

# Innate immune dysregulation and autoimmunity: Sex differences and impact on organ damage in women with lupus

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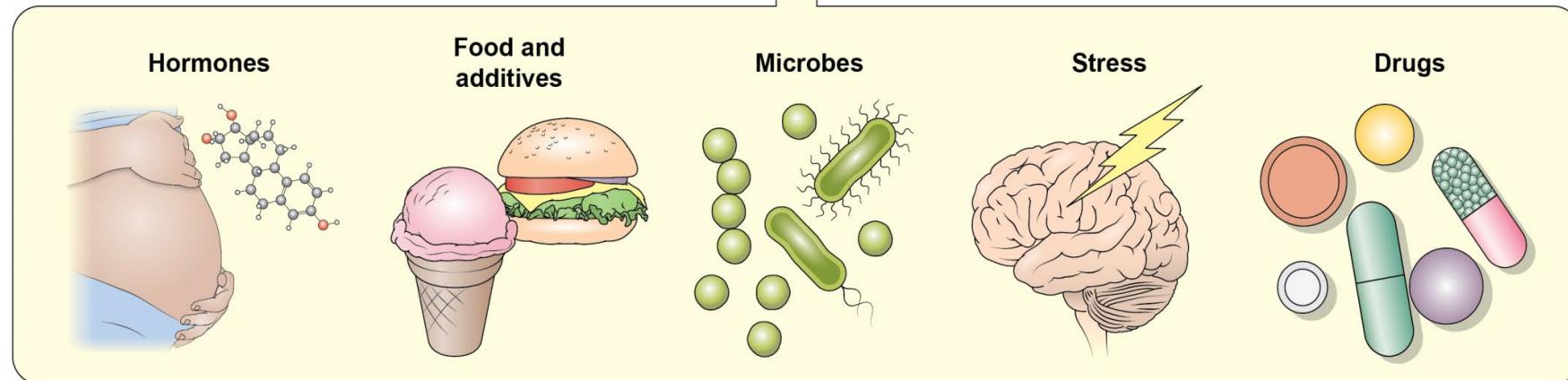
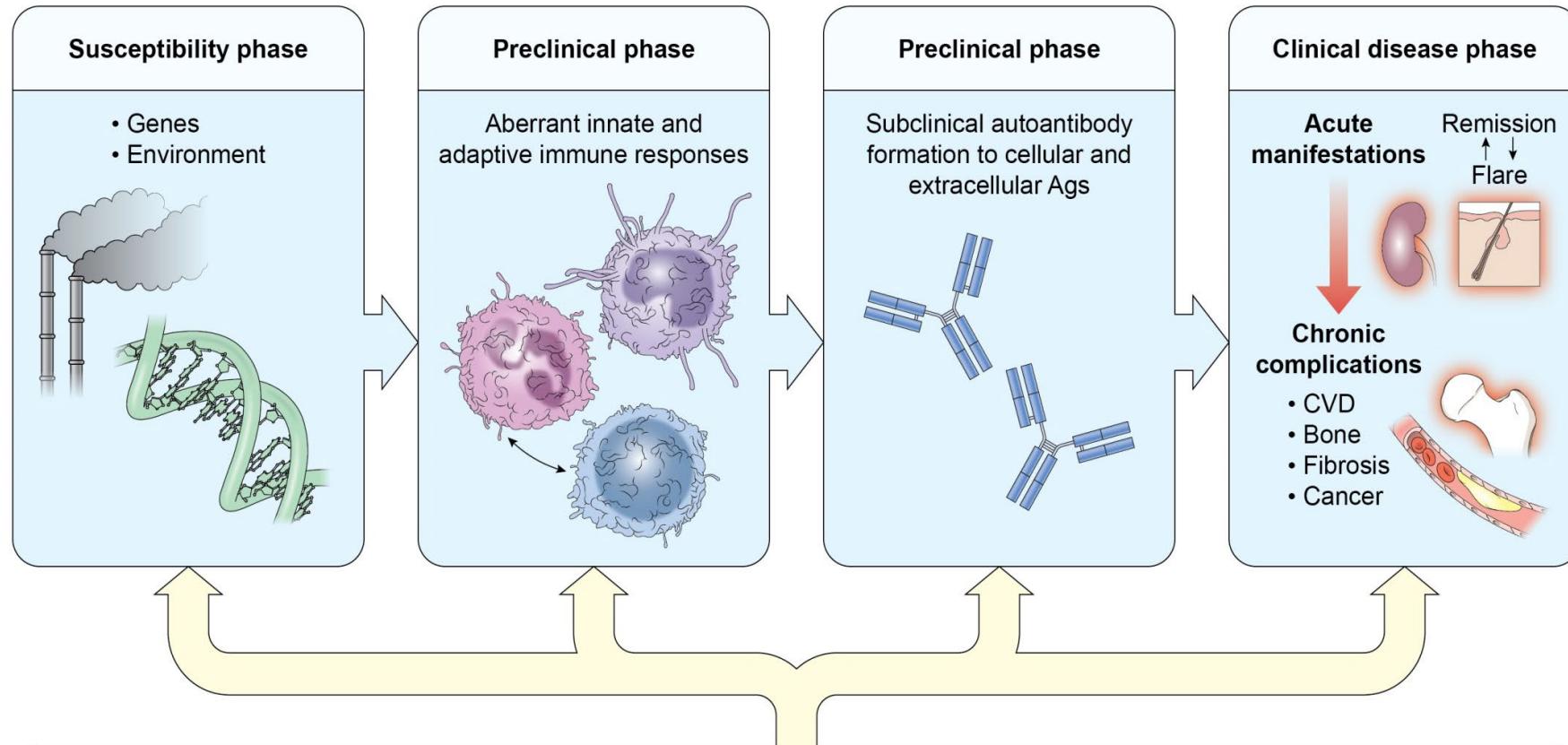
NIAMS/NIH

# Systemic autoimmune diseases

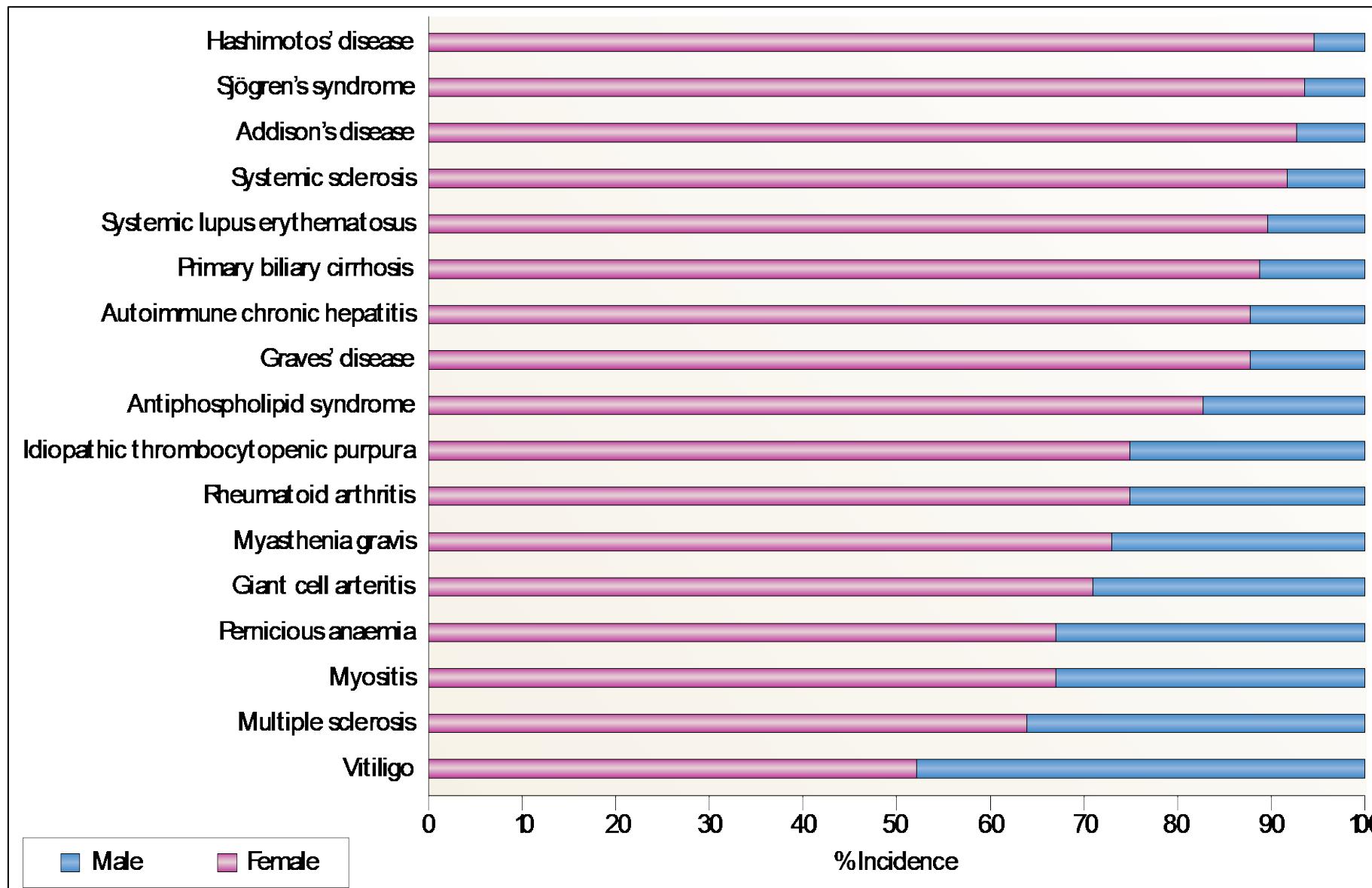
- Systemic lupus erythematosus
- Rheumatoid arthritis
- ANCA-associated vasculitis
- Antiphospholipid Syndrome
- Primary Sjögren's syndrome
- Idiopathic inflammatory myopathies
- Progressive systemic sclerosis
- Goodpasture syndrome
- Giant cell arteritis
- Takayasu's arteritis
- Behcet's disease
- Juvenile idiopathic arthritis
- Spondyloarthropathies
- Mixed connective tissue disease
- Psoriasis/psoriatic arthritis



