IFMi
Institut Français de Micro-immunothérapie

Mardi 25 février 2025

de 19h30 à 20h30

Epstein-Barr : quand le stress réveille un virus dormant

WebMi#32

Par le Dr Pascal Mensah

À LA POURSUITE DU

NINJA VIRAL

Rejoindre l'annuaire DetectEBV, c'est...

Aider les patients à sortir de l'errance médicale

Déja plus de 250 patients ont cherché un soignant compétent sur les 6 derniers mois... Ils ont besoin de vous !

Donner de la visibilité à votre expertise

Soyez facilement identifié par les patients en quête d'un accompagnement adapté.

Simple, rapide et gratuit

En quelques clics, rejoignez l'annuaire et faites partie du réseau des soignants engagés pour faire avancer la prise en charge de l'EBV.

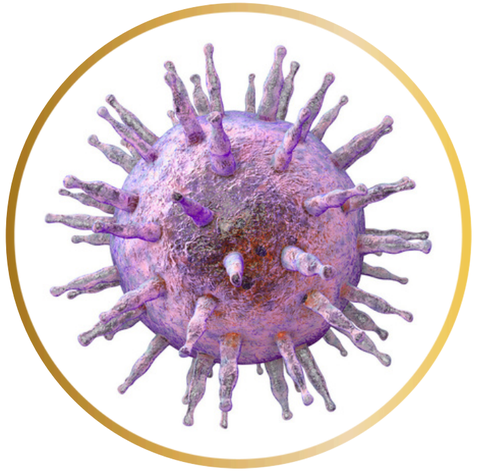
C'est par ici !

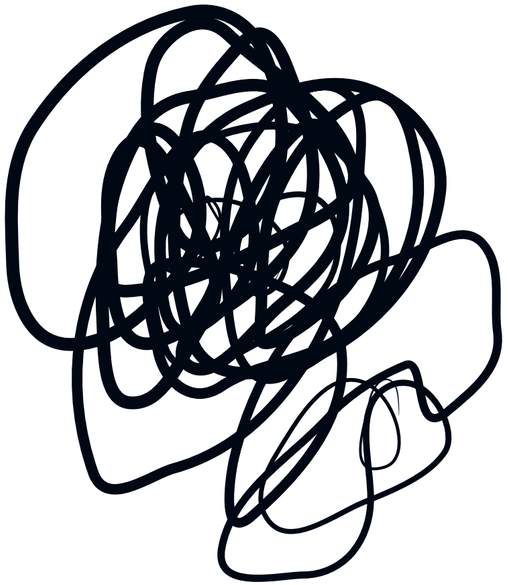
Adoptez le "Réflexe EBV" !

detect EBV

EPSTEIN-BARR COLLABORATIVE GROUP

EBV et Stress



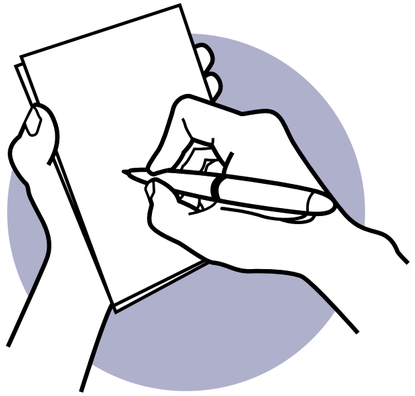


WebMi#32

Par le Dr Pascal Mensah

IFMi
Institut Français de
Micro-immunothérapie

Take home message



- le stress peut induire les **axes HPA et SAM.**
- entraînant la **production de cortisol.**
- peut provoquer **l'activation du génome de l'EBV latent.**

- **2L-EBV, 2L-MISEN et 2L-MIREG**

> In medicine, “**stress**” is defined by the body’s non-specific response to an **any extra demand** by physical, psychological or pharmacological events.

Par le Dr Pascal Mensah

Question : le stress réactive-t-il l'EBV latent ?

WebMi#32

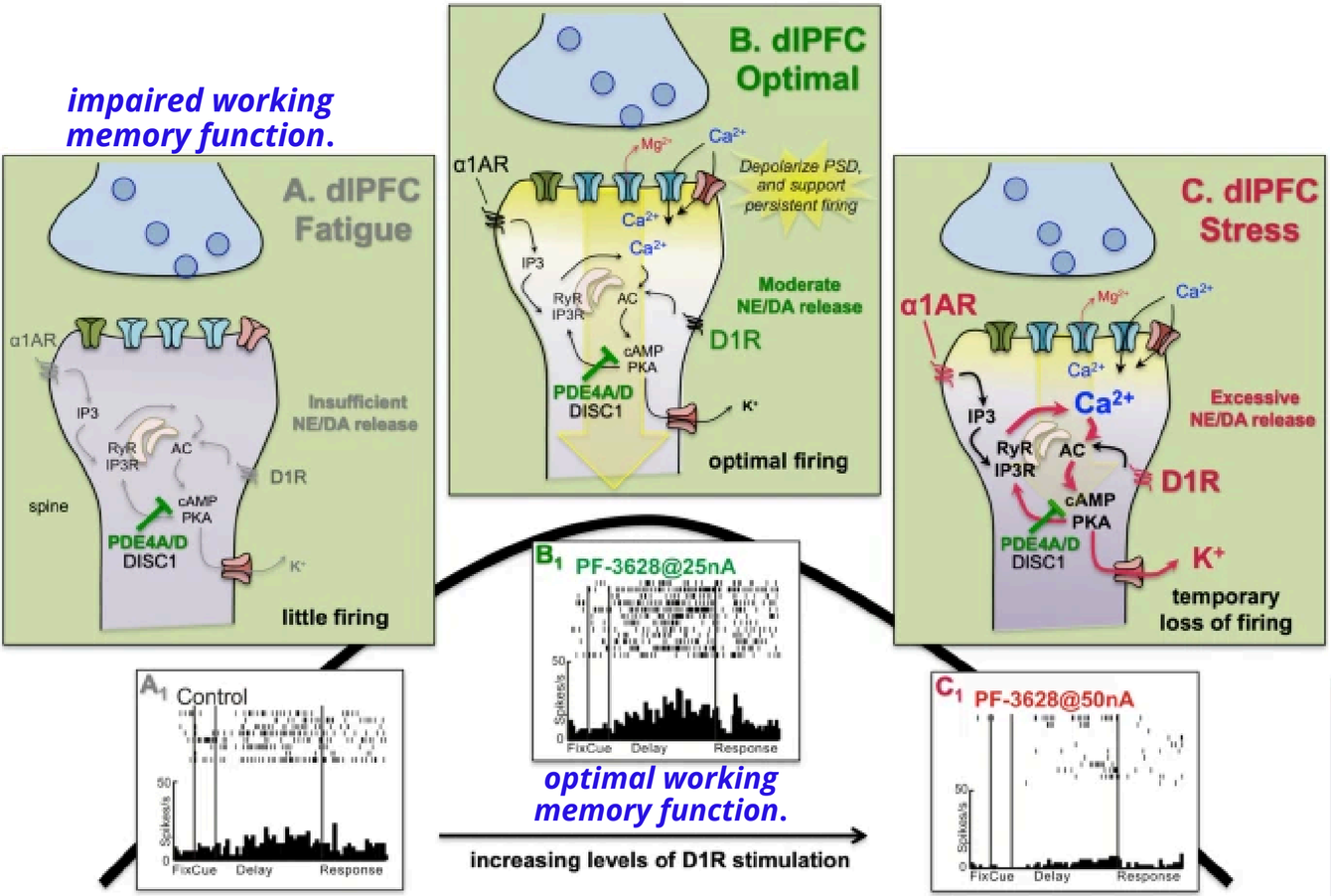
Par le Dr Pascal Mensah

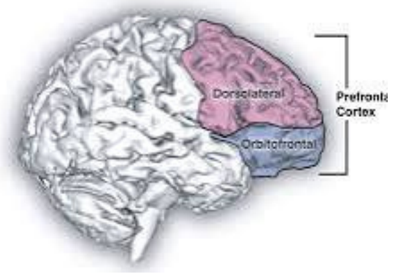
IFMi
Institut Français de Micro-immunothérapie

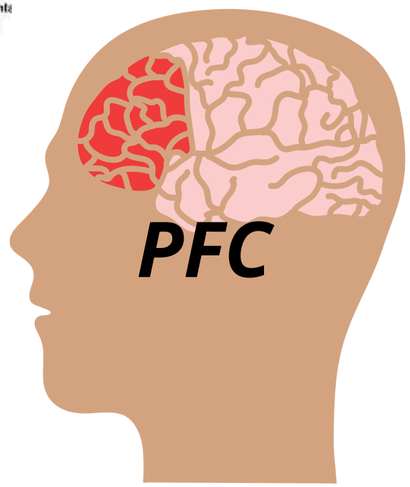

Réponse : YES !

Why

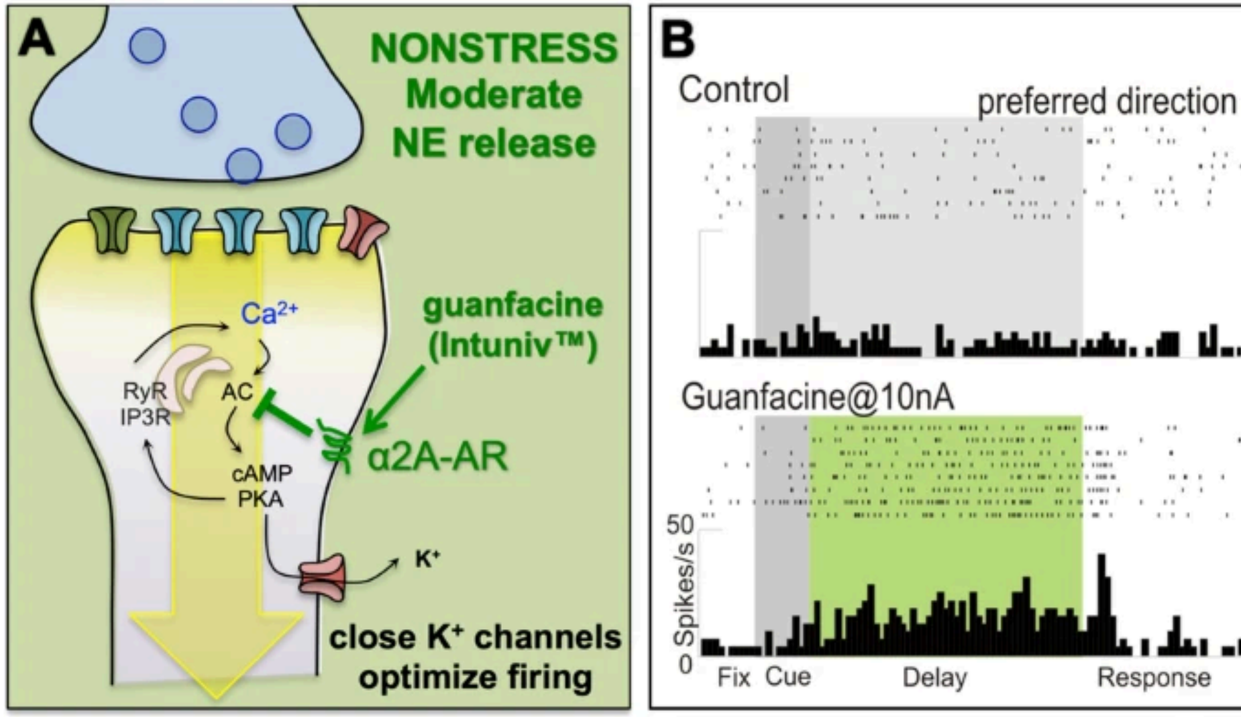
Narrow Inverted-U Dose Response in dlPFC

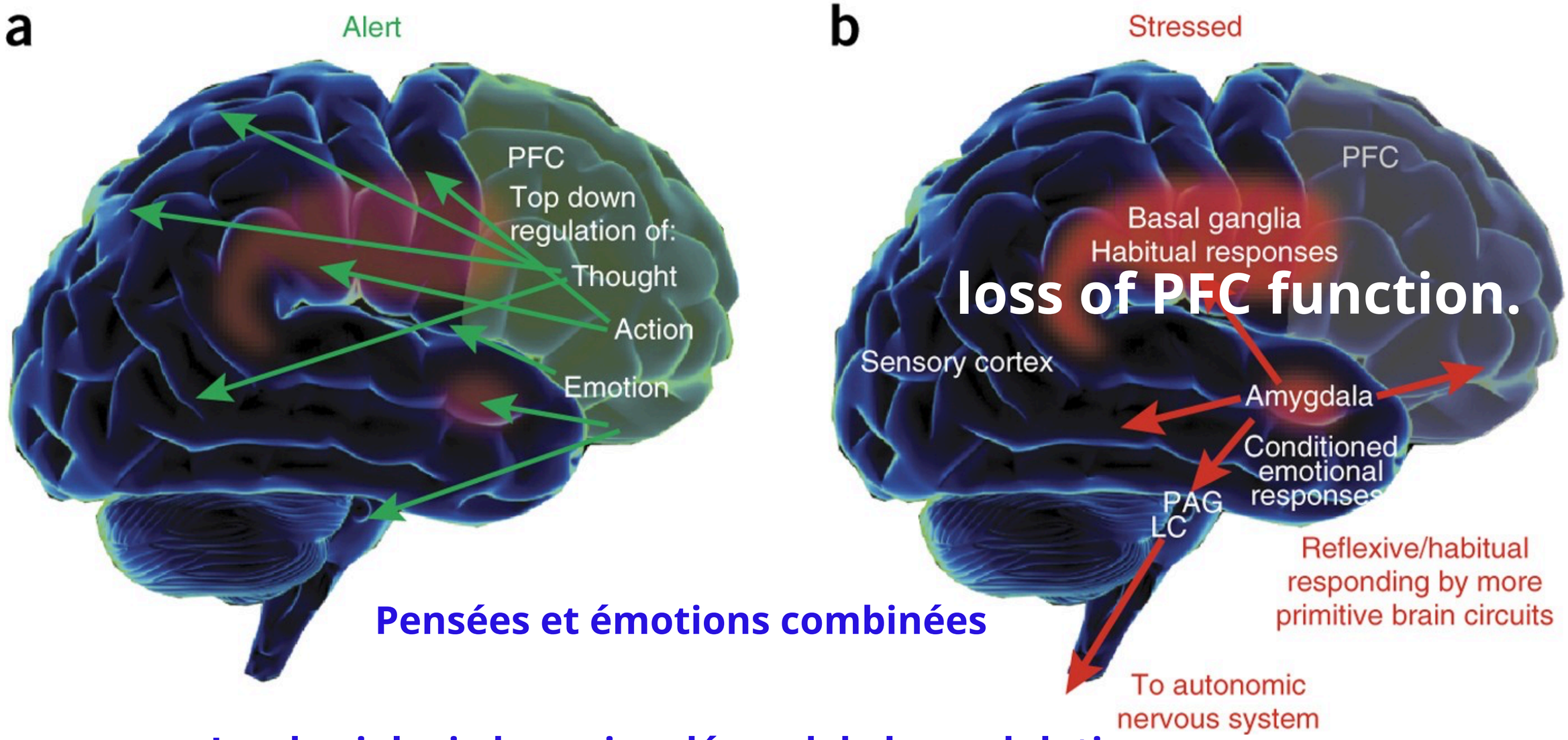






Beneficial NE α2A-AR actions in dlPFC





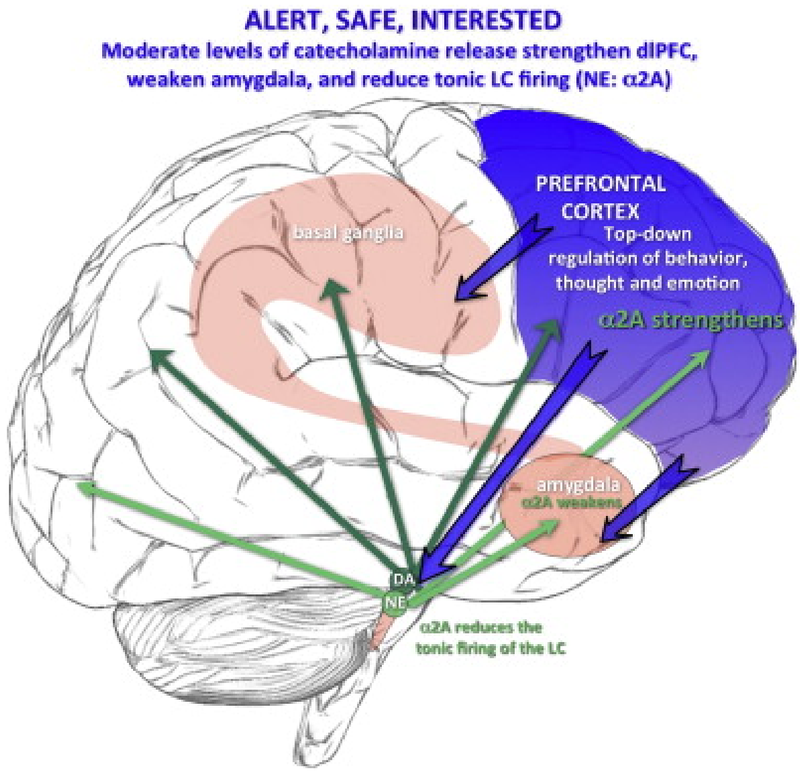
loss of PFC function.

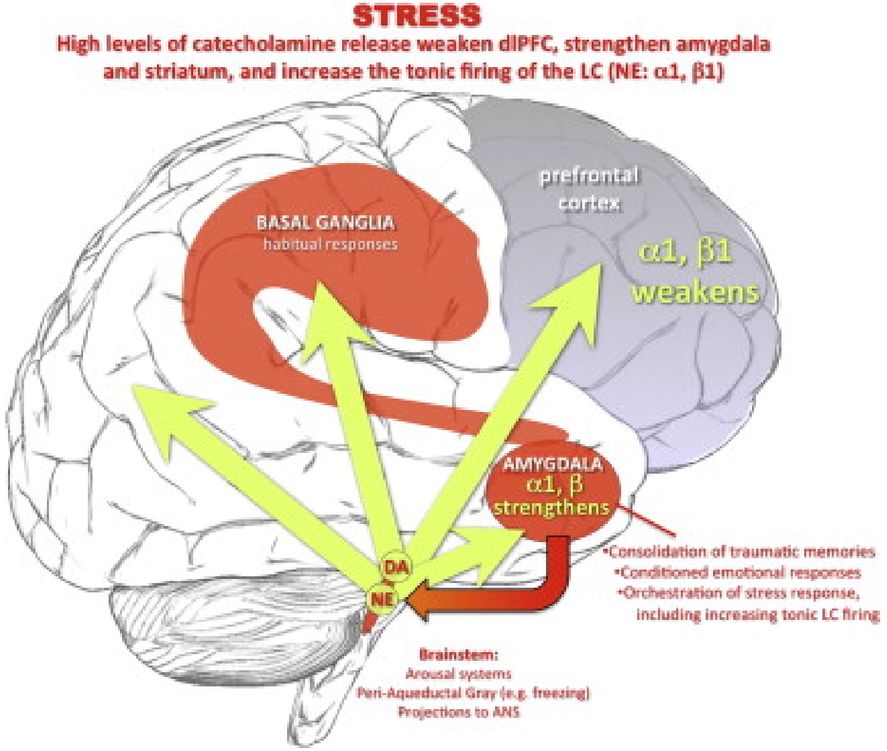
Pensées et émotions combinées

La physiologie humaine dépend de la modulation continuelle de l'expression émotionnelle

Arnsten, A. Stress weakens prefrontal networks: molecular insults to higher cognition. Nat Neurosci 18, 1376–1385 (2015). https://doi.org/10.1038/nn.4087

IFMi Institut Français de Micro-immunothérapie





Dans des conditions d'excitation sans stress, lorsque le sujet est alerte, en sécurité et intéressé, le cortex préfrontal hautement évolué (surligné en bleu) assure une régulation descendante du comportement, de la pensée et des émotions.

