1.358
(Google Scholar)

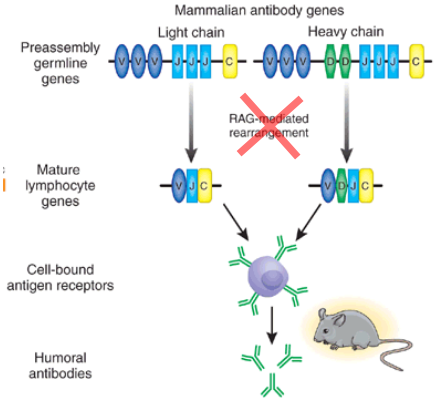
Sistema Imune Adaptativa – Linfócitos T *(CD4 ?)*

A hipertensão é acompanhada do aumento de infiltrado vascular de Linfócitos T.



Sistema Imune Adaptativa – Linfócitos (células T e B)

Entendendo o modelo

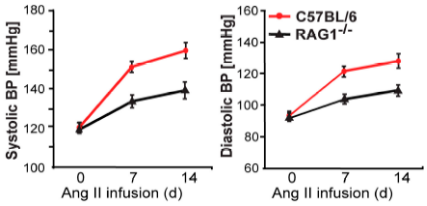


Recombination activating 1 gene (RAG-1): catalyzes the V(D)J recombination reaction of immunoglobulin and T cell receptor genes.

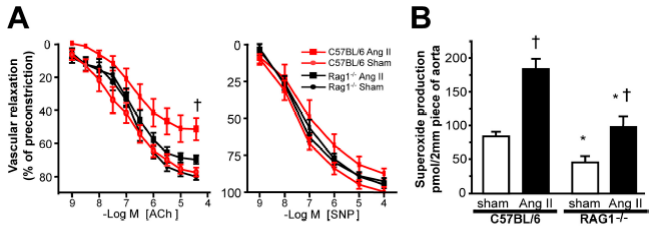
RAG-1-deficient mice show arrest of B and T cell differentiation, which occurs at an early stage.

Sistema Imune Adaptativa – Linfócitos (células T)

Camundongos destituídos de Linfócitos T e B (RAG$^{-/-}$) não desenvolvem hipertensão e são protegidos da prejuízo do relaxamento induzida por Ang-II.

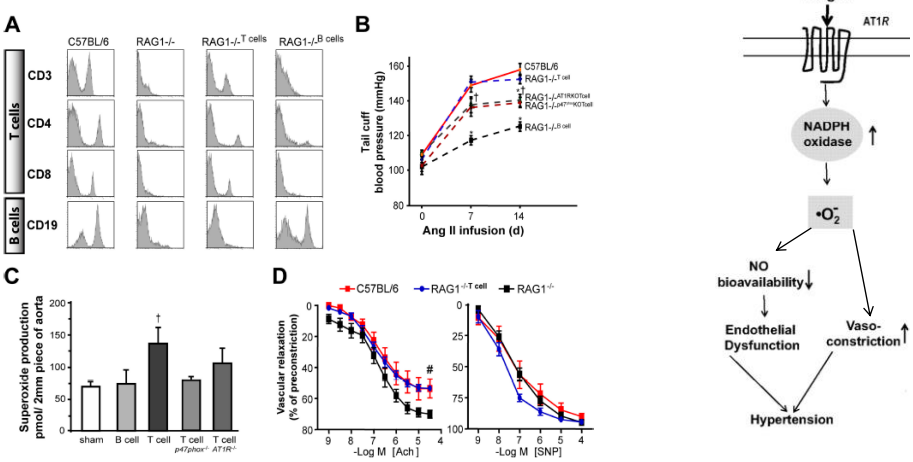


- Ang-II (490 ng/min/kg S.C.)
- Pletismografia de cauda
- Reatividade aórtica



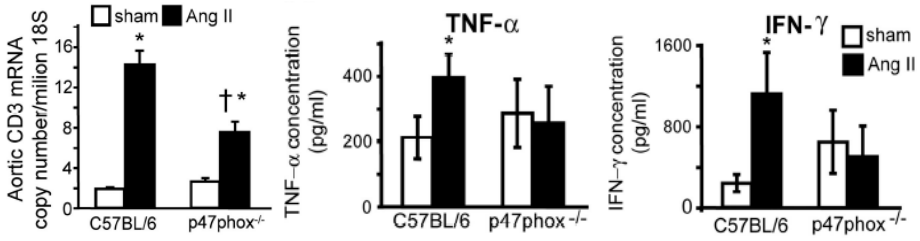
Sistema Imune Adaptativa – Linfócitos (células T)

A transferência adotiva de **células T** (e não de céls. B) de controles WT para camundongos RAG$^{-/-}$ restaurou o efeito hipertensivo.

