

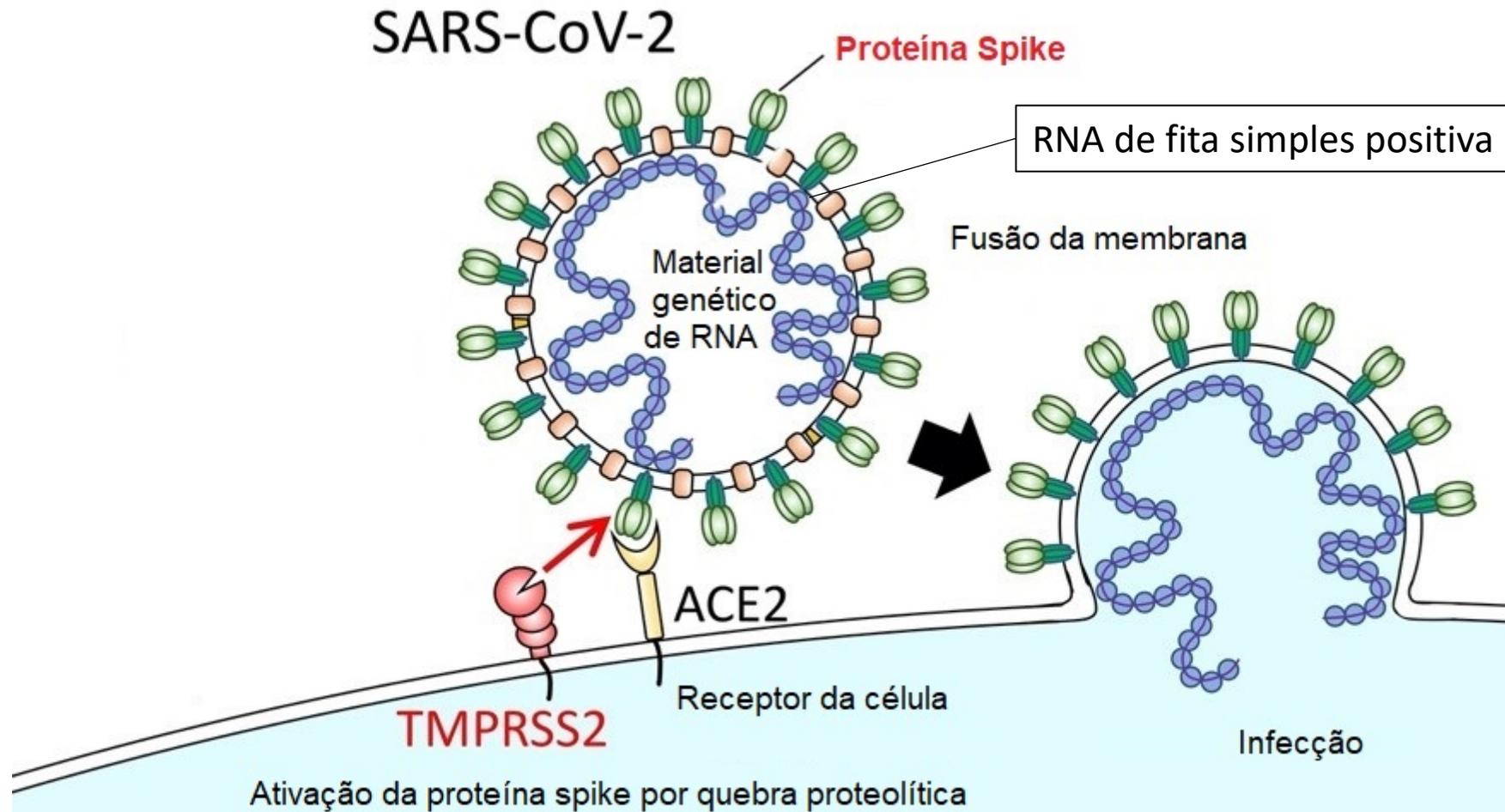
Imunidade aos microrganismos

Sars-Cov-2

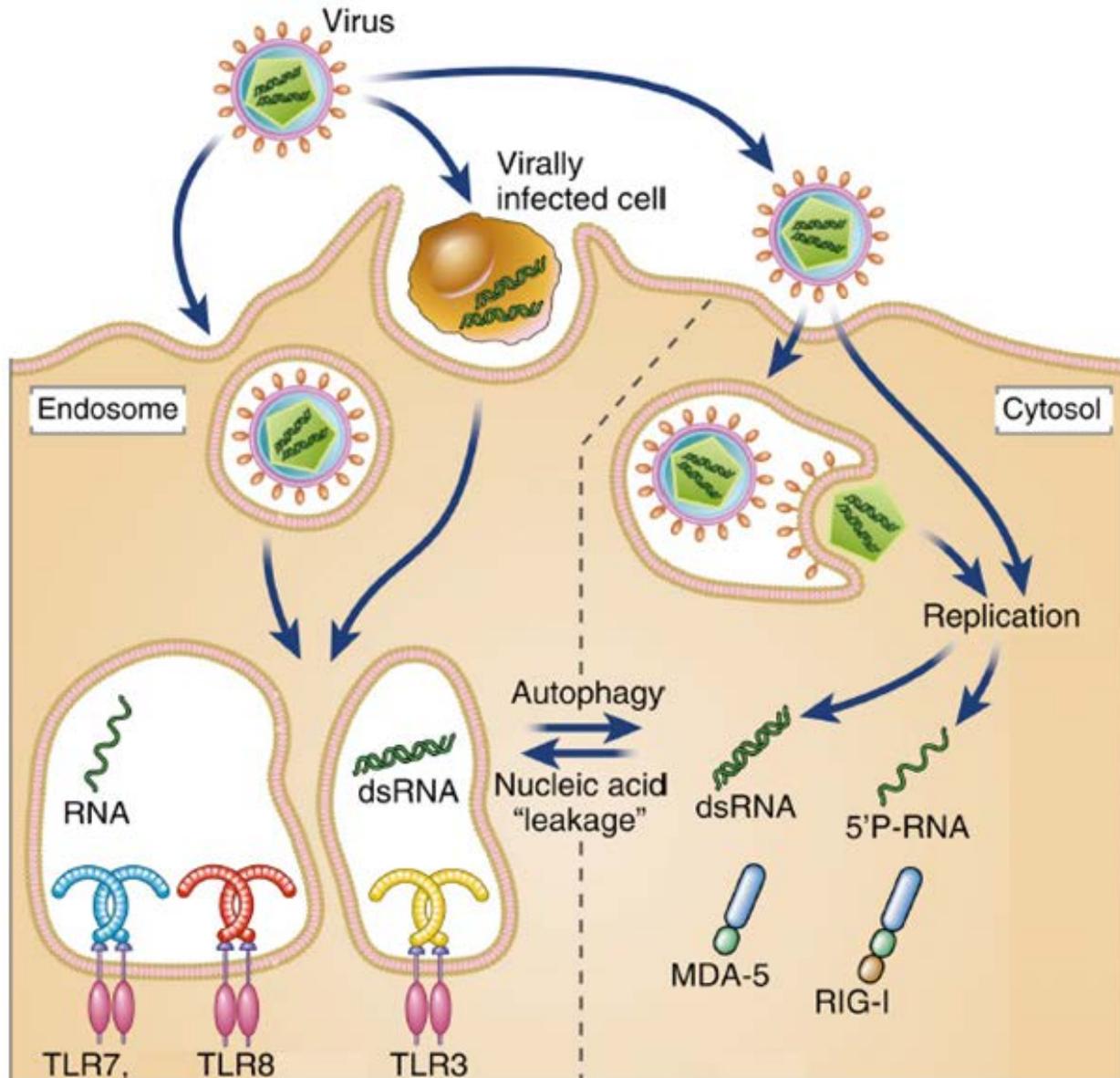
Disciplina integrada: Microbiologia, Imunologia e Parasitologia

Prof. Dr. Diego Luís Costa

Sars-Cov-2



Receptores de imunidade inata que reconhecem material genético de Sars-Cov2

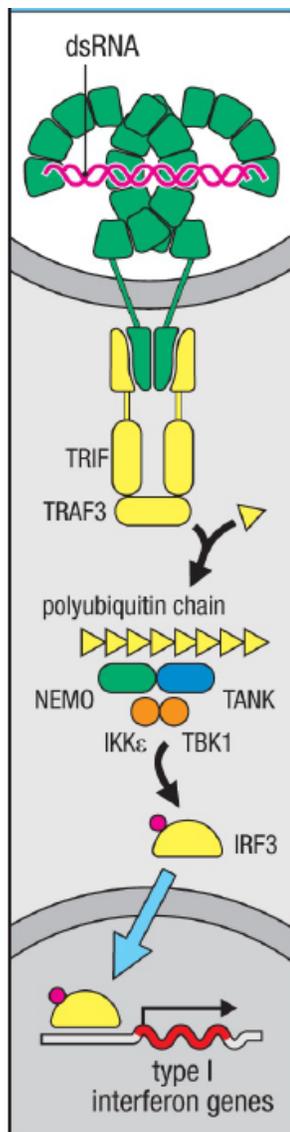


RIG-I, MDA5 – Detectam RNA de fita simples, RNA de dupla fita ou RNA complexado a DNA no citosol.

TLR3 – Detecta RNA de dupla fita no endossoma.

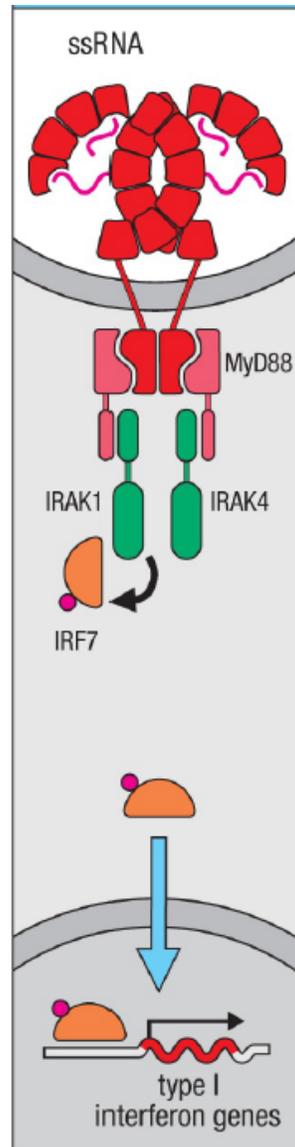
TLR7, 8 – Detectam RNA de fita simples no endossoma

Receptor Tipo Toll 3 – TLR3



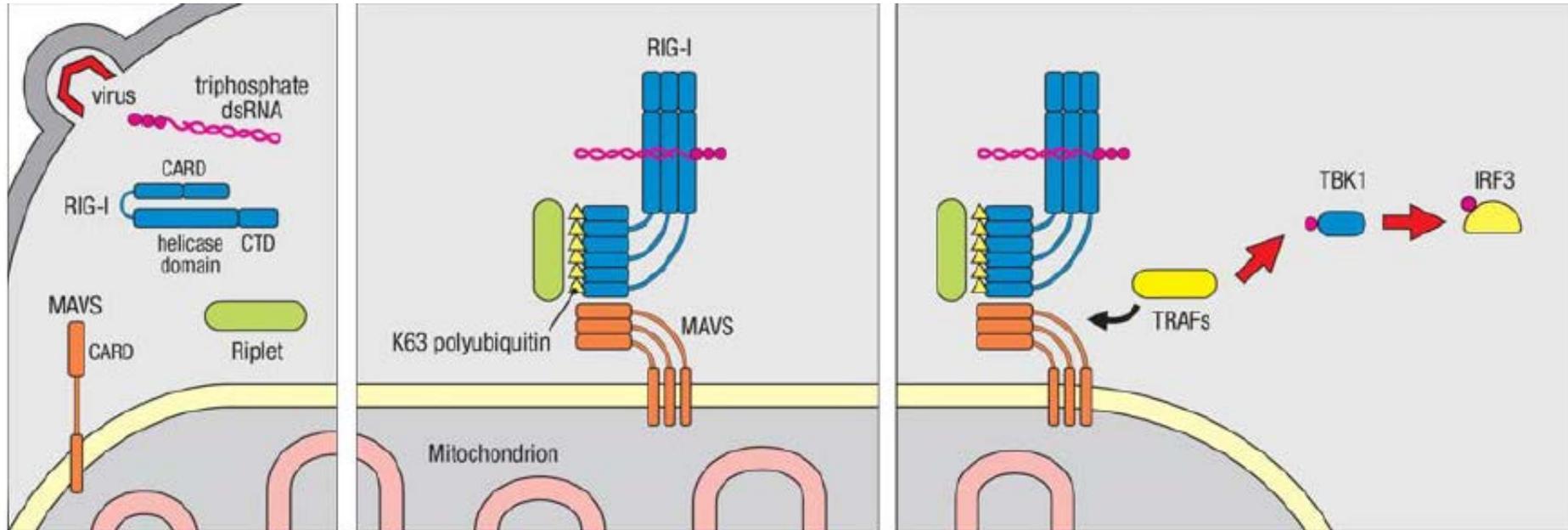
- TLR3 reconhece RNA de dupla fita.
- Advindo do genoma de vírus com RNA de dupla fita ou replicação de vírus com RNA de fita simples.
- Ativação de molécula adaptadora TRIF.
- Ativação de fator de transcrição IRF3.
- Ligação à região promotora de IFN α e IFN β (IFN do tipo I).

Receptores Tipo Toll 7 e 8 – TLR7 e 8



- TLR7 e 8 reconhecem RNA de fita simples curtos.
- TLR7 – RNA + guanosina / TLR8 – RNA + uridina.
- Ativação de molécula adaptadora MyD88.
- Ativação de fator de transcrição IRF7.
- Ligação à região promotora de IFN α e IFN β (IFN do tipo I).

Receptores RIG-I (RIG-I like receptors - RLRs)



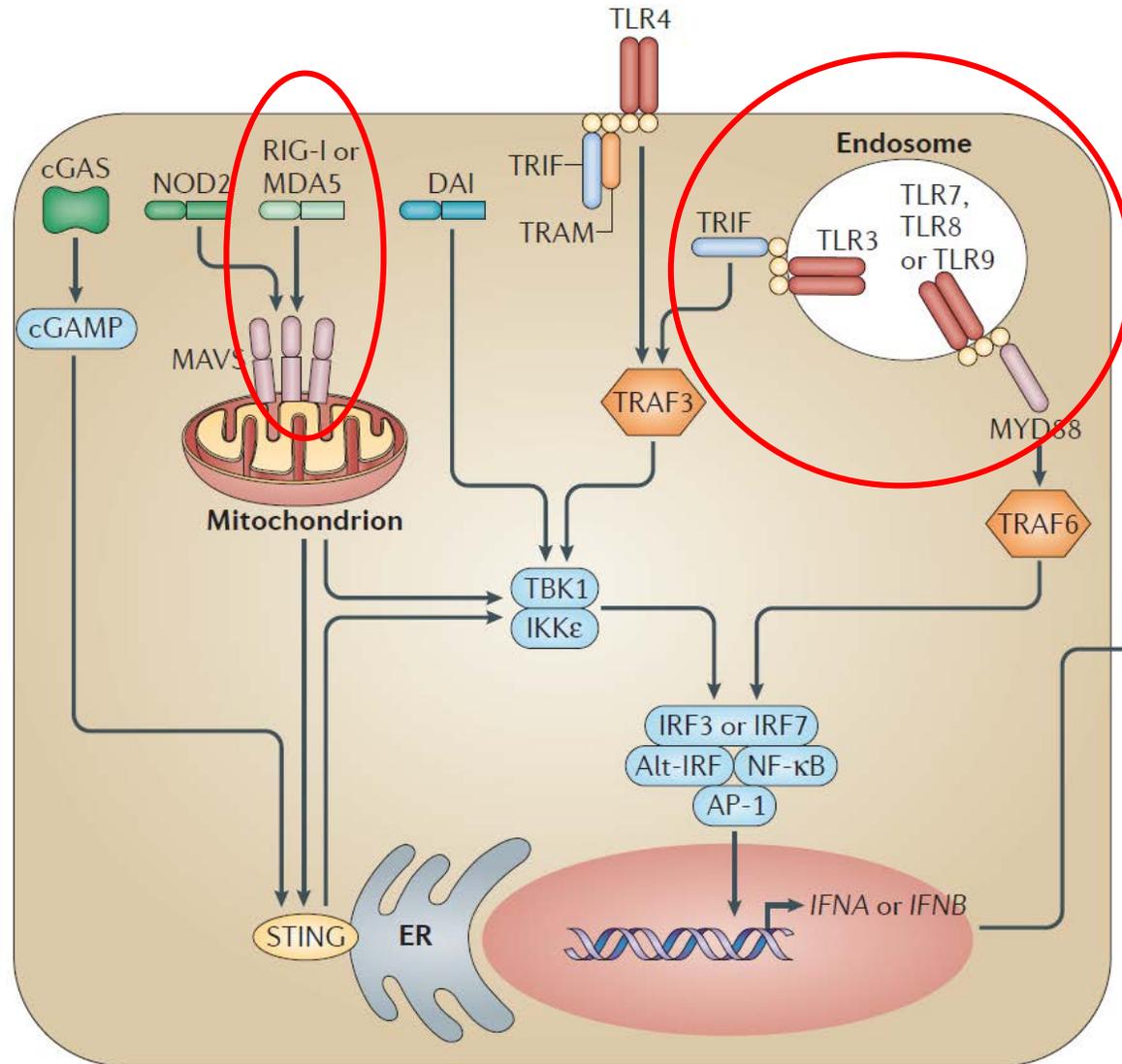
RIG-I, MDA5 – Detectam RNA de fita simples, RNA de dupla fita ou RNA complexado a DNA no citosol.

RIG-I – RNA com adição de motivo trifosfato na cauda 5'

MDA5 - RNA dupla fita ou RNA longo

IRF3 - Ativação de fator de transcrição IRF3 e ligação à região promotora de IFN α e IFN β (IFN do tipo I).