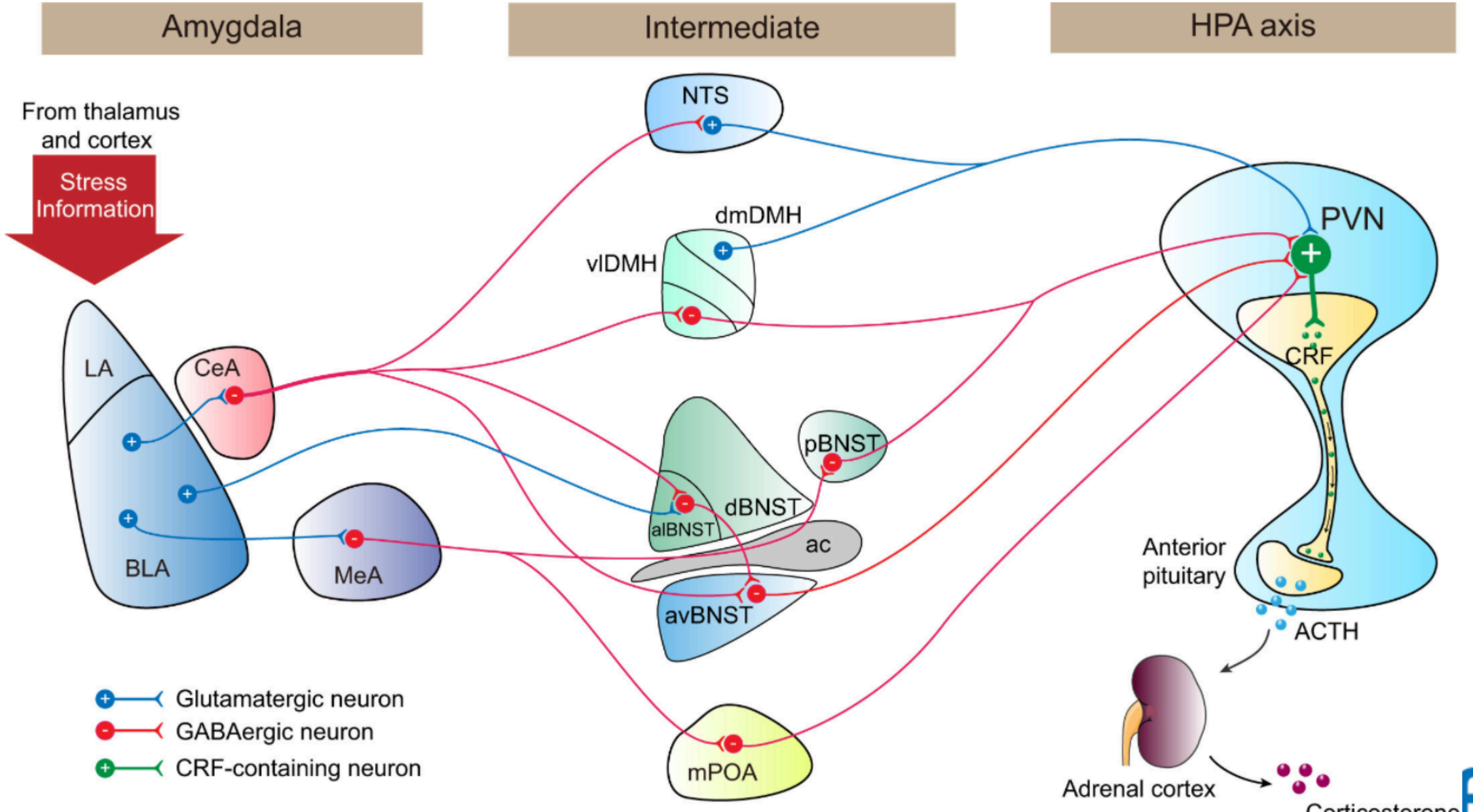
Il orchestre la réponse comportementale par le biais de connexions étendues, par exemple à l'amygdale, aux ganglions de la base et au tronc cérébral, y compris les neurones catécholamines.

Dans des conditions de stress incontrôlable, il y a des niveaux élevés de libération de catécholamines dans le cerveau, ce qui affaiblit la fonction PFC mais renforce les réponses (affectives) de l'amygdale et les réponses habituelles des ganglions de la base.

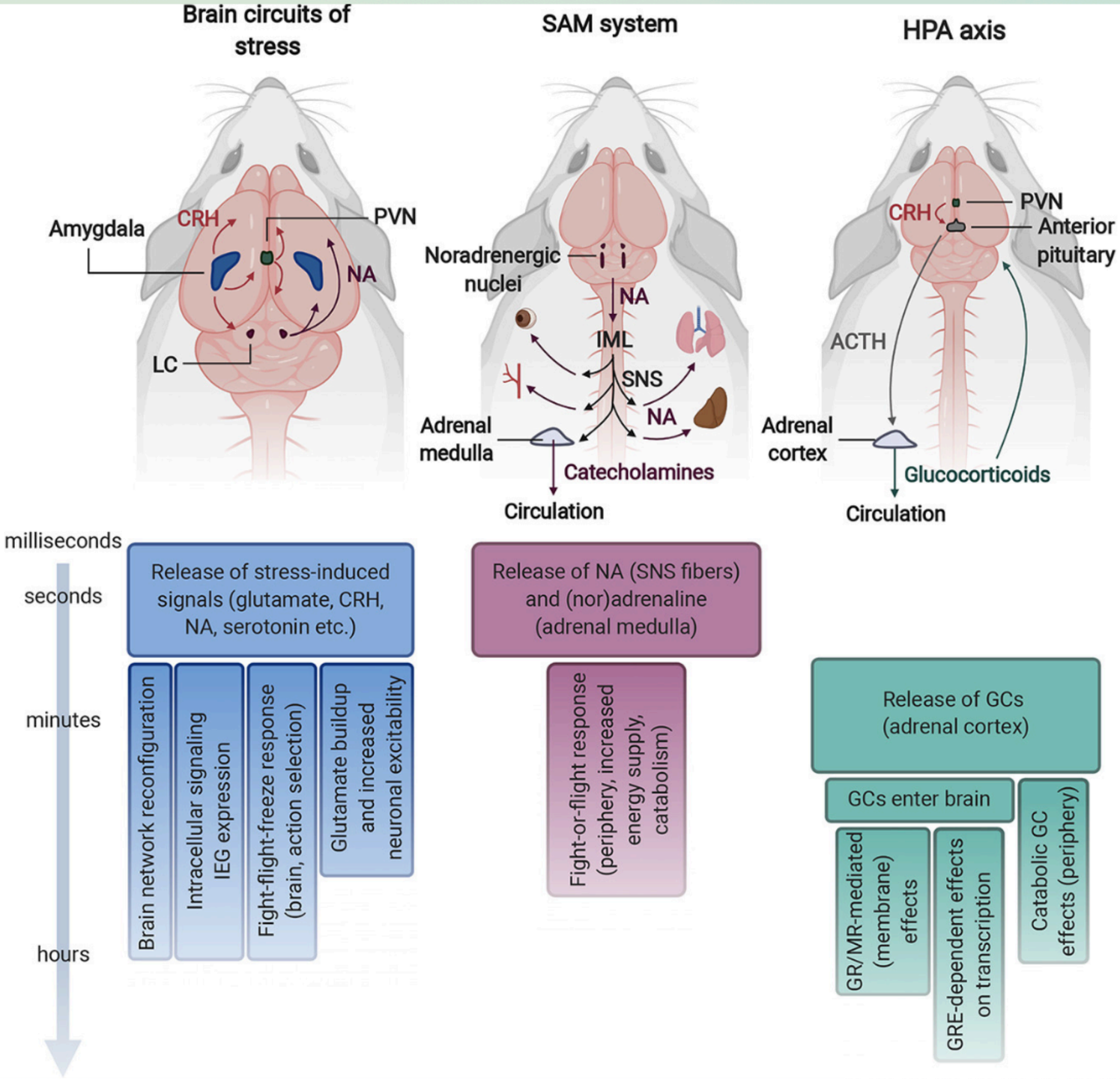
L'amygdale active la catécholamine dans des conditions de stress psychologique et coordonne d'autres aspects de la réponse au stress (par exemple, des projections vers le gris périaqueducal). L'activation de l'amygdale du locus coeruleus via CRF augmente la décharge tonique.

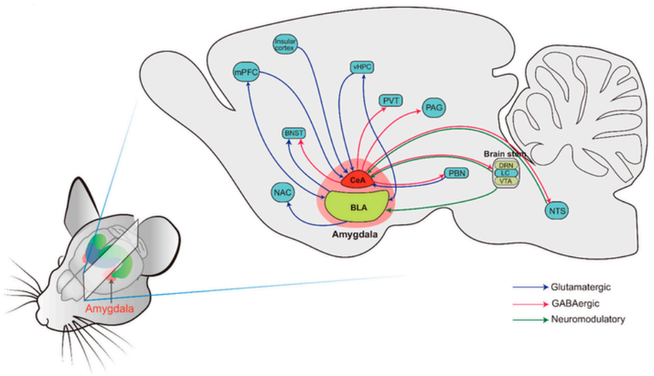
Des niveaux élevés de libération d'NE, qui engagent les récepteurs alpha-1 et bêta de plus faible affinité, qui améliorent l'amygdale et affaiblissent la fonction PFC, produisant ainsi un cercle vicieux qui maintient des circuits primitifs en contrôle du comportement.

Amy F.T. Arnsten, Murray A. Raskind, Fletcher B. Taylor, Daniel F. Connor,
The effects of stress exposure on prefrontal cortex: Translating basic research into successful treatments for post-traumatic stress disorder,
Neurobiology of Stress,
Volume 1,
2015,



Institut Français de Micro-immunothérapie

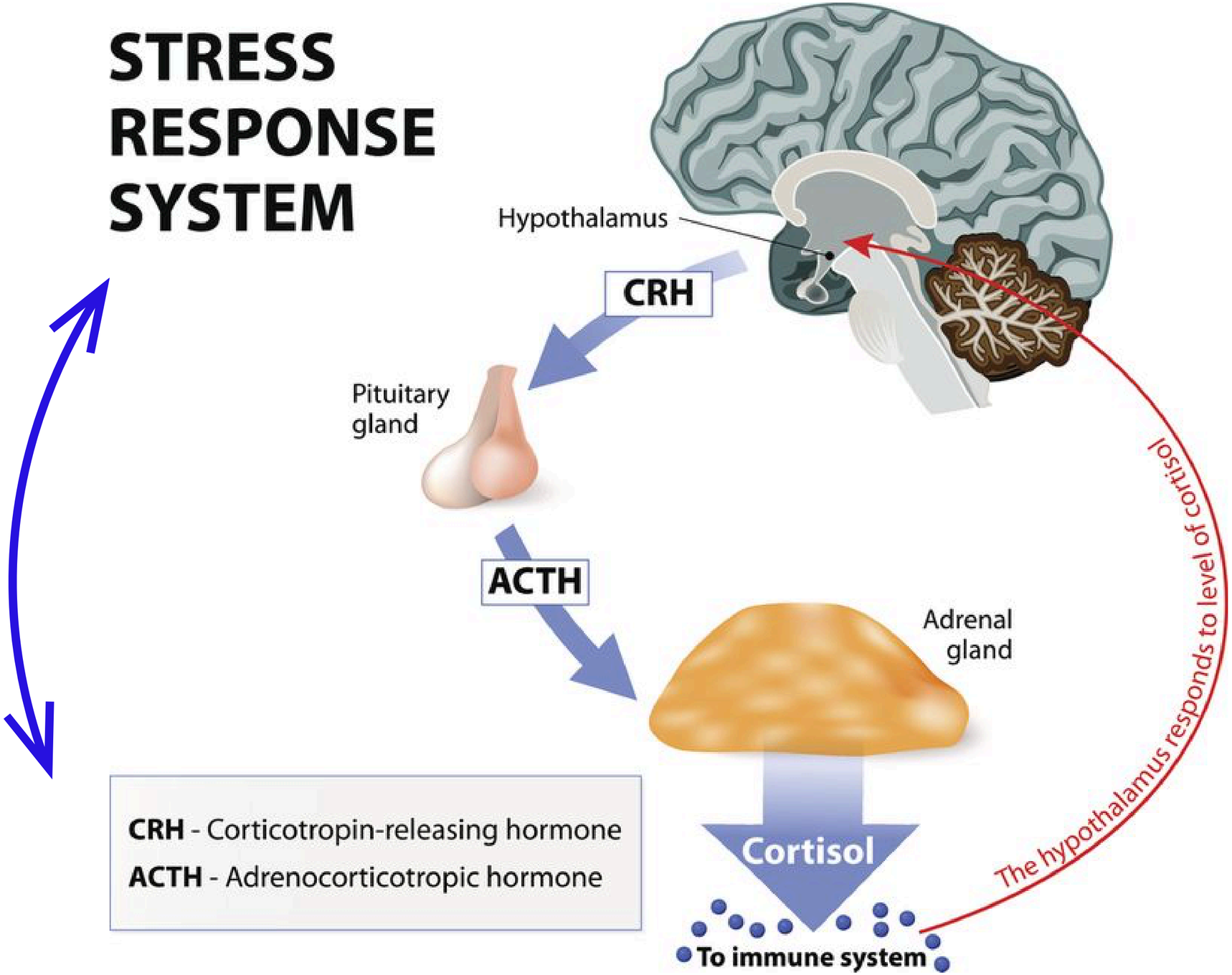




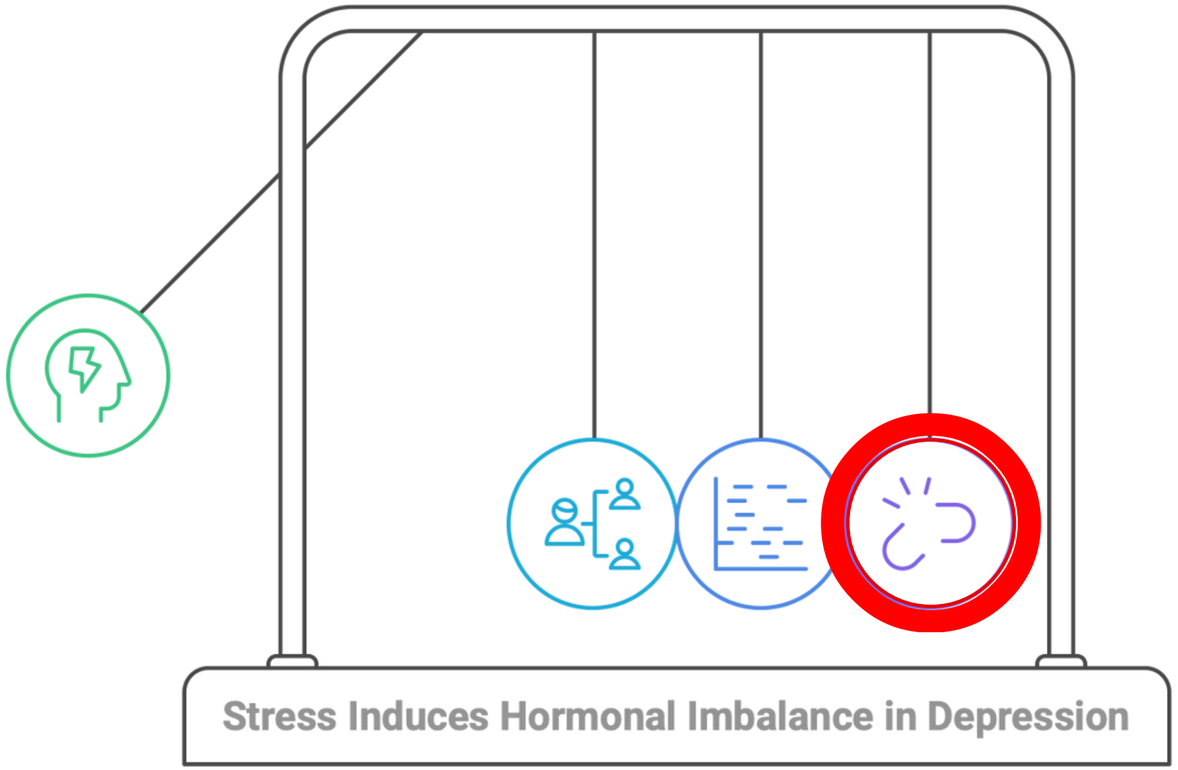
Amalia Floriou-Servou, Lukas von Ziegler, Rebecca Waag, Christa Schläppi, Pierre-Luc Germain, Johannes Bohacek,
The Acute Stress Response in the Multiomic Era,
Biological Psychiatry,
Volume 89, Issue 12,
2021,
Pages 1116-1126,
ISSN 0006-3223,

IFMi
Institut Français de Micro-immunothérapie

Cortisol


STRESS RESPONSE SYSTEM
Hypothalamus
CRH
Pituitary gland
ACTH
Adrenal gland
Cortisol
To immune system
The hypothalamus responds to level of cortisol
CRH - Corticotropin-releasing hormone
ACTH - Adrenocorticotropic hormone

