Rôle physiopathologique des interférons dans le lupus systémique

Auto-immunité physiologique

Phénomène naturel

Lymphocytes B / T

BCR **TCR**

reconnaître spécifiquement des antigènes

lymphocytes B/T autoréactifs
faible affinité

éliminer la production de
clone auto-réactif
forte affinité
ou
la production
d'autoanticorps

tolérance du système immunitaire

Permet la régulation de l'homéostasie du système immunitaire

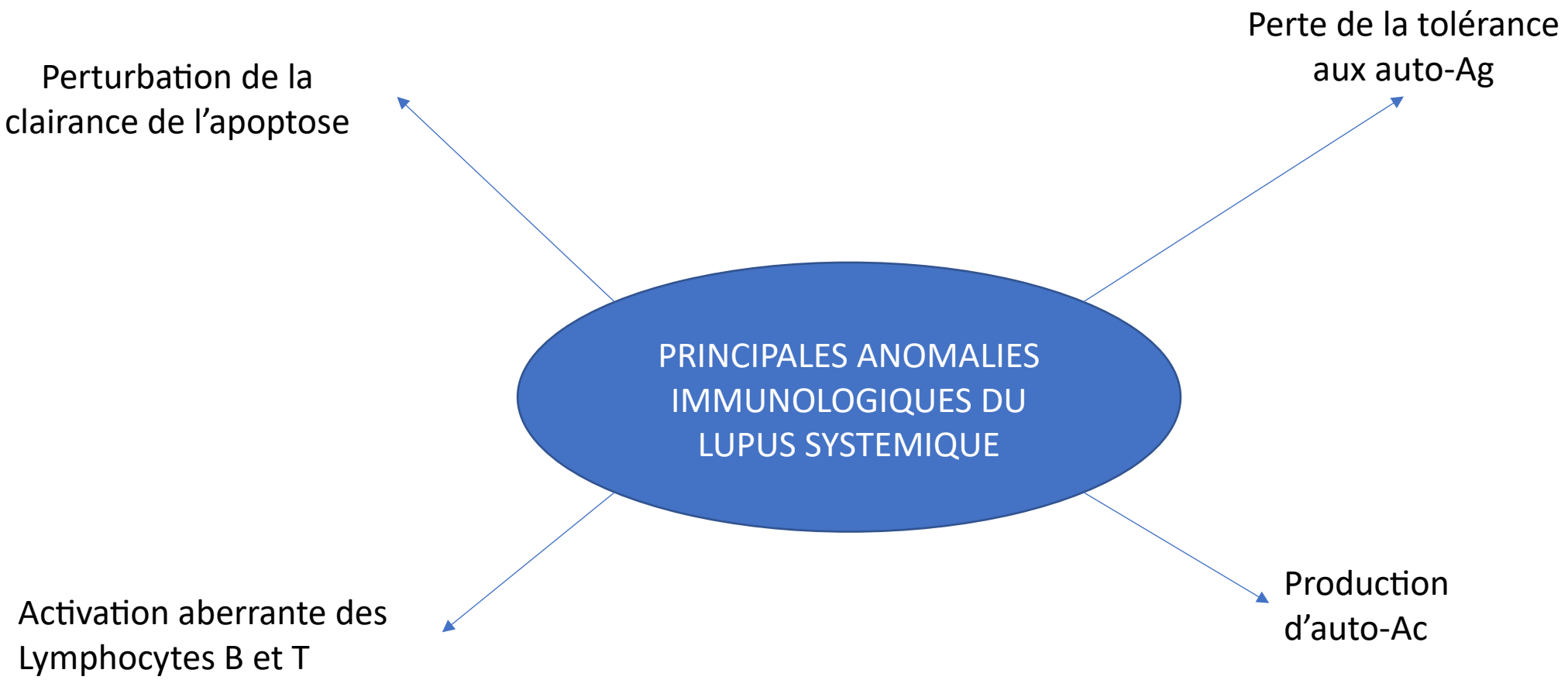
Auto-immunité pathologique

Défaillance du contrôle de l'auto-immunité

prolifération de lymphocytes B auto-agressifs de forte affinité

prolifération de lymphocytes T auto-agressifs de forte affinité

déclenchement
d'une maladie auto-immune


Perturbation de la clairance de l'apoptose
Perte de la tolérance aux auto-Ag
PRINCIPALES ANOMALIES IMMUNOLOGIQUES DU LUPUS SYSTEMIQUE
Activation aberrante des Lymphocytes B et T
Production d'auto-Ac

Il y a 3 Types d'interferons

- Considérée comme une famille de cytokines clés dans la réponse immunitaire innée [1,2]
- Ces 3 types ont des rôles communs et distincts dans l'immunité[1,2]

TYPE I[1-3]

- IFN-α (12 subtypes)
- IFN-β
- IFN-κ
- IFN-ε
- IFN-ω

Regulates immune response against viruses[1,2] and can also be produced in response to some types of bacteria[1]

Signals through the IFN-α receptor[1]

TYPE II[1,3]

- IFN-γ

Contributes to the immune responses against bacterial pathogens, such as mycobacteria[2]

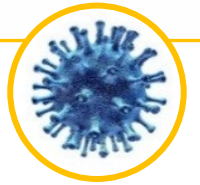
Signals through the IFN-γ receptor[1]

TYPE III[1,4]

- IFN-λ (4 subtypes)

Regulates responses against viruses[3]