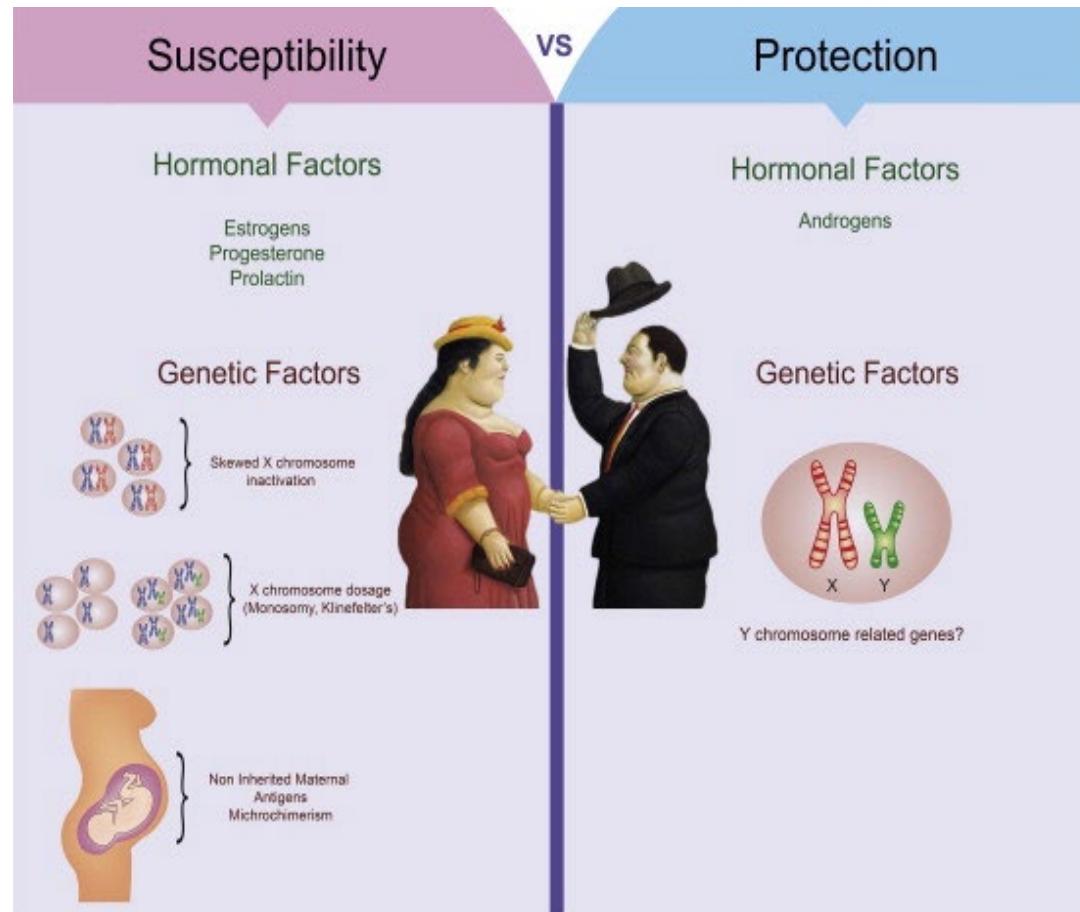
# Systemic Autoimmune Diseases

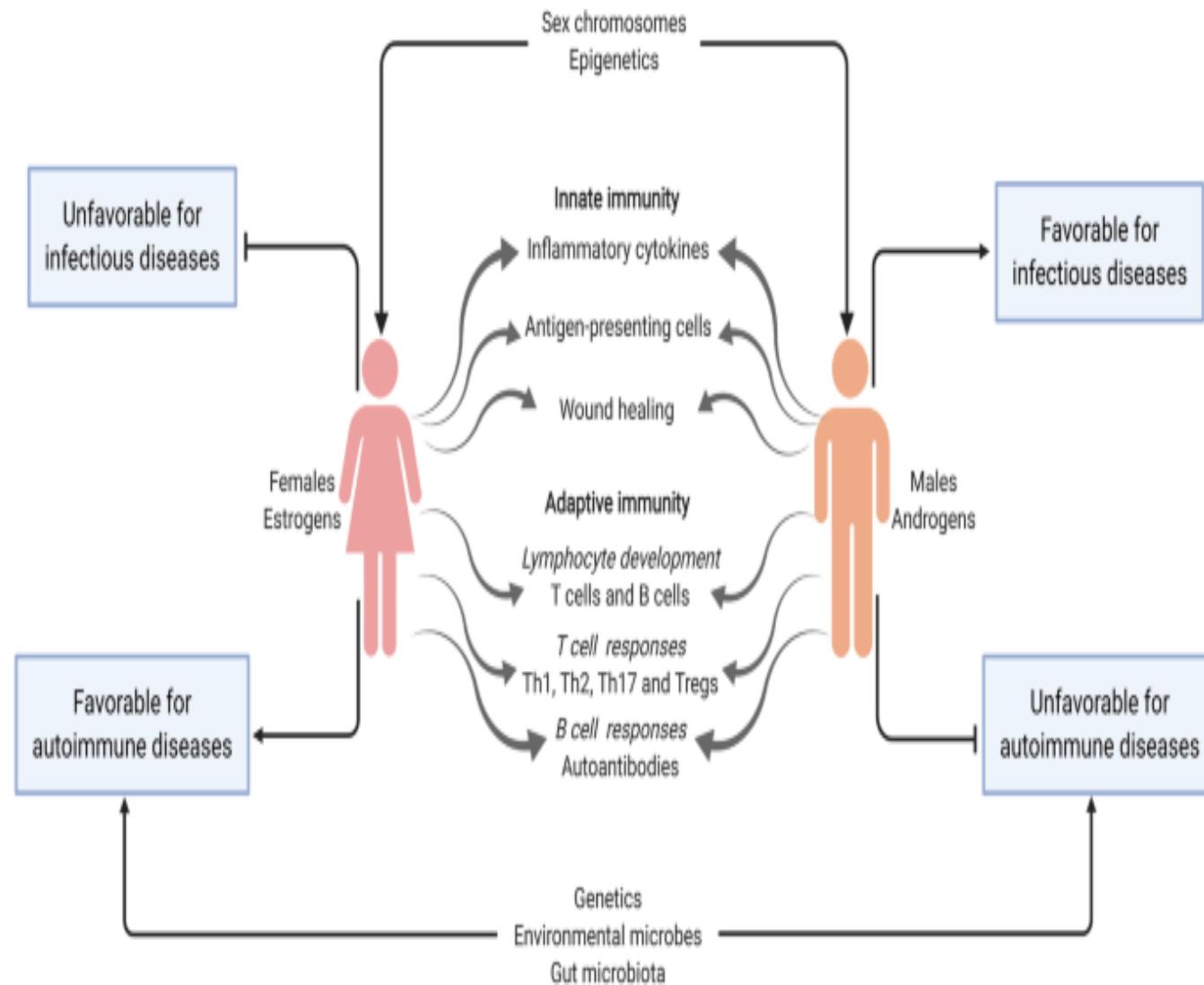


# Women and autoimmunity



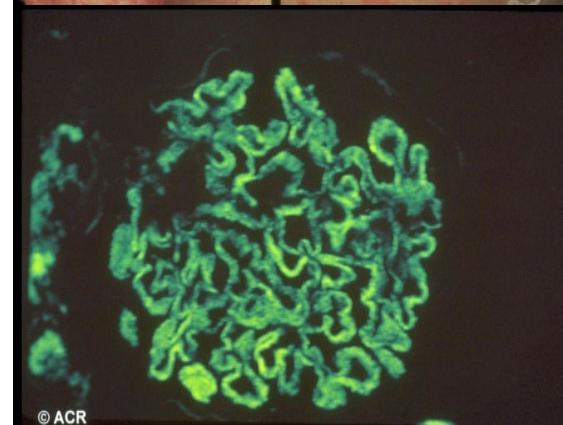
# Predisposition to autoimmunity in females





# Systemic lupus erythematosus (SLE)

- Autoimmune syndrome that affects primarily women of childbearing age.
- Profound clinical heterogeneity with periods of flare and remission.
- Autoantibodies to nucleic acids and/or proteins binding nucleic acids.
- Dysregulation in the type I IFN pathway.
- Premature cardiovascular disease is an important cause of morbidity and mortality.



### **Genetic mechanisms**

- SLE-associated SNPs
- Differential expression of genes and miRNAs
- X chromosome complement