Conséquence d'une cortisolémie chronique élevée



Stress

Continuous mental strain

CRH Overproduction

Excess corticotropin-releasing hormone

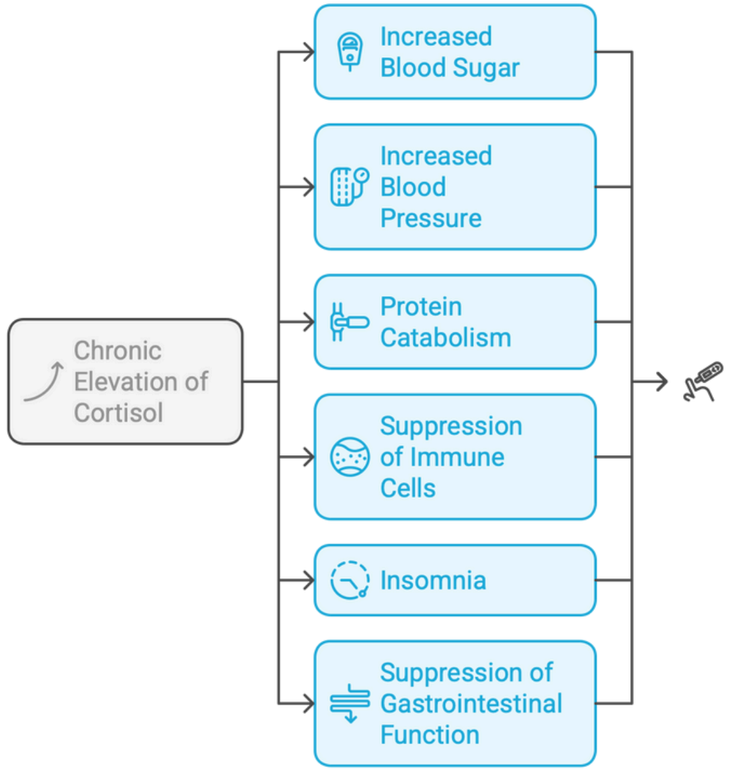
Cortisol Surge

Increased cortisol levels in bloodstream

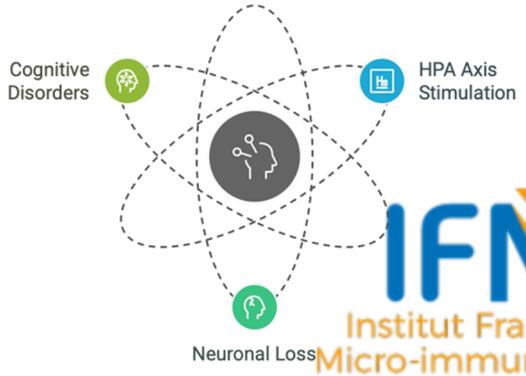
Feedback Loop Failure

Ineffective hormonal regulation

Effects of Chronic Cortisol Elevation



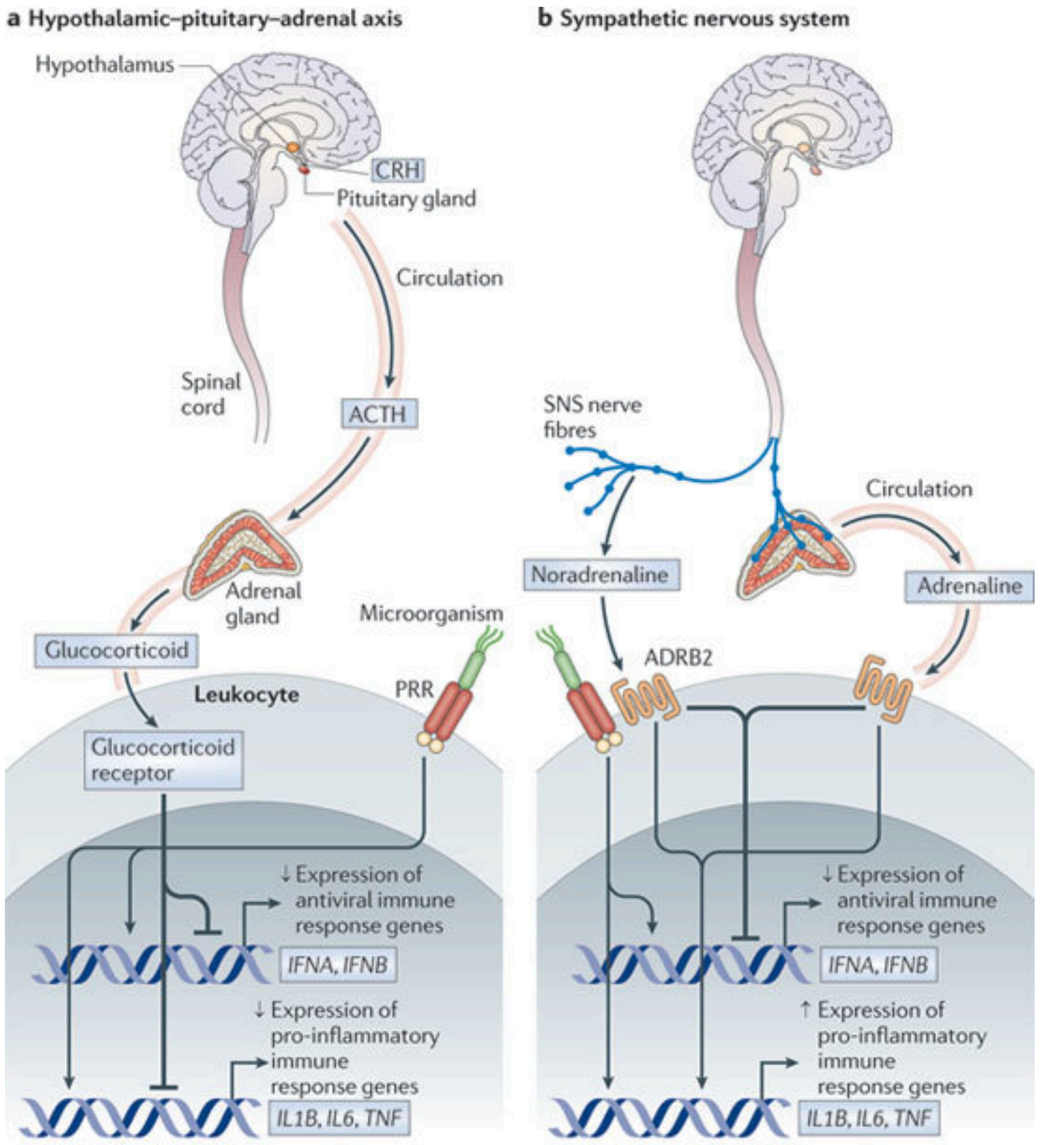
Impact of HPA Axis Stimulation



IFMi
Institut Français de Micro-immunothérapie

Cortisolémie et immunité innée

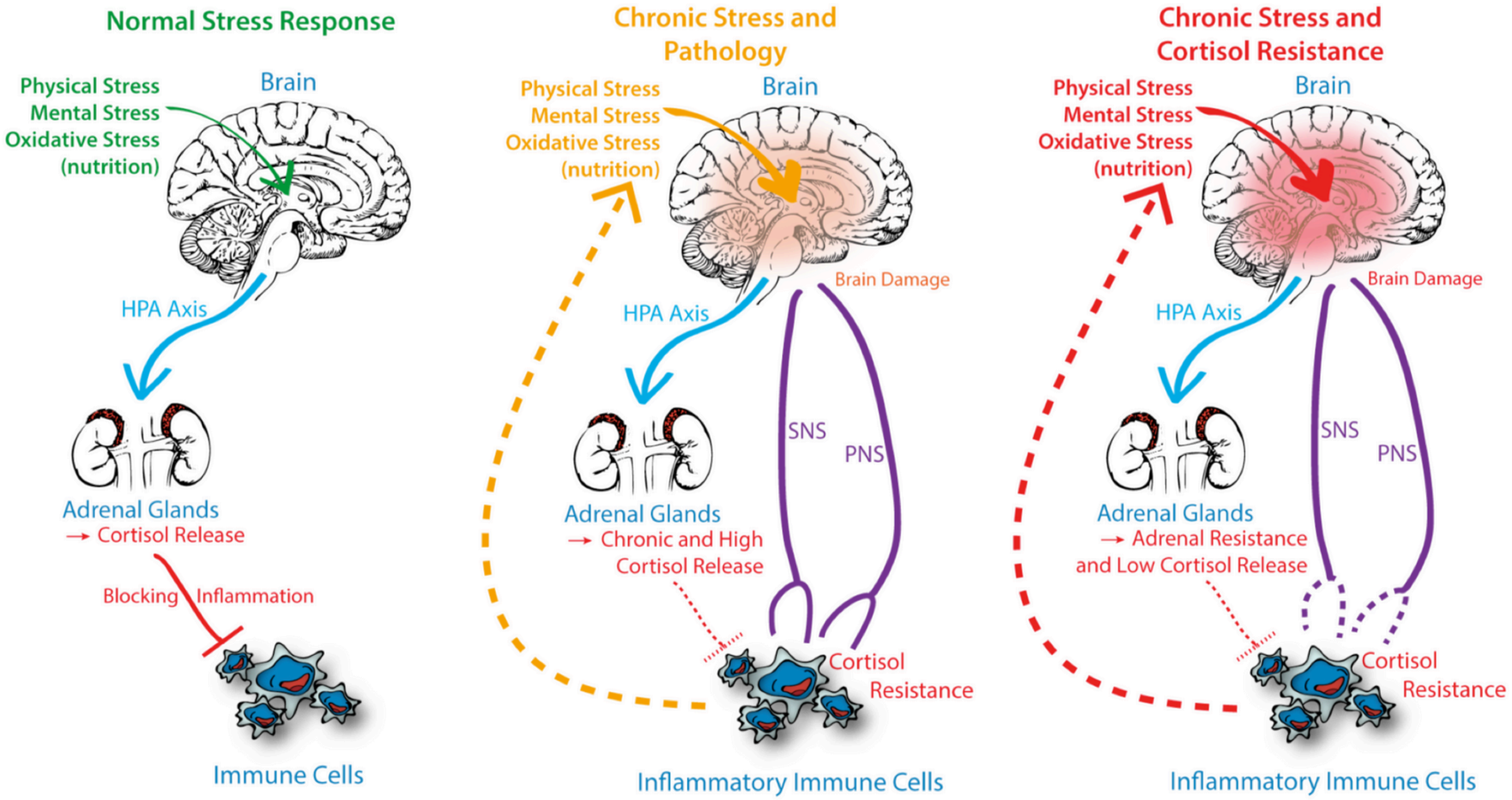
- moins de défense anti-virale
- plus d'inflammation



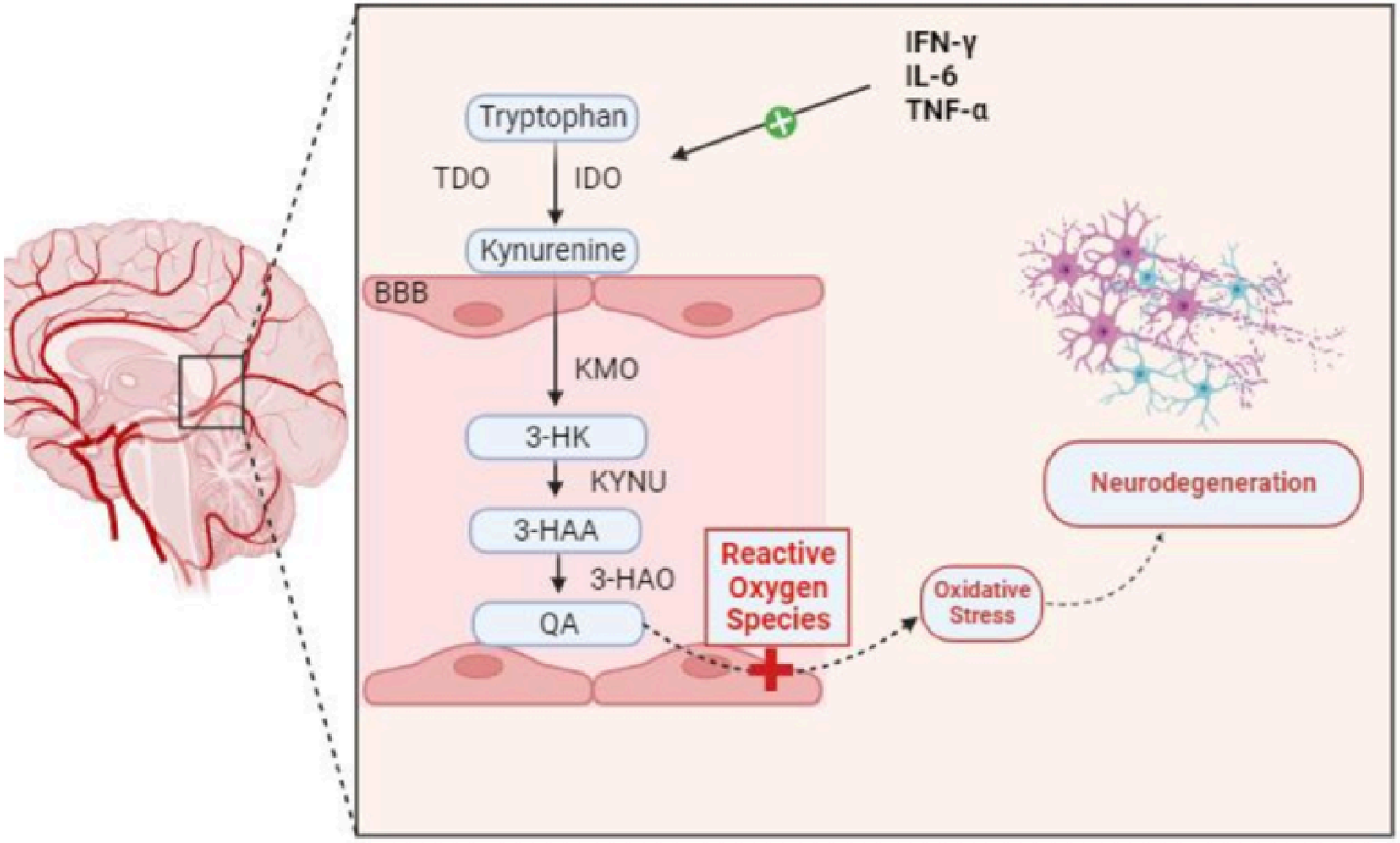
Nature Reviews | Immunology

Par le Dr Pascal Mensah

IFMi
Institut Français de Micro-immunothérapie


Normal Stress Response
Physical Stress
Mental Stress
Oxidative Stress
(nutrition)
Brain
HPA Axis
Adrenal Glands
→ Cortisol Release
Blocking Inflammation
Immune Cells
Chronic Stress and Pathology
Physical Stress
Mental Stress
Oxidative Stress
(nutrition)
Brain
Brain Damage
HPA Axis
SNS
PNS
Adrenal Glands
→ Chronic and High Cortisol Release
Cortisol Resistance
Inflammatory Immune Cells
Chronic Stress and Cortisol Resistance
Physical Stress
Mental Stress
Oxidative Stress
(nutrition)
Brain
Brain Damage
HPA Axis
SNS
PNS
Adrenal Glands
→ Adrenal Resistance and Low Cortisol Release
Cortisol Resistance
Inflammatory Immune Cells

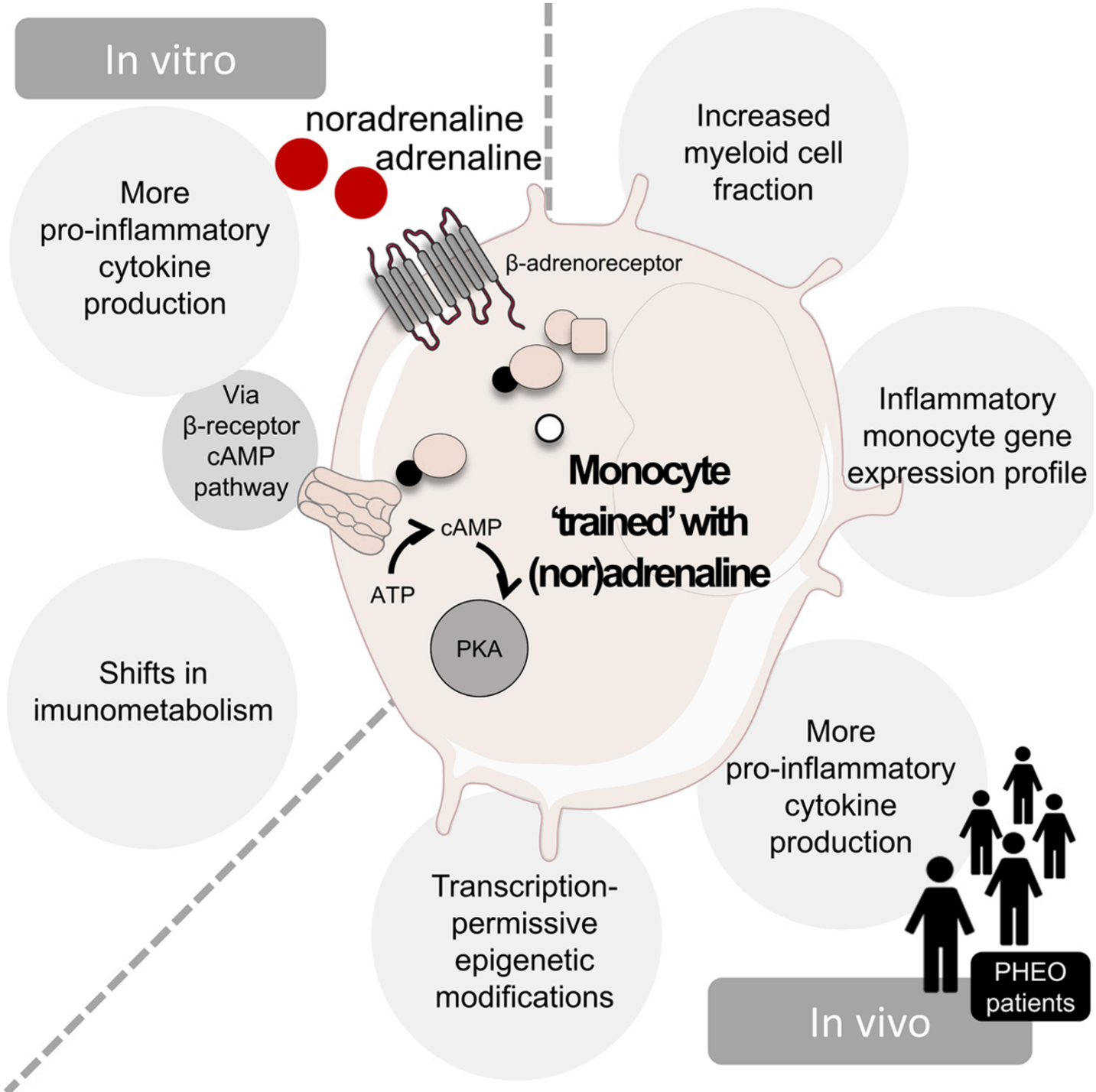
CORTISOL RESISTANCE



ıre 2. Pro-inflammatory cytokines, including TNF-α, IFN-γ, and IL-6, activate IDO, whic

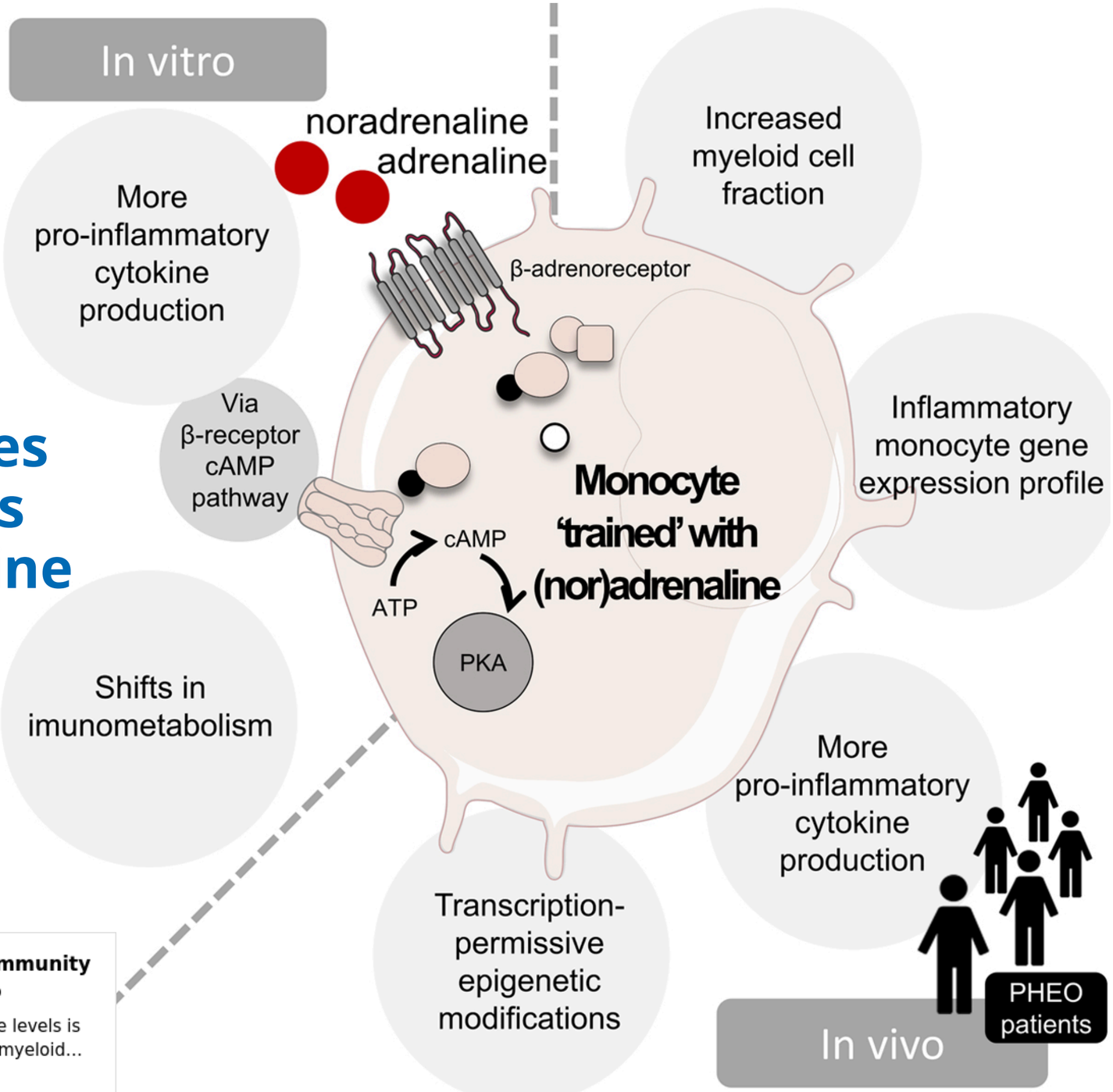
Pathak, Suhrud & Nadar, Rishi & Kim, Shannon & Liu, Keyi & Govindarajulu, Manoj & Cook, Preston & Alexander, Courtney & Dhanasekaran, Muralikrishnan & Moore, Timothy. (2024). **The Influence of Kynurenine Metabolites on Neurodegenerative Pathologies.** International Journal of Molecular Sciences. 25. 853. 10.3390/ijms25020853.