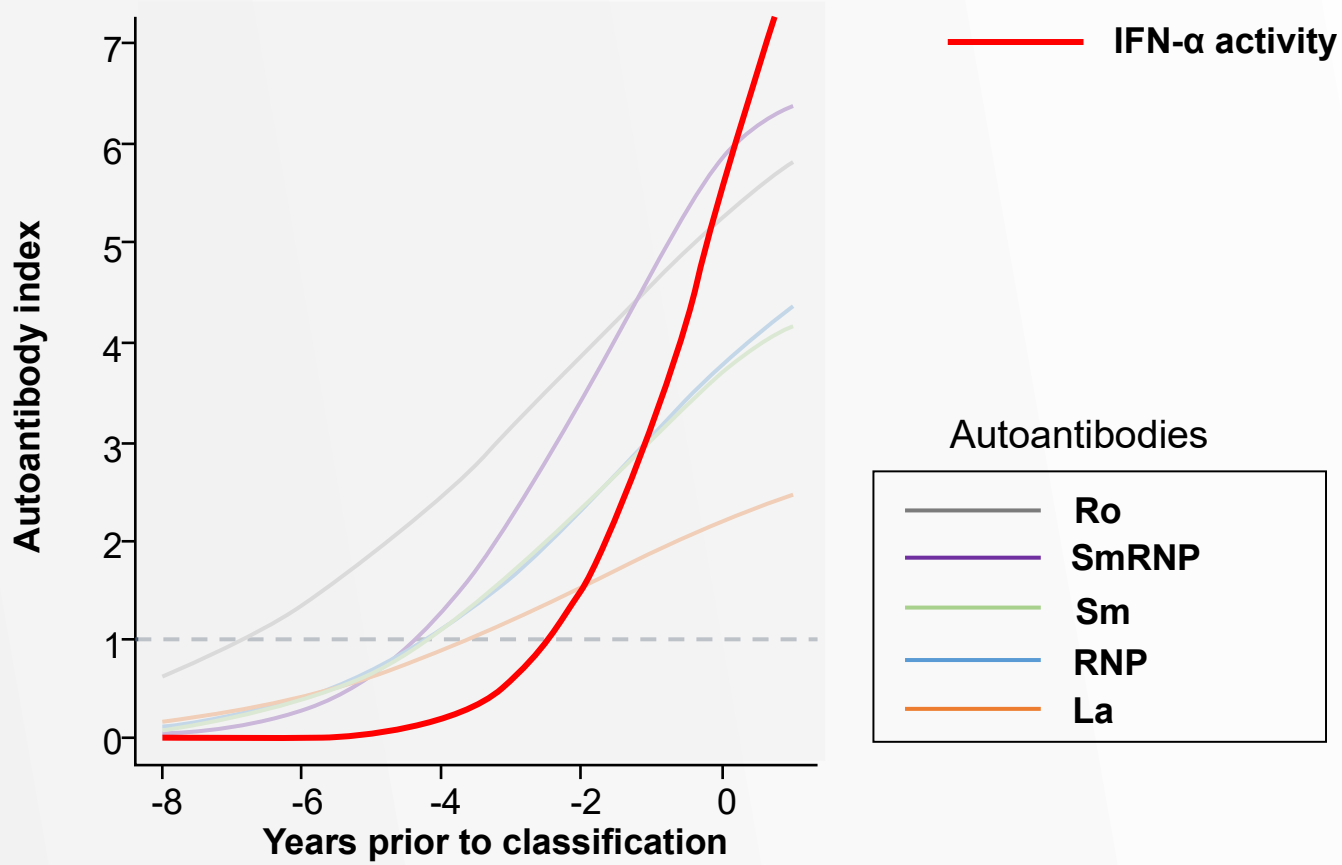
Signals through the IFN-λ receptor[1,3]



1. Rönnblom L, Leonard D. *Lupus Sci Med*. 2019;6(1):e000270. 2. Schoggins JW, F1000Res 2018;7:309. 3.Sozzani S, et al. *Autoimmunity*. 2010;43(3):196-203. 4. Egli A, et al. *Emerg Microbes Infect*. 2014;3(7):e51.

Les autoanticorps et l'IFN de type I sont présents bien avant les manifestations cliniques du LS

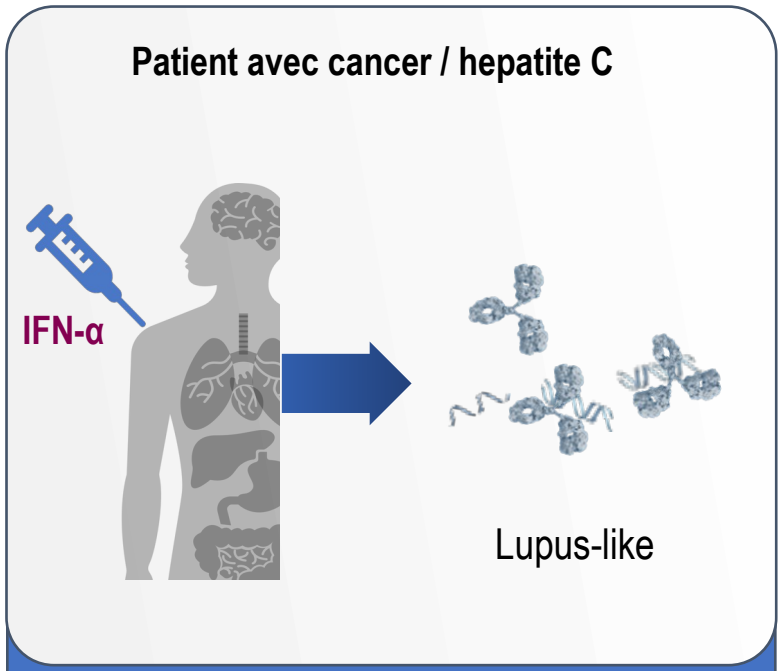
Longitudinal changes in serum level/activity preceding SLE classification in patients with SLE (n=55)[a]