### **Estrogen exposure**

- Increased estrogen action
- Hyperresponsive adaptive and innate immune system



### **Epigenetic mechanisms**

- DNA methylation
- Histone modification

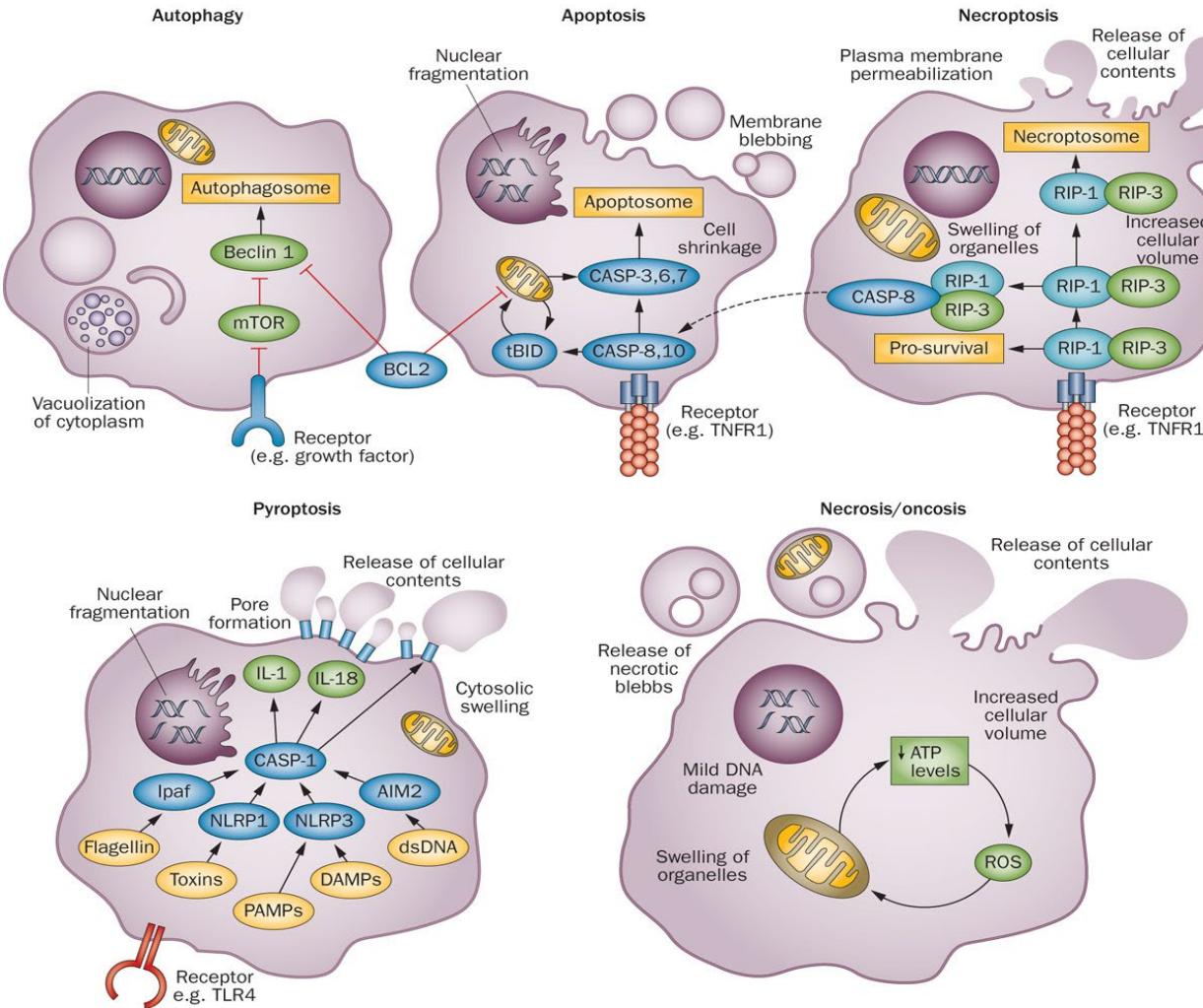


### **Microbiota gut changes**

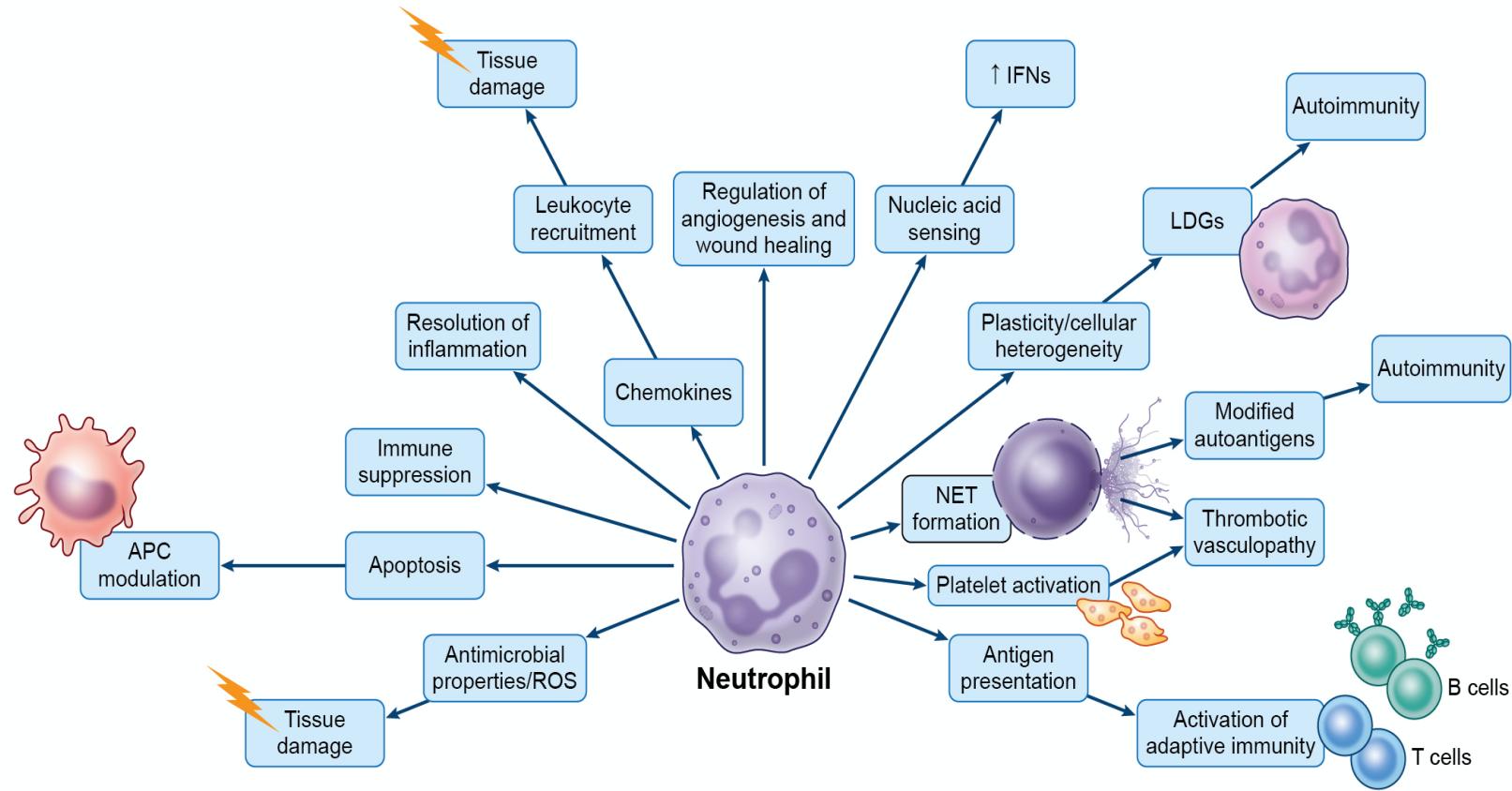
- Various strains