inflammatory changes of myeloid cells with Noradrenaline



IFMi
Institut Français de Micro-immunothérapie

modifications inflammatoires des cellules myéloïdes avec la noradrénaline

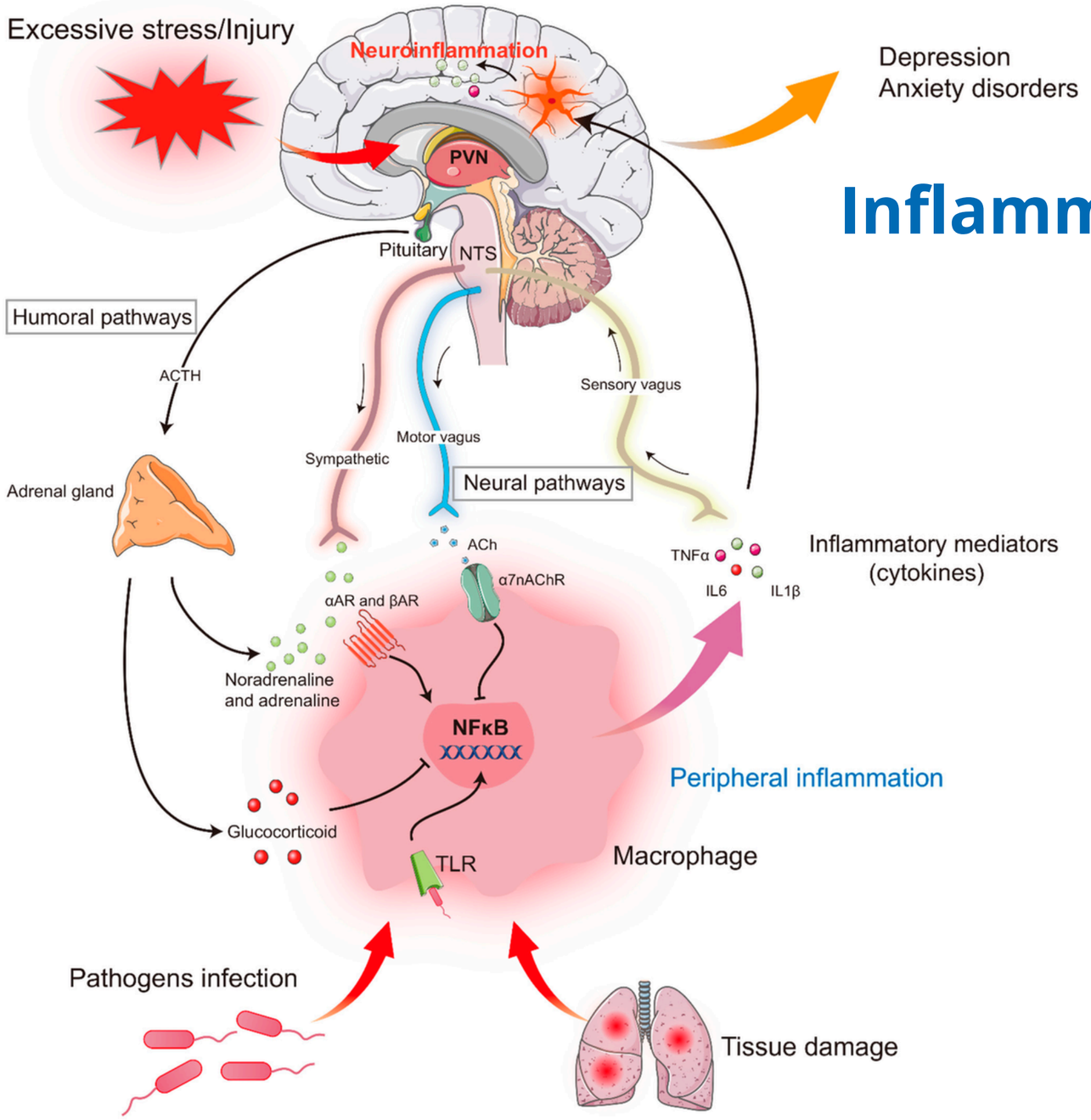


Catecholamines Induce Trained Immunity in Monocytes In Vitro and In Vivo

Rationale: Exposure to high catecholamine levels is associated with inflammatory changes of myeloid...

Circulation Research / Jul 3, 2020

IFMi
Institut Français de Micro-immunothérapie



Inflammation périphérique induite par le stress.

L'amygdale est essentielle dans la régulation de l'activation des axes HPA et SAM, qui sont les signes distinctifs de la réponse au stress.

Il convient de noter que contrairement à l'effet inhibiteur du cortex préfrontal et de l'hippocampe sur l'activation de l'axe HPA, l'amygdale agit principalement comme un activateur de l'axe HPA

Hu, P.; Lu, Y.; Pan, B.-X.; Zhang, W.-H. New Insights into the Pivotal Role of the Amygdala in Inflammation-Related Depression and Anxiety Disorder. *Int. J. Mol. Sci.* 2022, *23*, 11076. https://doi.org/10.3390/ijms231911076

IFMi
Institut Français de Micro-immunothérapie

Activation de l’axe hypothalamo-hypophyso-surrénalien (HPA) et signalisation par les glucocorticoïdes

Karin, O., Raz, M., Tendler, A., Bar, A., Kohanim, Y., Milo, T., ... & Alon, U. (2020). a new model for the hpa axis explains dysregulation of stress hormones on the timescale of weeks. Molecular Systems Biology, 16(7). https://doi.org/10.15252/msb.20209510

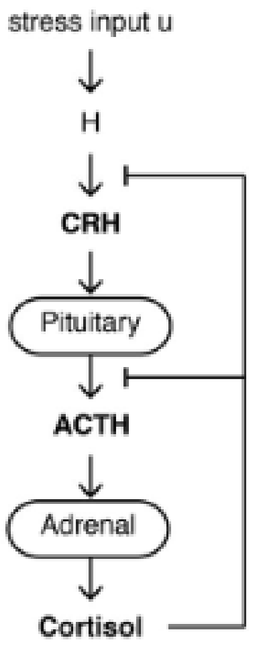
WebMi#32

Par le Dr Pascal Mensah

IFMi
Institut Français de Micro-immunothérapie

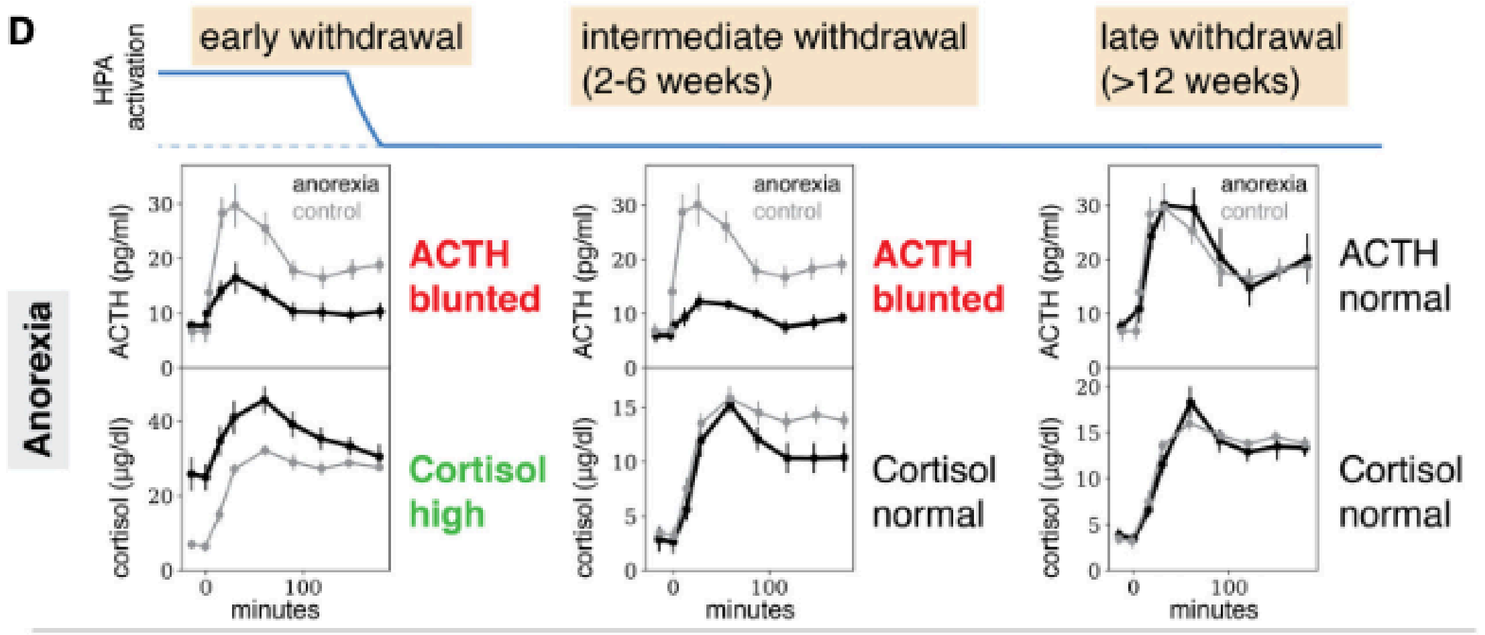
ACTH response is blunted for weeks after cortisol response normalizes

physiological and psychological stresses



Cortisol baseline is proportional

Three distinct phases of HPA axis

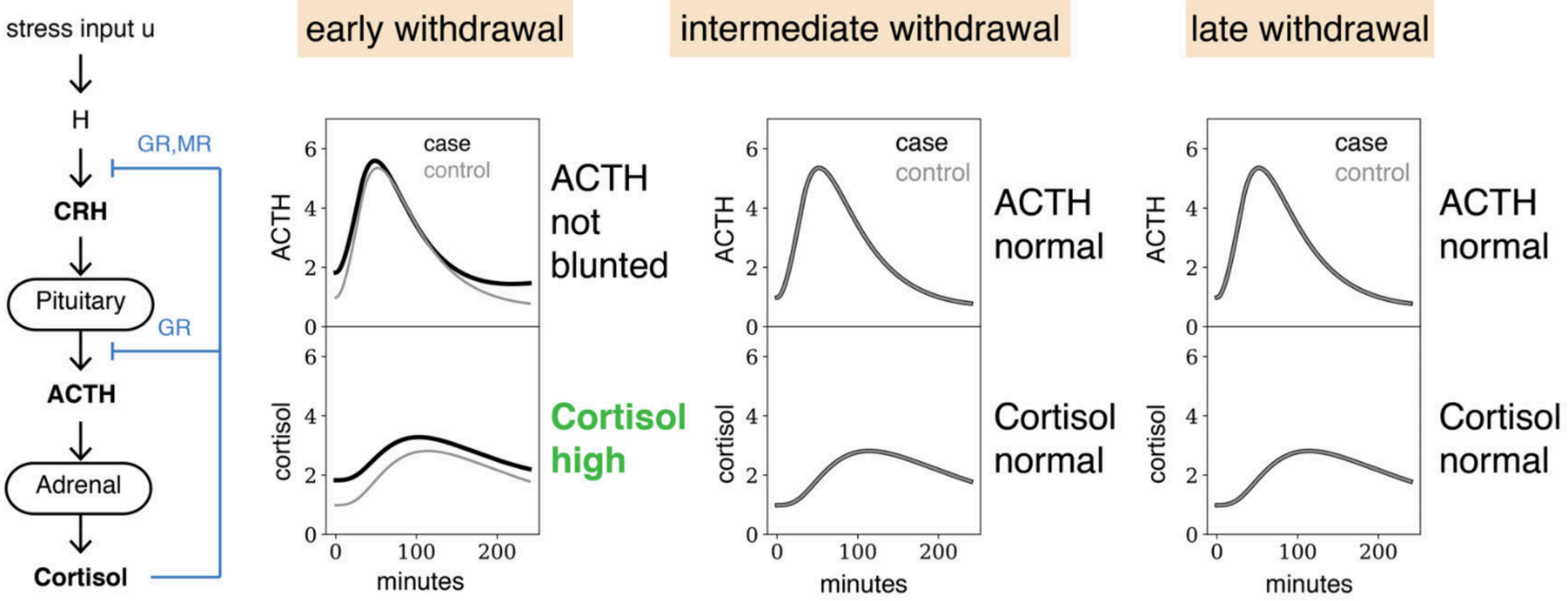


la rétroaction négative par GR protège l'axe HPA contre les changements importants de niveaux d'hormones et les réponses sur l'échelle de temps de quelques semaines après un apport de stress prolongé

Par le Dr Pascal Mensah

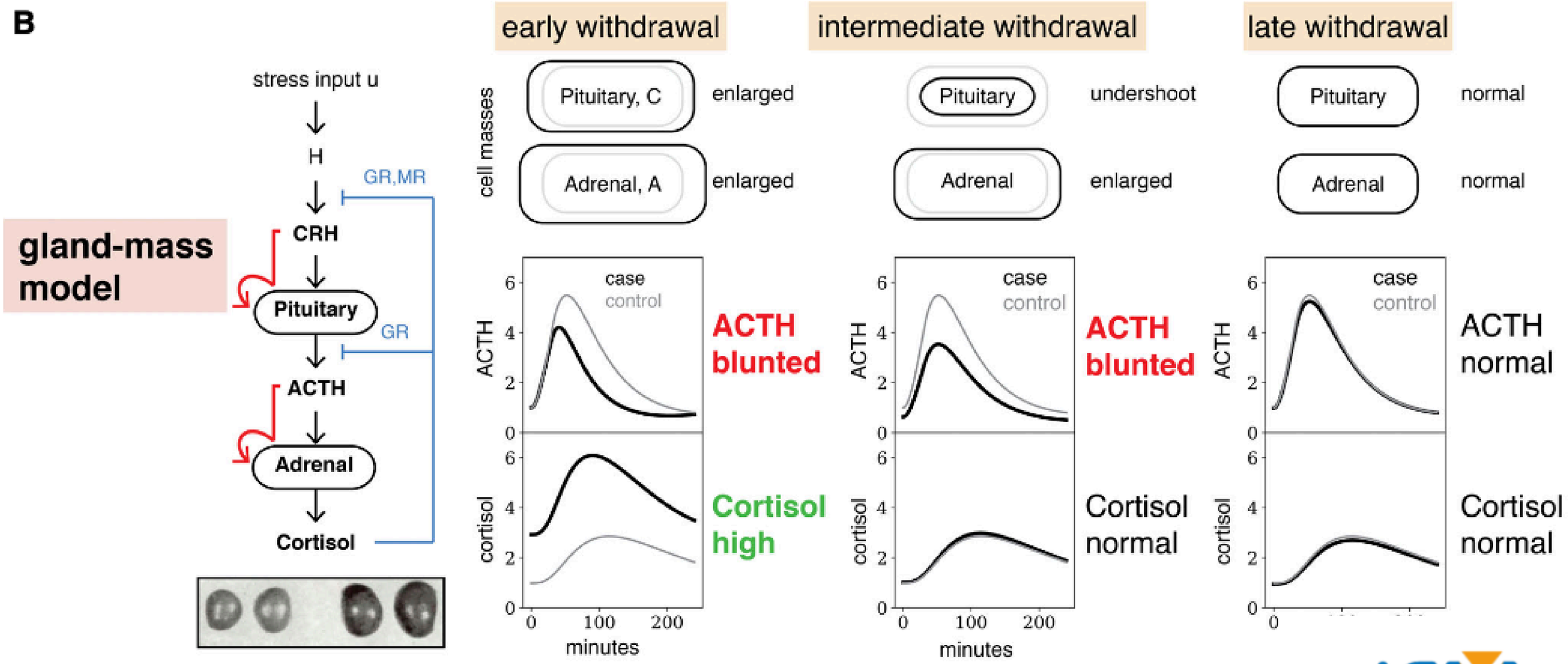
A

classic model



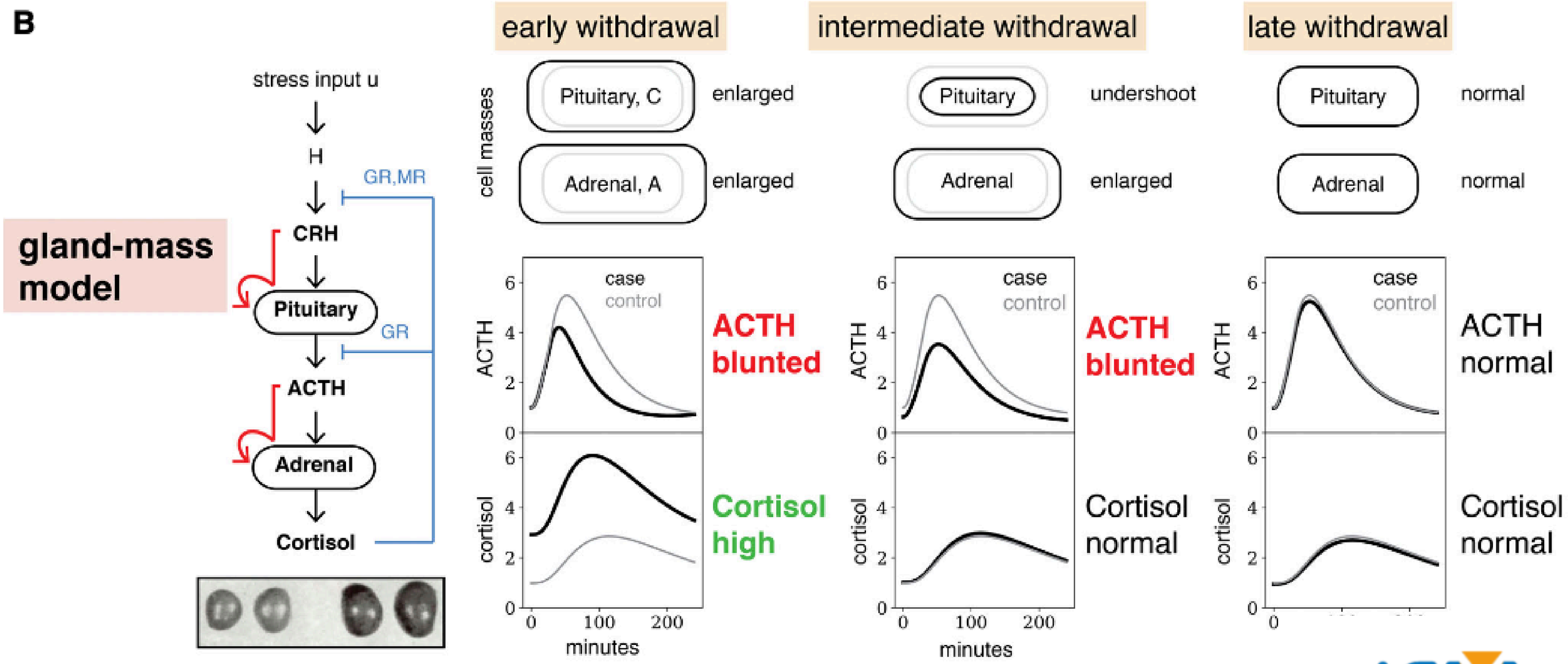
Par le Dr Pascal Mensah

Functional mass dynamics show ACTH blunting for weeks even after cortisol normalizes.



Par le Dr Pascal Mensah

La dynamique de masse fonctionnelle montre une diminution de l'ACTH pendant des semaines, même après la normalisation du cortisol.



Par le Dr Pascal Mensah

Comment les facteurs de stress psychologiques

affectent l'EBV latent.