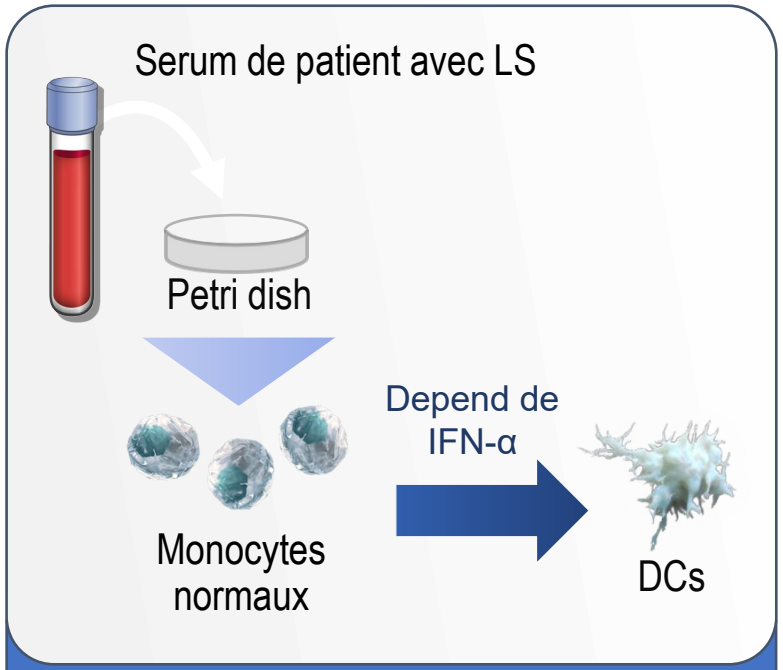
IFN = interferon; La = lupus antigen; RNP = ribonucleoprotein; SLE = systemic lupus erythematosus; Sm = anti-Smith.

[a]Munroe ME, et al. *Ann Rheum Dis.* 2016;75(11):2014-2021.

Les arguments pour impliquer les IFN dans la physiopathologie du LS



L'administration d'IFN-α peut induire l'autoimmunité[1]



Différentiation de DCs presentatrices d'antigene dépendant de l'IFN-α dans le LS peut déclencher l'autoimumunité[2]

Approximativement 60% à 80% des patients adultes avec un LS a une signature IFN Type I [3-6]

DC = cellule dendritique; IFN = interferon; LS = lupus systemique

1. Niewold T, Swedler WI. *Clin Rheumatol.* 2005;24(2):178-181. 2. Blanco P, et al. *Science*. 2001;294(5546):1540-1543. 3. Crow MK. *J Immunol.* 2014;192(12):5459-5468.
4. Lauwerys BR, et al. *Rheumatology (Oxford).* 2014;53(8):1369-1376. 5. Hoffman RW, et al. *Arthr Rheumatol.* 2017;69(3):643-654. 6.Becker AM, et al. *PLoS ONE*. 2013;8(6):e67003.

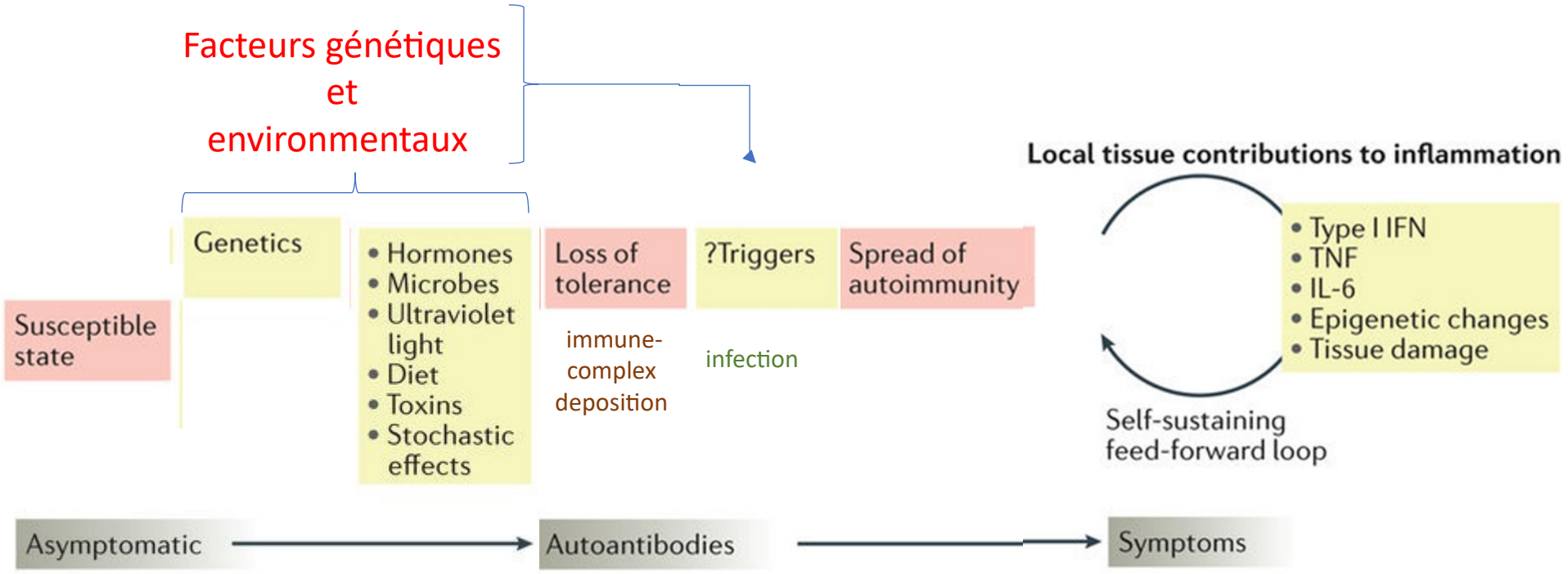
Les arguments pour impliquer les IFN dans la physiopathologie du LS (2)