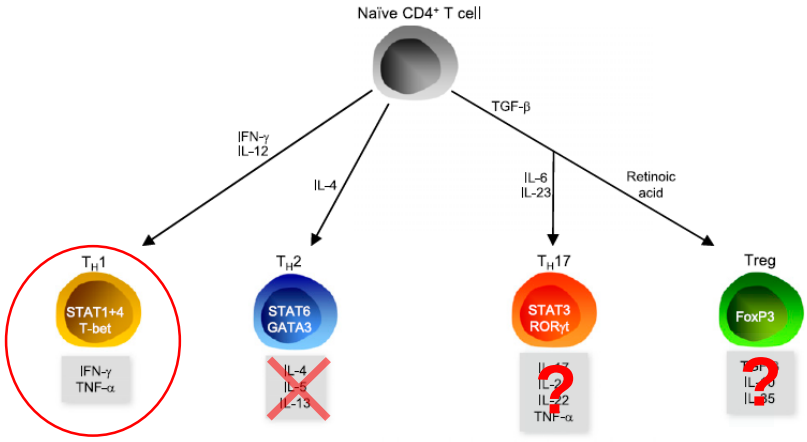


Sistema Imune Adaptativa – Linfócitos T *(CD4 ?)*

- Camundongos KO p47$^{phox-/-}$ apresentam redução da infiltração de céls. T.
- Céls. T circulantes de camundongos hipertensos produzem mais TNF-α e IFN-γ quando estimulados *in vitro*.



Sistema Imune Adaptativa – Células T



J Am Soc Nephrol 27: 677–686, 2016.

Sistema Imune Adaptativa – Células T

ARTICLES

nature immunology

Interleukin 17–producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages

Laurie E Harrington[1], Robin D Hatton[1], Paul R Mangan[1], Henrietta Turner[1], Theresa L Murphy[2], Kenneth M Murphy[2] & Casey T Weaver[1]

CD4+ T cells producing interleukin 17 (IL-17) are associated with autoimmunity, although the precise mechanisms that control their development are undefined. Here we present data that challenge the idea of a shared developmental pathway with T helper type 1 (T_H1) or T_H2 lineages and instead favor the idea of a distinct effector lineage we call 'T_H-17'. The development of T_H-17 cells from naive precursor cells was potently inhibited by interferon-γ (IFN-γ) and IL-4, whereas committed T_H-17 cells were resistant to suppression by T_H1 or T_H2 cytokines. In the absence of IFN-γ and IL-4, IL-23 induced naive precursor cells to differentiate into T_H-17 cells independently of the transcription factors STAT1, T-bet, STAT4 and STAT6. These findings provide a basis for understanding how inhibition of IFN-γ signaling enhances development of pathogenic T_H-17 effector cells that can exacerbate autoimmunity.

Nature Immunology volume 6, pages 1123–1132(**2005**).

Sistema Imune Adaptativa – Células T

Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®
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Interleukin 17 Promotes Angiotensin II Induced Hypertension and Vascular Dysfunction

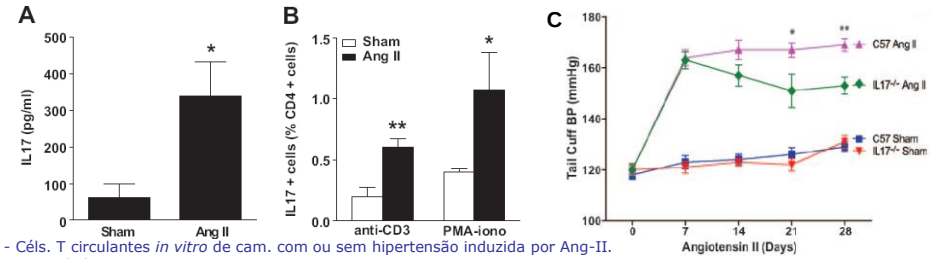
Meena S. Madhur, Heinrich E. Lob, Louise A. McCann, Yoichiro Iwakura, Yelena Blinder, Tomasz J. Guzik and David G. Harrison