- Altered gut microenvironment
- Increased permeability



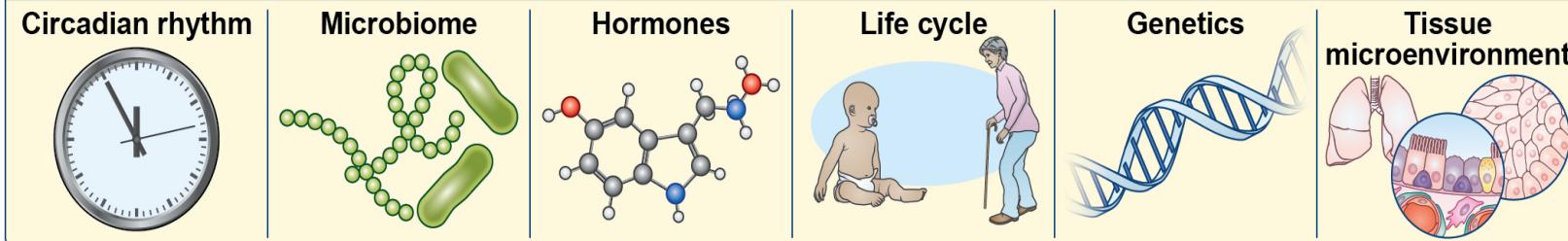
# AUTOANTIGEN GENERATION AND CELL DEATH: MANY WAYS TO DIE



# The life and death of the neutrophil



Regulated by:

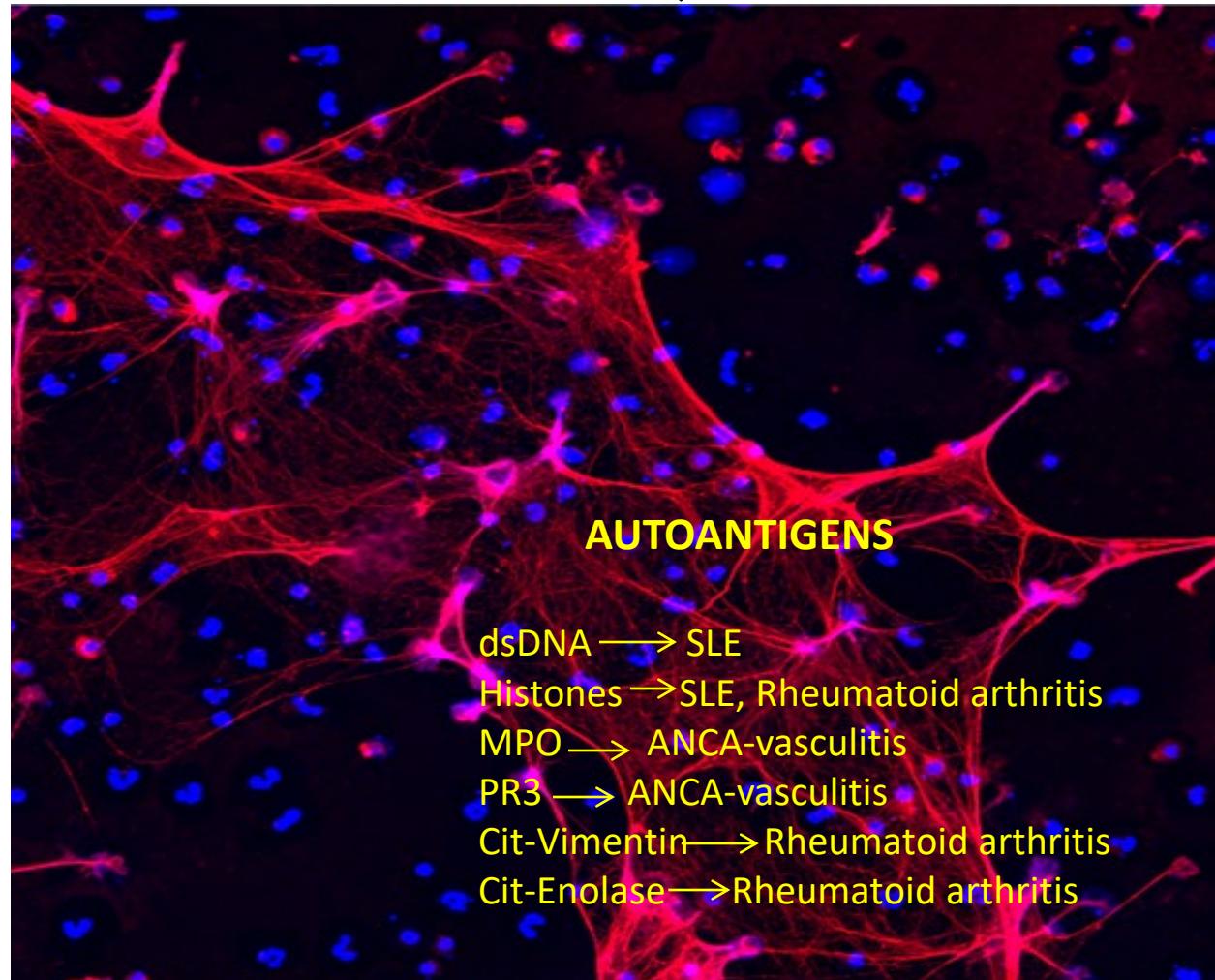
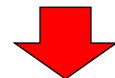