Imunidade inata antiviral

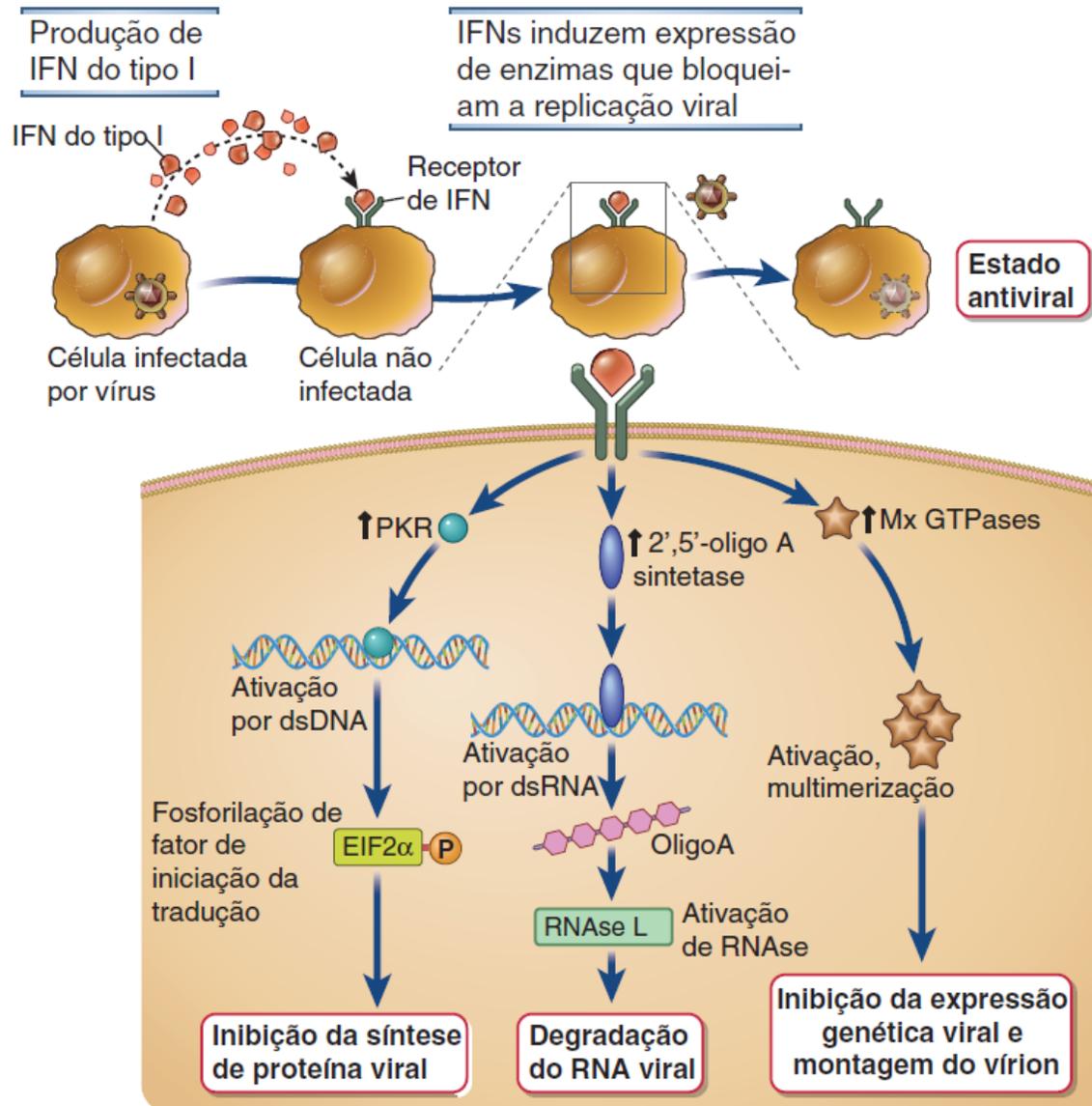


IFN α
IFN β

**Interferons
do tipo I**

“Interferem” com o processo de
replicação viral

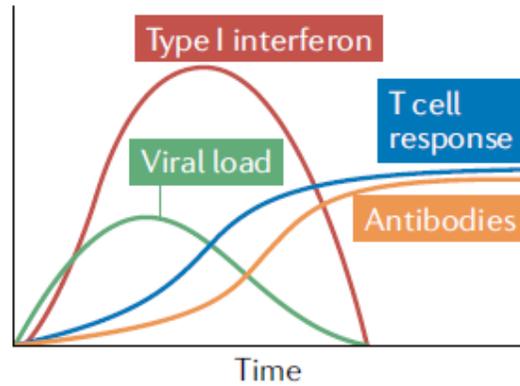
Indução de estado antiviral em células vizinhas



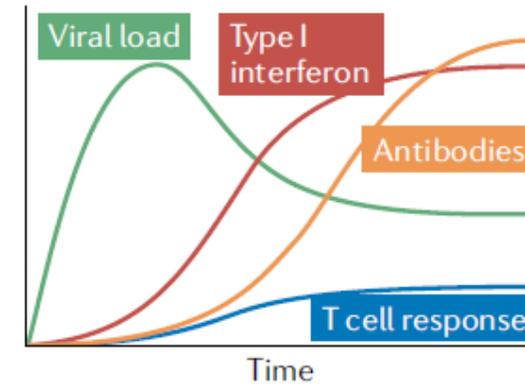
- Indução de expressão de enzimas que inibem replicação viral e montagem de vírions
- Aumento de expressão de moléculas de MHC de classe I
- Aumento de capacidade citotóxica de células NK
- Aumento de retenção de linfócitos T naíve em linfonodos

Covid-19 grave – defeitos na produção de IFN tipo I

a Early robust type I interferon response



b Delayed type I interferon response



• Viral clearance
• Normal-level T cell and B cell responses

Mild disease

• Young adults
• Low levels of viral exposure

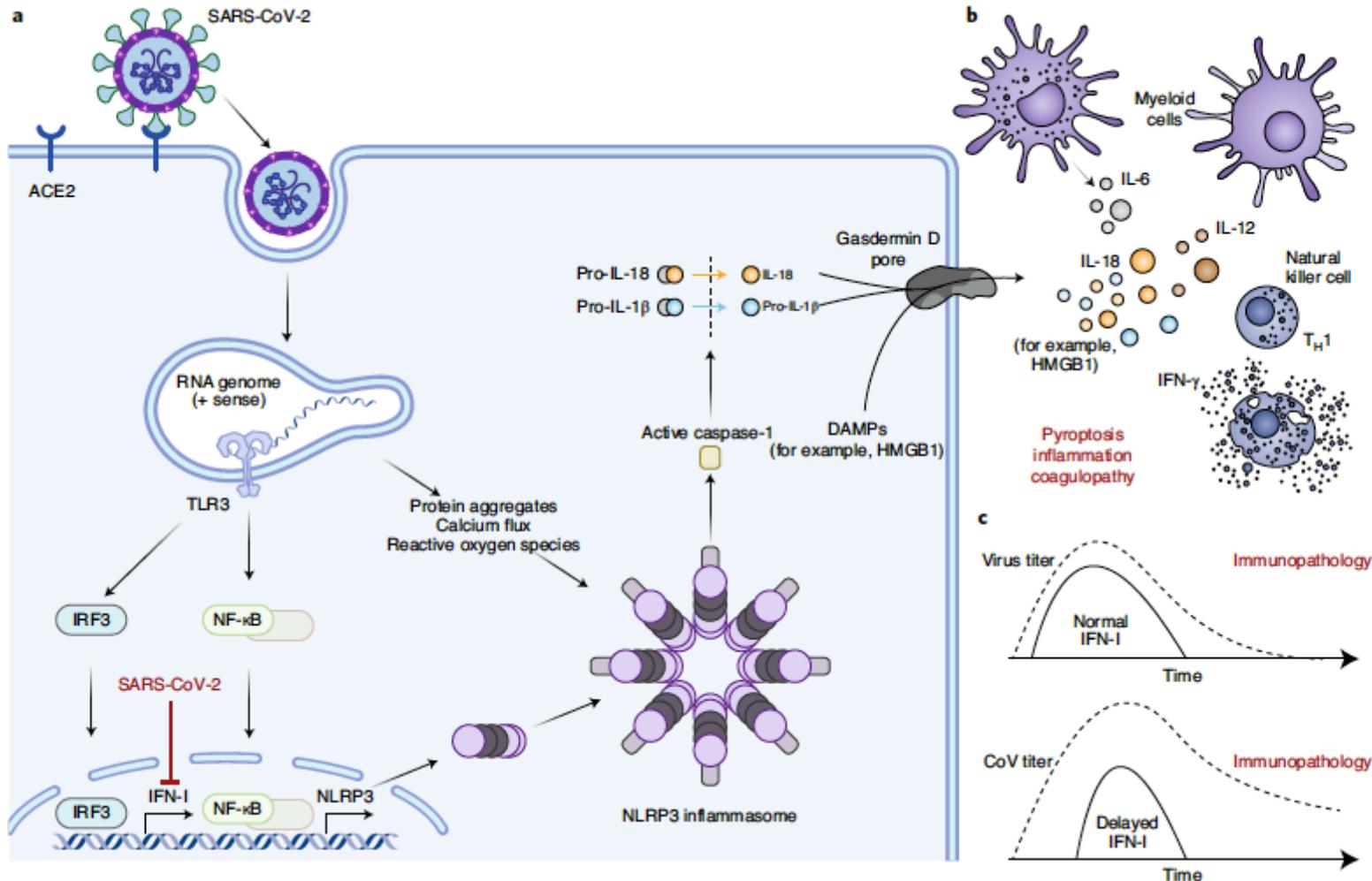
• Partial viral clearance
• T cell lymphopenia;
robust B cell response

Severe disease

• Older adults
• Higher levels of viral exposure

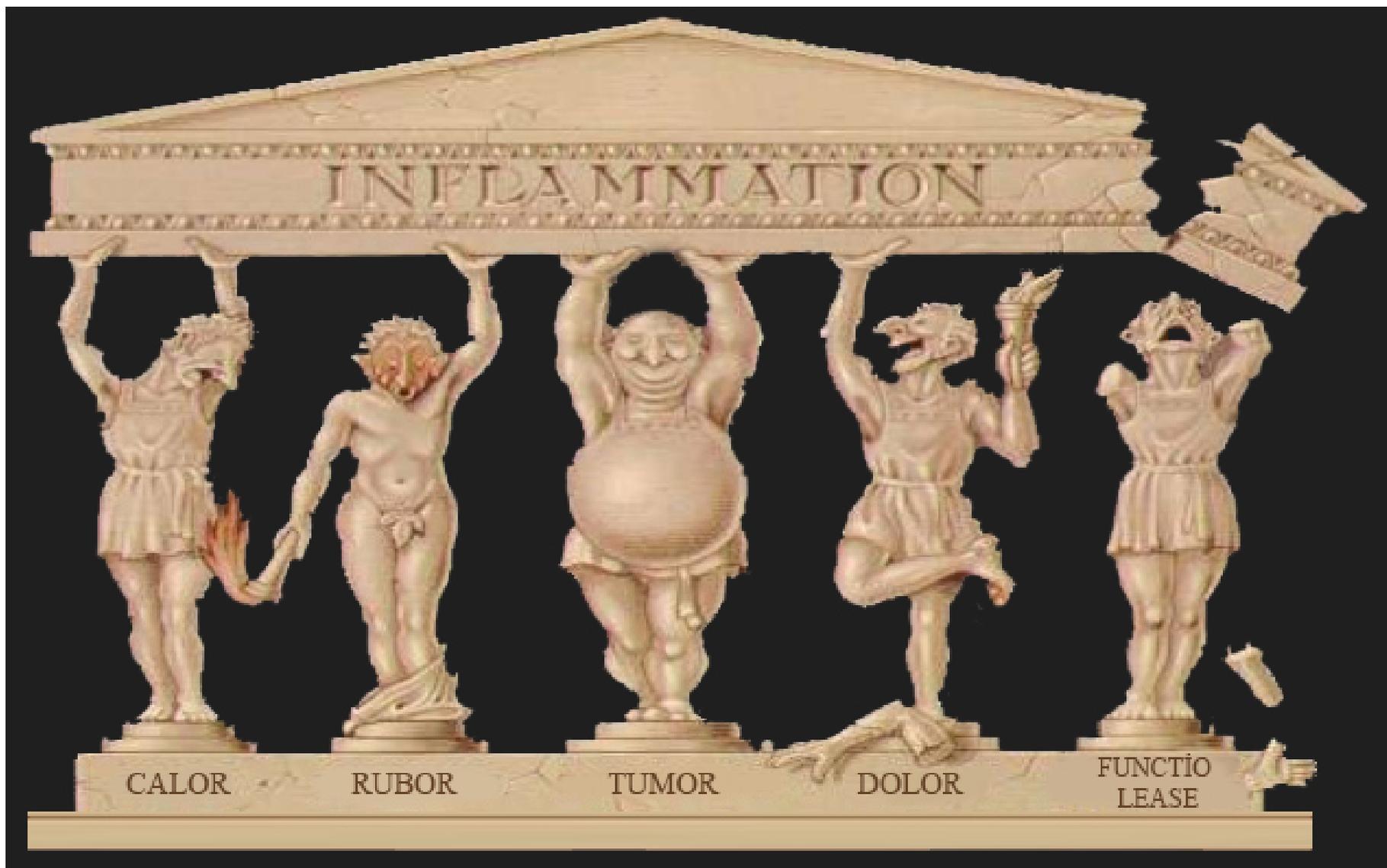
- Atraso na produção de IFN tipo I
- Deficiência na eliminação inicial do vírus
- Produção crônica elevada de IFN tipo I – biomarcador de gravidade da doença

Tempestade de citocinas inflamatórias

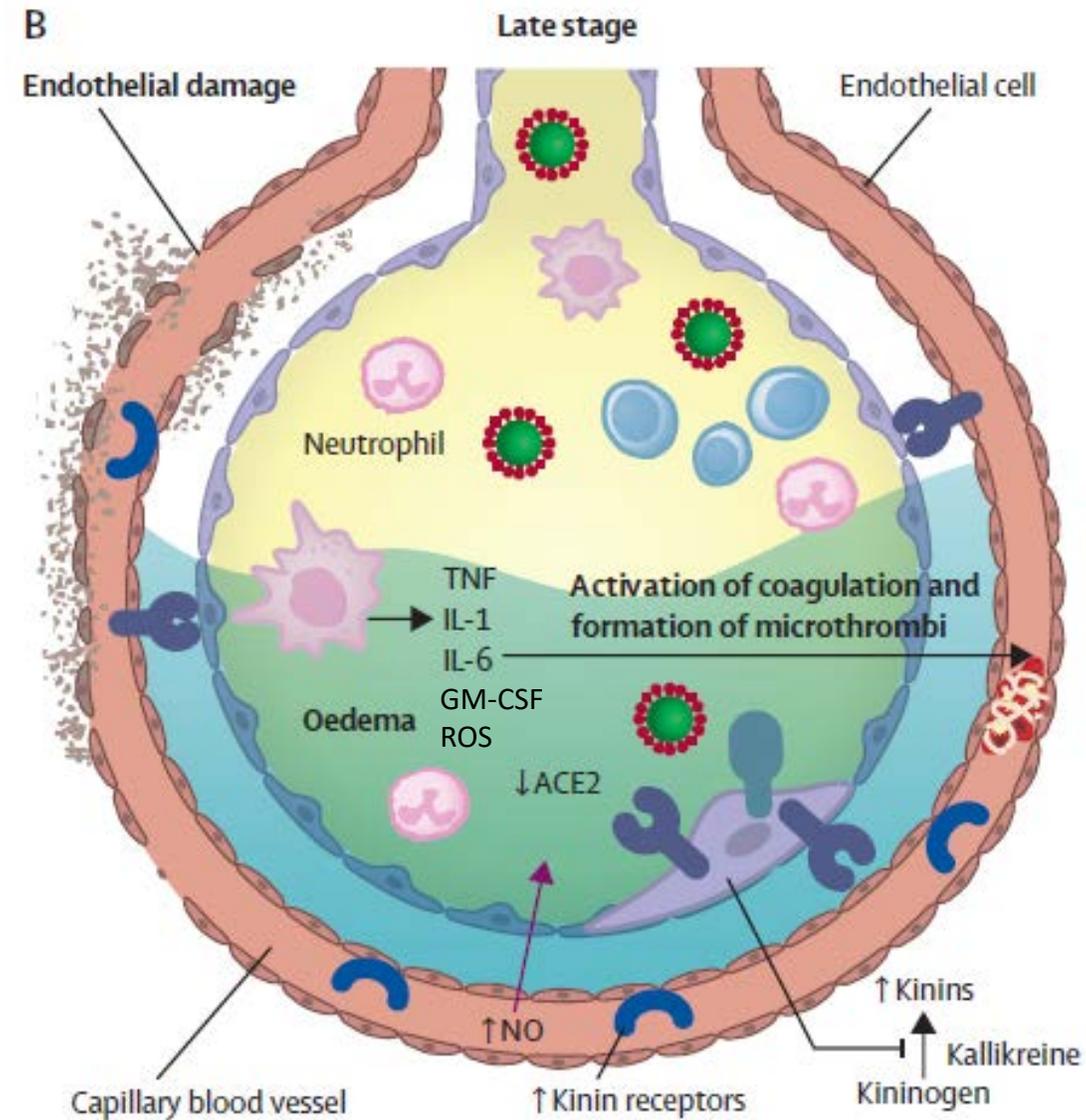


- Estresse celular e morte celular de células infectadas
- Liberação de DAMPs
- Ativação de receptores de imunidade inata e inflamassomas
- IL-6, TNF, IL-1β, GM-CSF