Hypertension 2010;55;500-507; originally published online Dec 28, 2009;
DOI: 10.1161/HYPERTENSIONAHA.109.145094
Hypertension is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514

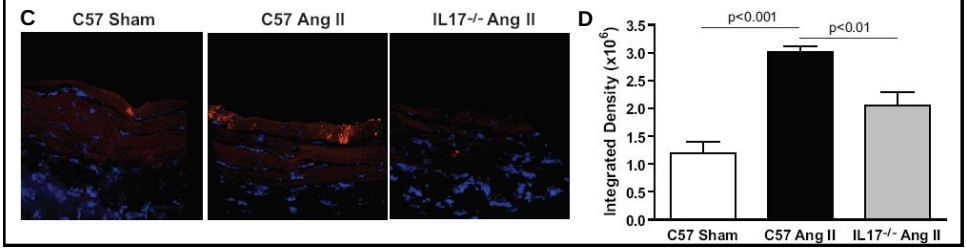
 Print ISSN: 0194-911X. Online ISSN: 1524-4563

Sistema Imune Adaptativa – Células T CD4 – Th17

- Células T de camundongos hipertensos expressam maiores níveis de IL-17.
- Camundongos KO IL17$^{-/-}$ são protegidos da hipertensão induzida por AngII.

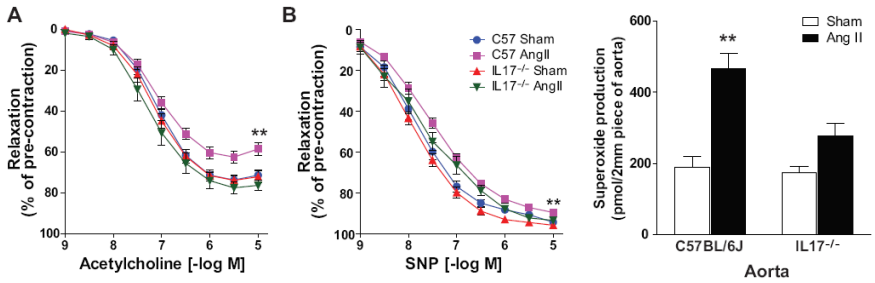


- Céls. T circulantes *in vitro* de cam. com ou sem hipertensão induzida por Ang-II.
- Estimuladas com Ac anti-CD3 ou PMA.



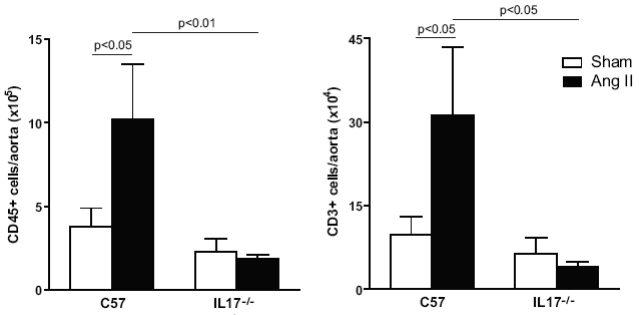
Sistema Imune Adaptativa – Células T CD4 – Th17

- Camundongos KO IL17$^{-/-}$ são protegidos do prejuízo do relaxamento vascular.
- O efeito protetor sobre a reatividade vascular está associado à menor produção de superóxido nas artérias dos camundongos KO IL17$^{-/-}$