GENE	NAME	PUTATIVE MECHANISM
FCGR (2A, 3A, 3B)	Fcγ receptor	Antibody and immune complex signaling
NCF2	Neutrophil cytosol factor 2	Defects in NOX-mediated ROS
TNFAIP3 (A20)	Tumor necrosis factor-α–induced protein 3	Disruption of protein's deubiquitinase activity, increased NET formation through PAD4 modulation
PTPN22	Protein tyrosine phosphatase, non-receptor type 22	Neutrophil activation, enhanced NET formation through PAD4 activation
DNASE1L3	Deoxyribonuclease γ	Defective nucleic acid degradation
TREX1	Three prime repair exonuclease 1	Defective nucleic acid degradation
ITGAM	Integrin α_M	Defective leukocyte adhesion and migration, enhanced IFN synthesis
IFIH1 (MDA5)	Type I Interferon induced with helicase C domain 1	RNA sensing, IFN signaling pathway
IRF5	IRF-5	IFN signaling pathway
IRF7	IRF-7	IFN signaling pathway
IRF8	IRF-8	IFN signaling pathway
TYK2	TYK2	IFN signaling pathway
STAT4	STAT4	IFN signaling pathway
TLR7	TLR-7	Endosomal TLR, RNA sensing, IFN signaling pathway
TLR8	TLR-8	Endosomal TLR, RNA sensing, IFN signaling pathway
TLR9	TLR-9	Endosomal TLR, DNA sensing, IFN signaling pathway

IFN = interferon; IRF = interferon-regulated factor; SLE = systemic lupus erythematosus; STAT = signal transducer and activator of transcription; TLR = Toll-like receptor; TYK = tyrosine-protein kinase 2.

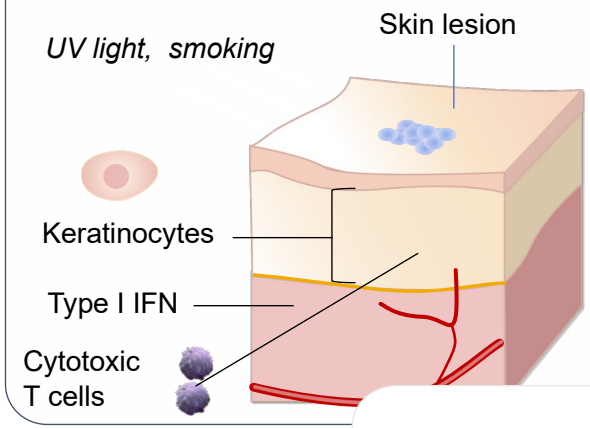
Gupta S, Kaplan MJ. *J Clin Invest*. 2021;131(3):e144918.

Les étapes de l'apparition du lupus systémique



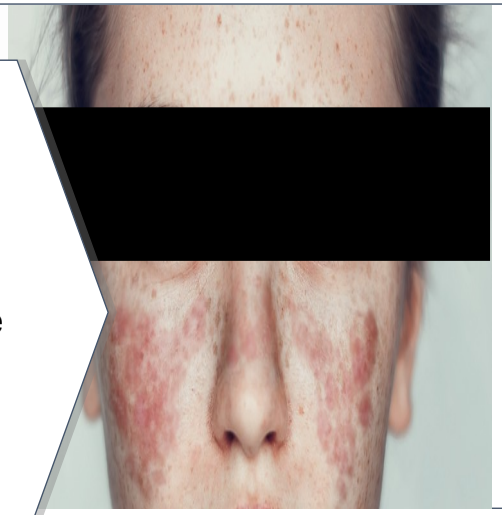
L’IFN de type I contribue aux manifestations cliniques du LS

SKIN[1]



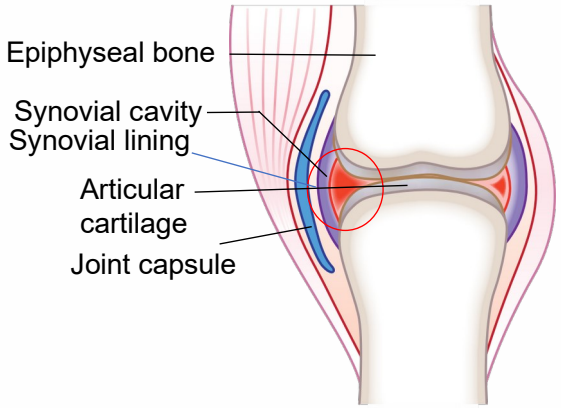
- Keratinocyte production of Type I and Type III IFNs[1]
- Increased expression of several Type I IFNs and Type I IFN–regulated genes[2,3]

Fully developed skin lesion (interface dermatitis)[1]



Mucocutaneous manifestations

JOINT[4,5]



- Increased expression of Type I IFN–inducible genes in synovial tissue[6,7]

Chronic synovial infiltrates[4]

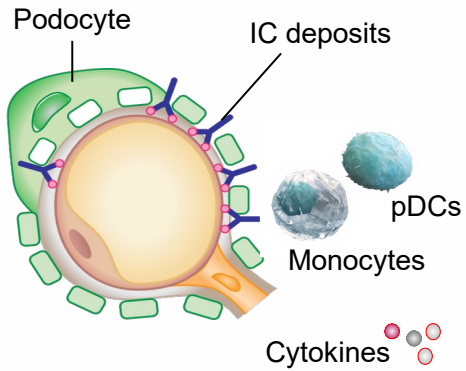
Lupus arthritis

IFN = interferon; SLE = systemic lupus erythematosus.

1. Wenzel J. *Nat Rev Rheumatol.* 2019;15(9):519-532. 2. Sarkar MK, et al. *Ann Rheum Dis.* 2018;77(11):1653-1664. 3. Berthier CC, et al. *J Clin Med.* 2019;8(8):1244. 4. Ceccarelli F, et al. *Semin Arthritis Rheum.* 2017;47(1):53-64. 5. Structure of synovial joints. Updated August 13, 2020. Accessed March 8, 2021. https://med.libretexts.org/@go/page/7516. 6. Nzeusseu Toukap A, et al. *Arthritis Rheum.* 2007;56(5):1579-1588. 7. Hubbard E, et al. *Sci Rep.* 2020;10(1):17361.