Sinais cardinais da inflamação

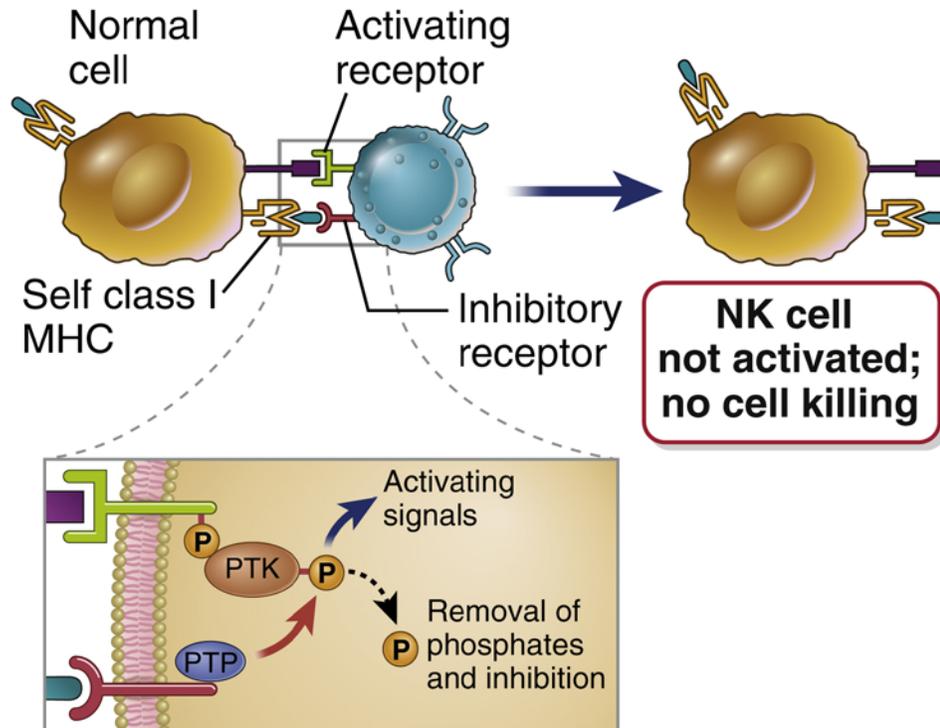


Tempestade de citocinas inflamatórias

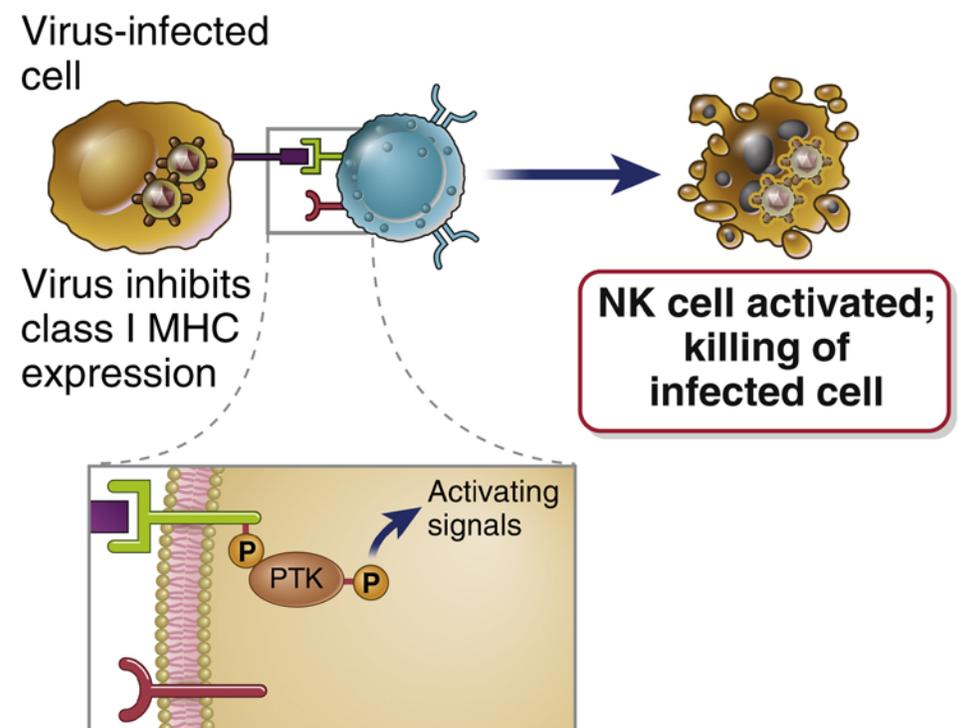


Ativação de células NK depende de balanço de sinais ativadores e inibidores

A Healthy cell; inhibitory receptor engaged

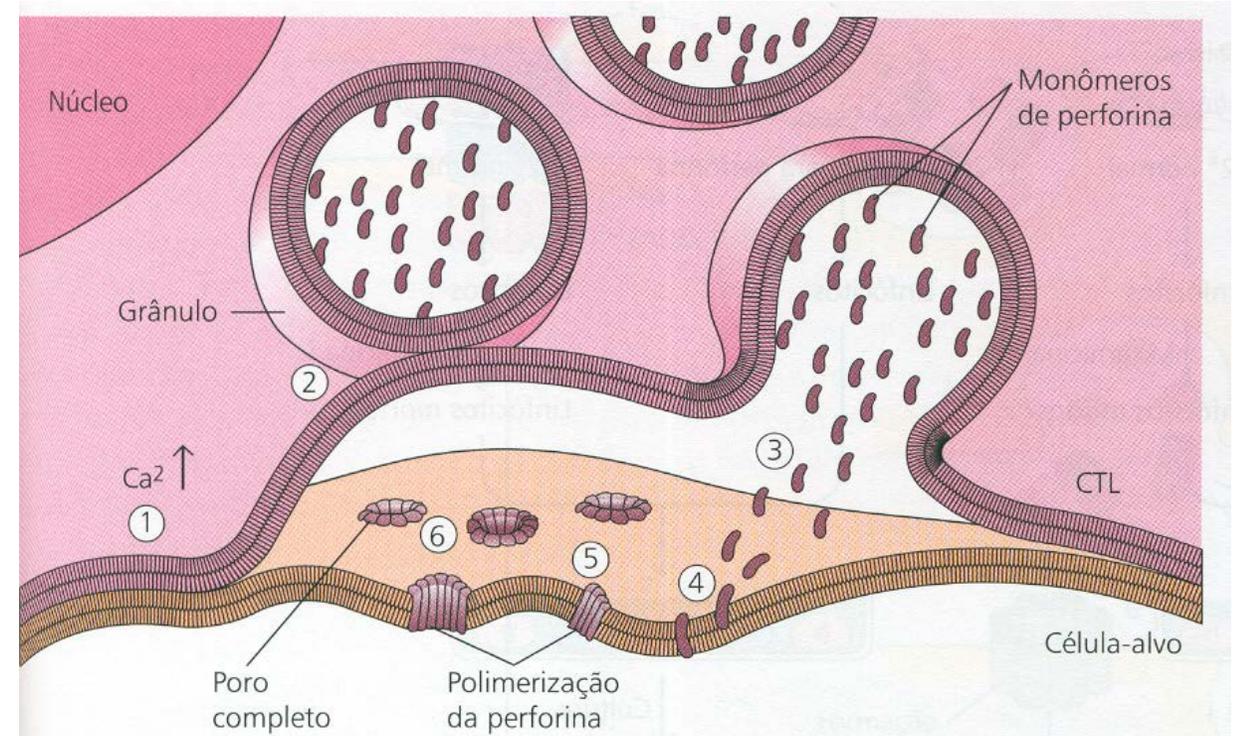
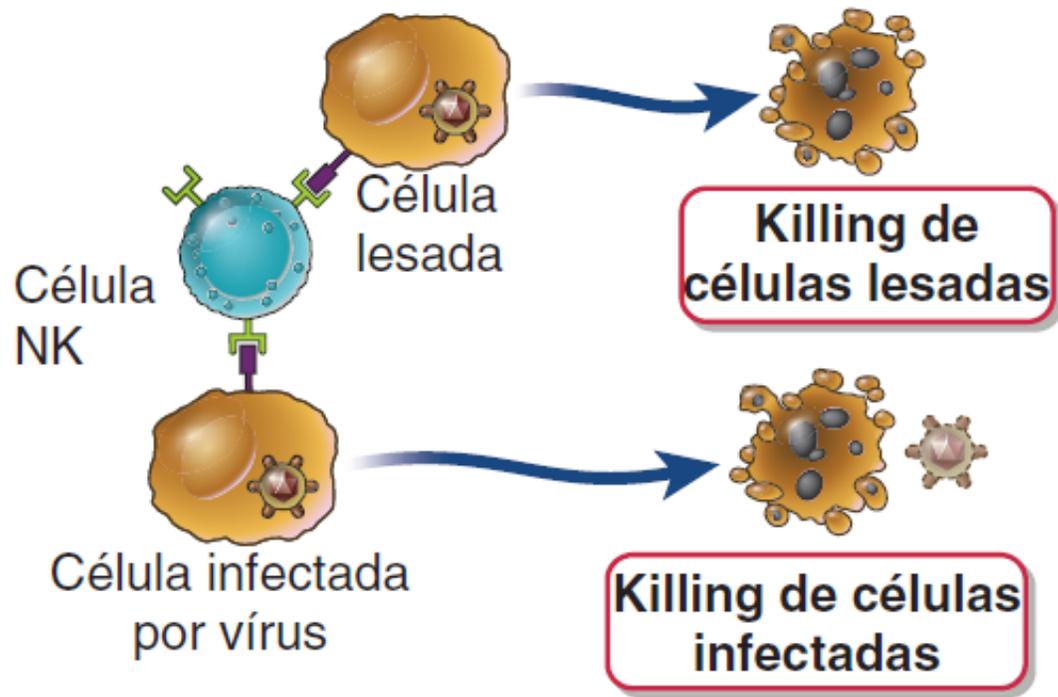


B Infected cell; inhibitory receptor not engaged



Ativação dependente de balanço entre sinais providos por receptores ativadores e receptores inibidores.

Células NK

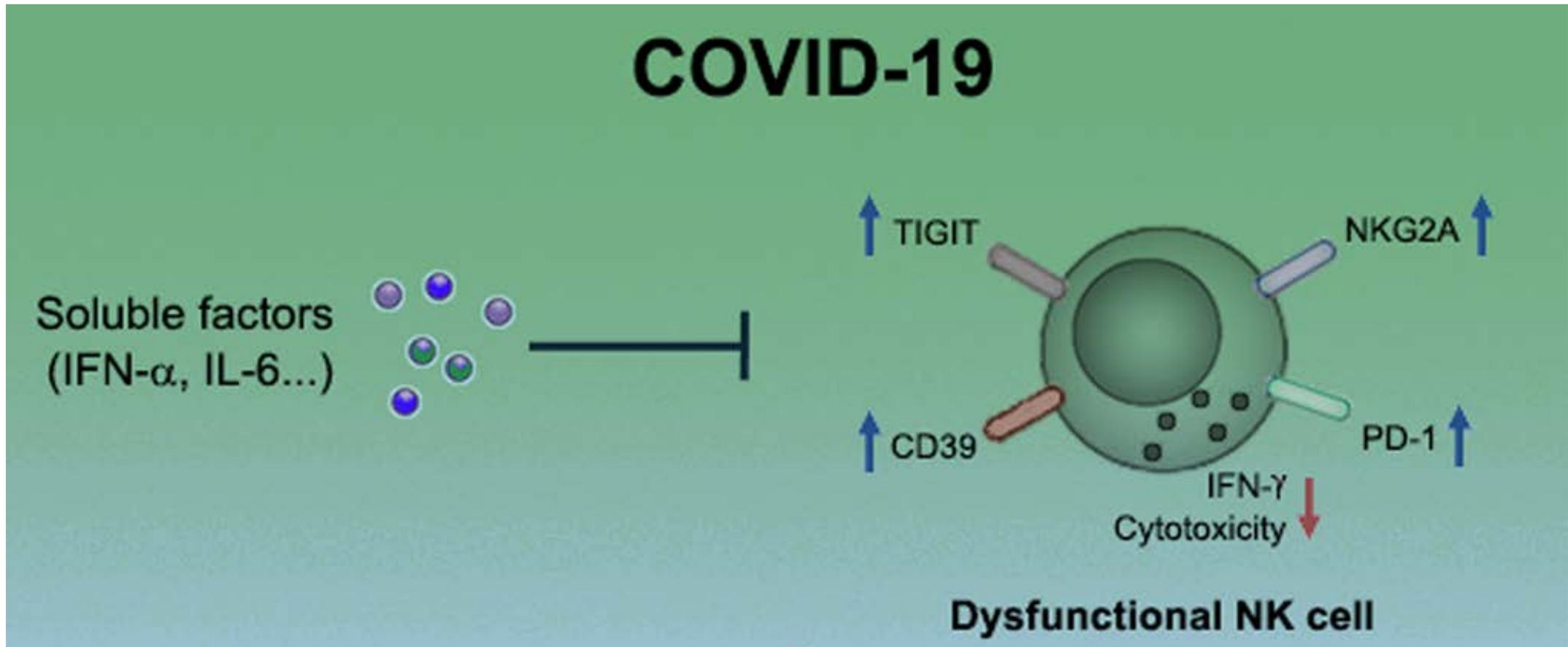


Liberação de conteúdo de grânulos citotóxicos

Perforina: formação de poros e transporte

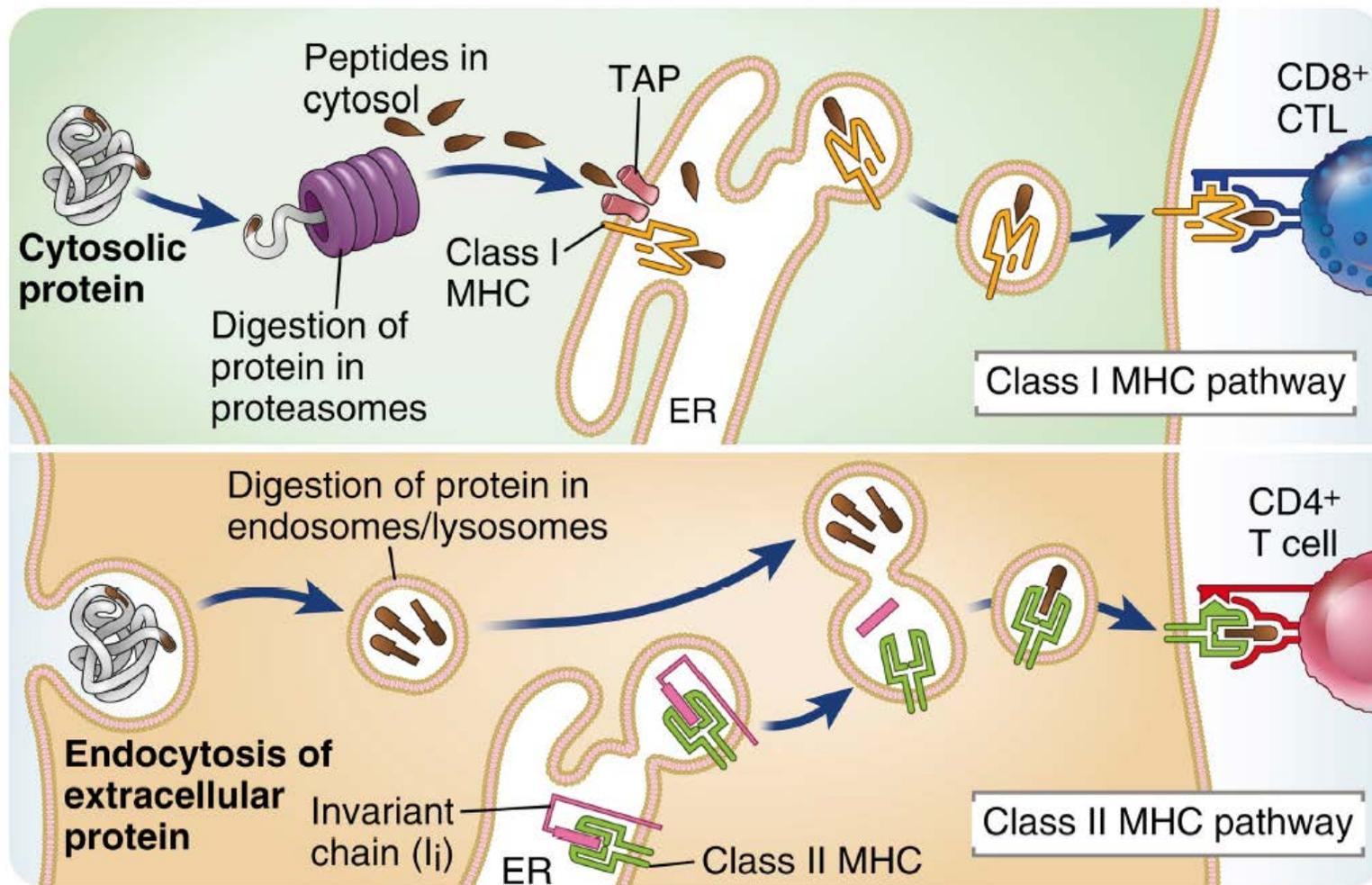
Granzima: ativa morte celular apoptótica por via de caspases

Disfunção de células NK em Covid grave



- Produção crônica de citocinas pro-inflamatórias induz expressão de receptores inibidores em células NK

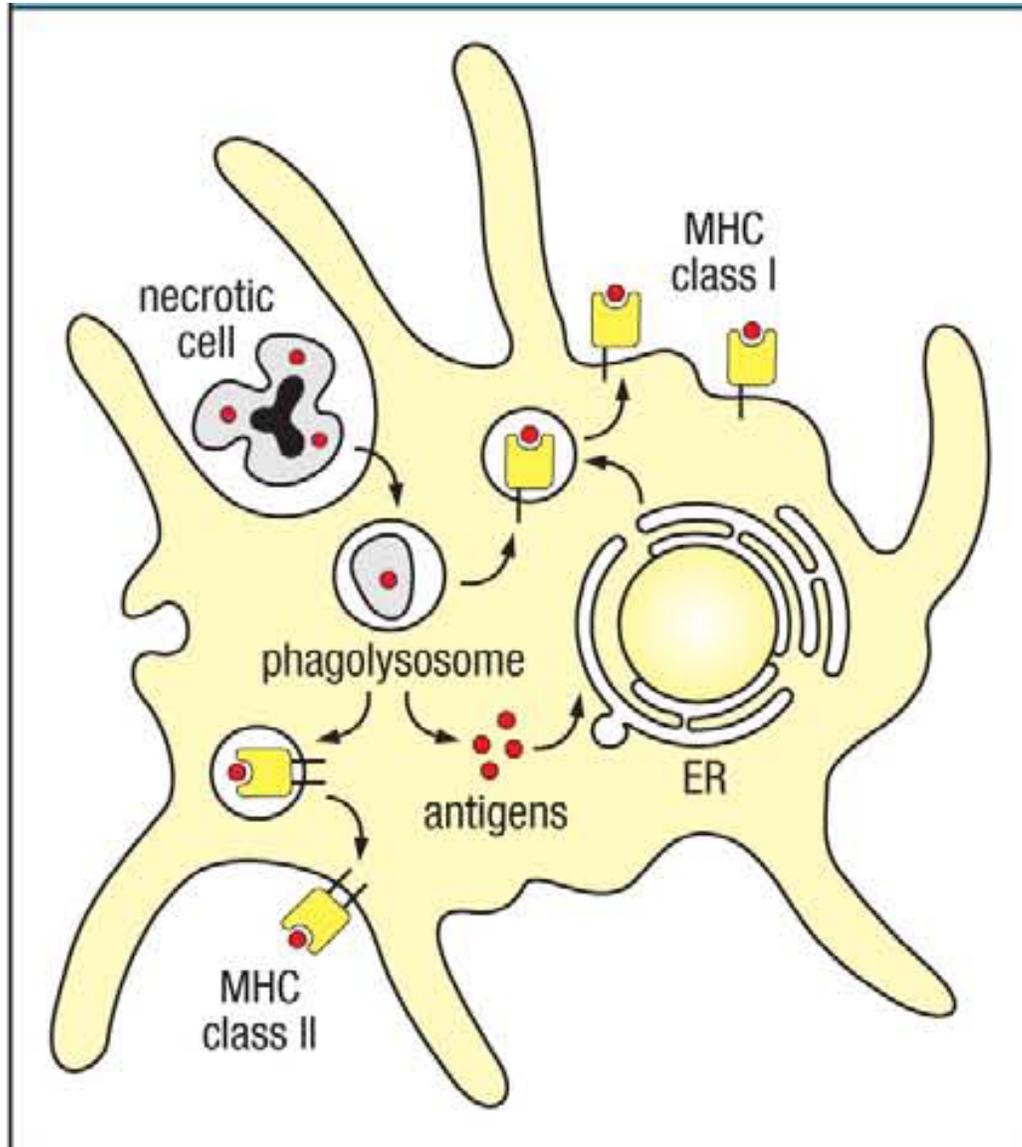
Imunidade adaptativa celular contra Sars-Cov2