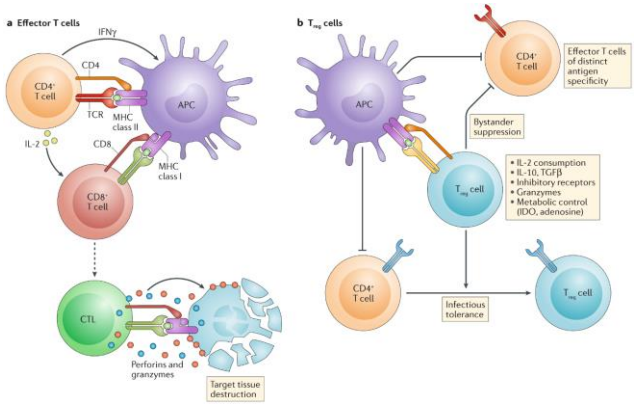
Sistema Imune Adaptativa – Células T CD4 – Th17

Aortas de camundongos KO IL17$^{-/-}$ apresentam menor infiltrado de céls. T



- Citometria de Fluxo das céls. de aortas (digestão com colagenase).

Sistema Imune Adaptativa – Células T Reguladoras (*T Reg*)

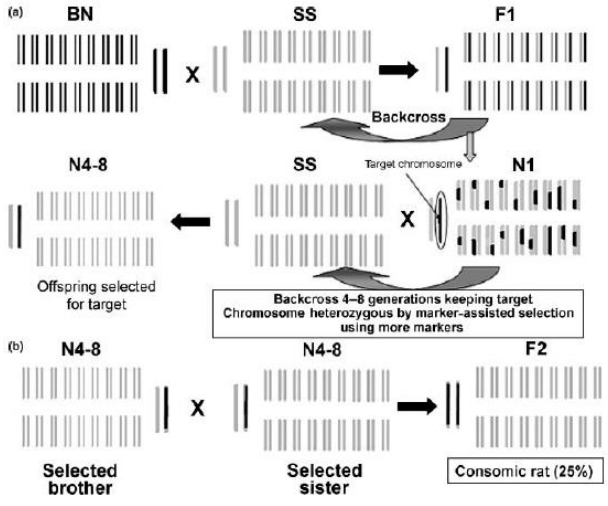


- ✓ Conferem tolerância imune
- ✓ Células T_{reg} corresponde a 5–7% das células T CD4$^+$
- ✓ Principais marcadores: *forkhead box P3* (FOXP3)$^+$ CD4$^+$ CD25$^+$
- ✓ Camundongos KO desenvolvem autoimunidade letal de múltiplos órgãos

Nature Reviews Immunology 20, 158–172(2020).

Sistema Imune Adaptativa – Células T Reguladoras (*T Reg*)

Entendendo o modelo



BN: controle normotenso

SS: Dahl sensível ao sal – hipertenso

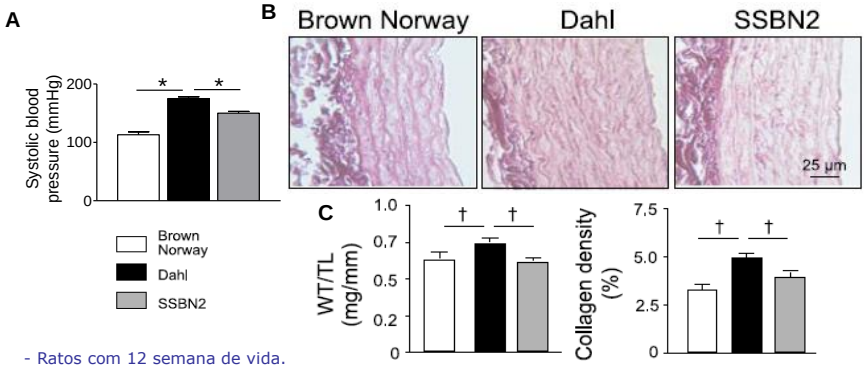
SSBN2: linhagem consômica (cromossomo 2 proveniente do BN)

Cromossomo 2: genes pró-inflamatórios (IL-2, IL-6, IL-7, IL-12)

Acta Physiol Scand 2004, 181, 585–592.

Sistema Imune Adaptativa – Células T Reguladoras (*T Reg*)

- Ratos *Dahl sensíveis ao sal* apresentaram modesta hipertensão e hipertrofia vascular. Ratos da linhagem consômica SSBN2 (possui cromossomo 2 proveniente do *background* normotenso) foram protegidos destes efeitos.