MICROBES  
PLATELETS

CYTOKINES  
COMPLEMENT

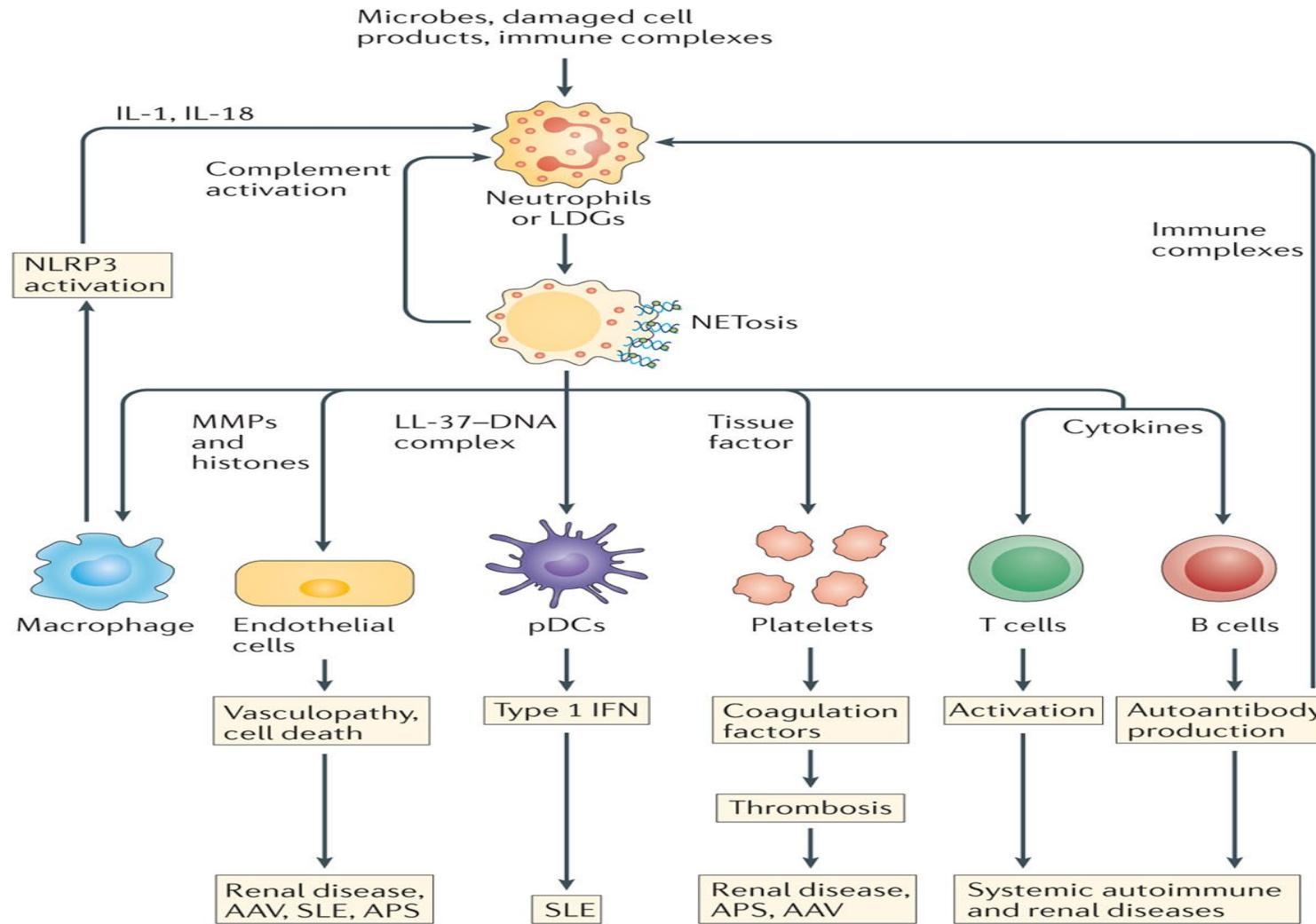
IMMUNE COMPLEXES  
MSU crystals

AUTOANTIBODIES  
DRUGS

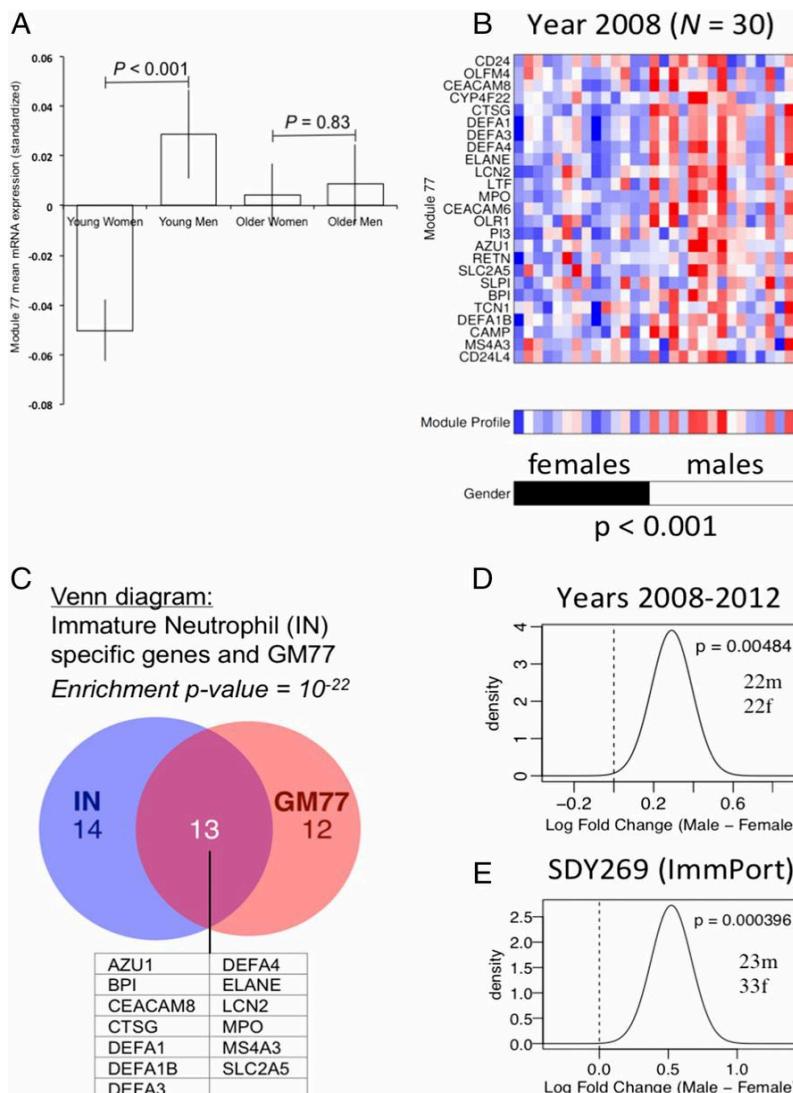


# NETs in the pathogenesis of SLE and beyond

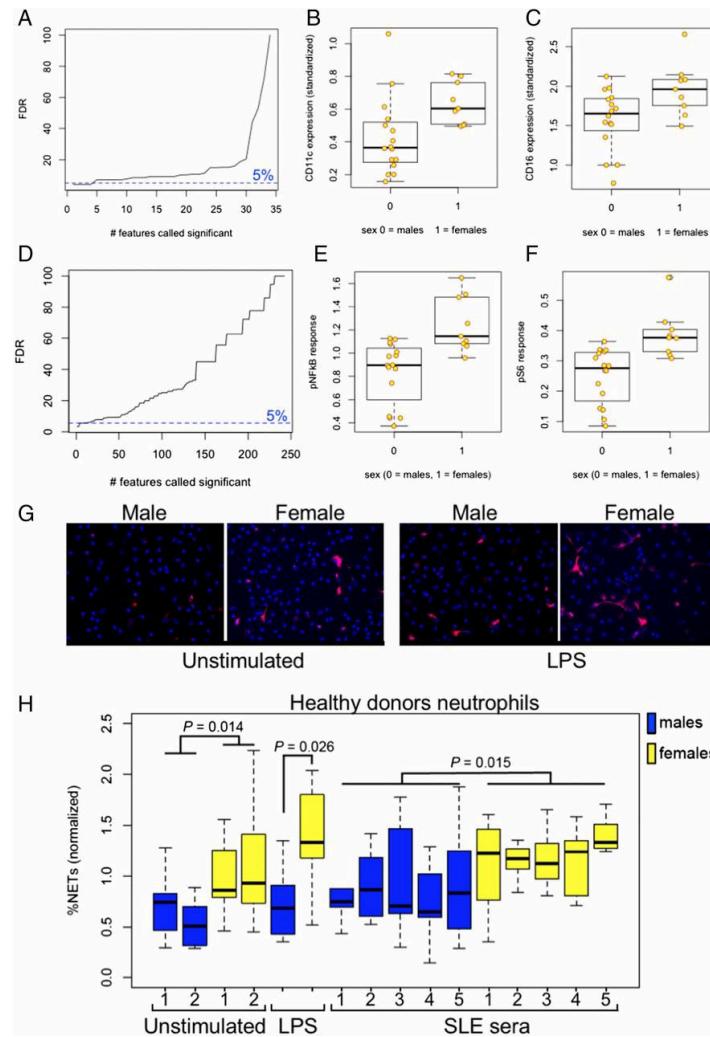
\*SLE  
\*RA  
\*AAV  
\*APS  
\*Psoriasis  
\*Gout  
\*Autoinflammation  
\*Job's syndrome  
\*Hidradenitis suppurativa  
\*DADA2  
\*VEXAS  
  