Apresentação de antígenos com MHC de classe I para linfócitos T CD8+ (citotóxico)-apresentação cruzada

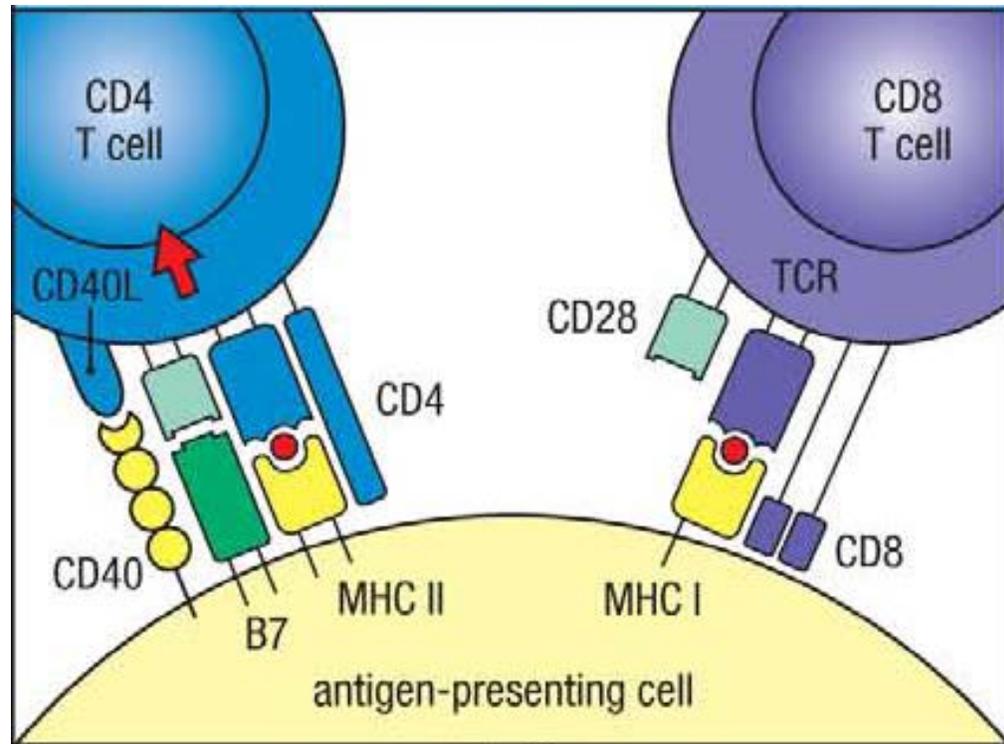
Apresentação de antígenos com MHC de classe II para linfócitos T CD4+ (T helper)

Ativação de linfócitos T CD8+ citotóxicos

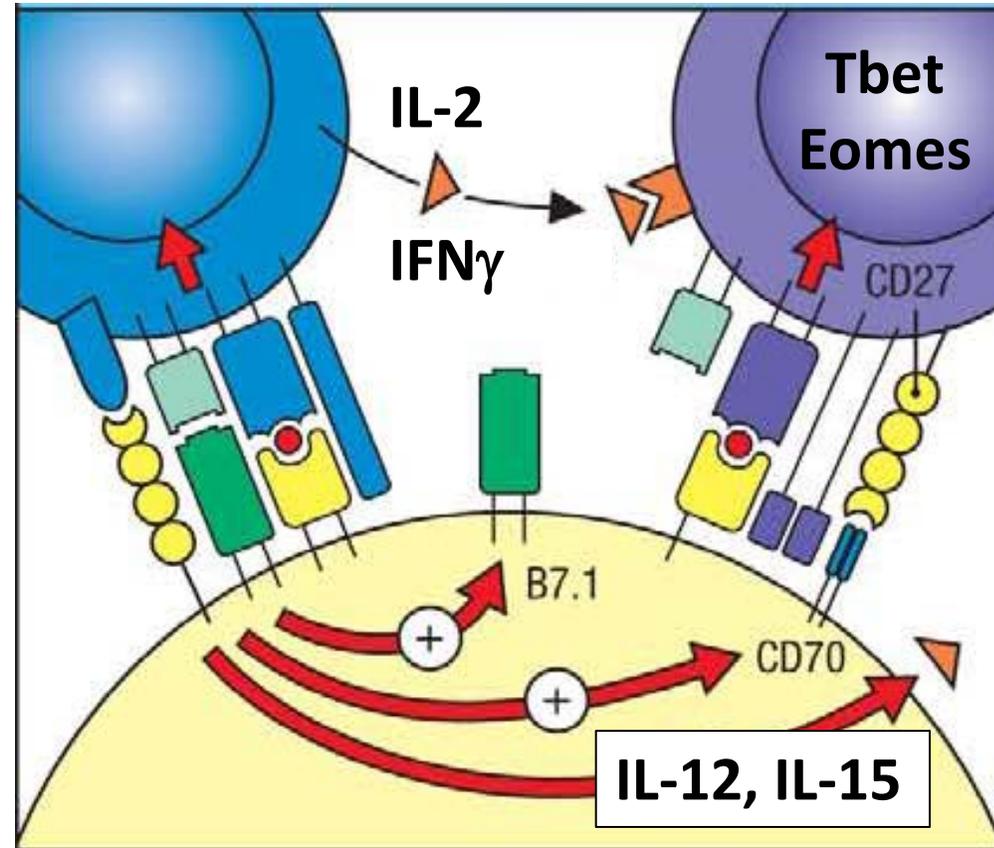


- Células dendríticas especializadas podem apresentar antígenos tanto para linfócitos T CD4+ (MHC II) quanto T CD8+ (MHC I) – **apresentação cruzada de antígenos.**

Ativação de linfócitos T CD8+ citotóxicos



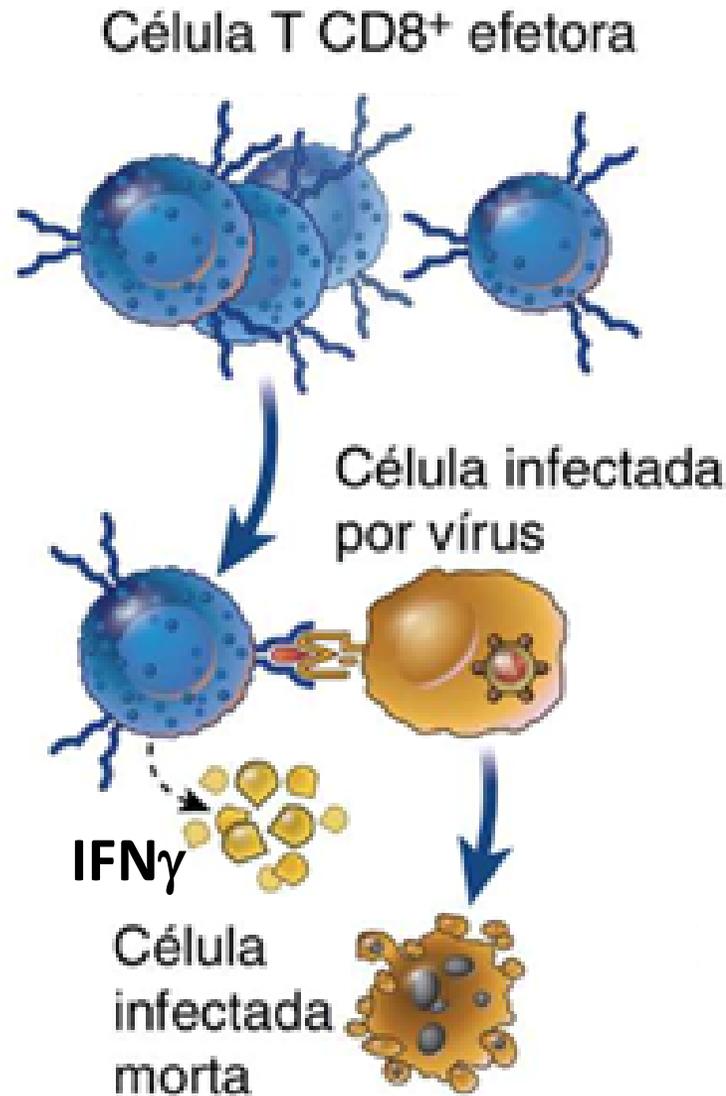
Licenciamento de APC por T CD4+ (CD40L-CD40) aumenta expressão de moléculas coestimuladoras para ativação concomitante de CD8+.



Produção de IL-2 por CD4+ é importante para ativação e expansão clonal concomitante de CD8+.

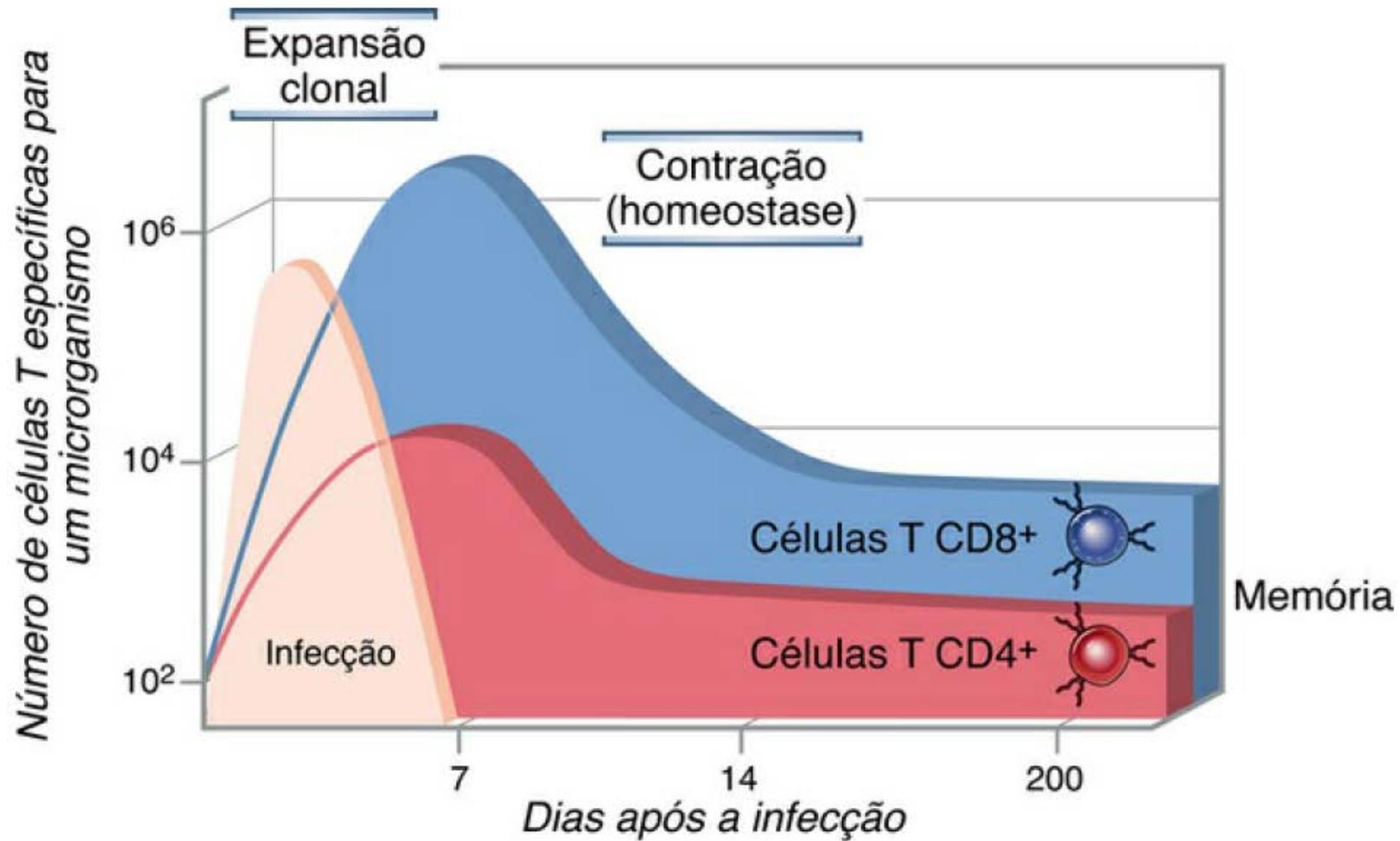
Produção de IFN γ por CD4+, junto à produção de IL-12 por APC, promove estabilização de fatores de transcrição e programação citotóxica.

Linfócitos T citotóxicos reconhecem antígenos virais expressos junto a moléculas de MHC de classe I em células infectadas



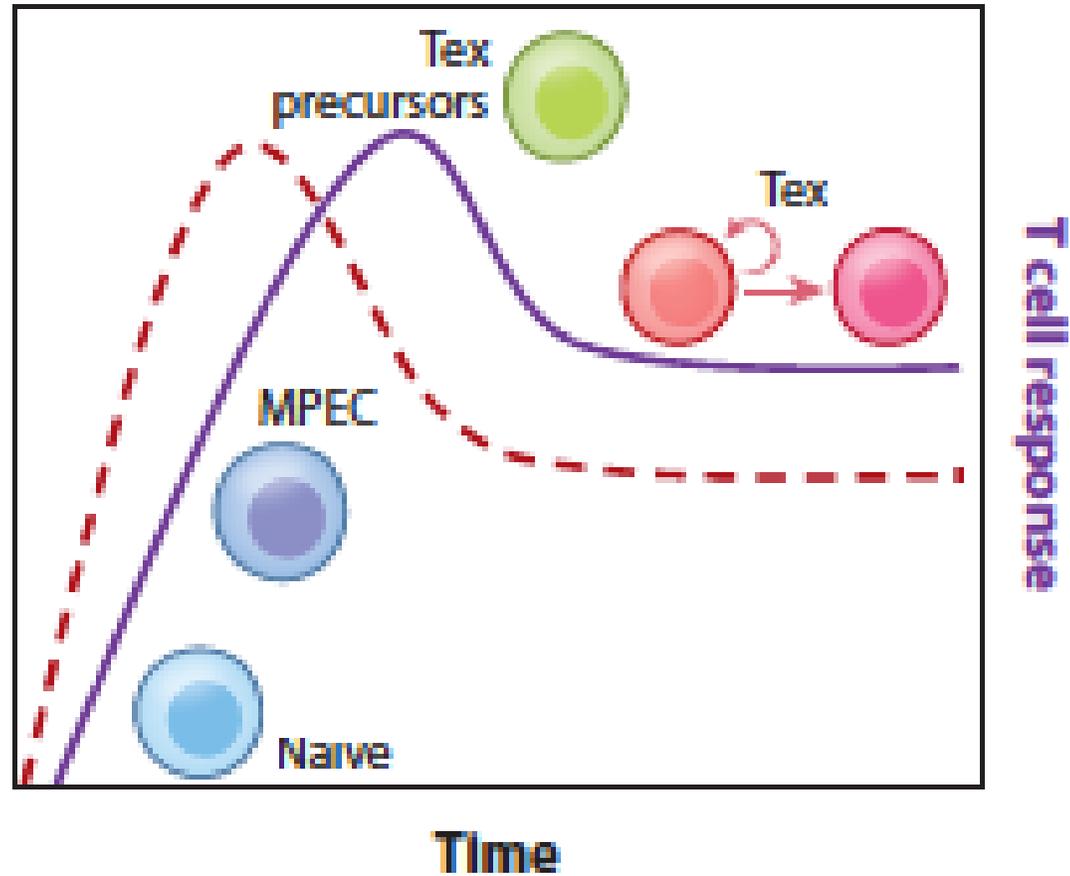
**CTL efetor e de memória:
pode responder ao vírus
por meio de secreção
de citocinas,
proliferação,
killing do alvo**