WebMi#32

Par le Dr Pascal Mensah

IFMi
Institut Français de Micro-immunothérapie

Impact of Psychological Stress on EBV Reactivation

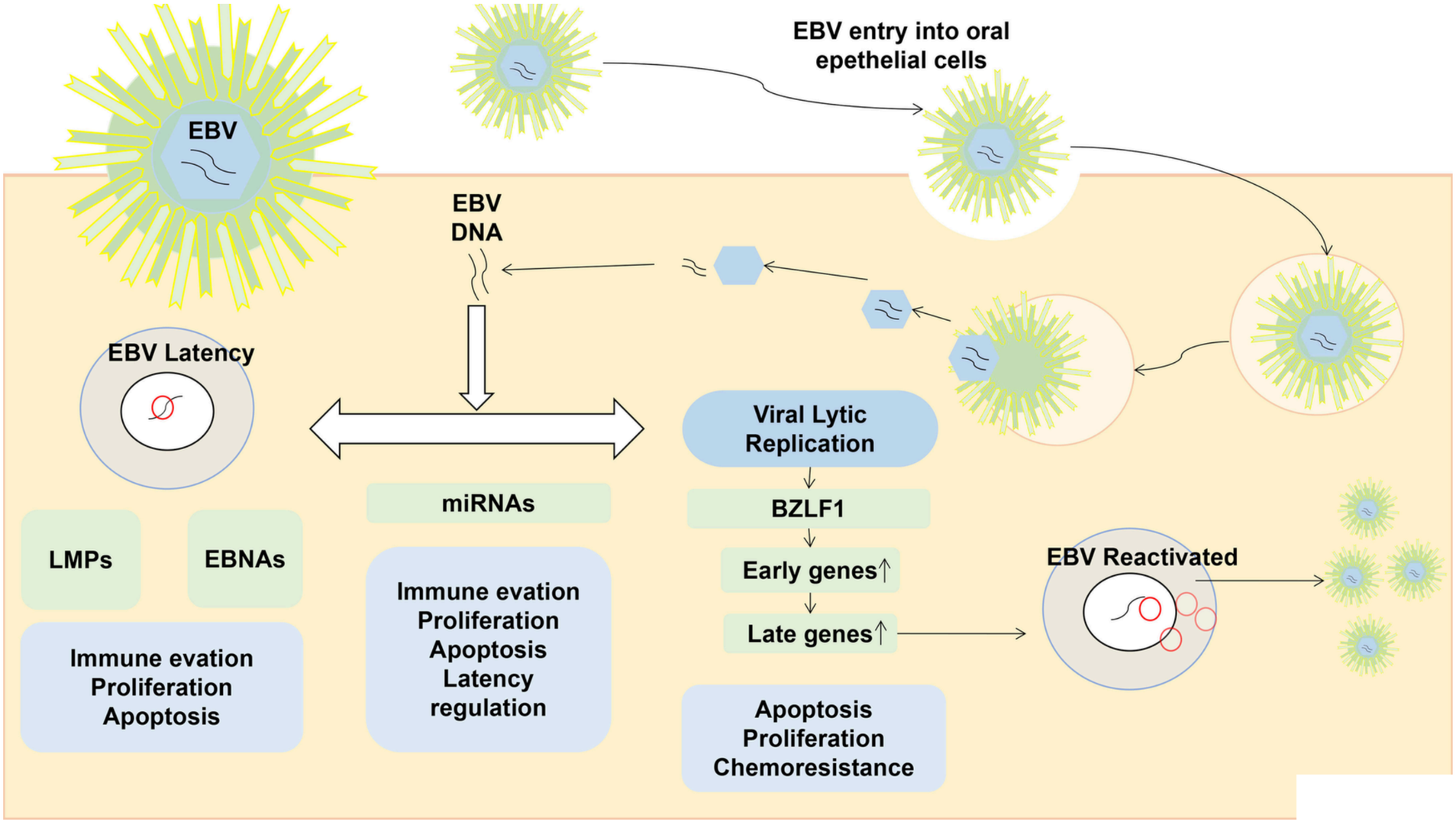
How do psychological stressors affect latent EBV?

They can induce the HPA and SAM axes, leading to cortisol production, which activates the latent EBV genome.

What is the goal of further studies on this topic?

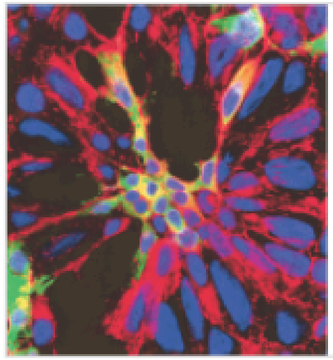
To understand the mechanisms of stress-associated reactivation of latent EBV and mitigate the adverse effects on EBV latency and related diseases.

IFMi
Institut Français de Micro-immunothérapie



Front. Cell. Infect. Microbiol. , 23 February 2022
Sec. Microbiome in Health and Disease
Volume 12 - 2022 |

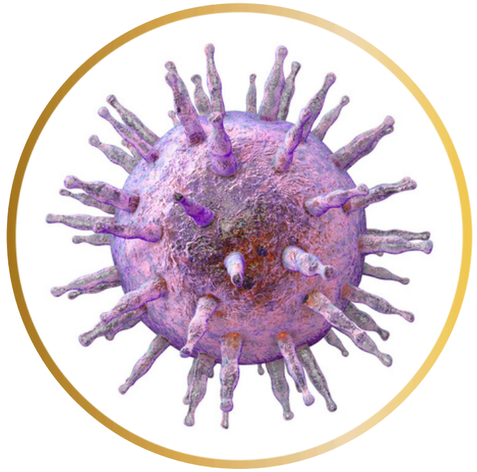
IFMi
Institut Français de Micro-immunothérapie

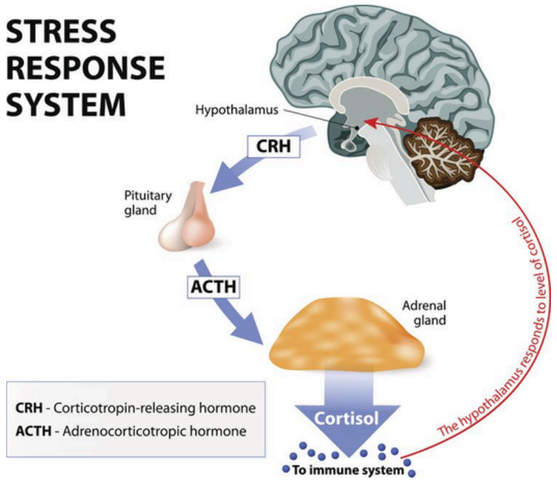


Epstein-Barr Virus BZLF1 Gene, a Switch from Latency to Lytic Infection, Is Expressed as an Imme...

ABSTRACT We demonstrate here that the Epstein-Barr virus (EBV) BZLF1 gene, a switch from latent infection to...

Journal of Virology / Jan 15, 2007





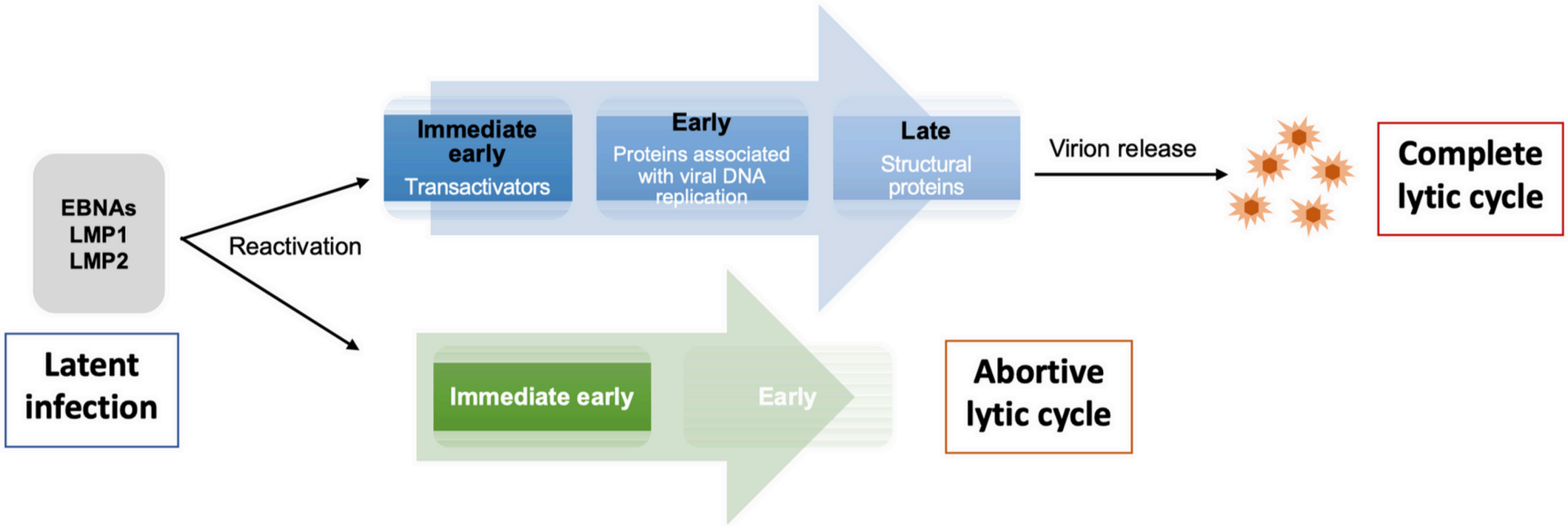
Glucocorticoids activate Epstein Barr Virus lytic replication through the upregulation of immediate early BZLF1 gene expression

Psychological stress-associated immune dysregulation has been shown to disrupt the steady state expression and reactivate latent herpes viruses. One such virus is the Epstein Barr virus (EBV), which is associated with several human m...

PubMed Central (PMC)

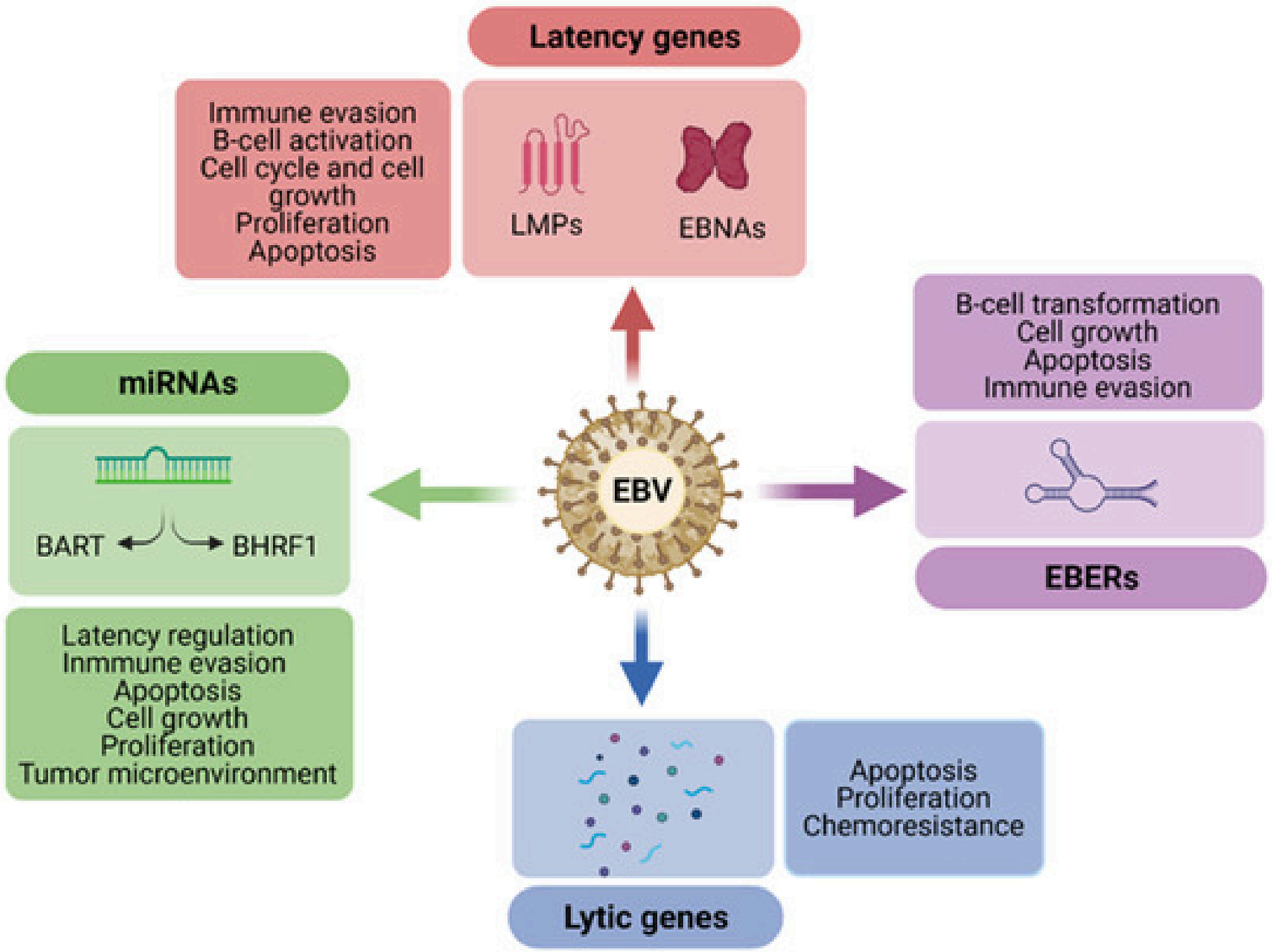
Published in final edited form as: Brain Behav Immun. 2010 May 11;24(7):1089–1096. doi:


Results



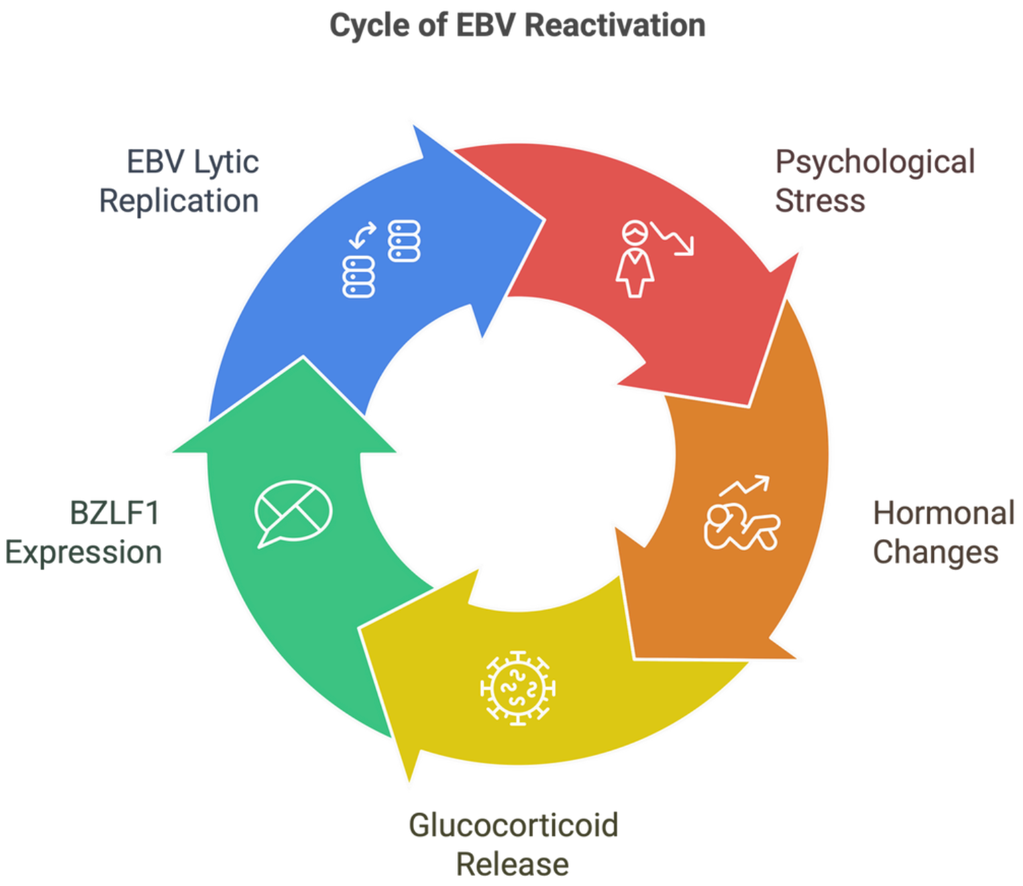
MDPI and ACS Style

Yap, L.F.; Wong, A.K.C.; Paterson, I.C.; Young, L.S. Functional Implications of Epstein-Barr Virus Lytic Genes in Carcinogenesis. Cancers 2022, 14, 5780. https://doi.org/10.3390/cancers14235780



Verdu-Bou, M.; Tapia, G.; Hernandez-Rodriguez, A.; Navarro, J.-T. Clinical and Therapeutic Implications of Epstein–Barr Virus in HIV-Related Lymphomas. Cancers 2021, 13, 5534. https://doi.org/10.3390/cancers13215534

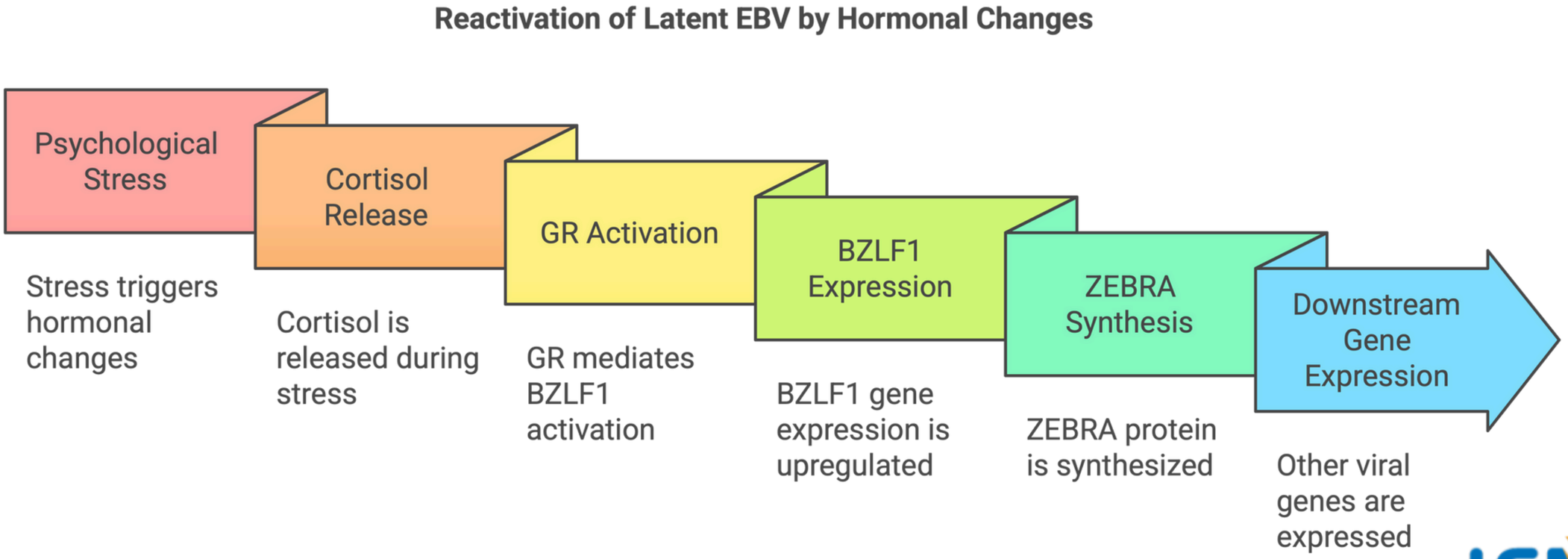
Les GC induisent l'expression précoce du gène BZLF1 de l'EBV dans les cellules de Daudi