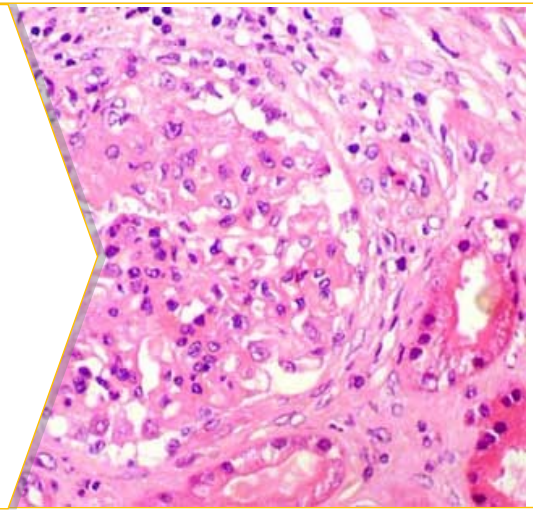
L'IFN de type I contribue aux manifestations cliniques du LS

KIDNEY[1-3]



- Accumulation of pDCs and expression of Type I IFN–inducible genes in kidney biopsies[4-6]

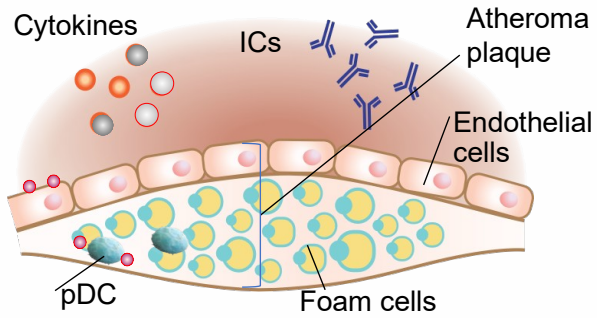
Increased nephron mass, inflammatory infiltrates, hypoxia, kidney fibrosis[1]



Lupus nephritis[a]

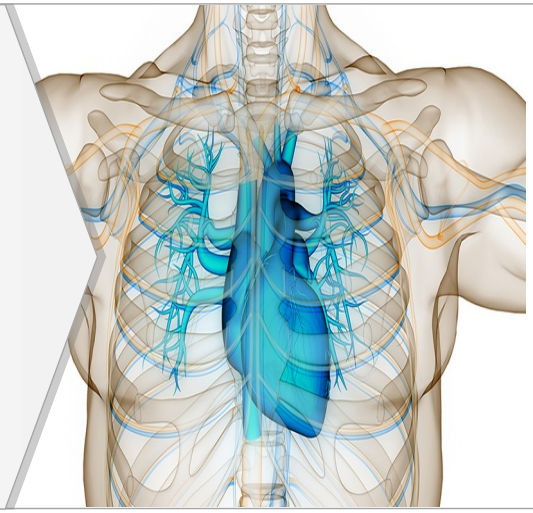
VASCULATURE[1-3]

Vascular injuries and thrombosis



- Type I IFN–induced endothelial damage and foam cell formation[2,3]

Premature atherosclerosis[1,2]



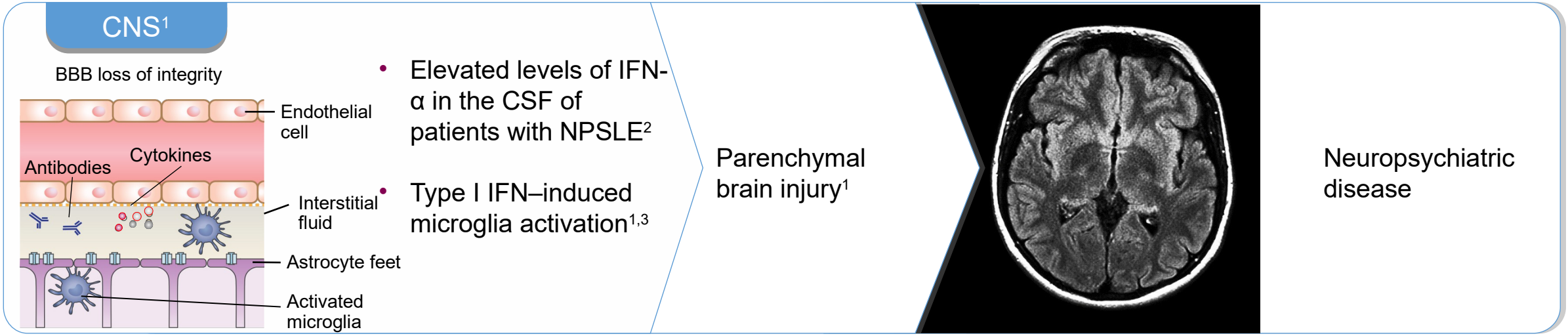
Cardiovascular disease

[a]Available at: https://kidneypathology.com/English_version/Lupus_nephritis.html with permission.

IC = immune complex; IFN = interferon; pDC = plasmacytoid dendritic cell; SLE = systemic lupus erythematosus.

1. Liu Z, Davidson A. *Nat Med*. 2013;18(6):871-882. 2. Crow M. *J Immunol.* 2014;192(12):5459-5468. 3. Tsokos GC. *Nat Immunol*. 2020;21(6):605-614. 4. Tucci M, et al. *Arthritis Rheum*. 2008;58(1):251-262. 5. Der E, et al. *Nat Immunol*. 2019;20(7):915-927. 6. Peterson KS, et al. *J Clin Invest.* 2004;113(12):1722-1733.