Resposta imune bem sucedida e eliminação do antígeno

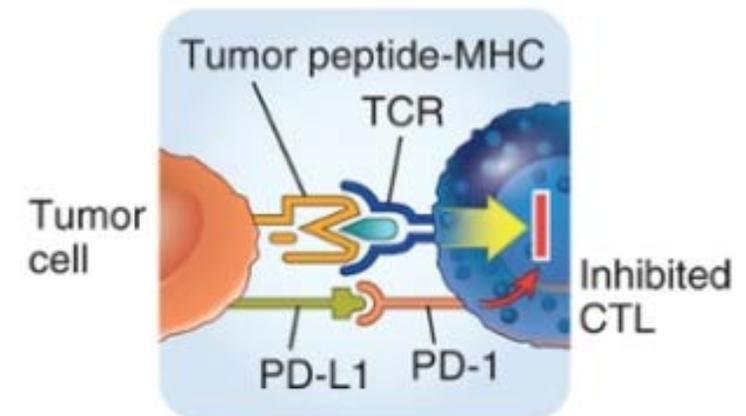
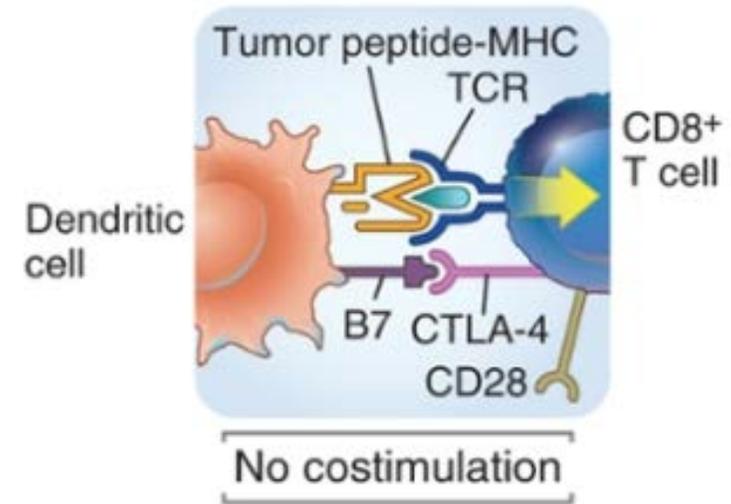
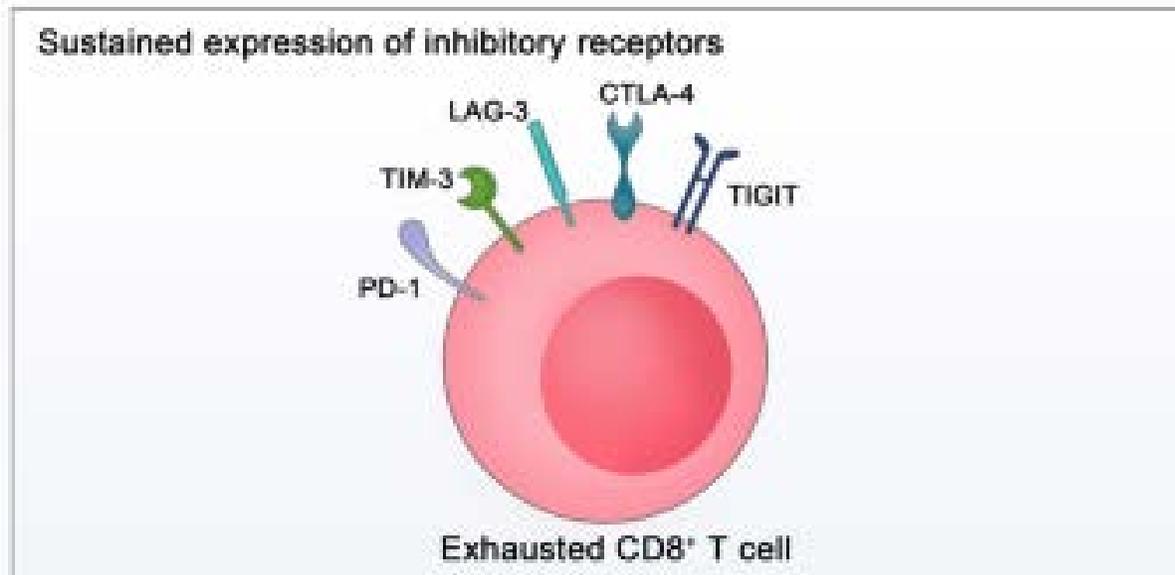
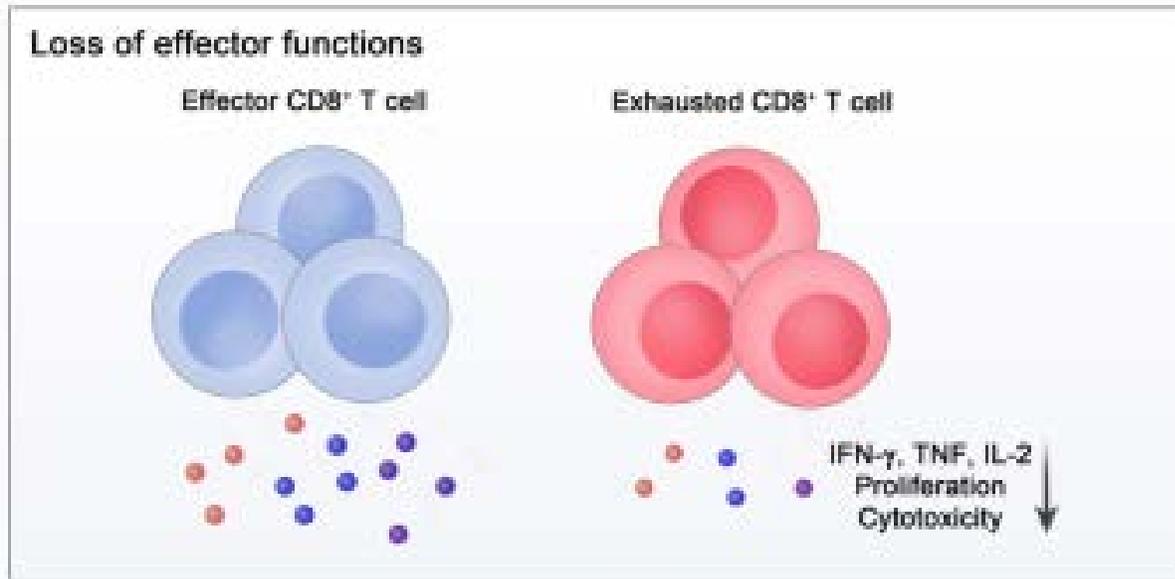


Exaustão de linfócitos T

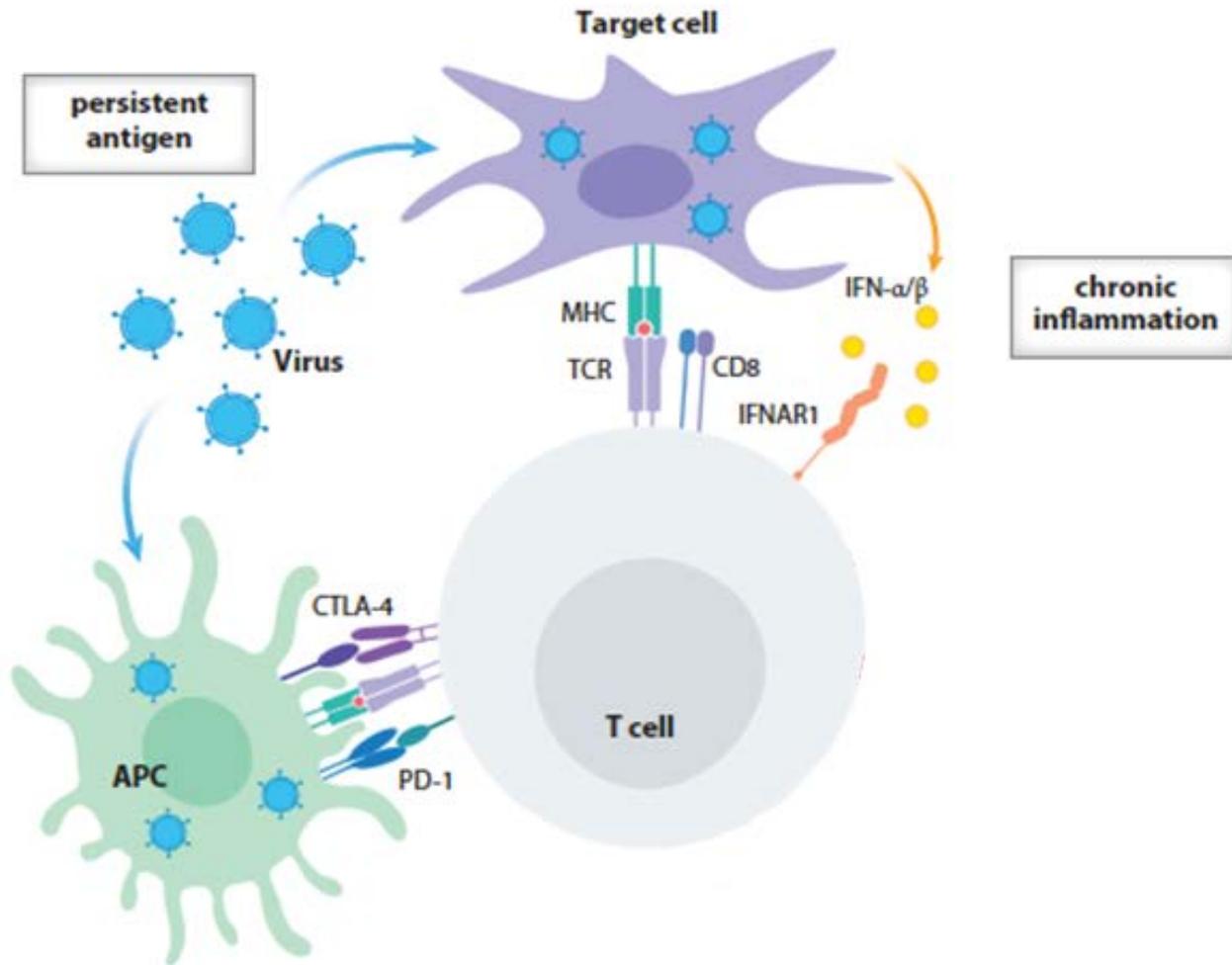
Falha na eliminação do antígeno e exposição crônica



Moléculas de “checkpoint inmunológico”



Exaustão celular de linfócitos T CD8⁺ citotóxicos



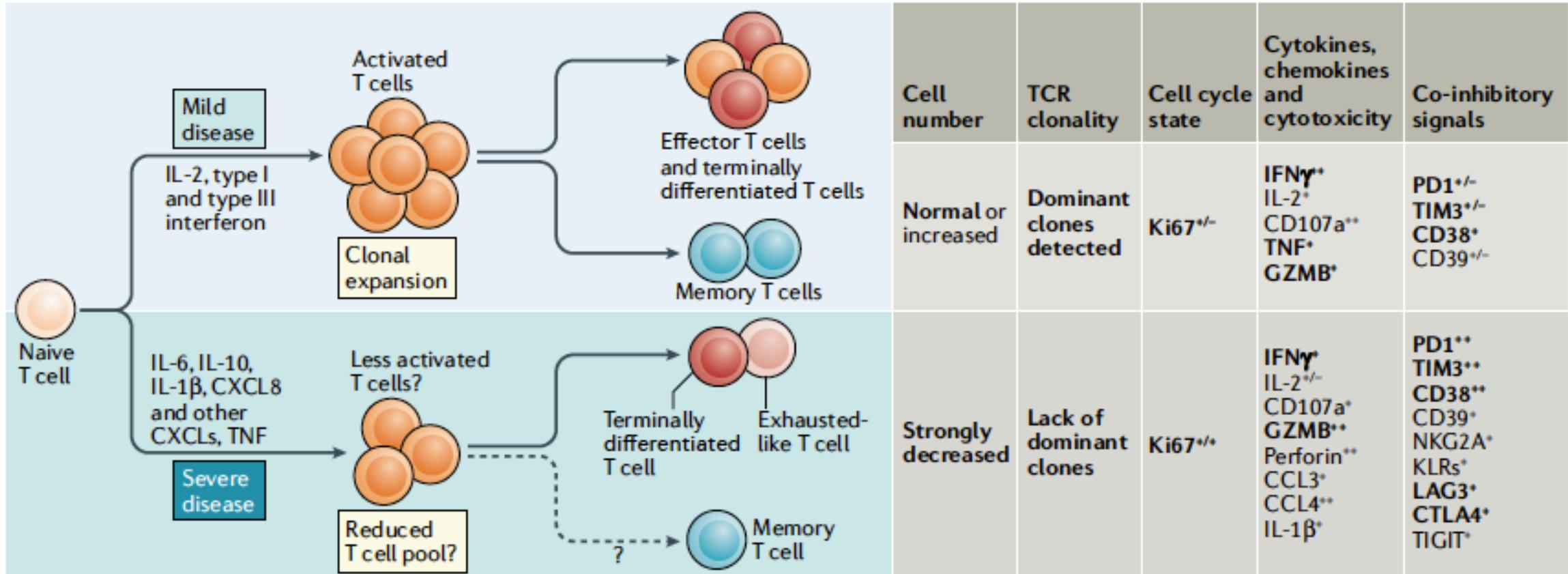
Expressão de receptores inibidores:

- PD1
- TIM3
- LAG3
- CTLA4
- TIGIT

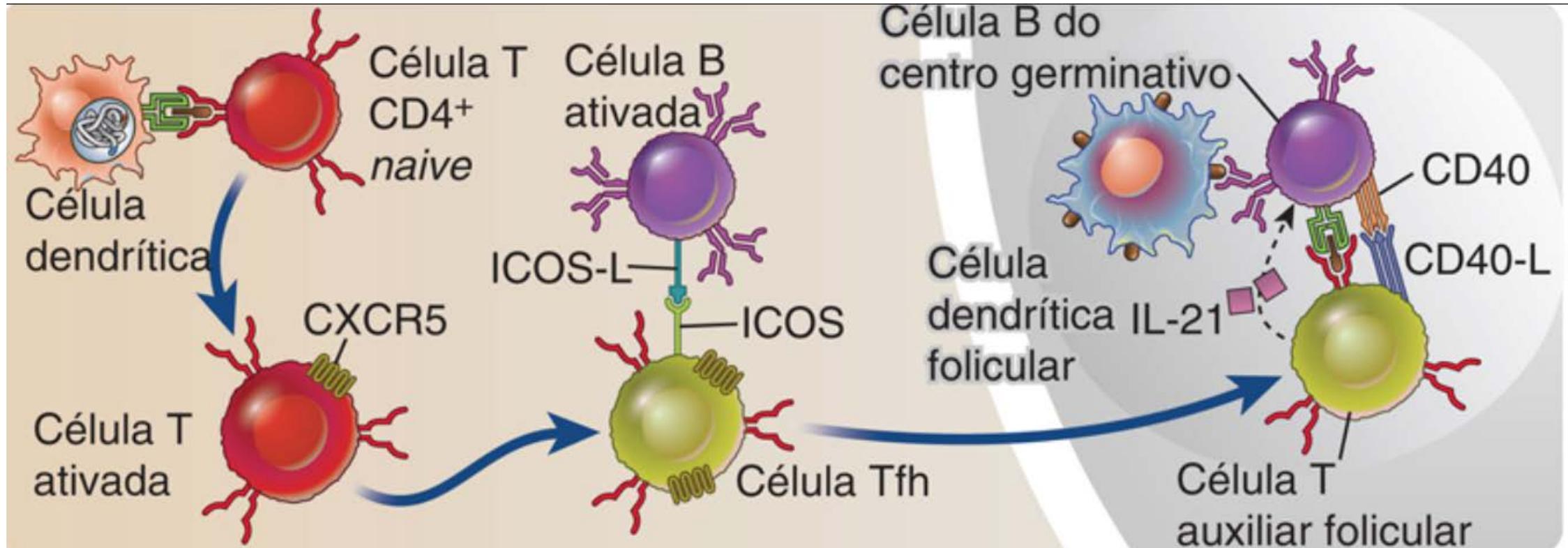
Baixa produção de citocinas e baixa citotoxicidade.

Disfunção de respostas mediadas por linfócitos T CD8⁺ na Covid grave

a Proposed CD8⁺ T cell response during COVID-19

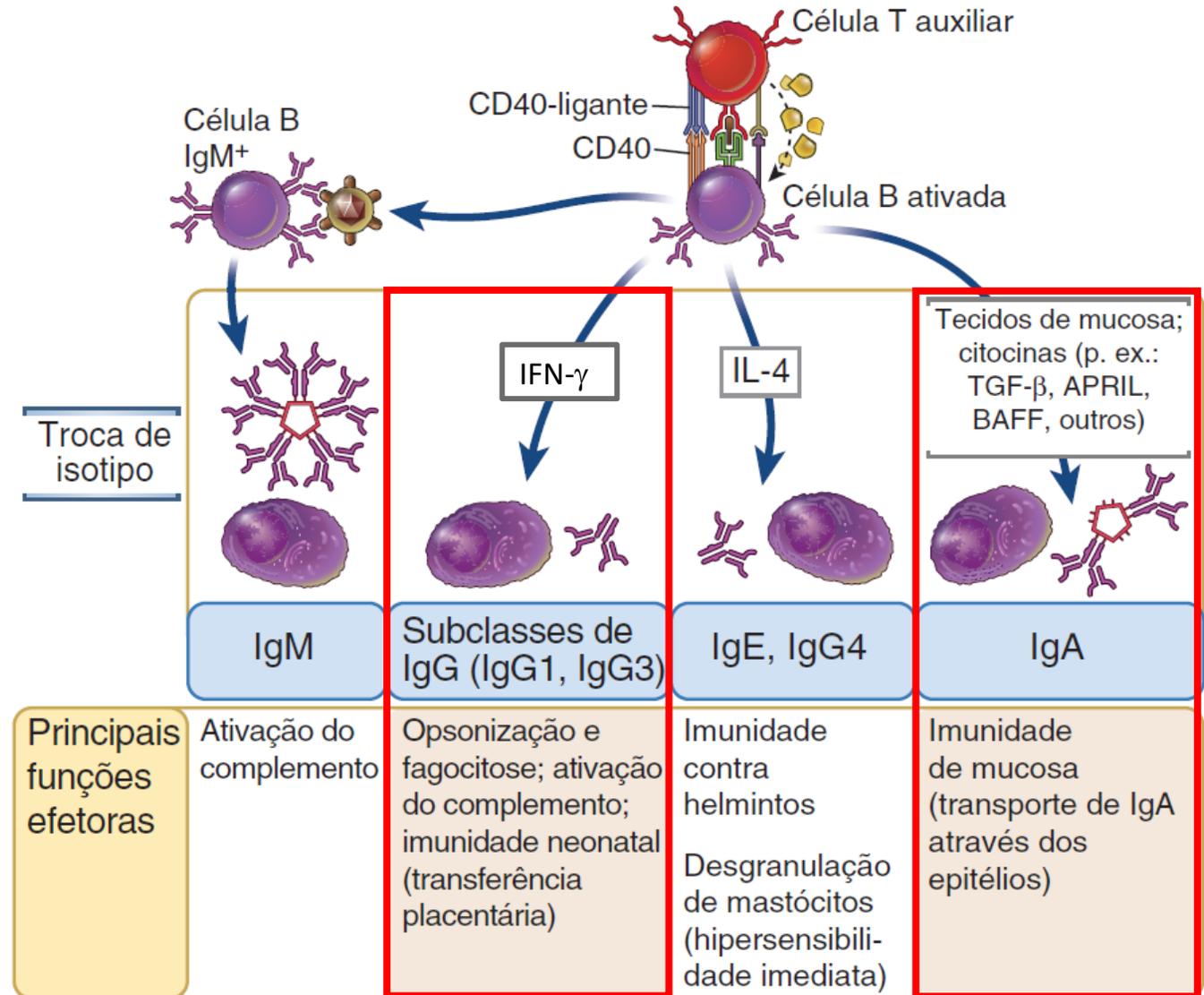
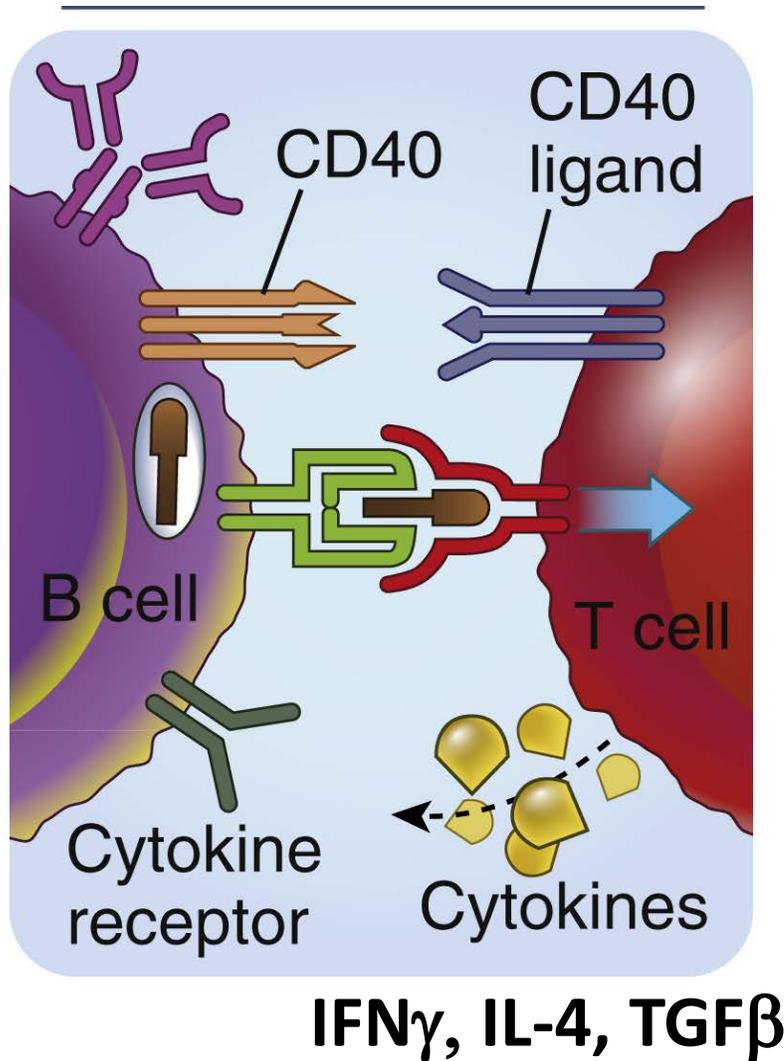