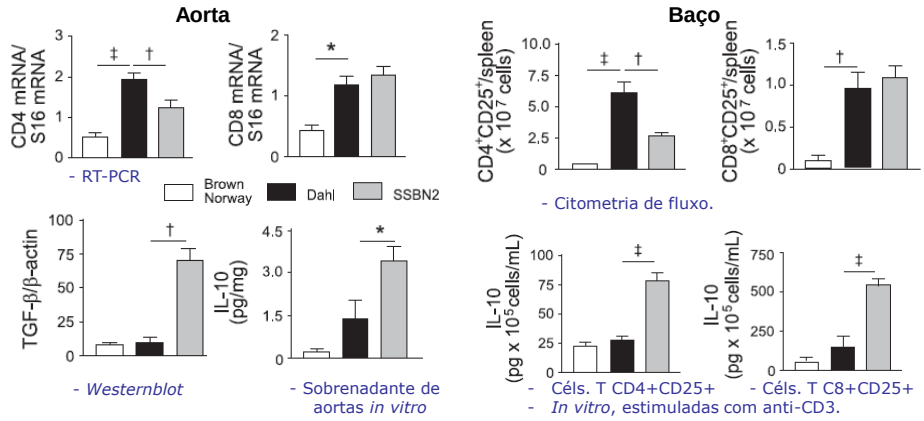
- Ratos com 12 semana de vida.
- Dieta normal (0,23% de sódio)→ avaliação dos fatores genéticos, independentemente dos ambientais, na indução da hipertensão.

Am J Physiol Heart Circ Physiol. 298: H938–H944, 2010.

Sistema Imune Adaptativa – Células T Reguladoras (*T Reg*)

- Aortas de ratos da linhagem consômica SSBN2 apresentaram menor infiltração de céls. T e níveis aumentados de citocinas do perfil *T reg*.

- Marcadores característico de *T reg* apareceram no baço dos ratos SSBN2.



Am J Physiol Heart Circ Physiol. 298: H938–H944, 2010.

Sistema Imune Adaptativa – Células T Reguladoras (*T Reg*)

Hypertension
Journal of the American Heart Association
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T Regulatory Lymphocytes Prevent Angiotensin II Induced Hypertension and Vascular Injury

Tlili Barhoumi, Daniel A. Kasal, Melissa W. Li, Layla Shbat, Pascal Laurant, Mario F. Neves, Pierre Paradis and Ernesto L. Schiffrin

Hypertension 2011;57;469-476; originally published online Jan 24, 2011;
DOI: 10.1161/HYPERTENSIONAHA.110.162941

Hypertension
Journal of the American Heart Association
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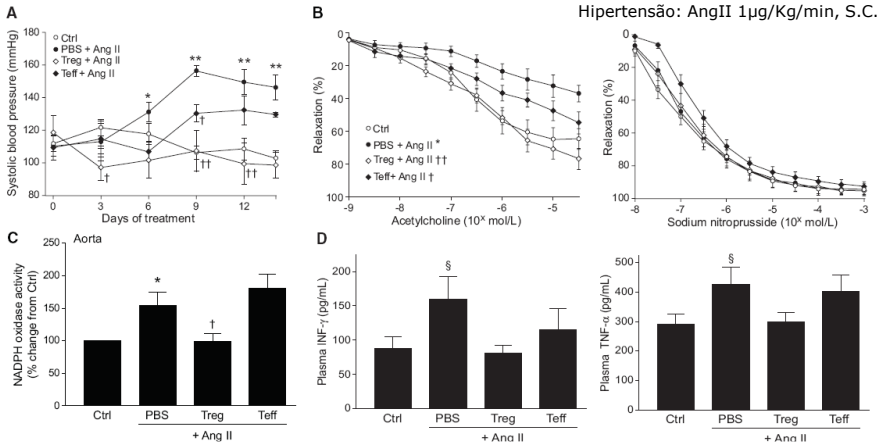
T Regulatory Lymphocytes Prevent Aldosterone-Induced Vascular Injury

Daniel A. Kasal, Tlili Barhoumi, Melissa W. Li, Naoki Yamamoto, Evguenia Zdanovich, Asia Rehman, Mario F. Neves, Pascal Laurant, Pierre Paradis and Ernesto L. Schiffrin

Hypertension 2012, 59:324-330: originally published online December 5, 2011
doi: 10.1161/HYPERTENSIONAHA.111.181123

Sistema Imune Adaptativa – Células T Reguladoras (*T Reg*)

- A transferência adotiva de *céls.* T_{Reg} preveniu a hipertensão, perda do relaxamento vascular, estresse oxidativo e liberação de citocinas induzidos pela hipertensão.