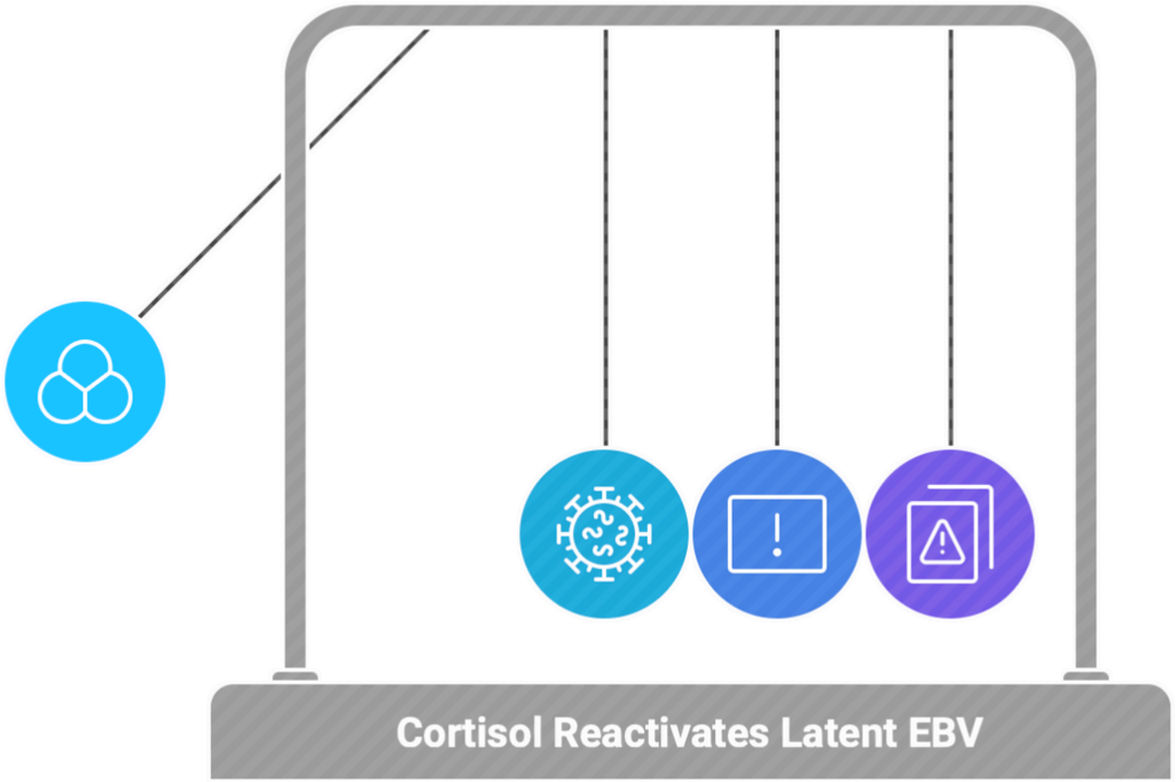
Par le Dr Pascal Mensah

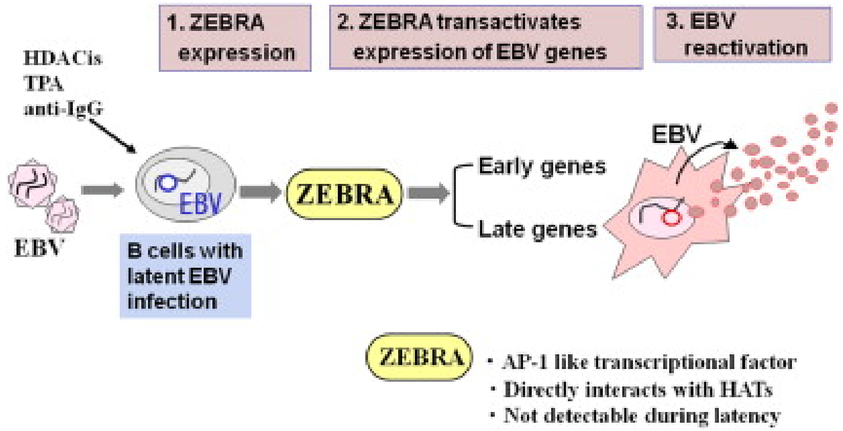
IFMi
Institut Français de Micro-immunothérapie

L'expression de ZEBRA induite par GC médie l'expression différentielle des EAs EBV



Par le Dr Pascal Mensah





Kenichi Imai, Yorimasa Ogata, Kuniyasu Ochiai,
Microbial interaction of periodontopathic bacteria and Epstein-Barr virus and their implication of periodontal diseases,
Journal of Oral Biosciences,
Volume 54, Issue 3,
2012,

Cortisol

Enhances EBV gene expression

BZLF1 Activation

Triggers viral replication

EA Expression

Increases EBV antigens

EBV Reactivation

Leads to disease potential

Par le Dr Pascal Mensah

IFMi
Institut Français de Micro-immunothérapie

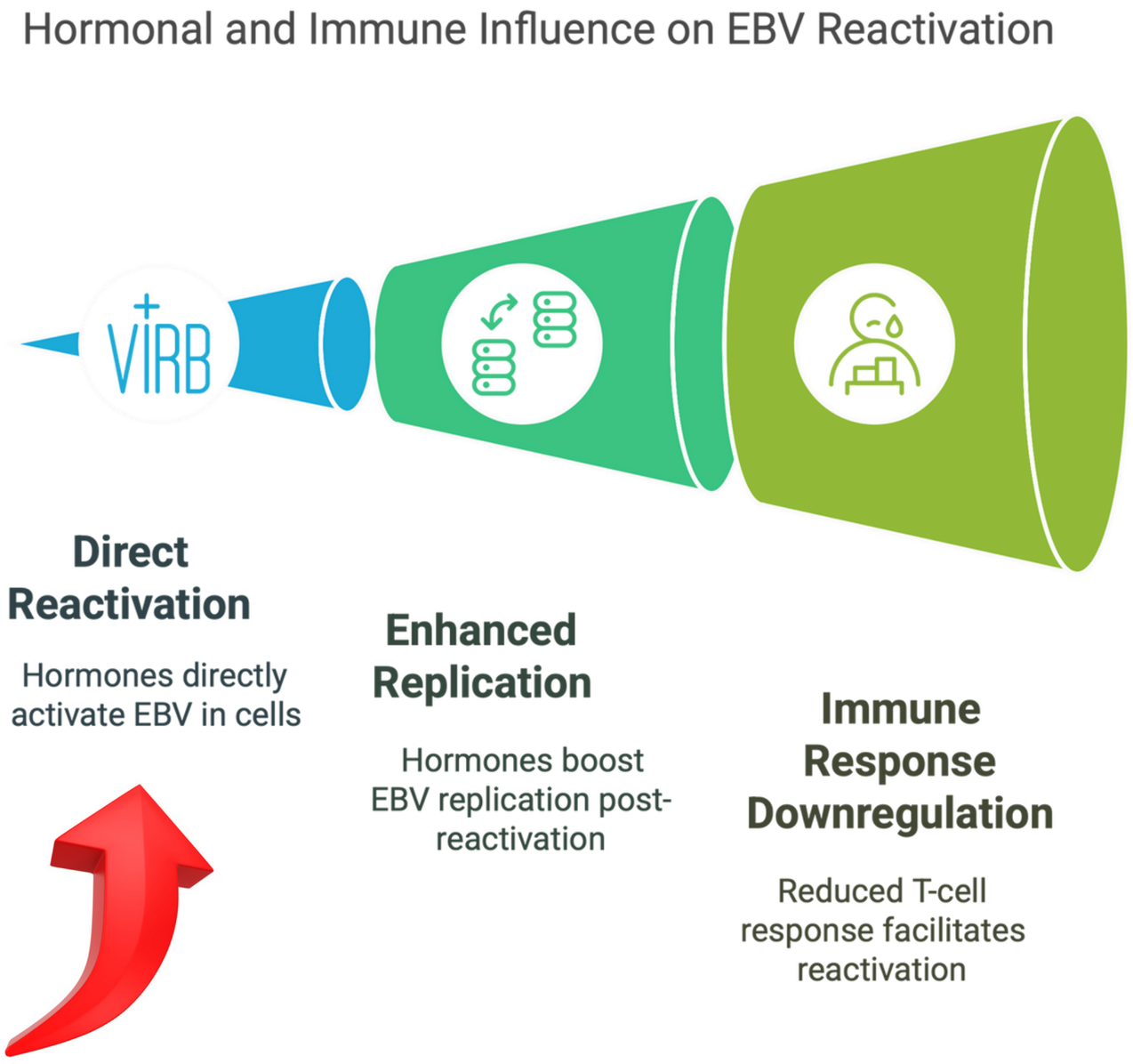
“

Here we further confirm that Dex and HC can reactivate latent EBV and that Dex can more efficiently induce reactivation by virtue of its greater potency compared to HC.

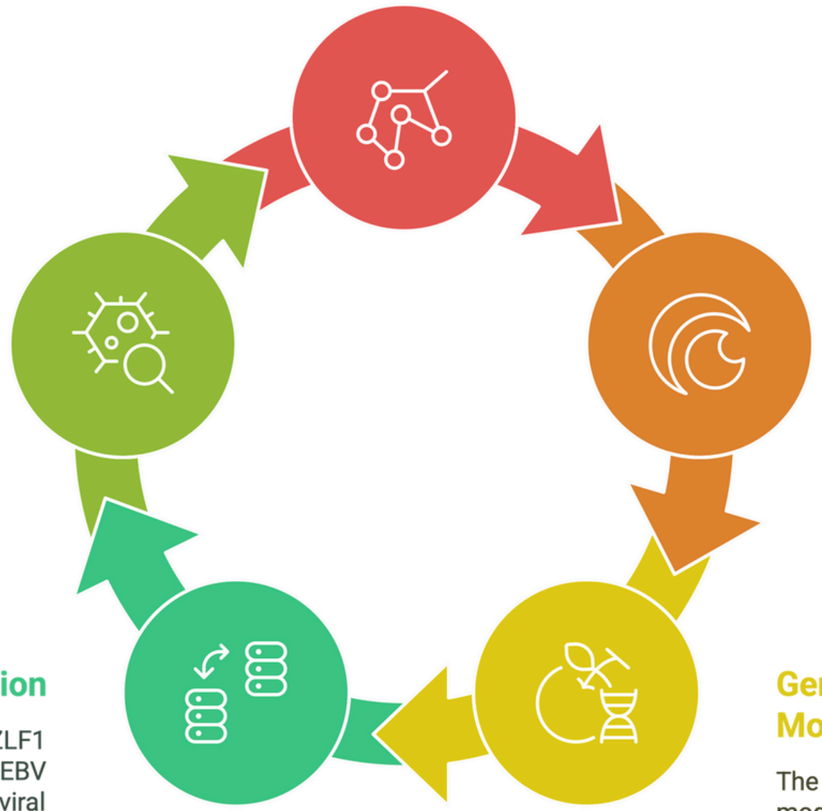
”

Par le Dr Pascal Mensah

Exposition à Dex or HC



Cycle of EBV Reactivation Induced by Stress



Stress Induction

Psychological stress activates the HPA axis, leading to cortisol production.

Cortisol Binding

Cortisol binds to glucocorticoid receptors (GR) in cells.

Gene Expression Modulation

The GR-cortisol complex modulates EBV gene expression, enhancing BZLF1 mRNA.

EBV Reactivation

Increased BZLF1 expression leads to EBV reactivation and viral replication.

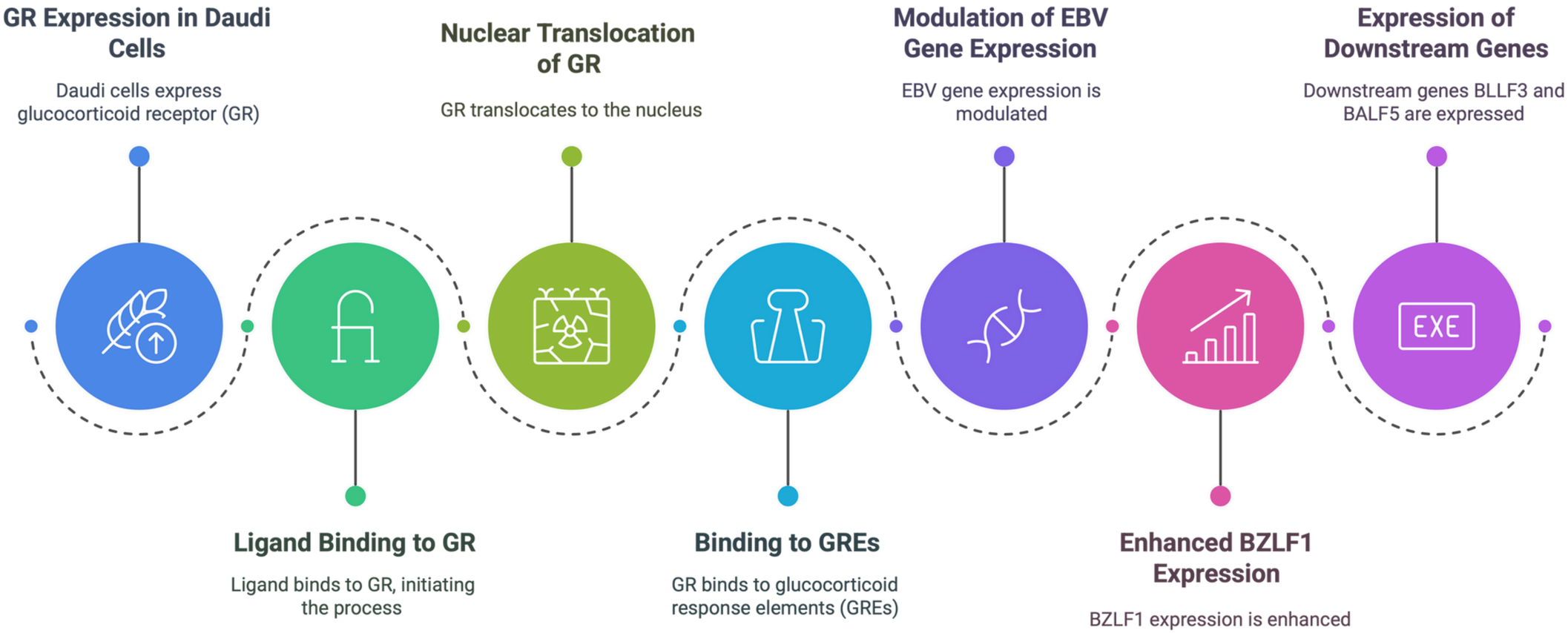
EA Antigen Expression

EBV early antigens (EAs) are expressed, indicating viral activity.

Par le Dr Pascal Mensah

IFMi
Institut Français de Micro-immunothérapie

EBV Reactivation and Gene Expression Modulation



Par le Dr Pascal Mensah

IFMi
Institut Français de Micro-immunothérapie

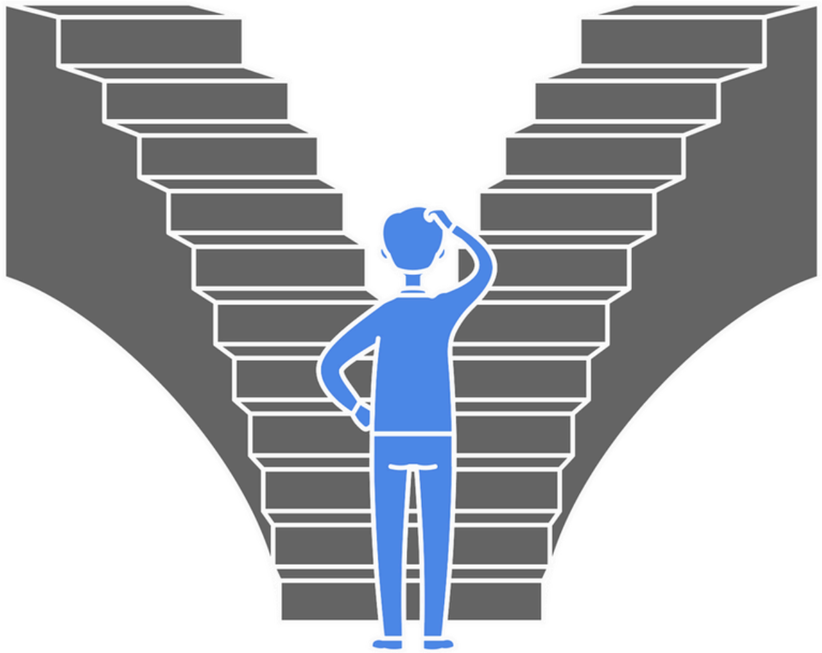
How do different treatments affect EBV reactivation?

GCs Induced Expression

Leads to limited EA expression and partial EBV reactivation.

TPA/NaB Induced Expression

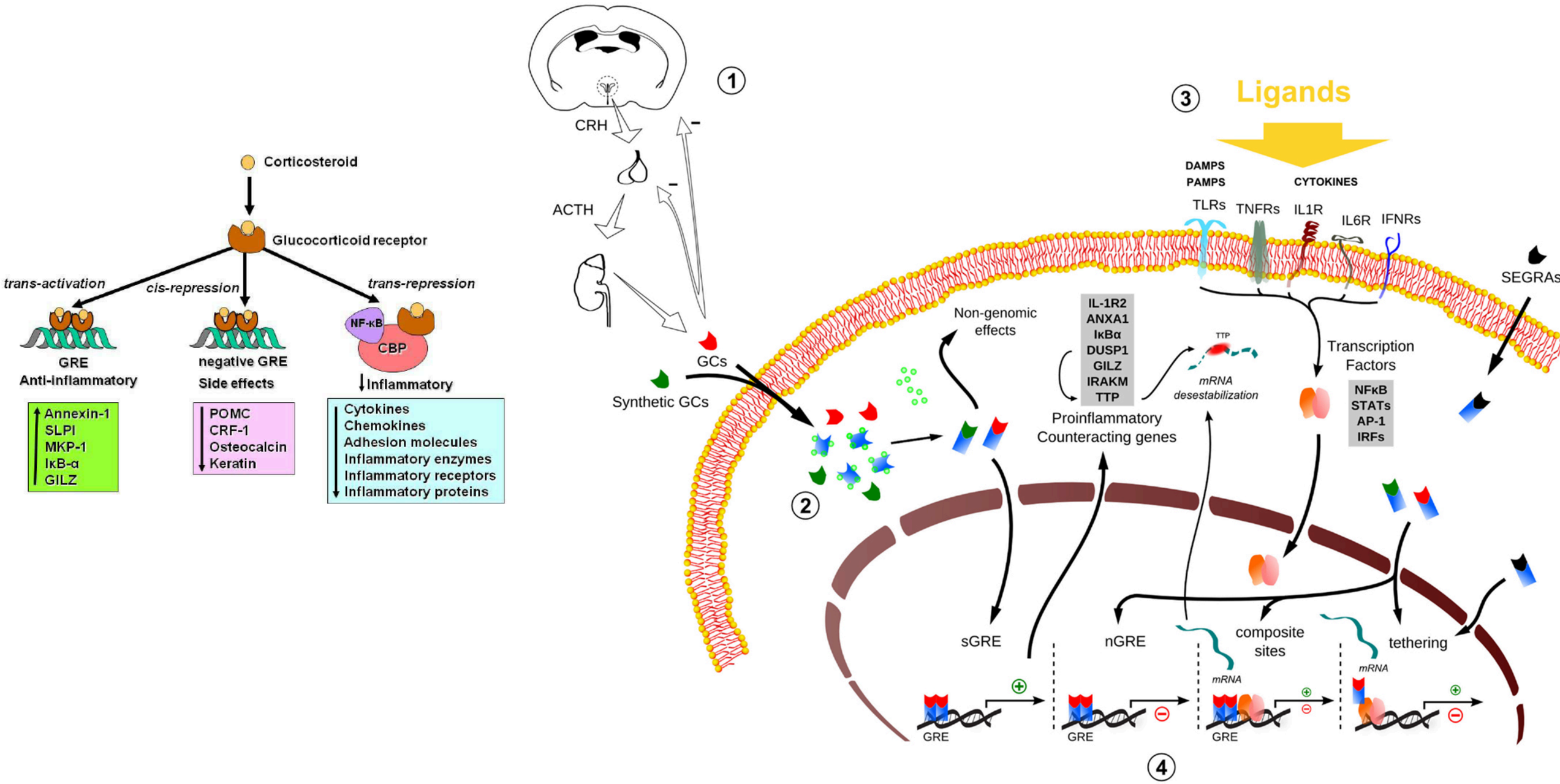
Results in a larger set of EBV EAs and complete reactivation.



Par le Dr Pascal Mensah

Nous, et d'autres, avons montré que le **stress** peut induire les axes HPA et SAM, entraînant la **production de cortisol**, dont nous avons montré dans cette étude (sous forme de HC) qu'il peut provoquer l'activation du génome de l'EBV latent.