Ativação de resposta adaptativa humoral contra Sars-Cov2

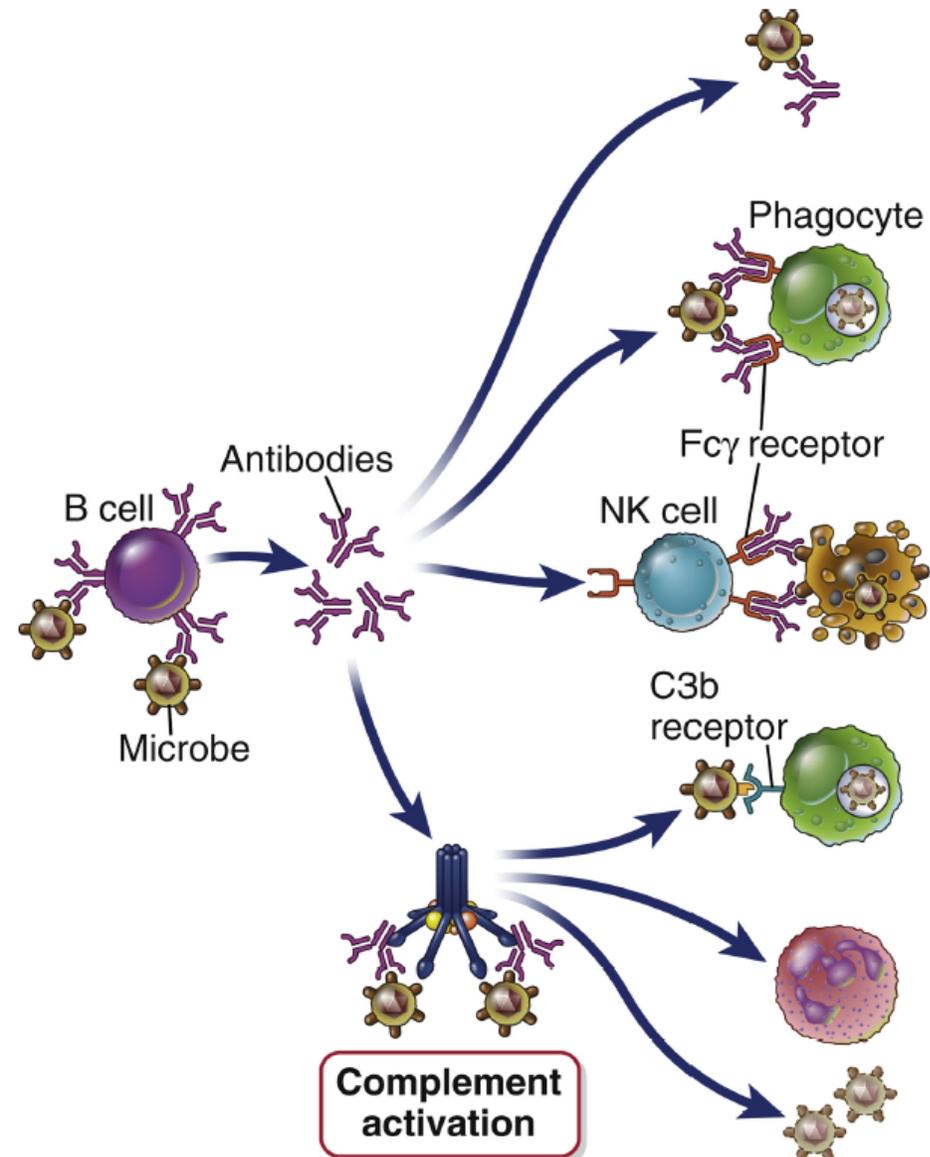


Ativação de linfócitos B específicos para proteínas virais auxiliada por linfócitos T CD4+ foliculares (Tfh) – Reação de centro germinativo – maturação de afinidade

Troca de isotipo de imunoglobulinas



Mecanismos efetores da imunidade humoral contra vírus



Neutralização viral – impede infecção das células pelos vírus

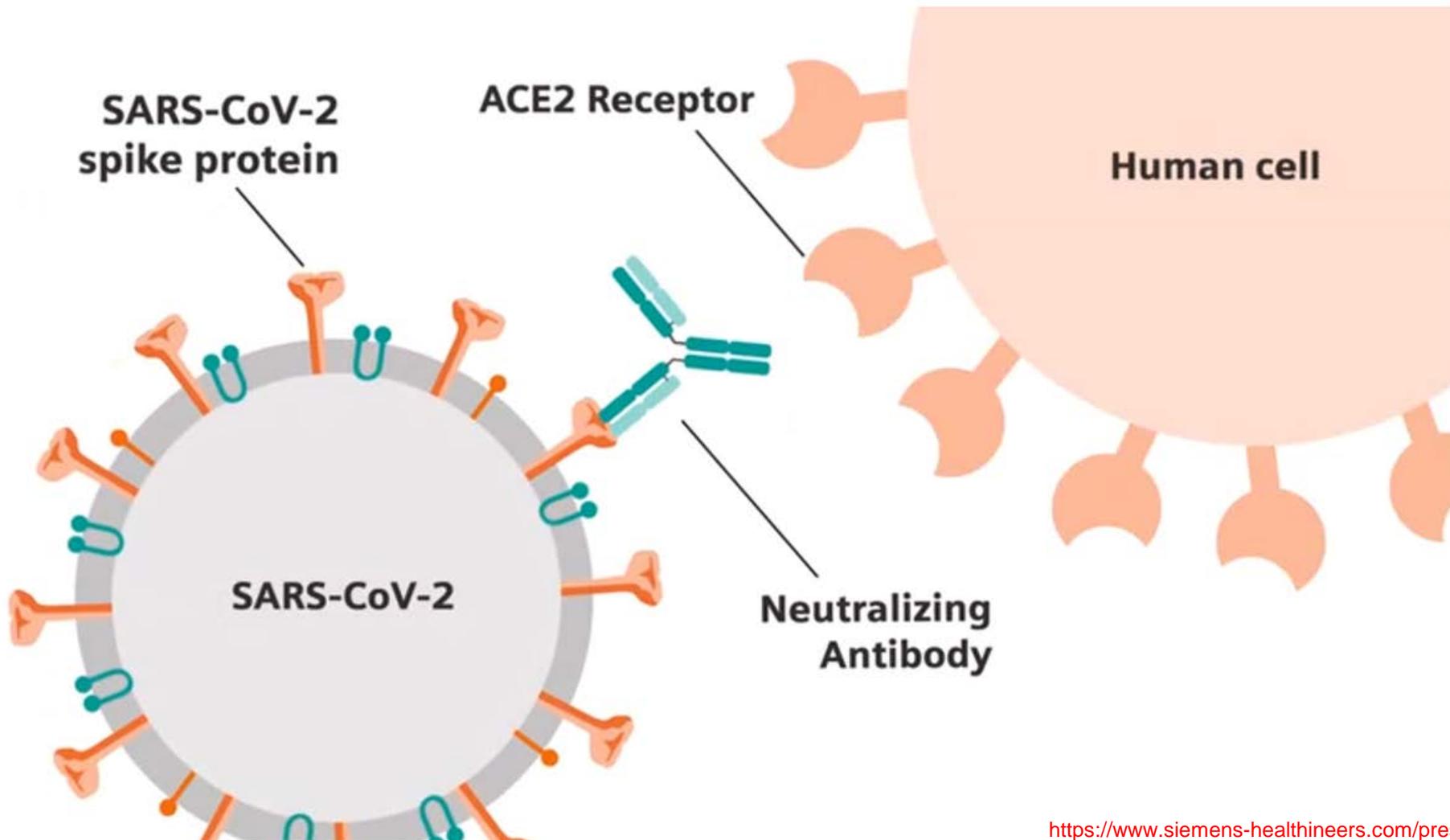
Opsonização viral – fagocitose de partículas virais – receptores de porções Fc (FcR) de fagócitos

Citotoxicidade celular dependente de anticorpos – receptores de porções Fc (FcR) de NK

Ativação de complemento e deposição de fragmentos de complemento – destruição de partículas virais e opsonização de partículas virais (fagocitose).

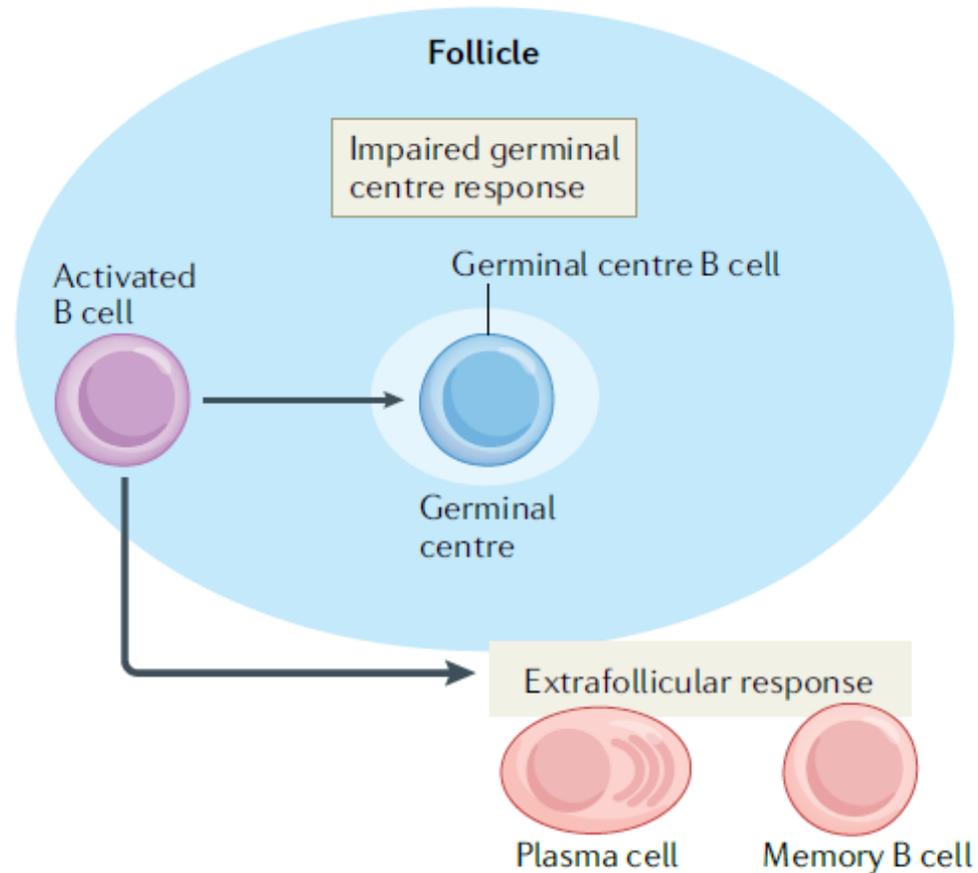
Neutralização Sars-Cov2

Indução de IgG neutralizante circulante e nos tecidos



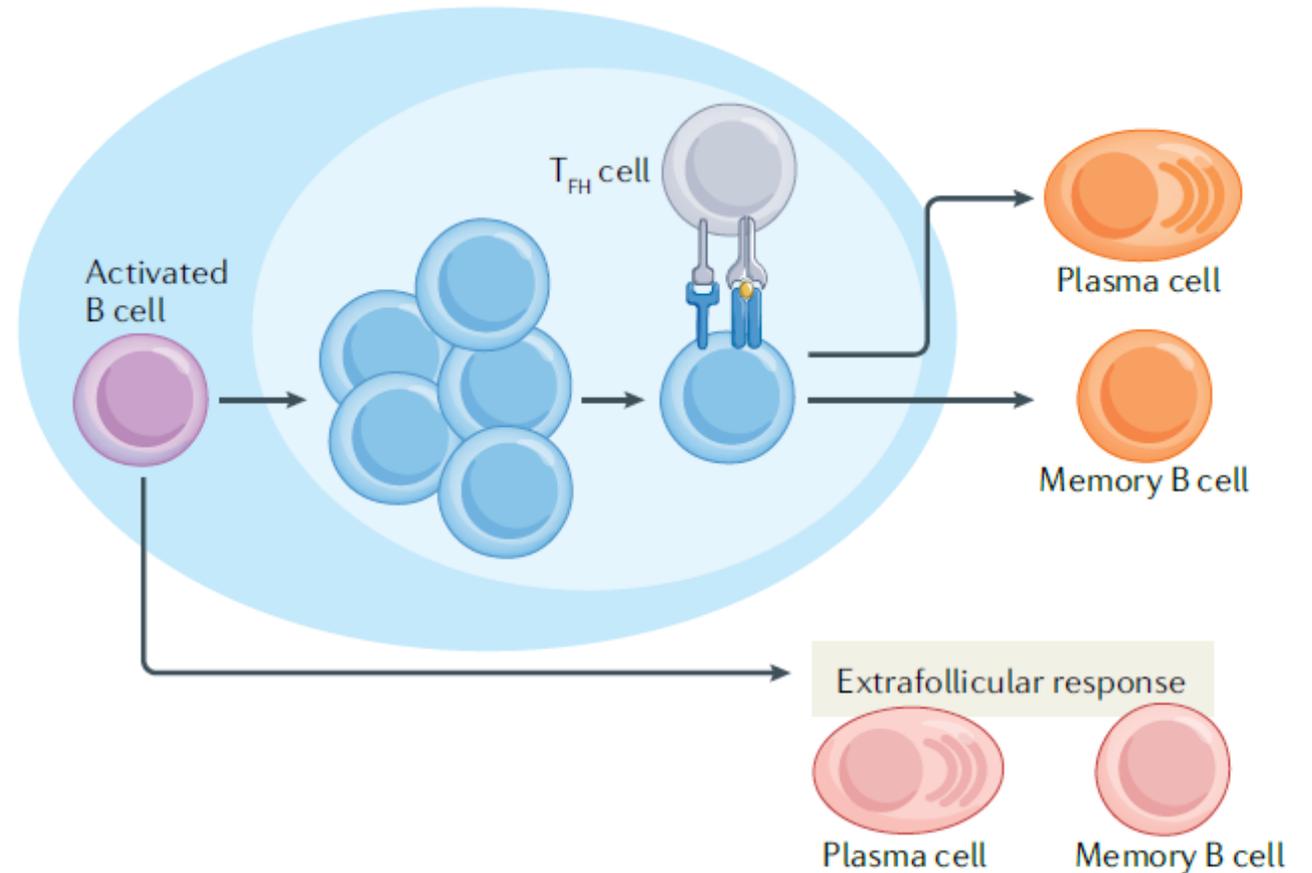
Disfunção de reações de centro germinativo em covid grave