\*Atherosclerosis  
\*Thrombosis  
\*Cancer  
\*TRALI  
\*Cystic fibrosis  
\*Metabolic Sx.  
\*Diabetes mellitus  
\*Gallbladder stones  
\*COVID-19



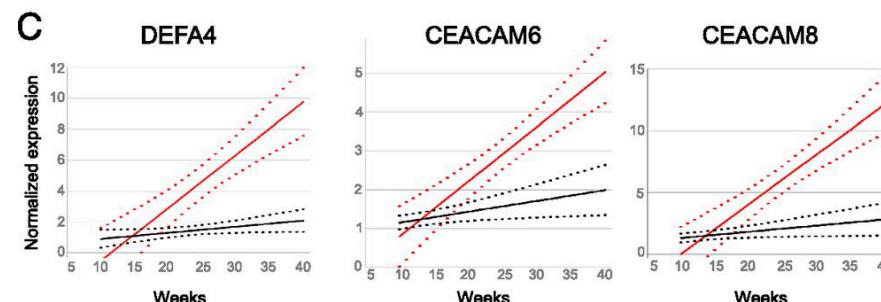
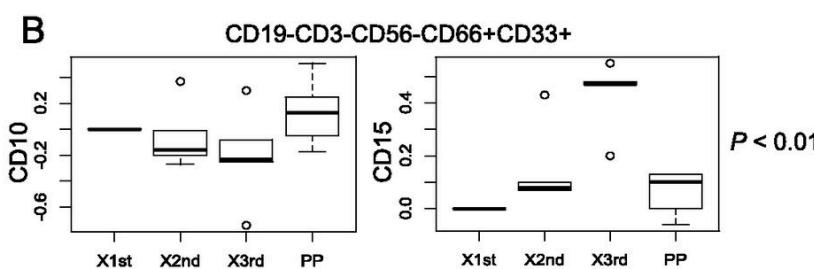
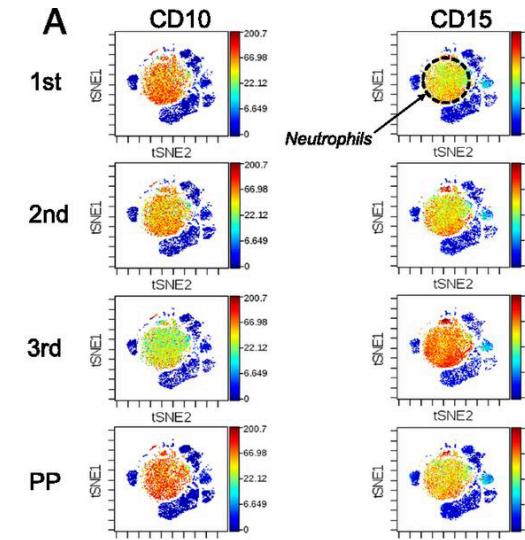
## Immature neutrophils in males compared with females



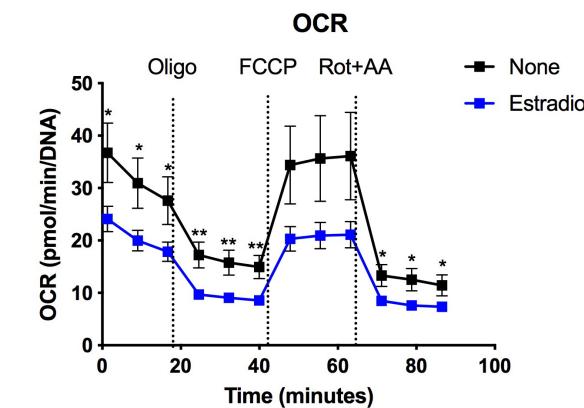
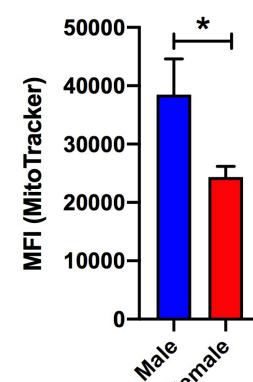
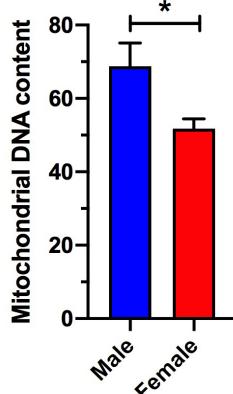
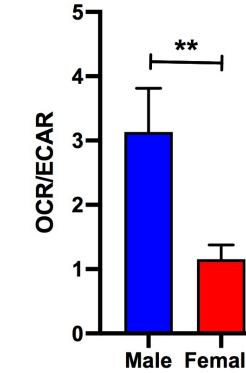
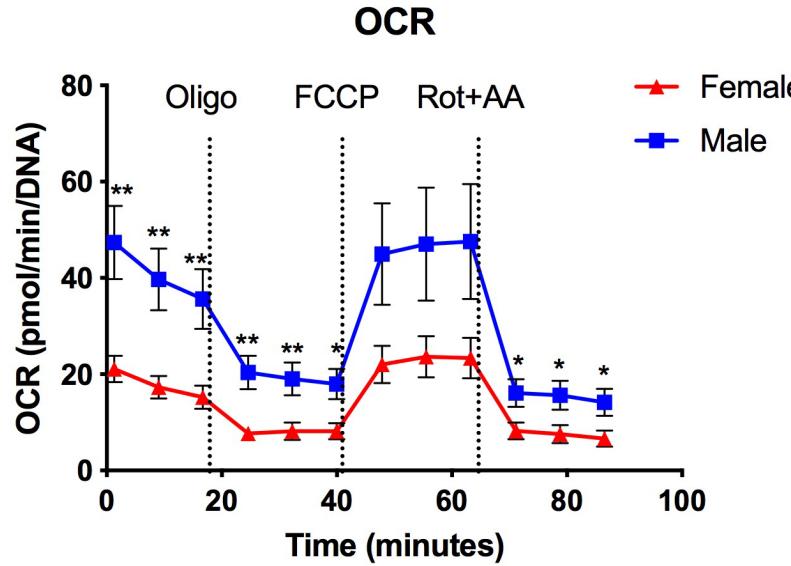
## Cell surface markers and functional analysis of male and female neutrophils