Hipertensão: AngII 1µg/Kg/min, S.C.

Obtenção das céls.T reg: baço→ seleção CD4+/CD25+ (T reg) ou CD4+CD25- (Teff - *comparator T effector*)→ administração I.V. 100 µL of PBS or $3x10^5$ céls.

Hypertension. 2011;57;469-476.

Sistema Imune Adaptativa – Células T (CD8)

Hypertension
Volume 64, Issue 5, November 2014, Pages 1108-1115
https://doi.org/10.1161/HYPERTENSIONAHA.114.04147

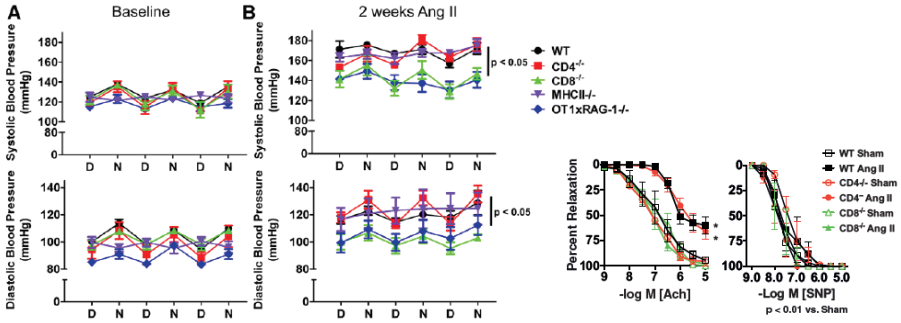
ORIGINAL ARTICLE - ADAPTIVE IMMUNITY AND HYPERTENSIONADAPTIVE IMMUNITY AND HYPERTENSION

Oligoclonal CD8+ T Cells Play a Critical Role in the Development of Hypertension

Daniel W. Trott*, Salim R. Thabet*, Annet Kirabo, Mohamed A. Saleh, Hana Itani, Allison E. Norlander, Jing Wu, Anna Goldstein, William J. Arendshorst, Meena S. Madhur, Wei Chen, Chung-I. Li, Yu Shyr, and David G. Harrison

Sistema Imune Adaptativa – Células T (CD8)

- Animais protegidos da hipertensão são o que não possuem Céls. T CD8+(ou defeito na apresentação de antígeno via MCH I).



Sistema Imune – Uma Oportunidade Terapêutica para ↓ PA?

BJP British Journal of Pharmacology

British Journal of Pharmacology (2019) **176** 2028–2048 2028

Themed Section: Immune Targets in Hypertension

REVIEW ARTICLE

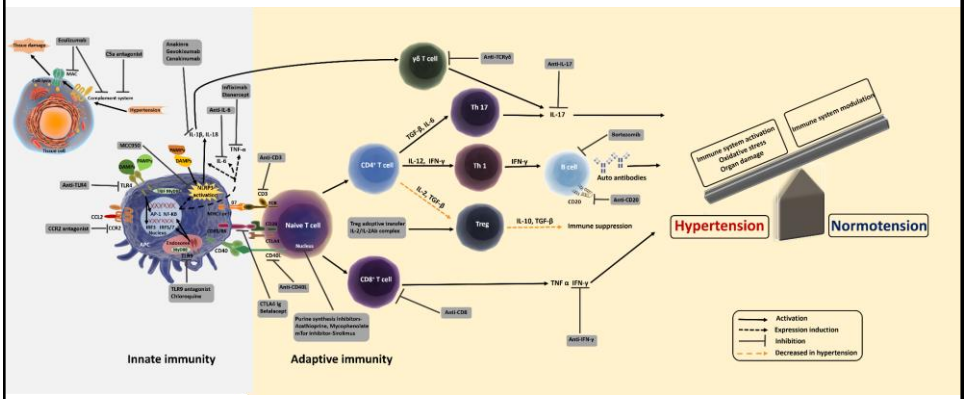
Hypertension: a new treatment for an old disease? Targeting the immune system