a Severe SARS-CoV-2 infection



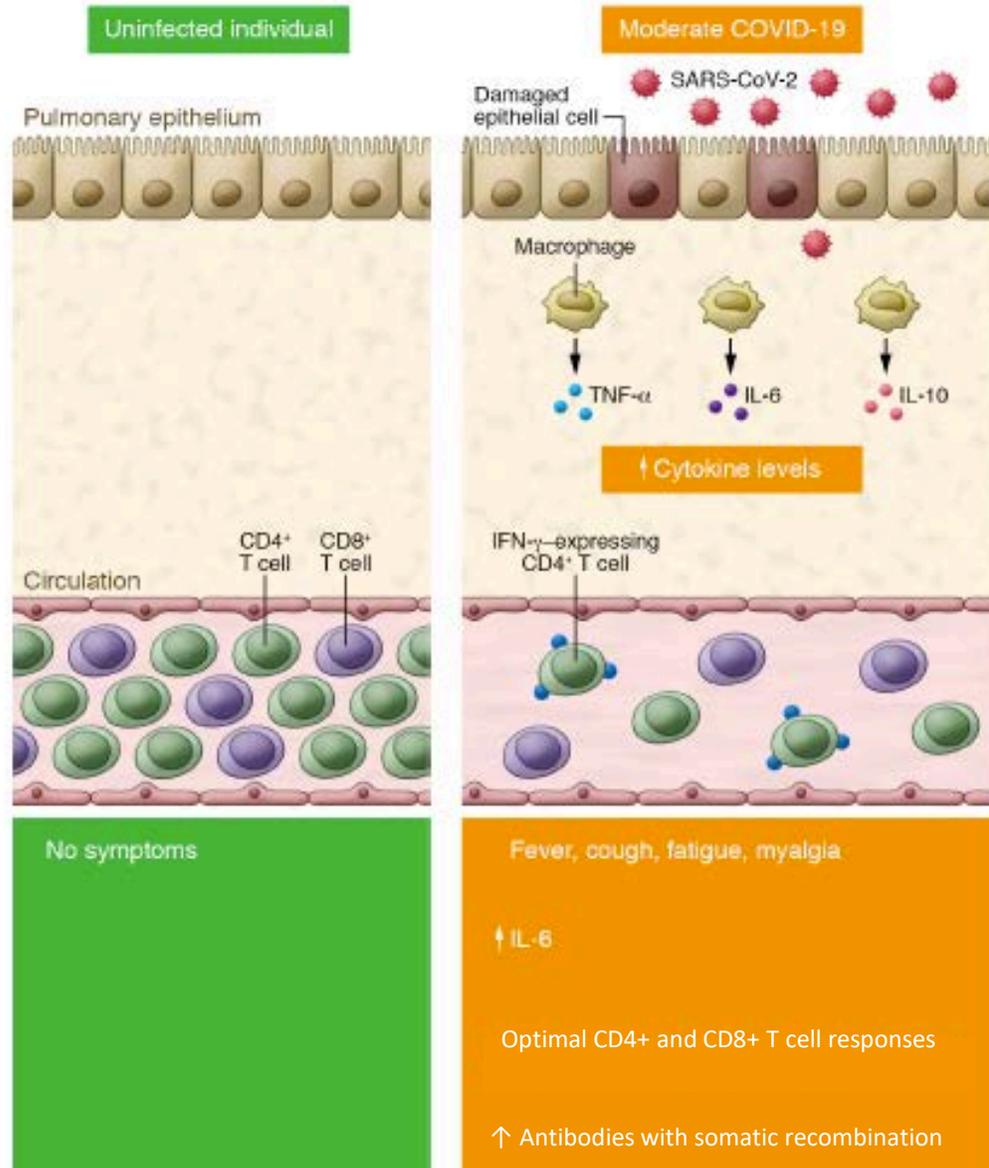
- Altos títulos de anticorpos
- Principalmente reações extrafoliculares
- Baixa afinidade de anticorpos e baixa geração de memória

b Mild SARS-CoV-2 infection

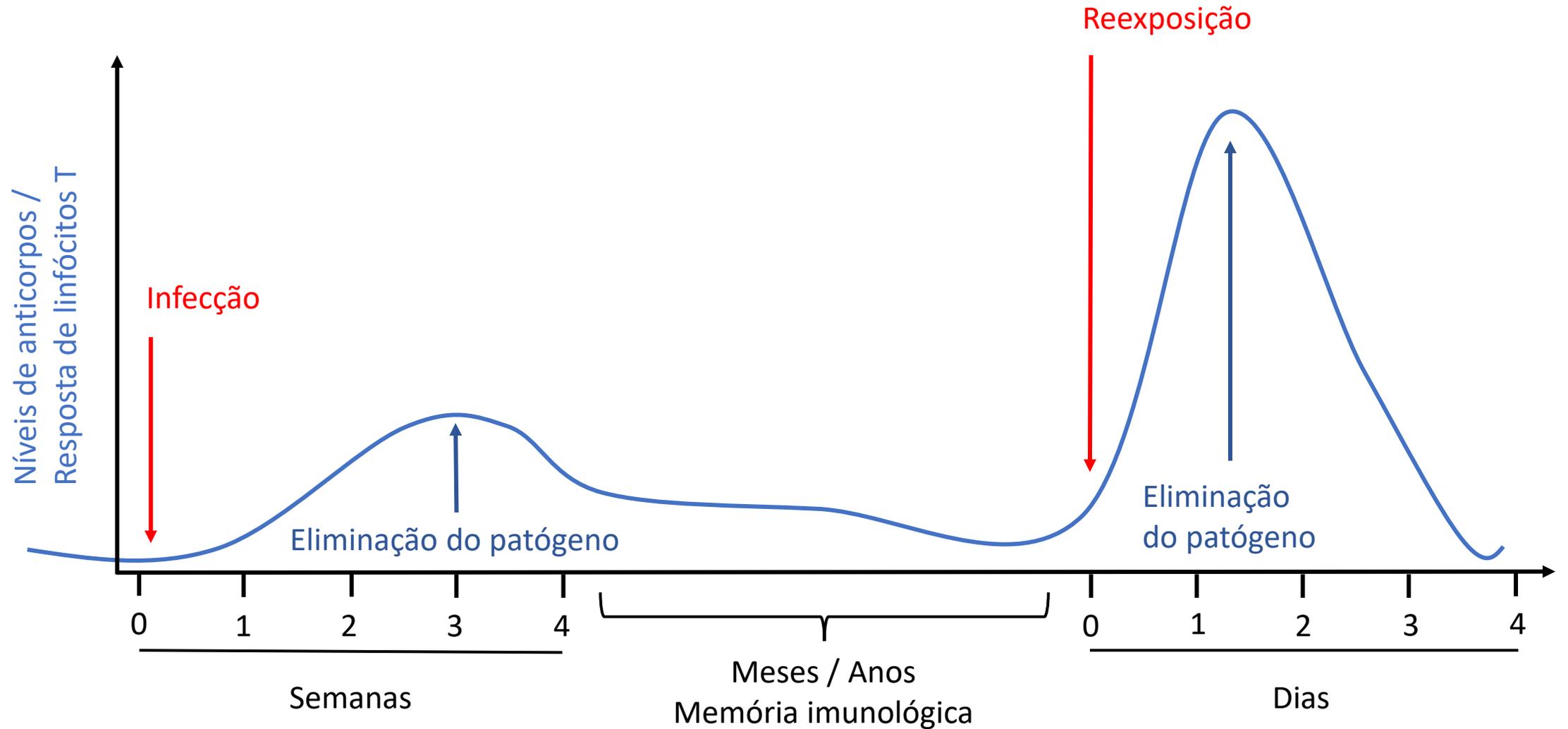


- Maior magnitude de reações foliculares
- Alta afinidade de anticorpos
- Geração de memória imunológica eficiente

Fases da resposta imune antiviral



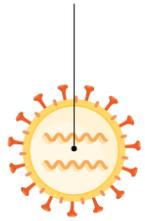
Memória imunológica



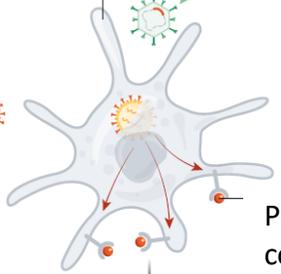
Vacinas para Covid-19 usadas no Brasil

Vacinas de vírus inativado

CORONAVAC
(Alum)



Célula apresentadora de antígeno

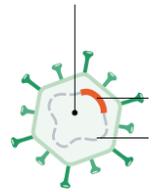


Peptídeos de coronavirus

Resposta imune

Vacinas de vetor viral

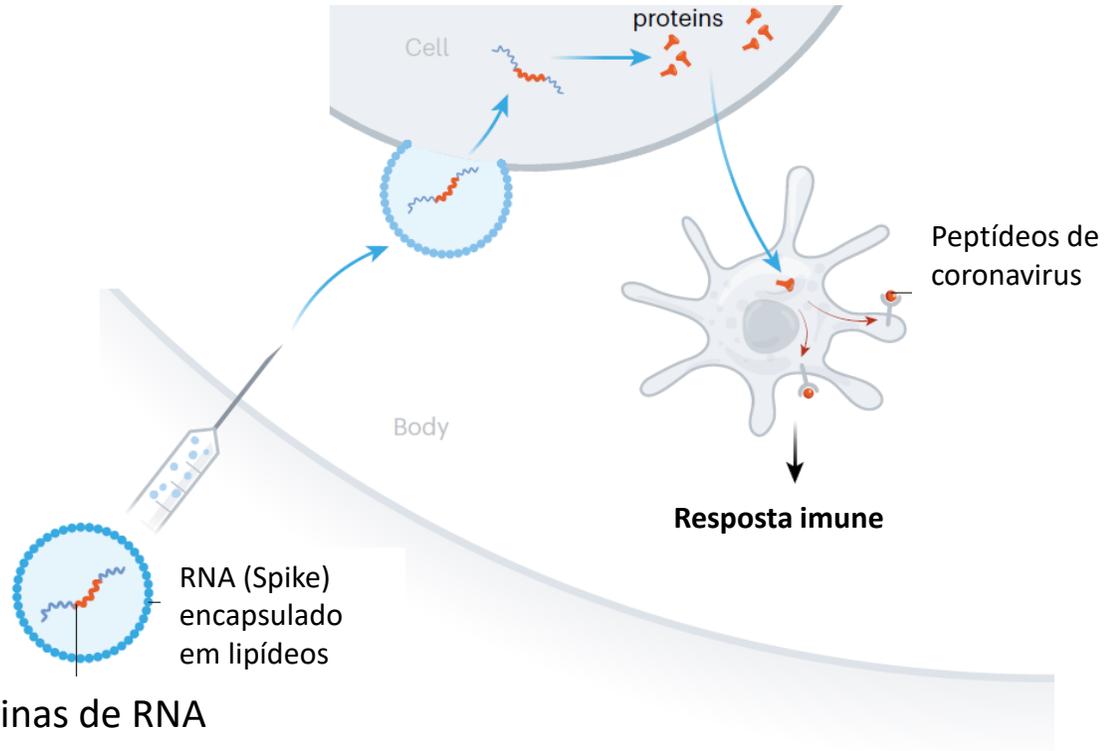
ASTRAZENECA (AZD1222)
JOHNSON & JOHNSON (Ad26.COV2-S)



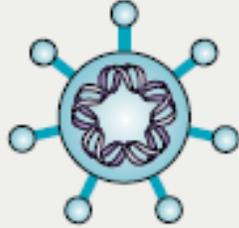
Gene da proteína Spike
Genes de adenovírus (alguns inativos)



Resposta imune



Sinovac - Coronavac

Type of vaccine		Licensed vaccines using this technology	First introduced
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	1896 (typhoid)

Vacinas de microrganismos inativados:

Prós: estabilidade e impossibilidade de reversão

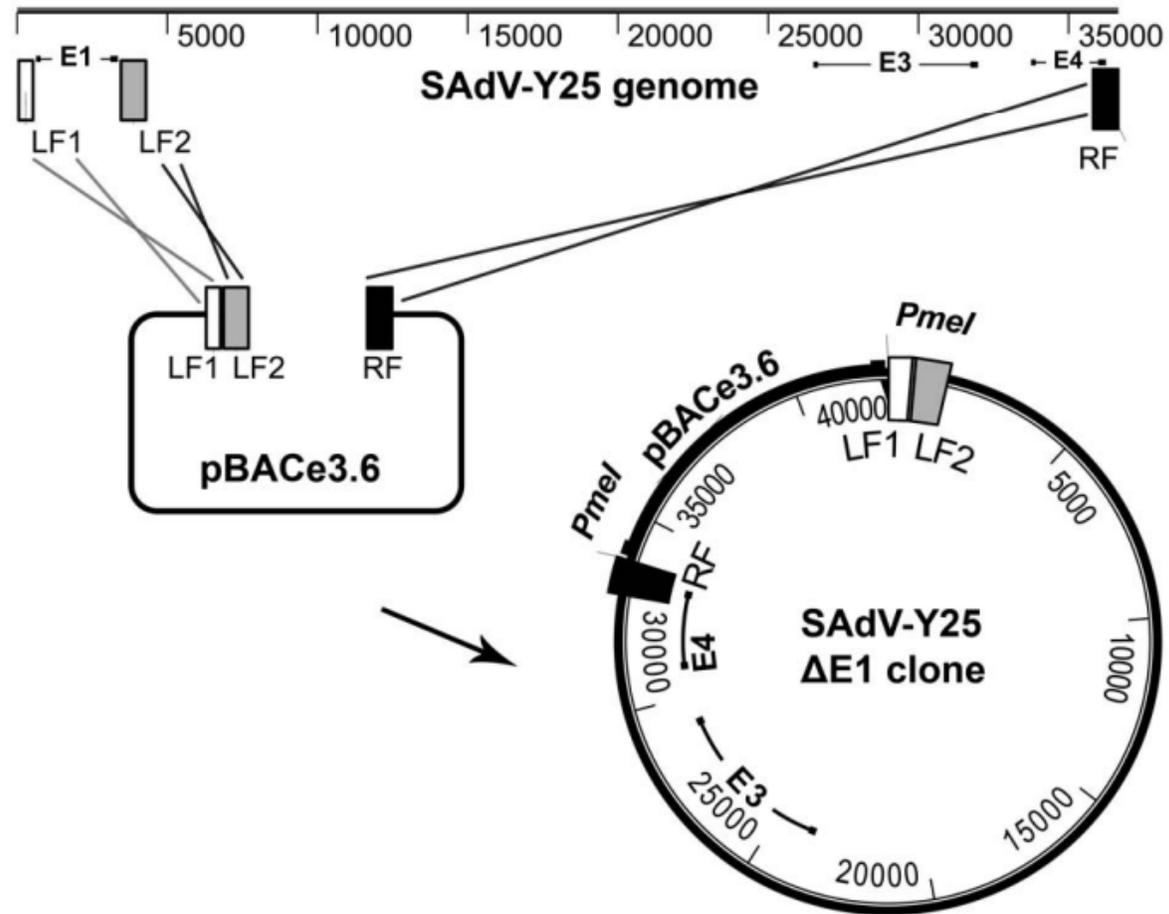
Contras: imunogenicidade mais baixa, necessidade de adjuvantes e doses de reforço

A Novel Chimpanzee Adenovirus Vector with Low Human Seroprevalence: Improved Systems for Vector Derivation and Comparative Immunogenicity

Matthew D. J. Dicks¹, Alexandra J. Spencer¹, Nick J. Edwards¹, Göran Wadell², Kalifa Bojang³, Sarah C. Gilbert¹, Adrian V. S. Hill¹, Matthew G. Cottingham^{1*}

¹ The Jenner Institute, University of Oxford, Oxford, United Kingdom, ² Department of Clinical Microbiology, University of Umeå, Umeå, Sweden, ³ Medical Research Council Laboratories, Fajara, The Gambia

AstraZeneca / Oxford – AZ1222



Clinical Assessment of a Novel Recombinant Simian Adenovirus ChAdOx1 as a Vectored Vaccine Expressing Conserved Influenza A Antigens

Richard D Antrobus¹, Lynda Coughlan¹, Tamara K Berthoud¹, Matthew D Dicks¹, Adrian VS Hill¹, Teresa Lambe¹ and Sarah C Gilbert¹

¹*The Jenner Institute, University of Oxford, Oxford, UK*

SCIENTIFIC REPORTS



OPEN

Chimpanzee Adenovirus Vaccine Provides Multispecies Protection against Rift Valley Fever

Received: 23 September 2015

Accepted: 08 January 2016

Published: 05 February 2016

George M. Warimwe^{1,2}, Joseph Gesharisha³, B. Veronica Carr⁴, Simeon Otieno³, Kennedy Otingah³, Danny Wright¹, Bryan Charleston⁴, Edward Okoth³, Lopez-Gil Elena⁵, Gema Lorenzo⁵, El-Behiry Ayman⁶, Naif K. Alharbi^{1,7}, Musaad A. Al-dubaib⁶, Alejandro Brun⁵, Sarah C. Gilbert¹, Vishvanath Nene³ & Adrian V. S. Hill¹

AstraZeneca / Oxford – AZ1222



www.nature.com/npjvaccines

BRIEF COMMUNICATION **OPEN**

Protective efficacy of a novel simian adenovirus vaccine against lethal MERS-CoV challenge in a transgenic human DPP4 mouse model

Vincent J. Munster¹, Daniel Wells ², Teresa Lambe², Daniel Wright², Robert J. Fischer¹, Trenton Bushmaker¹, Greg Saturday³, Neeltje van Doremalen ¹, Sarah C. Gilbert², Emmie de Wit ¹ and George M. Warimwe^{2,4,5}

AstraZeneca / Oxford – AZ1222

RESEARCH ARTICLE

A single-dose ChAdOx1-vectored vaccine provides complete protection against Nipah Bangladesh and Malaysia in Syrian golden hamsters

Neeltje van Doremalen^{1*}, **Teresa Lambe**², **Sarah Sebastian**², **Trenton Bushmaker**¹, **Robert Fischer**¹, **Friederike Feldmann**³, **Elaine Haddock**¹, **Michael Letko**¹, **Victoria A. Avanzato**^{1,4}, **Ilona Rissanen**⁴, **Rachel LaCasse**³, **Dana Scott**³, **Thomas A. Bowden**⁴, **Sarah Gilbert**^{2*}, **Vincent Munster**¹

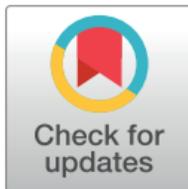
1 Laboratory of Virology, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rocky Mountain Laboratories, Hamilton, MT, United States of America, **2** The Jenner Institute, University of Oxford, Oxford, United Kingdom, **3** Rocky Mountain Veterinary Branch, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, MT, United States of America, **4** Division of Structural Biology, Wellcome Centre for Human Genetics, University of Oxford, Oxford, United Kingdom