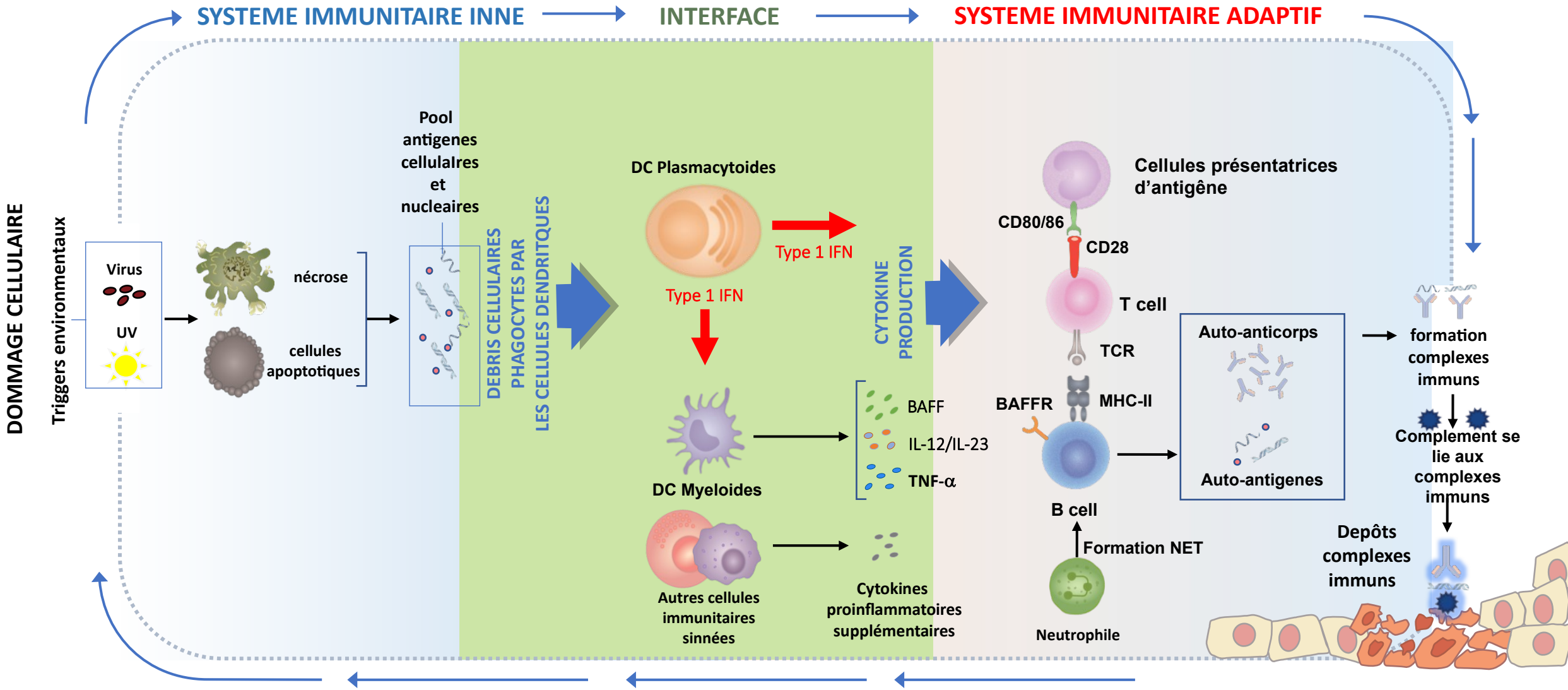
L’IFN de type I contribue aux manifestations cliniques du LS



BBB = brain-blood barrier; CNS = central nervous system; CSF = cerebrospinal fluid; IFN = interferon; NPSLE = neuropsychiatric SLE; SLE = systemic lupus erythematosus.

1. Schwartz N, et al. *Nat Rev Rheumatol.* 2019;15(3):137-152. 2. Shiozawa S, et al. *Arthritis Rheum.* 1992;35(4):417-422. 3. Rönnblom L, Leonard D. *Lupus Sci Med*. 2019;6(1):e000270.

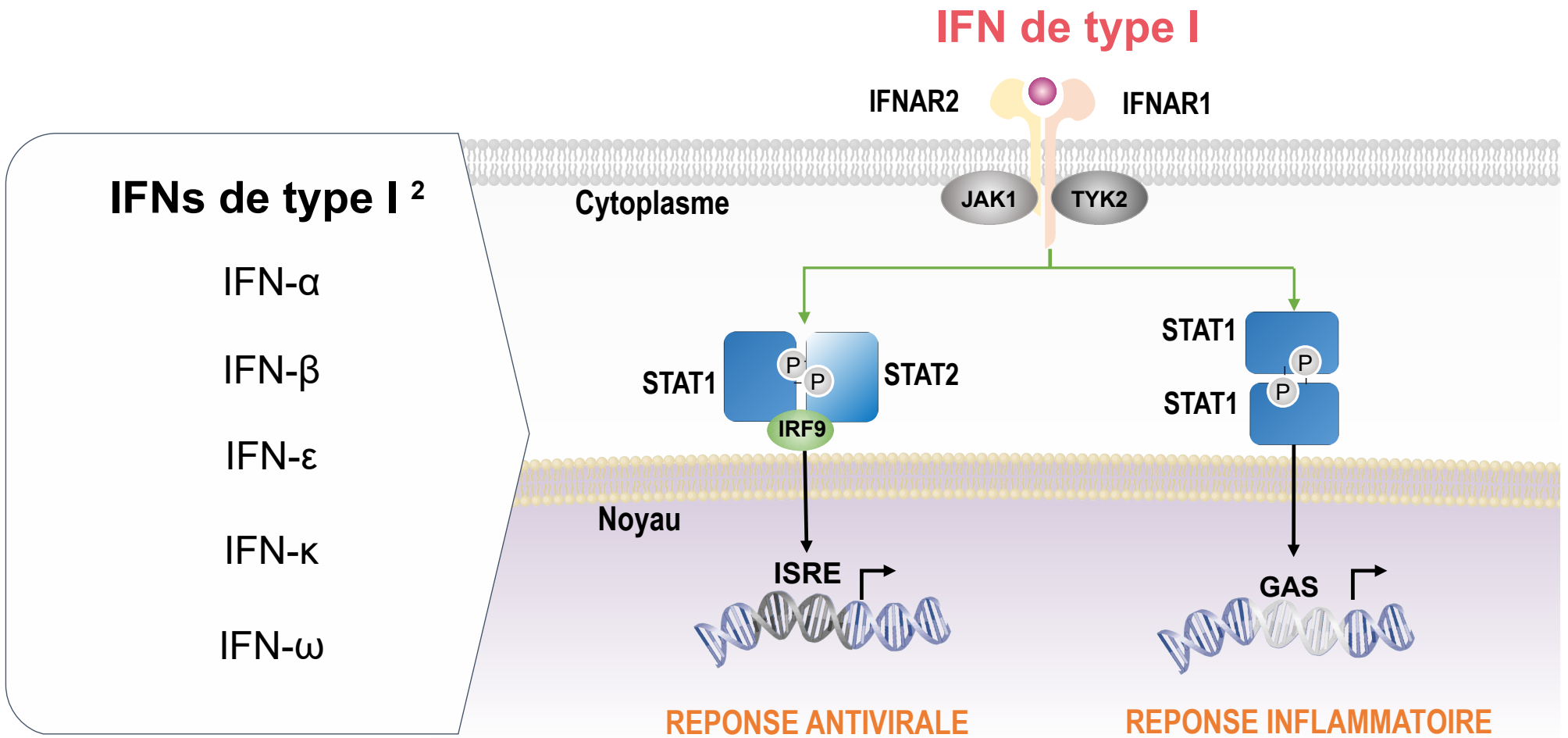
L'IFNs de type-I interagit avec cellules immunitaires qui contribuent à la pathogénèse du LS