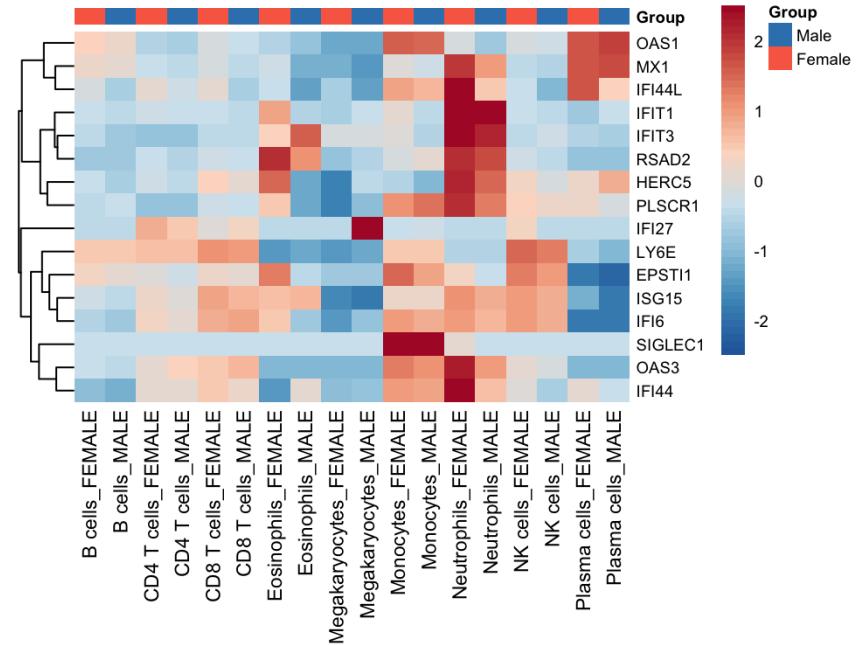
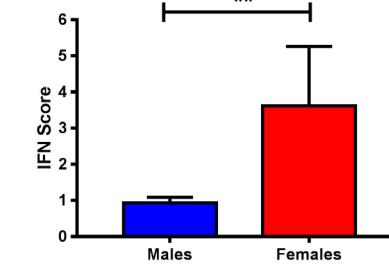
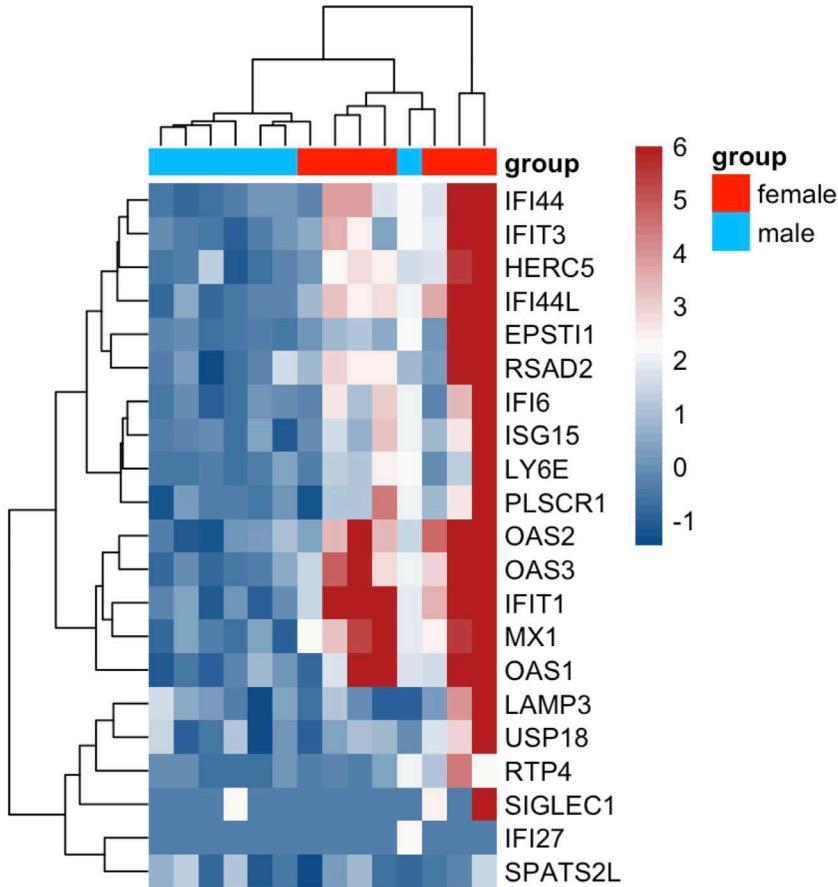
## Neutrophil phenotype in pregnancy



# Male and female neutrophils differ in immunometabolism



# Female neutrophils upregulate type I-IFN regulated genes



# Sex hormones and neutrophils

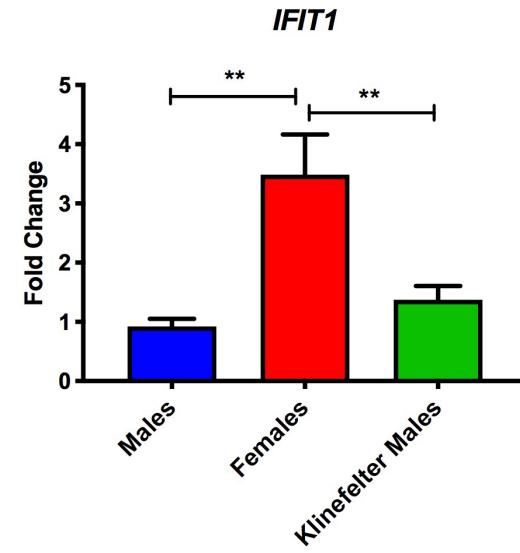
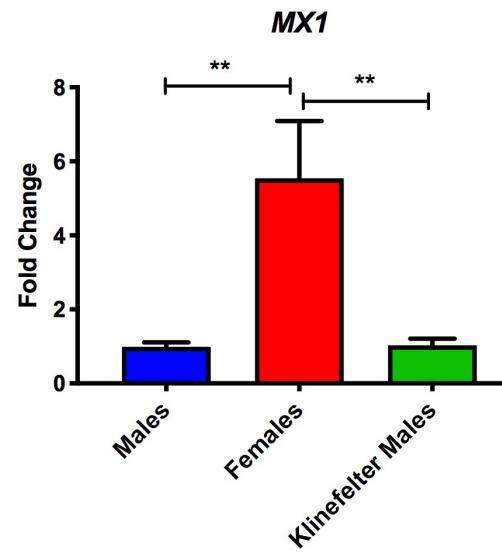
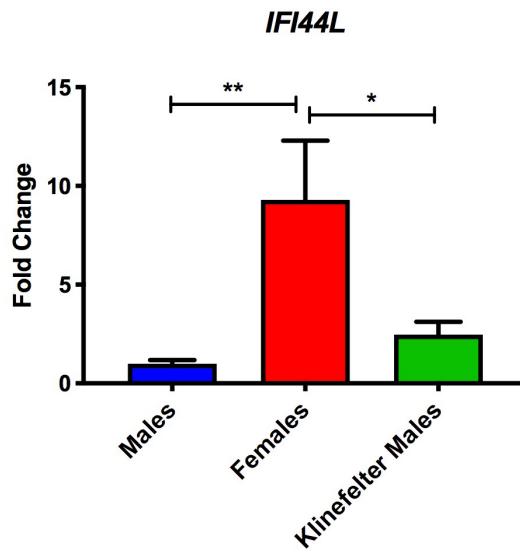
Table 3 | Effects of sex steroid hormones on innate and adaptive immunity