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Received: February 11, 2019

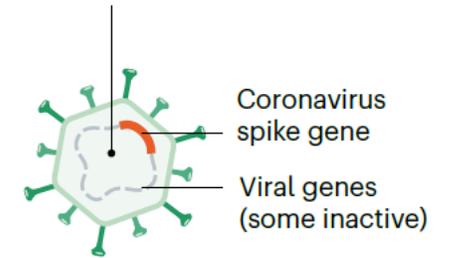
Accepted: May 13, 2019

Published: June 6, 2019



AstraZeneca / Oxford – AZ1222

Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK



Merryn Voysey, Sue Ann Costa Clemens*, Shabir A Madhi*, Lily Y Weckx*, Pedro M Folegatti*, Parvinder K Aley, Brian Angus, Vicky L Baillie, Shaun L Barnabas, Qasim E Bhorat, Sagida Bibi, Carmen Briner, Paola Cicconi, Andrea M Collins, Rachel Colin-Jones, Clare L Cutland, Thomas C Darton, Keertan Dheda, Christopher J A Duncan, Katherine R W Emary, Katie J Ewer, Lee Fairlie, Saul N Faust, Shuo Feng, Daniela M Ferreira, Adam Finn, Anna L Goodman, Catherine M Green, Christopher A Green, Paul T Heath, Catherine Hill, Helen Hill, Ian Hirsch, Susanne H C Hodgson, Alane Izu, Susan Jackson, Daniel Jenkin, Carina C D Joe, Simon Kerridge, Anthonet Koen, Gaurav Kwatra, Rajeka Lazarus, Alison M Lawrie, Alice Lelliott, Vincenzo Libri, Patrick J Lillie, Raburn Mallory, Ana V A Mendes, Eveline P Milan, Angela M Minassian, Alastair McGregor, Hazel Morrison, Yama F Mujadidi, Anusha Nana, Peter J O'Reilly, Sherman D Padayachee, Ana Pittella, Emma Plested, Katrina M Pollock, Maheshi N Ramasamy, Sarah Rhead, Alexandre V Schwarzbald, Nisha Singh, Andrew Smith, Rinn Song, Matthew D Snape, Eduardo Sprinz, Rebecca K Sutherland, Richard Tarrant, Emma C Thomson, M Estée Török, Mark Toshner, David P J Turner, Johan Vekemans, Tonya L Villafana, Marion E E Watson, Christopher J Williams, Alexander D Douglas*, Adrian V S Hill*, Teresa Lambe*, Sarah C Gilbert*, Andrew J Pollard* on behalf of the Oxford COVID Vaccine Trial Group†*

Pfizer / Biontech BNT162b2

Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 6077–6081, August 1989
Biochemistry

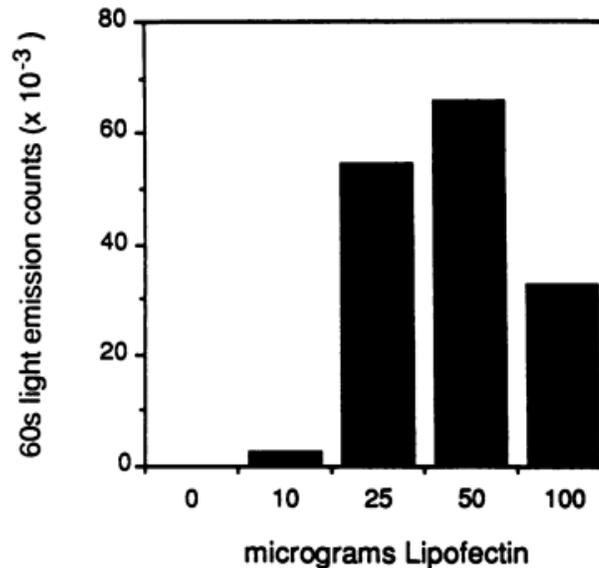
Cationic liposome-mediated RNA transfection

[cationic lipid vesicles/*N*-[1-(2,3-dioleoyloxy)propyl]-*N,N,N*-trimethylammonium chloride (DOTMA)/translation]

ROBERT W. MALONE*^{†‡}, PHILIP L. FELGNER[‡], AND INDER M. VERMA*[§]

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Communicated by Giuseppe Attardi, May 12, 1989



**Reversal of Diabetes Insipidus in Brattleboro Rats:
Intrahypothalamic Injection of Vasopressin mRNA**

GUSTAV F. JIRIKOWSKI,* PIETRO PAOLO SANNA,
DOMINIQUE MACIEJEWSKI-LENOIR, FLOYD E. BLOOM

Década de 1990:

- Tecnologia muito cara
- Instabilidade de moléculas de mRNA
(mesmo encapsulada em lipídeos)
- Intensa resposta inflamatória

“RNA was so hard to work with,” says Matt Winkler, who founded one of the first RNA-focused lab supplies companies, Ambion, in Austin, Texas, in 1989. “If you had asked me back [then] if you could inject RNA into somebody for a vaccine, I would have laughed in your face.”

Pfizer / Biontech BNT162b2

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Vol. 279, No. 13, Issue of March 26, pp. 12542–12550, 2004
Printed in U.S.A.

mRNA Is an Endogenous Ligand for Toll-like Receptor 3*

Received for publication, September 12, 2003, and in revised form, January 15, 2004
Published, JBC Papers in Press, January 16, 2004, DOI 10.1074/jbc.M310175200

Katalin Karikó^{‡§}, ~~Houping Ni[¶]~~, John Capodici[¶], Marc Lamphier[¶], and Drew Weissman[¶]

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Immunity, Vol. 23, 165–175, August, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.immuni.2005.06.008

Suppression of RNA Recognition by Toll-like Receptors: The Impact of Nucleoside Modification and the Evolutionary Origin of RNA

Katalin Karikó,¹ Michael Buckstein,² Houping Ni,²
and Drew Weissman²

¹Department of Neurosurgery

²Department of Medicine

University of Pennsylvania School of Medicine

Philadelphia, Pennsylvania 19104



Uridina / Pseudouridina

BioNTech - 2012

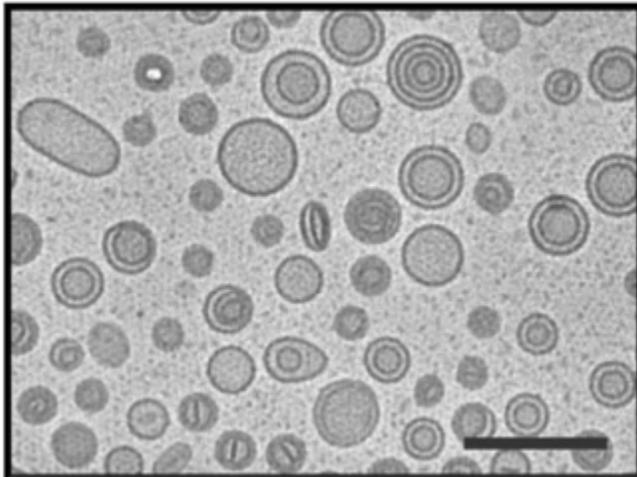
Pfizer / Biontech BNT162b2

Pharmaceutical Research, Vol. 22, No. 3, March 2005 (© 2005)
DOI: 10.1007/s11095-004-1873-z

Research Paper

A Scalable, Extrusion-Free Method for Efficient Liposomal Encapsulation of Plasmid DNA

Lloyd B. Jeffs,¹ Lorne R. Palmer,¹ Ellen G. Ambegia,¹ Cory Giesbrecht,¹ Shannon Ewanick,¹ and Ian MacLachlan^{1,2}



- Método mais eficiente de produção de nanopartículas lipídicas contendo ácidos nucleicos
- Meia vida após inóculo in vivo muito maior

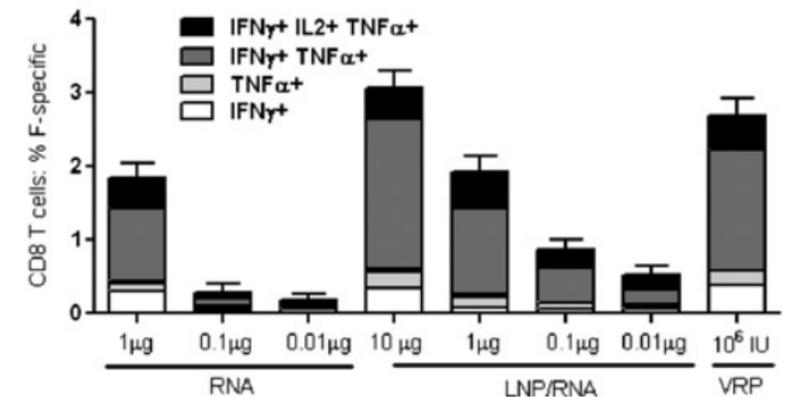
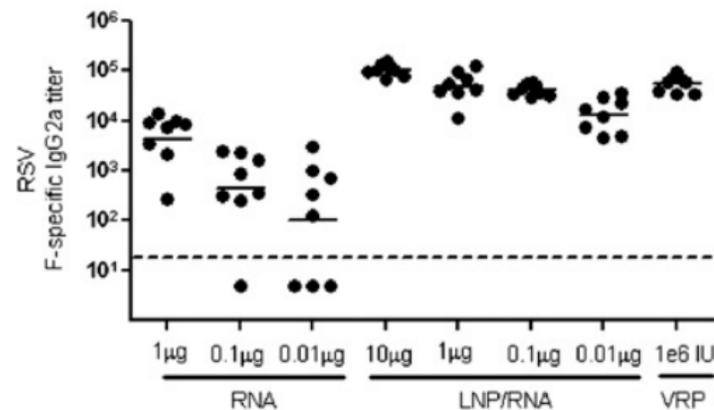
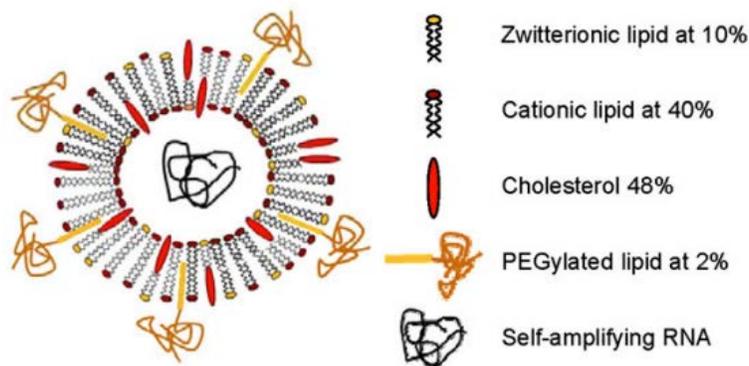
Nonviral delivery of self-amplifying RNA vaccines

Andrew J. Geall^{a,1}, Ayush Verma^a, Gillis R. Otten^a, Christine A. Shaw^a, Armin Hekele^a, Kaustuv Banerjee^a, Yen Cu^a, Clayton W. Beard^a, Luis A. Brito^a, Thomas Krucker^b, Derek T. O'Hagan^a, Manmohan Singh^a, Peter W. Mason^a, Nicholas M. Valiante^a, Philip R. Dormitzer^a, Susan W. Barnett^a, Rino Rappuoli^a, Jeffrey B. Ulmer^a, and Christian W. Mandl^a

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Edited by John J. Mekalanos, Harvard Medical School, Boston, MA, and approved July 26, 2012 (received for review April 4, 2012)

14604–14609 | PNAS | September 4, 2012 | vol. 109 | no. 36



Pfizer / Biontech BNT162b2

Molecular Therapy

Original Article

2017



Preclinical and Clinical Demonstration of Immunogenicity by mRNA Vaccines against H10N8 and H7N9 Influenza Viruses

Kapil Bahl,¹ Joe J. Senn,² Olga Yuzhakov,¹ Alex Bulychev,² Luis A. Brito,² Kimberly J. Hassett,¹ Michael E. Laska,² Mike Smith,² Örn Almarsson,² James Thompson,² Amilcar (Mick) Ribeiro,¹ Mike Watson,¹ Tal Zaks,² and Giuseppe Ciaramella¹

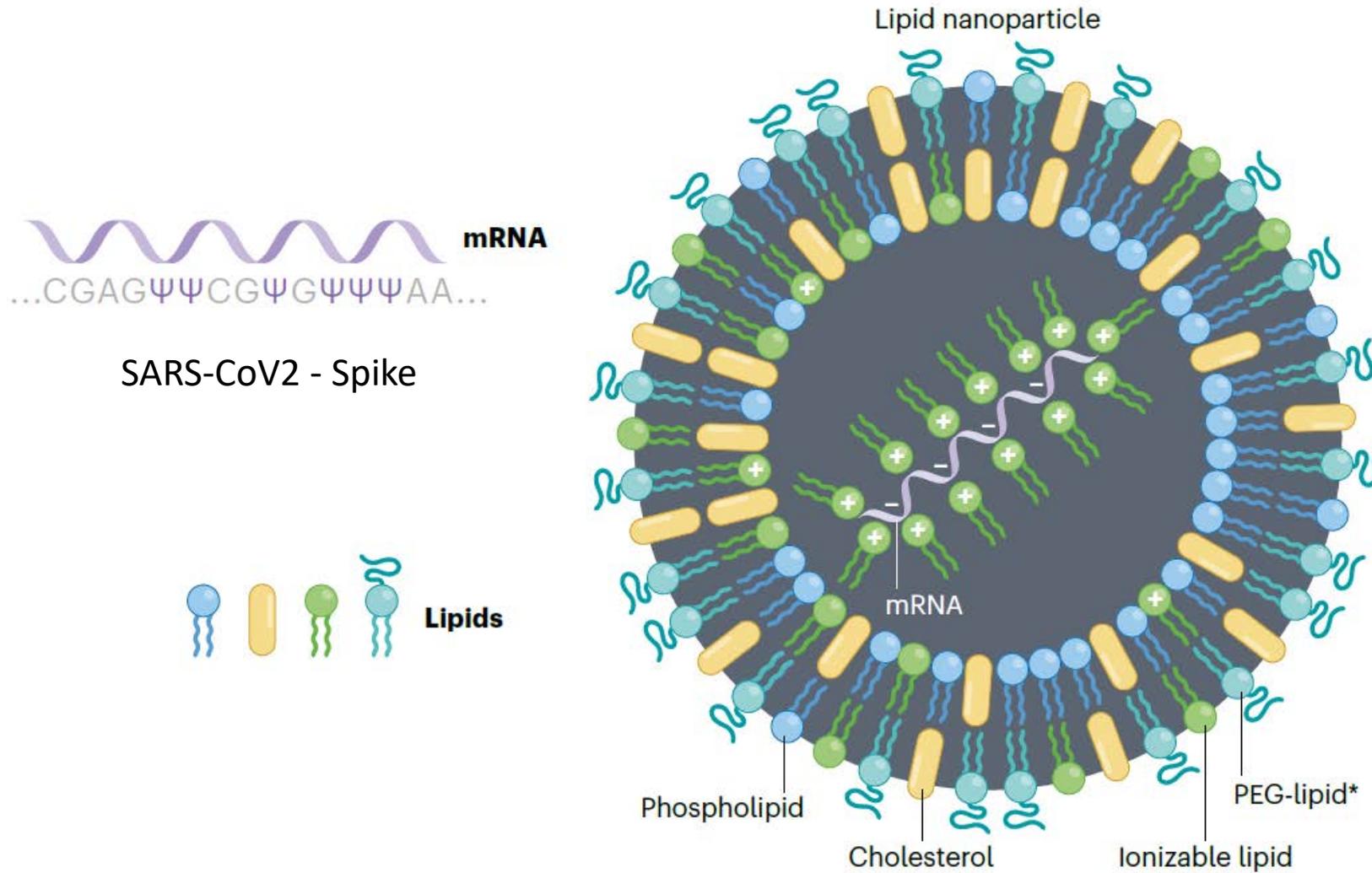
¹Valera, A Moderna Venture, 500 Technology Square, Cambridge, MA 02139, USA; ²Moderna Therapeutics, 200 Technology Square, Cambridge, MA 02139, USA

Início de 2020:

A empresa Moderna já tinha 9 protótipos de vacinas de RNA em testes clínicos

A empresa BioNTech já tinha 8 anos de experiência em desenvolvimento de tecnologia para tratamento com mRNA

Pfizer / Biontech BNT162b2



Pfizer / Biontech BNT162b2

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Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D.,
Alejandra Gurtman, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Gonzalo Pérez Marc, M.D.,
Edson D. Moreira, M.D., Cristiano Zerbini, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D.,
Satrajit Roychoudhury, Ph.D., Kenneth Koury, Ph.D., Ping Li, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Ph.D.,
Robert W. Frenc, Jr., M.D., Laura L. Hammitt, M.D., Özlem Türeci, M.D., Haylene Nell, M.D., Axel Schaefer, M.D.,
Serhat Ünal, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D., Philip R. Dormitzer, M.D., Ph.D.,
Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group*

Pfizer / Biontech BNT162b2

The Nobel Prize in Physiology or Medicine 2023



© Nobel Prize Outreach. Photo:
Clément Morin
Katalin Karikó

Prize share: 1/2



© Nobel Prize Outreach. Photo:
Clément Morin
Drew Weissman

Prize share: 1/2

Graus de proteção das vacinas usadas contra Covid-19 no Brasil

Vaccine manufacturer (vaccine name) ^a	Platform	Clinical trial regime	Total trial size	Efficacy	End point measure	Eligibility	Duration of follow up for phase III trial	Circulating genotypes at location and time of trial	Results by severity
Pfizer–BioNTech (BNT162b2) ²	mRNA	2 doses (21 days apart)	43,548	95%	Symptomatic COVID-19 and positive RT–PCR test result	>16 years old	Up to 24 months after second dose (NCT04368728)	B.1.351, P.1, B.1.427/B.1.419, P.2 and B.1.526	100% effective in preventing CDC-defined severe disease; 95.3% effective in preventing FDA-defined severe disease
AstraZeneca–University of Oxford (AZD1222 (Vaxzevria, also called Covishield when manufactured by SII under license)) ⁴	Viral vector	2 doses (<6 weeks apart) 2 doses (>12 weeks apart)	17,178	55% 81% (Pooled efficacy 67%)	Symptomatic COVID-19 and positive NAAT result	≥18 years old (WHO); ≥40 years old and not pregnant in UK	24 months after first dose (NCT04516746) 12 months after second dose (NCT04400838, NCT04536051 and NCT04516746)	B.1.1.7, B.1.351, P.1, B.1.427/B.1.429, P.2, B.1.526 and C.37	100% efficacy against hospitalization
Johnson & Johnson ^b (Ad26.COV2-S) ^{5,51}	Viral vector	1 dose	44,325	66%	Symptomatic COVID-19 and positive RT–PCR test result	≥18 years old	25 months (NCT04505722) and 27 months (NCT04614948) after first dose	B.1.351, P.1, B.1.427/B.1.429, P.2, B.1.526 and C.37	85.4% efficacy against severe–critical disease occurring ≥28 days after vaccination
Sinovac Biotech (CoronaVac) ⁷	Inactivated virus	2 doses (14 days apart; 14 or 28 days apart in Chile)	2,300 (Chile); 13,000 (Turkey); 12,688 (Brazil)	Multiple studies in different countries: 50.7% (Brazil), 56.5% (Chile), 65% (Indonesia), 78% (Brazil) and 91% (Turkey)	Symptomatic, virologically confirmed COVID-19 occurring from 2 weeks after the second dose up to 1 year after the first dose	≥18 years old	12 months after first dose	P.1 and P.2	51% efficacy against symptomatic SARS-CoV-2 infection; 100% efficacy against severe disease; 100% efficacy against hospitalization from 14 days after second dose

Questões