Correspondence Dr Fernando S. Carneiro, Department of Pharmacology, Ribeirão Preto Medical School, University of São Paulo, Av Bandeirantes, 3900 Ribeirão Preto, São Paulo 14049-900, Brazil. E-mail: fsilvac@usp.br

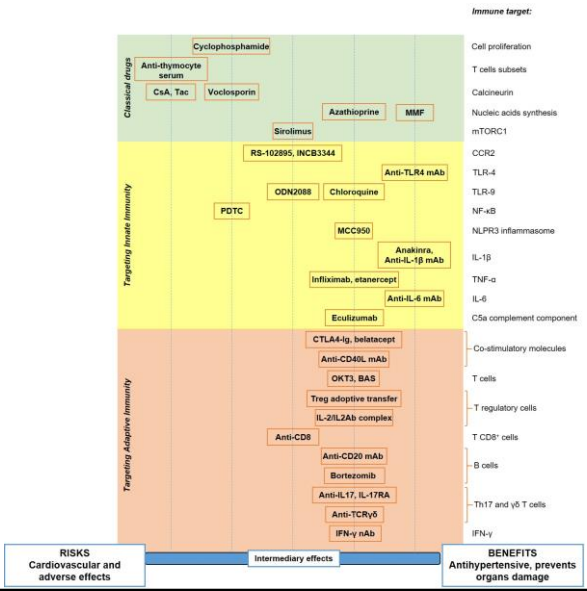
Received 28 March 2018; **Revised** 14 June 2018; **Accepted** 24 June 2018

Gisele Facholi Bomfim[3,*], Stefany Bruno Assis Cau[1,*], Alexandre Santos Bruno[1], Aline Garcia Fedoce[2] and Fernando S Carneiro[2]

Sistema Imune – Uma Oportunidade Terapêutica para ↓ PA?

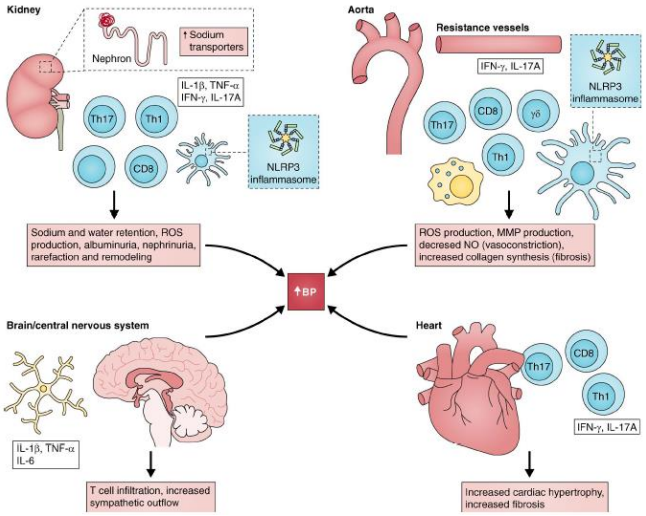


Sistema Imune – Uma Oportunidade Terapêutica para ↓ PA?



Sistema Cardiovascular e Sistema Imune

Considerações Finais



J Exp Med **(2018)** 215 (1): 21–33.

Sistema Cardiovascular e Sistema Imune

Considerações Finais

- ✓ O sistema imune está envolvido na fisiopatologia de outras doenças cardiovasculares além da hipertensão (nota: aterosclerose).
- ✓ Na hipertensão, nem sempre há envolvimento com o ↑ da PA, mas há com lesão em órgãos-alvo.
- ✓ Há muito avanço sobre outros tipos celulares (NK, γδ) e sobre as citocinas que participam do desenvolvimento da hipertensão.
- ✓ Doenças inflamatórias (periodontites) e autoimunes (lúpus, artrite reumatoide, psoríase, etc.) tem sido consideradas fatores de risco para o desenvolvimento de doenças cardiovasculares. **(*Free Radic Biol Med*.2018 Sep;125:104-115)**

Obrigado!

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