Andre Machado , Anunciato Aparecida Kataryna Olimpio , Rosenstock Tatiana Rosado , Glezer Isaias
Gene Expression Control by Glucocorticoid Receptors during Innate Immune Responses
Frontiers in Endocrinology, VOLUME=7/ 2016
=https://www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2016.00031

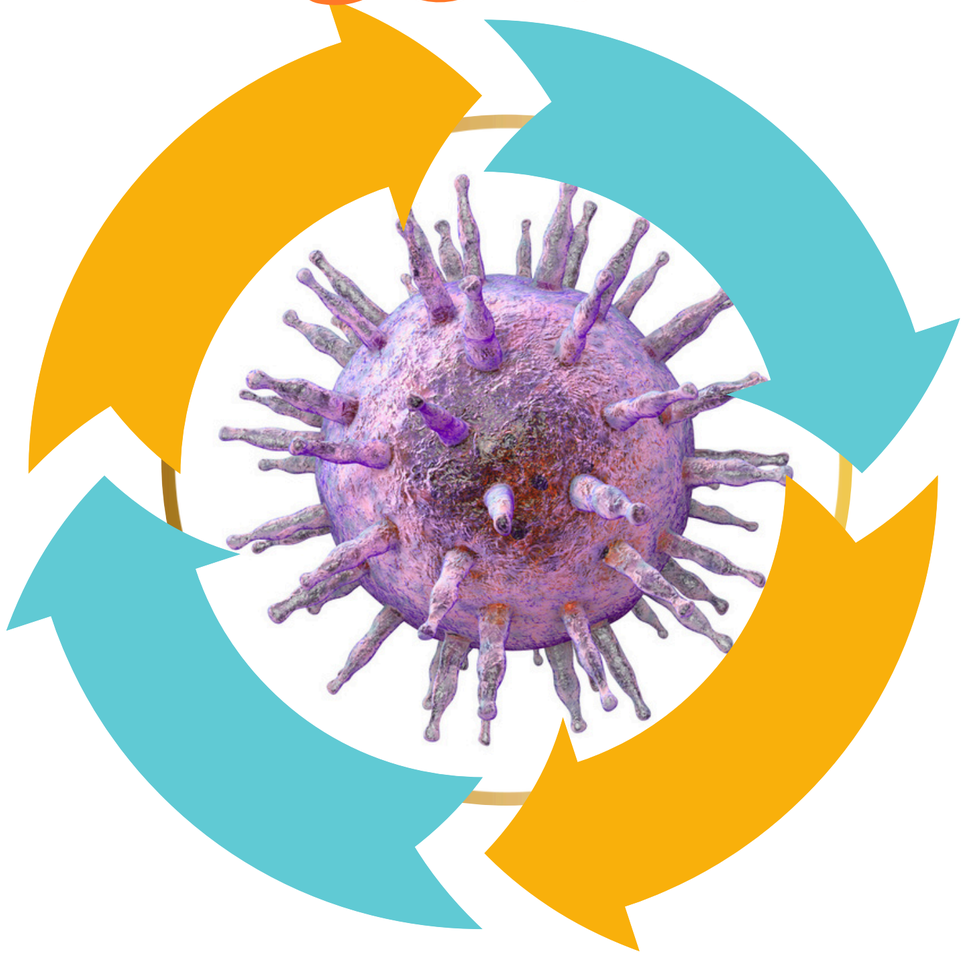


Il n' y a pas que le stress psychologique à prendre en compte, le stress oxidatif aussi active la réactivation de l'EBV !

Par le Dr Pascal Mensah

EBV

ROS



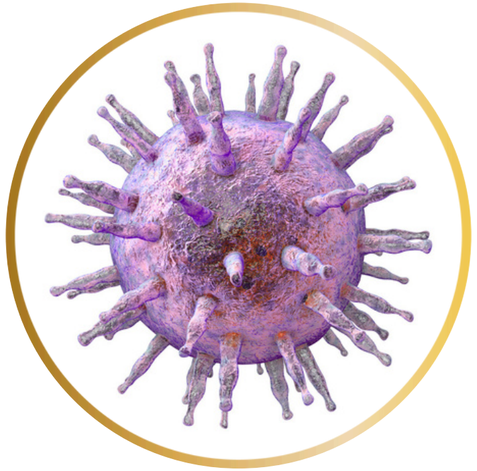
Reactivation

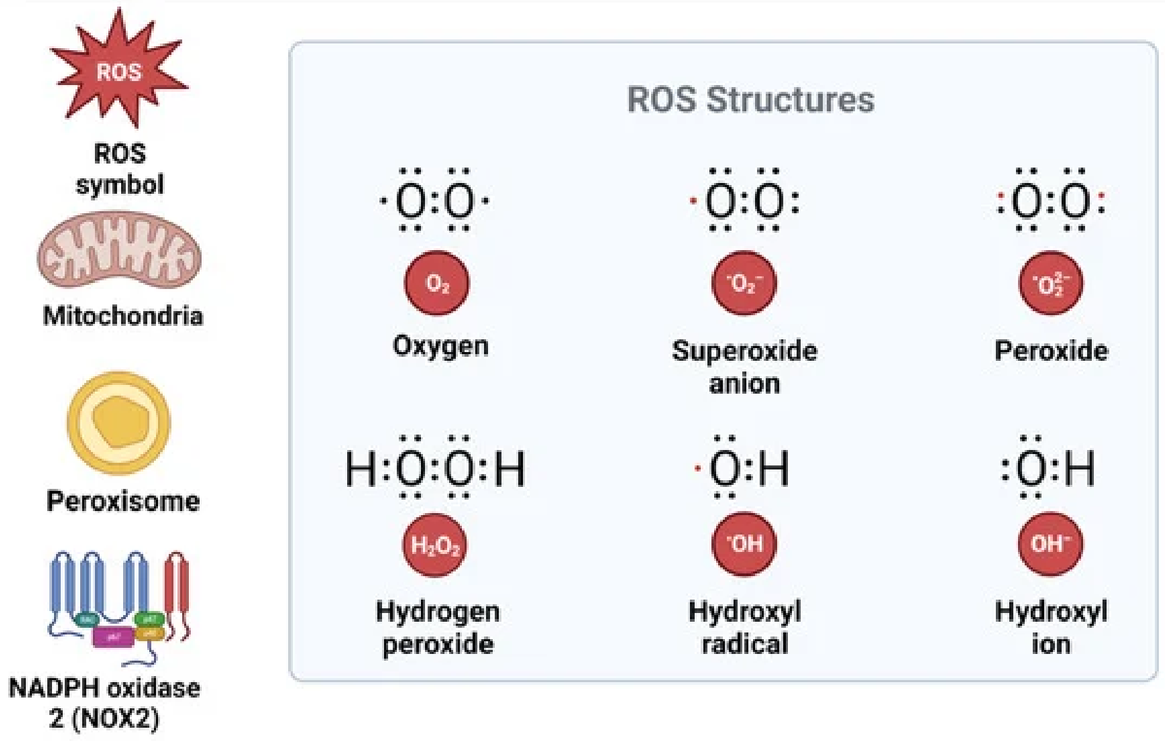
WebMi#32

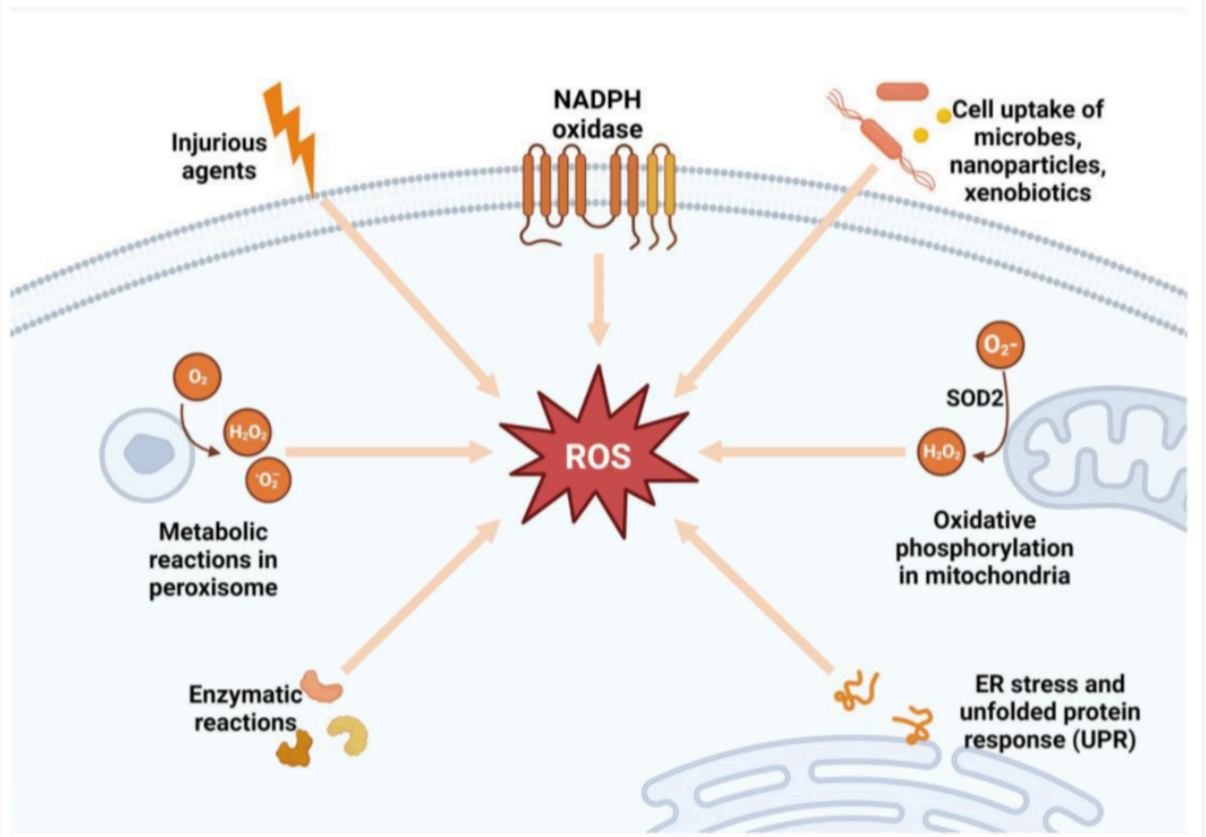
Par le Dr Pascal Mensah

IFMi
Institut Français de
Micro-immunothérapie

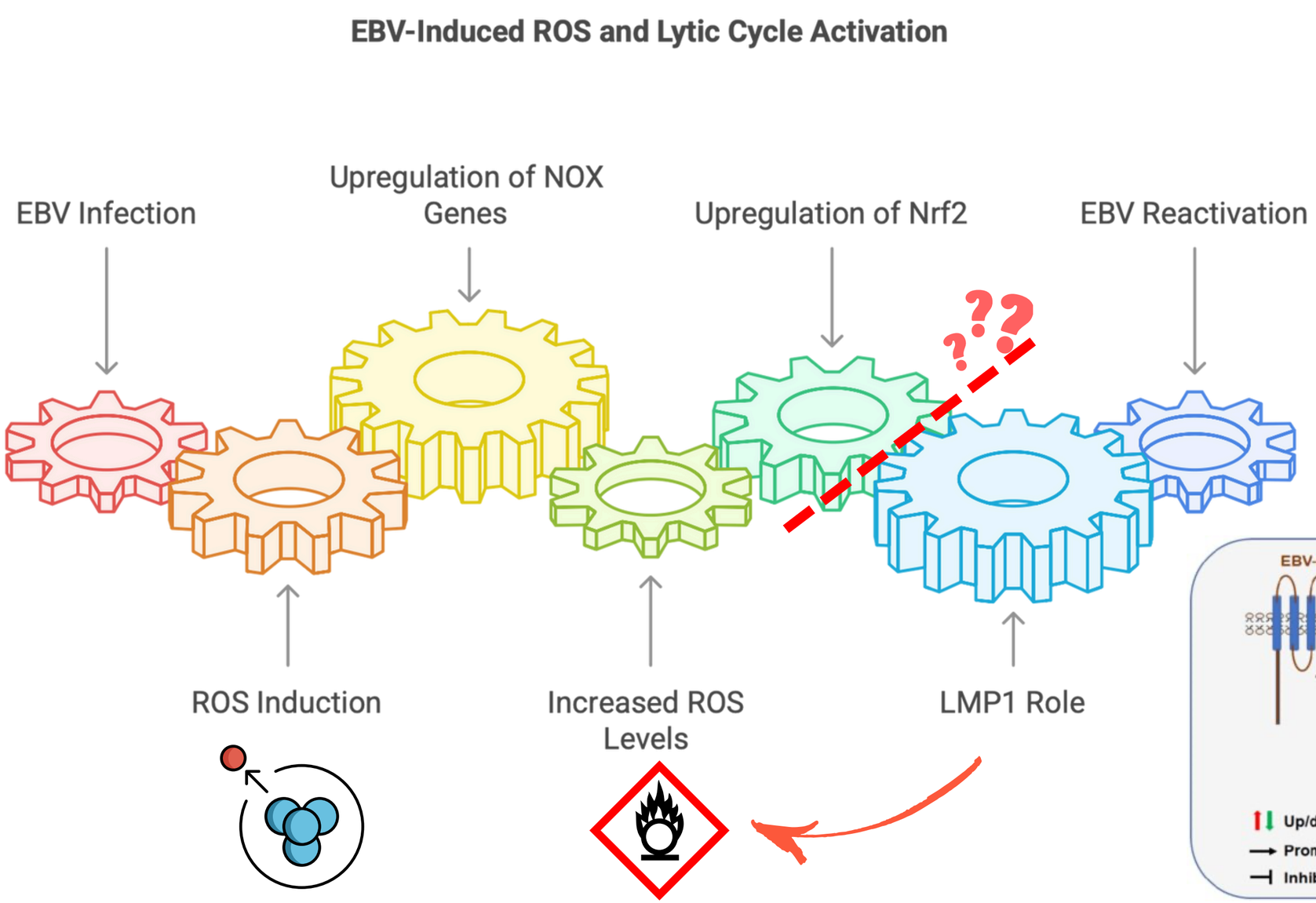
ROS

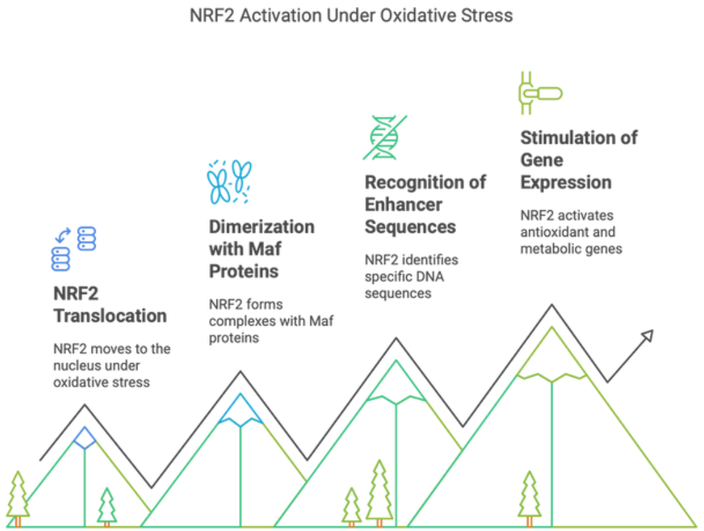


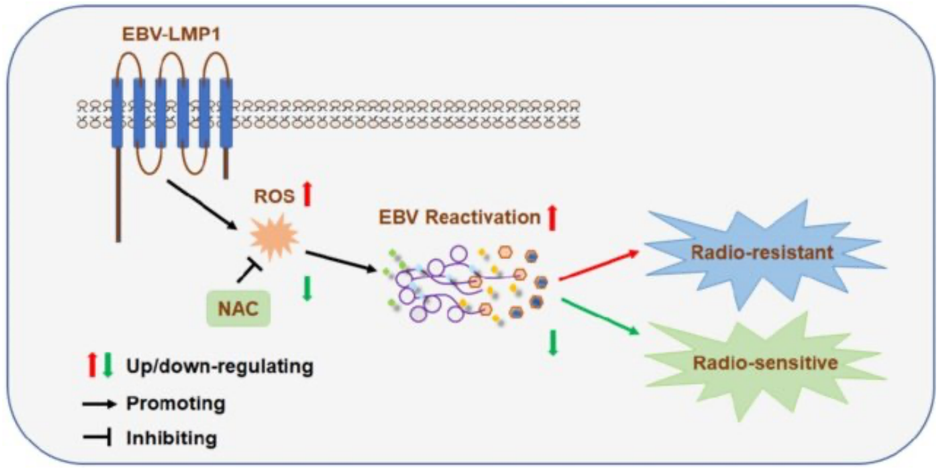




Masenga, S.K.; Kabwe, L.S.; Chakulya, M.; Kirabo, A. Mechanisms of Oxidative Stress in Metabolic Syndrome. Int. J. Mol. Sci. 2023, 24, 7898. https://doi.org/10.3390/ijms24097898

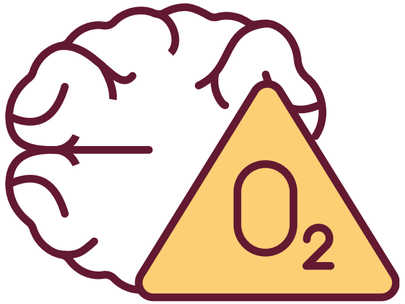


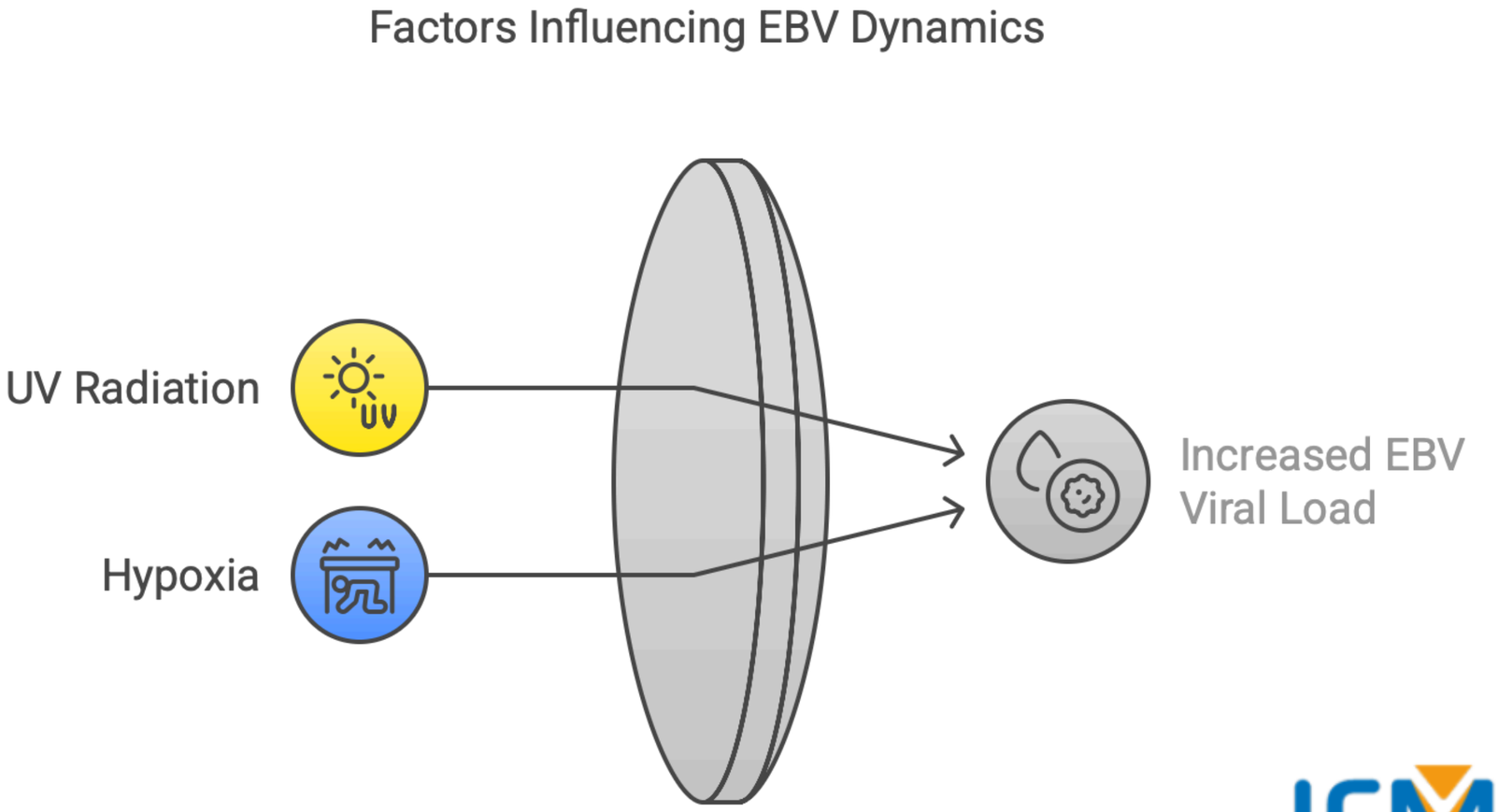




Hu, Jianmin & Li, Yueshuo & Hongde, Li & Shi, Feng & Xie, Longlong & Zhao, Lin & Tang, Min & Luo, Xiangjian & Jia, Weihua & Fan, Jed & Zhou, Josh & Gao, Qiang & Qiu, Shuangjian & Wu, Weizhong & Zhang, xin & Liao, Weihua & Bode, Ann & Cao, Ya. (2020). Targeting Epstein-Barr virus oncoprotein LMP1-mediated high oxidative stress suppresses EBV lytic reactivation and sensitizes tumors to radiation therapy. Theranostics. 10. 11921-11937. 10.7150/thno.46006.

l'hypoxie et la radiothérapie ont toutes deux augmenté la charge virale du EBV.