BAFF = B-cell activating factor; BAFFR = BAFF receptor; CD = cluster of differentiation; DC = dendritic cell; IFN = interferon; IL = interleukin; MHC-II = major histocompatibility complex II; NET = neutrophil extracellular trap; TCR = T cell receptor; TNF-α = tumor necrosis factor alpha; UV = ultraviolets.

1. Kim J-M et al. *Int J Mol Sci*. 2015;16(6):14158-14170. 2. Rönnblom L, Elkon KB. *Nat Rev Rheumatol*. 2010;6(6):339-347. 3. Wahren-Herlenius M, Dörner T. *Lancet*. 2013;382(9894):819-831. 4. Dennis GJ. *Clin Pharmacol Ther*. 2012;91(1):143-149. 5. Rönnblom L. Upsala *J Med Sci*. 2011;116(4):227-237.

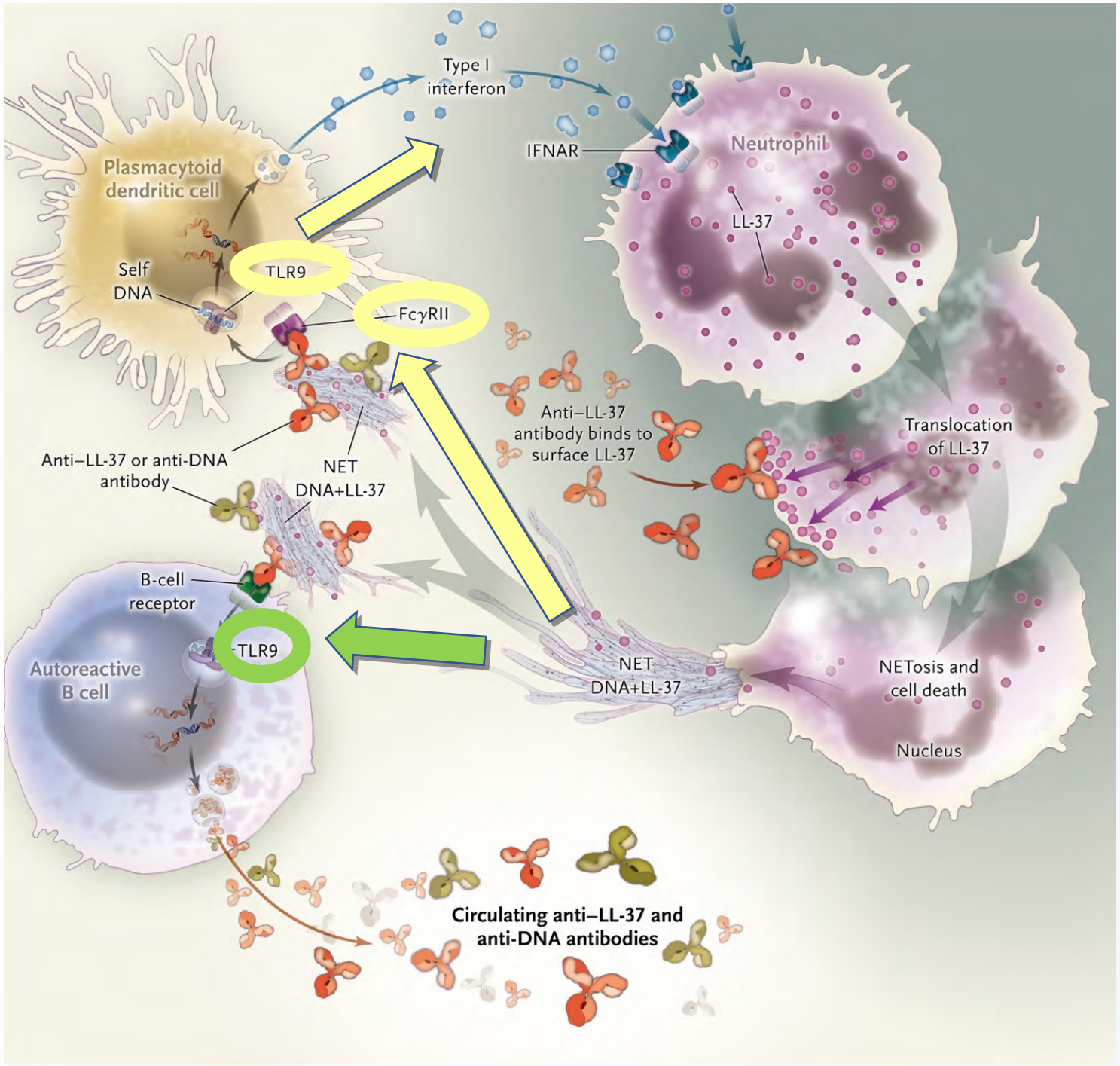
L'activation de l'IFN de type I et l'expression des genes stimulant l'IFN [1,2]