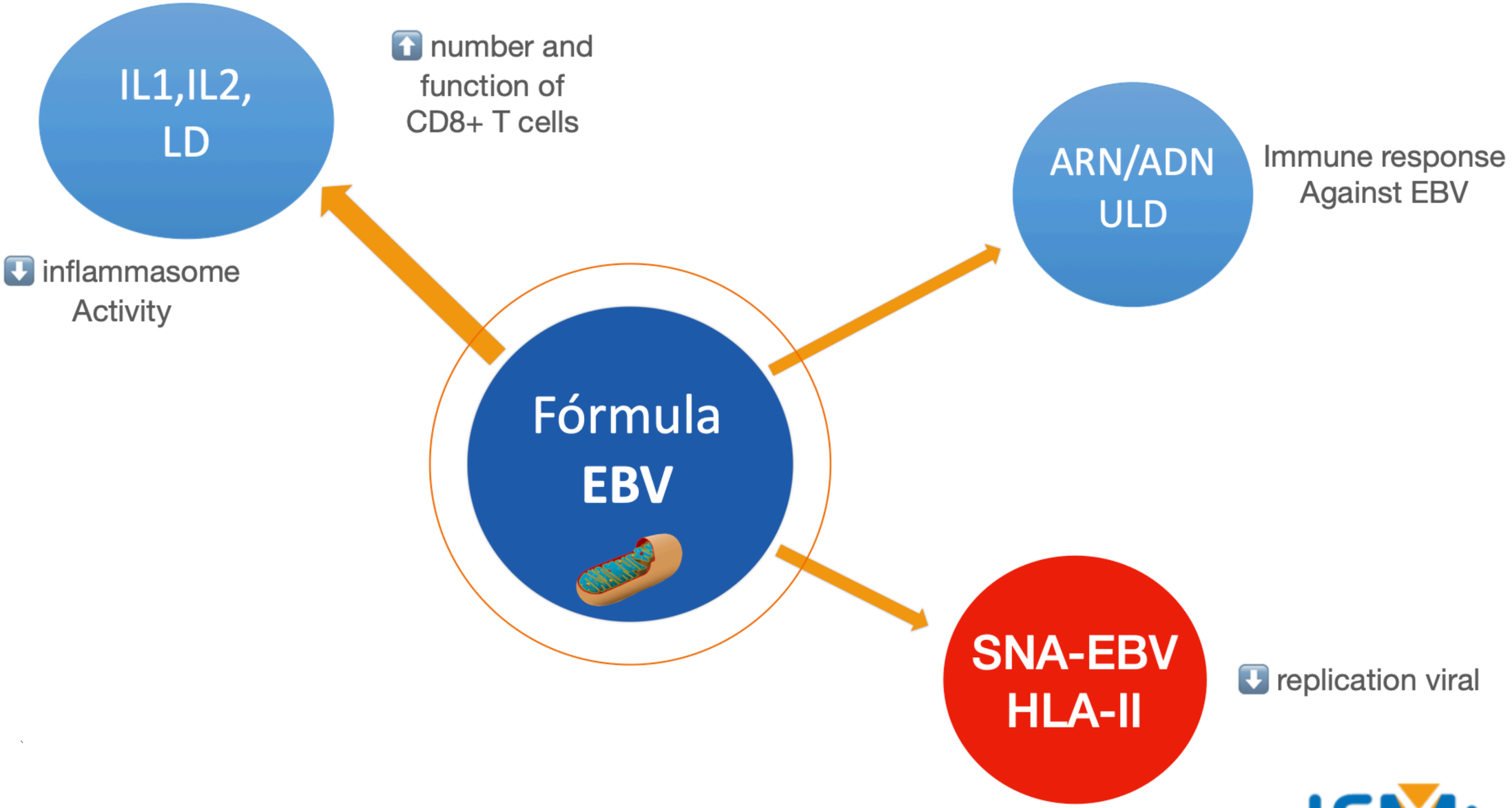
Par le Dr Pascal Mensah

IFMi
Institut Français de
Micro-immunothérapie

bMi#32

Pascal Mensah

IFMi
Institut Français de
Micro-immunothérapie



Par le Dr Pascal Mensah

IFMi
Institut Français de
Micro-immunothérapie

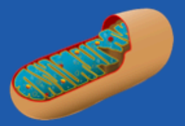
RNA

⬇️ IFN-I activity
and loss of CD28

IL2

⬆️ telomerase
activity

Fórmula MISEN



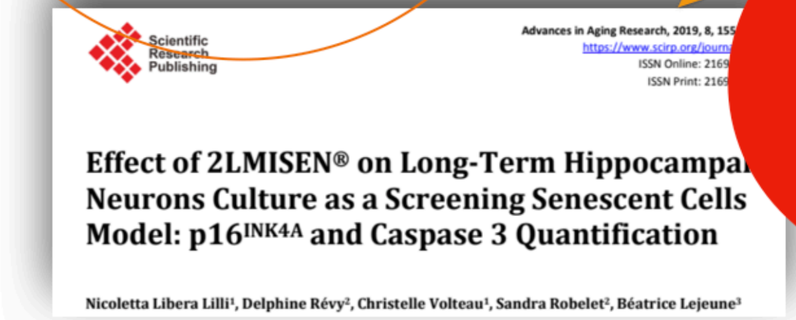
SNA-MISEN/ HLA-I/II

- regulating gene of ageing-specific expression

- ⬆️ Telomerase activity

DHEA

Moderate Cortisol/
DHEA ratio.



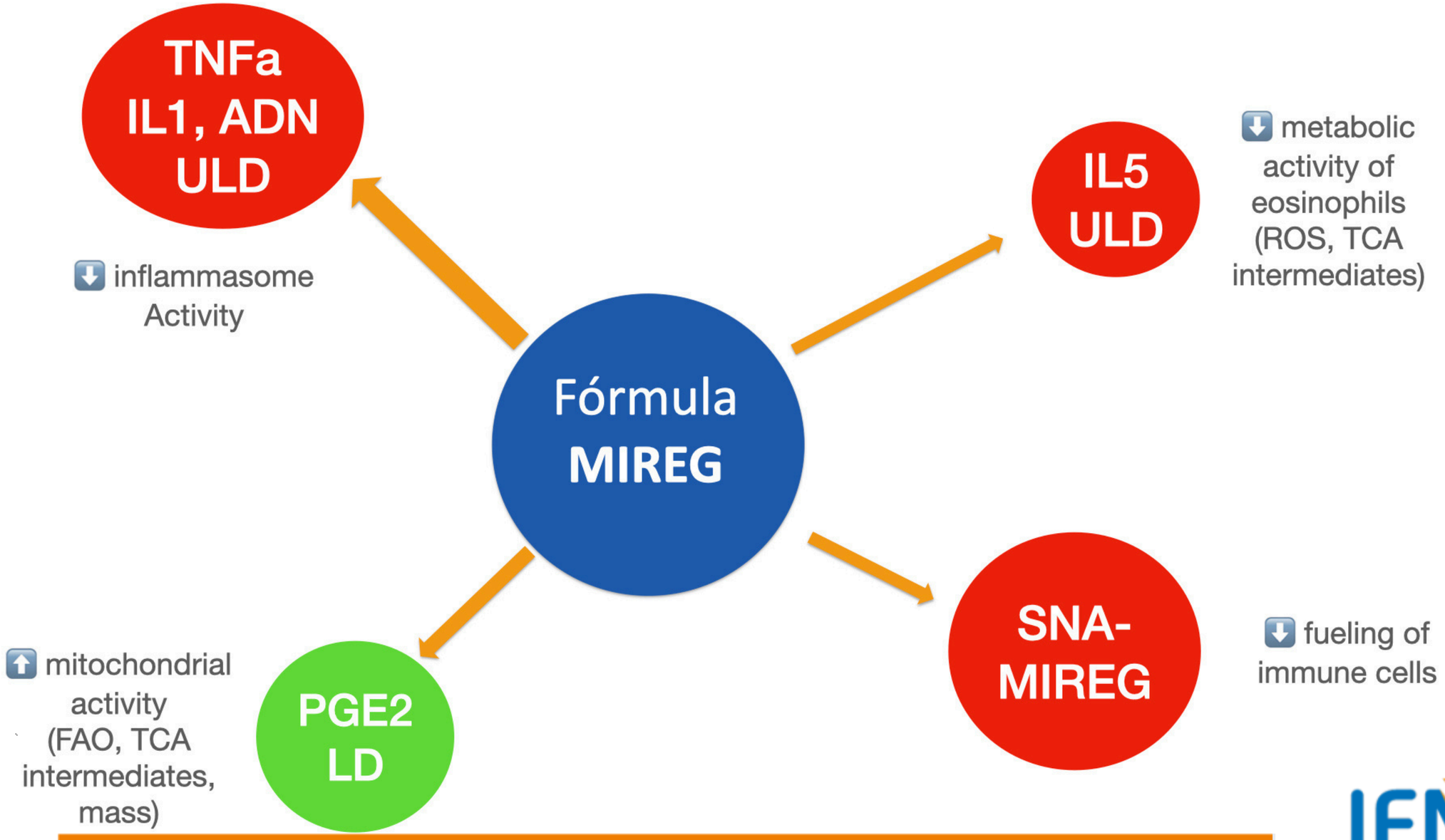
Scientific Research Publishing

Advances in Aging Research, 2019, 8, 155
https://www.scirp.org/journ
ISSN Online: 2169
ISSN Print: 2169

Effect of 2LMISEN® on Long-Term Hippocampal Neurons Culture as a Screening Senescent Cells Model: p16INK4A and Caspase 3 Quantification

Nicoletta Libera Lilli[1], Delphine Révy[2], Christelle Volteau[1], Sandra Robelet[2], Béatrice Lejeune[3]

x



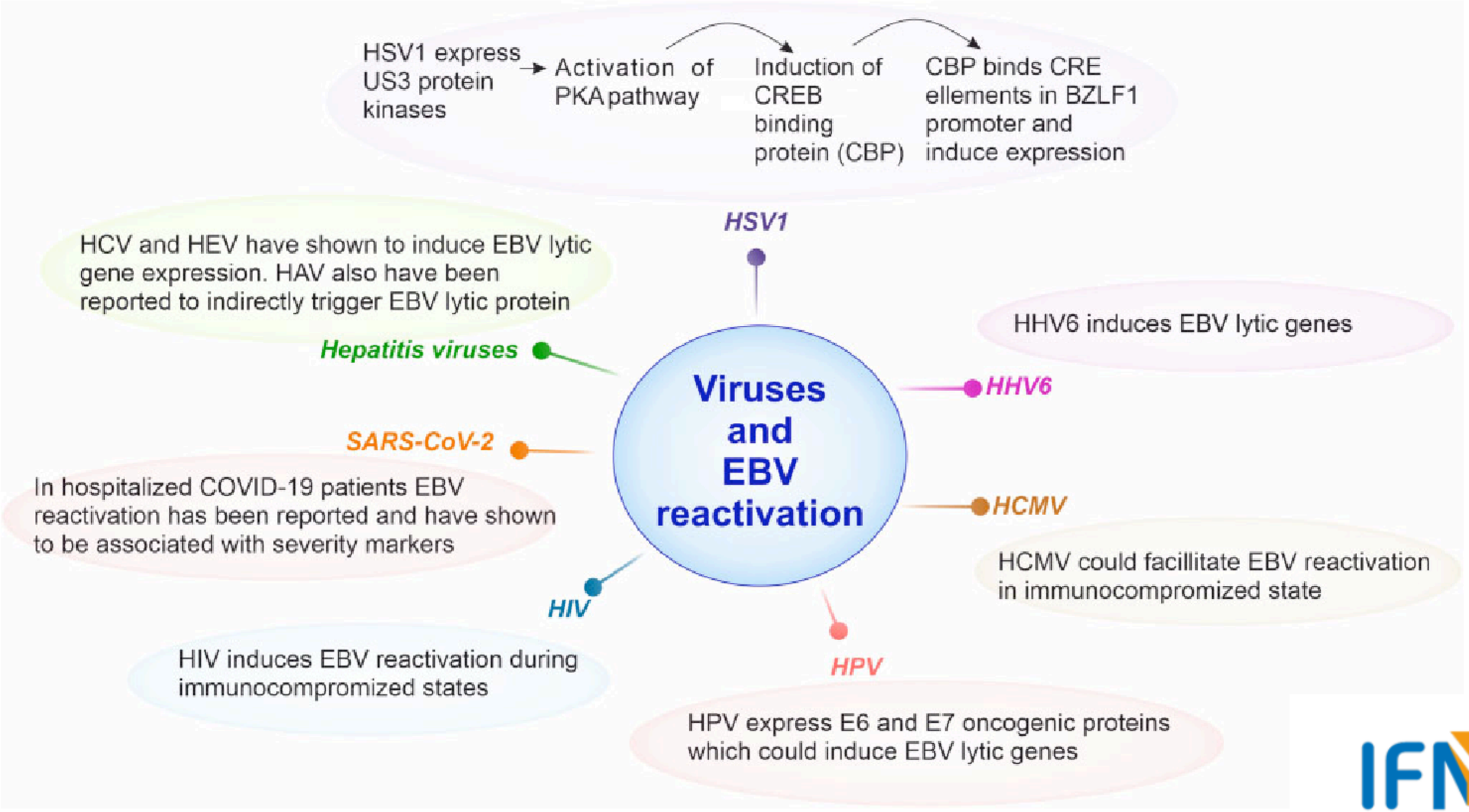
Par le Dr Pascal Mensah

IFMi
Institut Français de Micro-immunothérapie

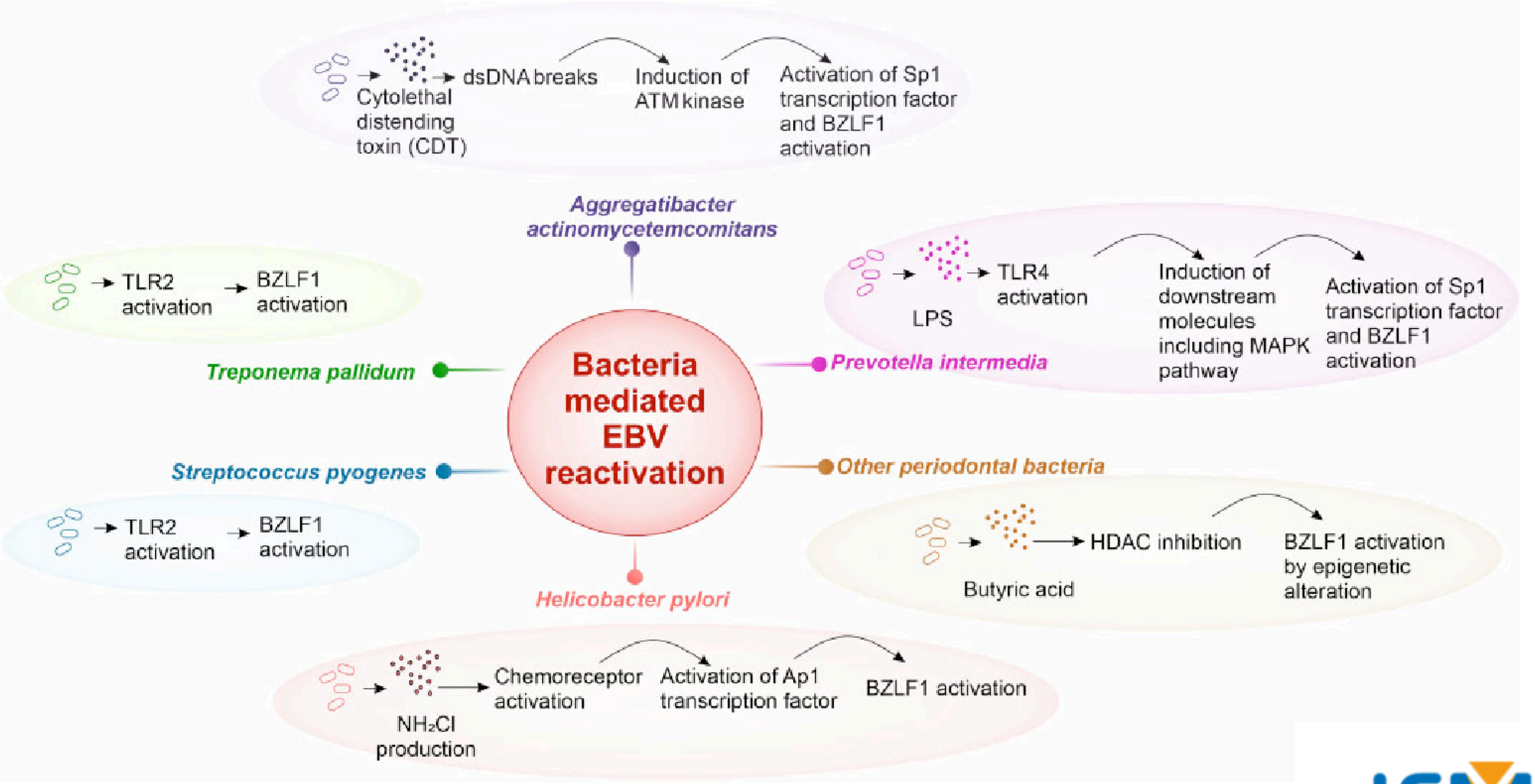
NEXT

Par le Dr Pascal Mensah

IFMi
Institut Français de
Micro-immunothérapie

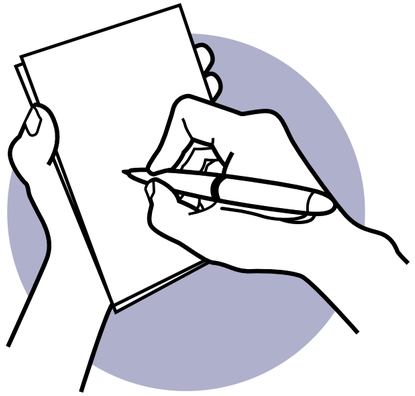


IFMi
Institut Français de Micro-immunothérapie



IFMi
Institut Français de Micro-immunothérapie

Take home message



- le stress peut induire les **axes HPA et SAM.**
- entraînant la **production de cortisol.**
- peut provoquer **l'activation du génome de l'EBV latent.**

- **2L-EBV, 2L-MISEN et 2L-MIREG**


FINISH