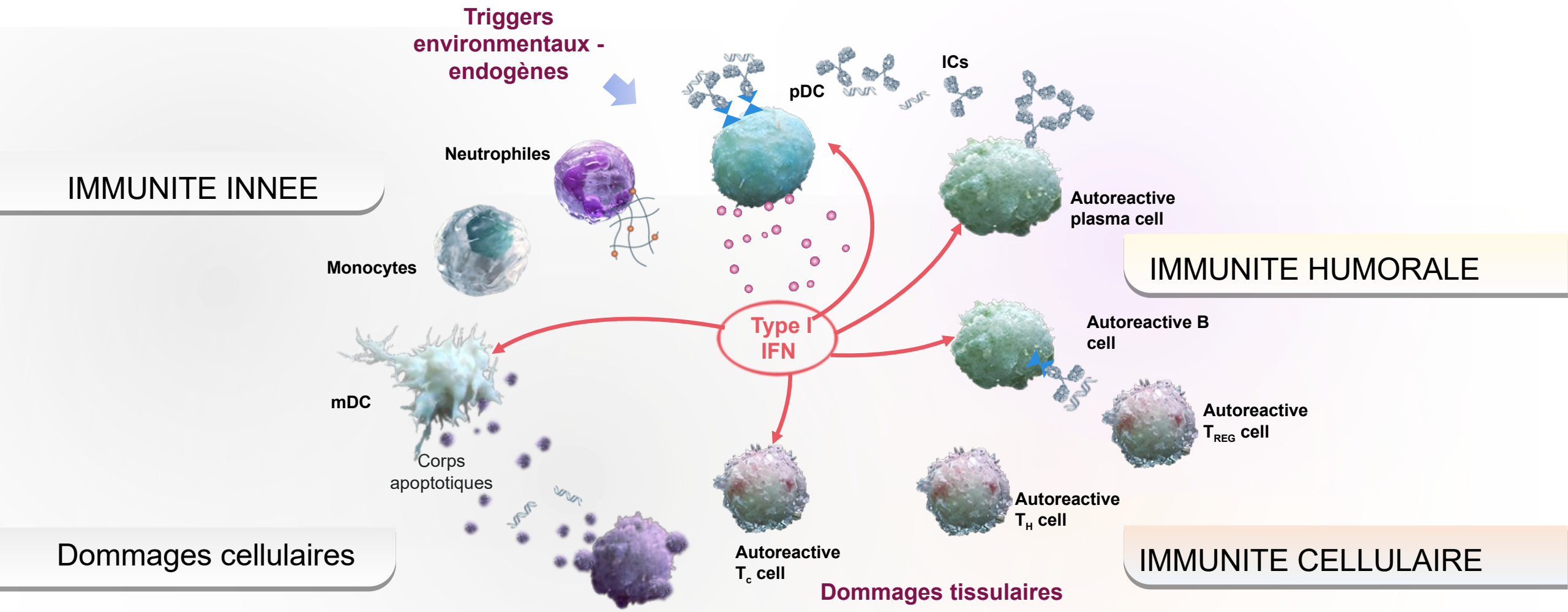
GAS = gamma interferon–activated sequence; IFN = interferon; IFNAR = interferon-α/β receptor; IRF= interferon regulatory factor; ISRE = interferon-stimulated response element; JAK = Janus kinase; P = phosphate; STAT = signal transducer and activator of transcription; TYK = tyrosine kinase.

1. Ivashkiv LB, Donlin LT. *Nat Rev Immunol*. 2014;14(1):36-49. 2. Rönnblom L, Leonard D. *Lupus Sci Med*. 2019;6 (1):e000270.

NETs (Neutrophil Extracellular Traps)



L'IFN de type I est un élément central dans la pathogénèse du LS[1-10]



IC = immune complex; IFN = interferon; mDC = myeloid dendritic cell; pDC = plasmacytoid dendritic cell; SLE = systemic lupus erythematosus; T_C = cytotoxic T; T_H = T helper; T_{REG} = regulatory T.

1. Crow MK. *J Immunol*. 2014;192 (12):5459-5468. 2. Wahren-Herlenius M, Dörner T. *Lancet*. 2013;382(9894):819-831. 3. Kim JM, et al. *Int J Mol Sci*. 2015;16(6):14158-14170. 4. Tsokos GC. *Nat Immunol*. 2020;21(6):605-614. 5.Bertsias G, et al. EULAR Textbook of Rheumatic Diseases. 1st ed. BMJ/EULAR; 2012:476-505. 6.Rönnblom L, Leonard D. *Lupus Sci Med*. 2019;6(1):e000270. 7. Liu Z, Davison A. *Nat Med*. 2012;18(6):871-882. 8. Fitzgerald-Bocarsly P, et al. *Cytokine Growth Factor Rev*. 2008;19(1):3-19. 9. Chan VS, et al. *Autoimmun Rev*. 2012;11(12):890-897. 10. Rönnblom L. *Ups J Med Sci*. 2011;116(4):227-237. 11. Mustelin T, et al. *Front Immunol*. 2019;10:1028. 12. Hansen ML, et al. *Mol Immunol*. 2011;48(15-16):2087-2093. 13. Rönnblom L, et al. *Lupus*. 2008;17(5):394–399. 14. Mak A, Kow NY. *J Immunol Res*. 2014;2014:419029

Au total

SLE may be driven by heterogeneous pathways of immune dysregulation that eventually converge into a loosely shared clinical phenotype[1]

SLE pathophysiology is multifactorial, involving cells of the innate and adaptive arms of the immune system, driving organ damage[1]

Type I IFN is a central driver of SLE pathophysiology[2]

Type I IFN represents a key area of ongoing research that is advancing understanding of SLE[2-4]

1. Gupta S, Kaplan MJ. *J Clin Invest*. 2021;131(3):e144918. 2. Crow MK. *J Immunol.* 2014;192(12):5459-5468. 3. Lauwerys BR, et al. *Rheumatology (Oxford).* 2014;53(8):1369-1376. 4. Rönnblom L, Leonard D. *Lupus Sci Med.* 2019;6(1):e000270.