Immune component	Effect of sex hormones*		
	Oestradiol	Progesterone	Androgens
TLRs	↑TLR4, TLR7 and TLR9	↓TLR3 and TLR7	↓TLR4
Macrophages	↑TLR4	↓iNOS and NO ↑FIZZ1 and YM1	↓iNOS/ NO ↓TNF
NF-κB	↓Activity	↓Activity	↓Activity
DCs	↑Activation ↑TLR7 and TLR9 ↑CCL2 ↓CXCL10 ↓IFN $\alpha$	↓CD40, CD80, CD86 and ↑CD11c ↑IL-18 and IL-10	ND
Neutrophils	↑Numbers ↑Degranulation ↑Elastase release	ND	↑Numbers ↓Kinases and leukotriene formation
NK cells	↑IFN $\gamma$ ↑Granzyme B ↓FASL	↑Numbers ↑Apoptosis (caspase dependent)	ND
Eosinophils	↓Numbers ↓Mobilization	↑Numbers	ND
Inflammatory cytokines	Low oestrogen: ↑IL-1 $\beta$ , IL-6, and TNF High oestrogen: ↓L-1 $\beta$ , IL-6 and TNF	↓TNF and IFN $\gamma$ ↑IL-6	↑IL-1 $\beta$ and IL-2 ↓TNF
Suppressive cytokines	↑IL-4, IL-10 and TGF $\beta$	↑IL-4, IL-5 and TGF $\beta$	↑IL-10 and TGF $\beta$
Chemokines	↓CCL2 ↑CXCL1	↓CXCL2	↓CCL3
T <sub>H</sub> 1 cells	Low oestradiol: ↑Activity	↓Activity	↓IFN $\gamma$
T <sub>H</sub> 2 cells	High oestradiol: ↑Activity	↑Activity	↓IL-4 and IL-5 ↓GATA3
T <sub>H</sub> 17 cells	↓Numbers ↓IL-17	↓Percentages	↑IL-17
T <sub>reg</sub> cells	↑Numbers	↑Percentages	↑Numbers
CD8 $^+$ T cells	↑Response	↓Response	↓Numbers ↓Activity
B cells	↑IgG and IgM	↓CD80 and CD86	ND
Antibody responses	↑Response	↑Total antibody ↓Autoantibodies	↓Response

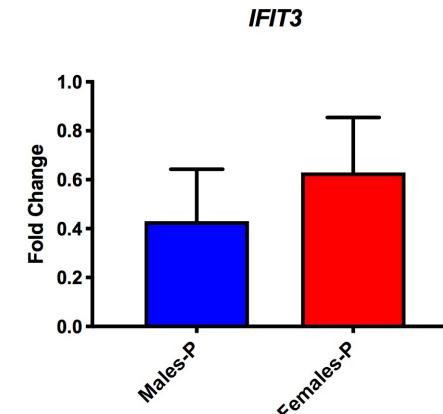
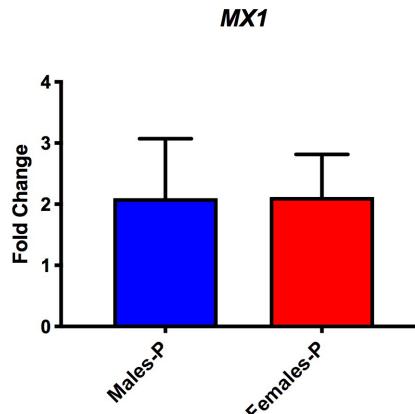
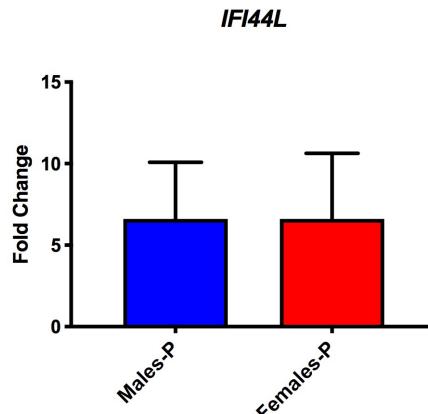
CCL, CC-chemokine ligand; CXCL, CXC-chemokine ligand; DCs, dendritic cells; FASL, FAS ligand; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; ND, not defined; NF-κB, nuclear factor-κB; NK, natural killer; NO, nitric oxide; TGF $\beta$ , transforming growth factor-β; T<sub>H</sub>, helper; TLR, Toll-like receptor; TNF, tumour necrosis factor; T<sub>reg</sub>, regulatory T. \*There is growing evidence that immune cells have sex hormone receptors and can respond directly to the presence, absence or changes in the concentrations of sex steroid hormones. Androgens (including testosterone), oestrogens (including 17 $\beta$ -oestradiol), and progesterone can have distinct and overlapping effects on the recruitment and activity of diverse immune cell populations in humans, rodents and primary cell culture systems. Generally, testosterone and progesterone are anti-inflammatory, suppressing several of the immune responses necessary for inflammation. Oestradiol has bipotential effects: low concentrations of oestradiol (for example, during the follicular stage of the reproductive cycle) can be pro-inflammatory, whereas high concentrations of oestradiol (for example, during the luteal phase of the reproductive cycle or during pregnancy) can be anti-inflammatory.

# Sex differences in neutrophil biology are likely regulated by hormones

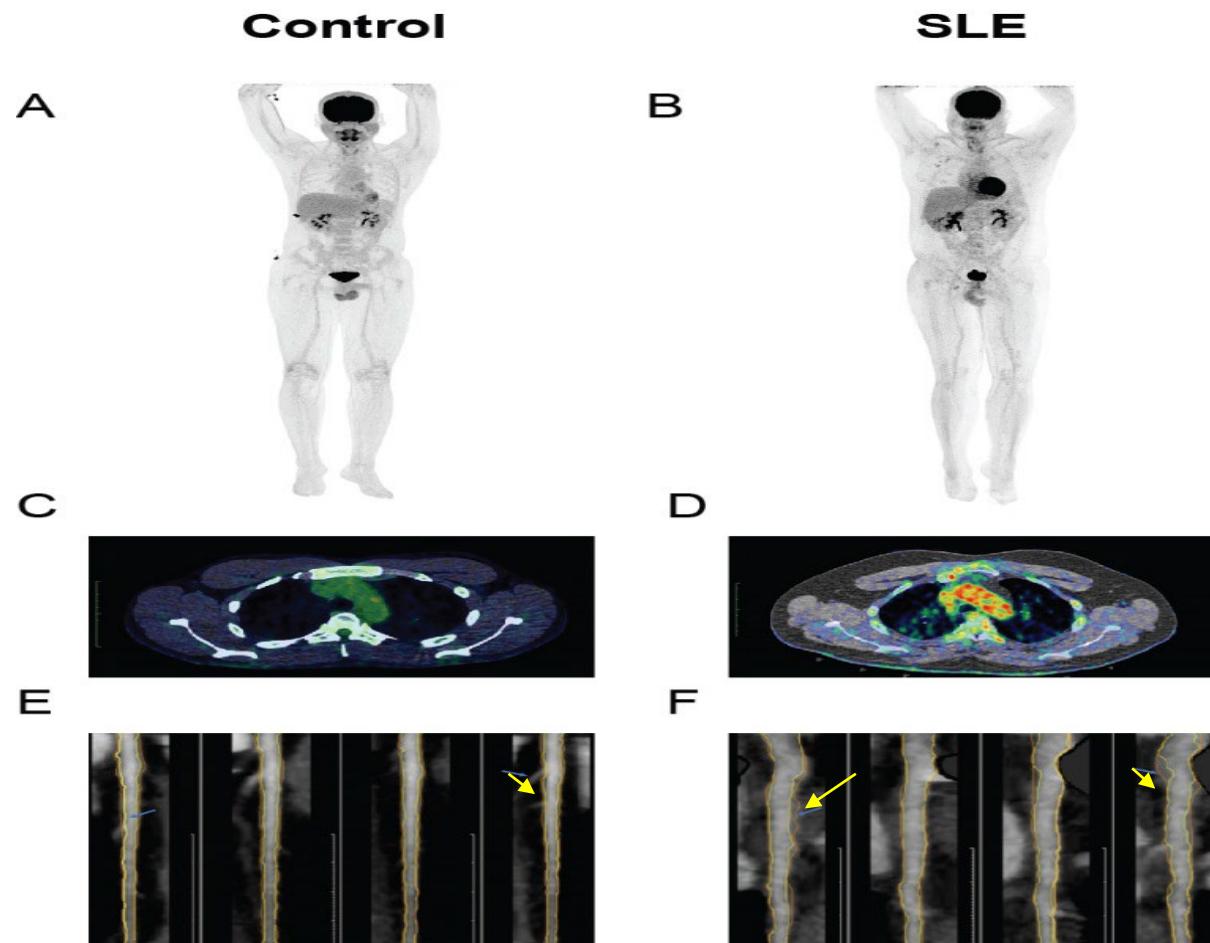
## Klinefelter's syndrome



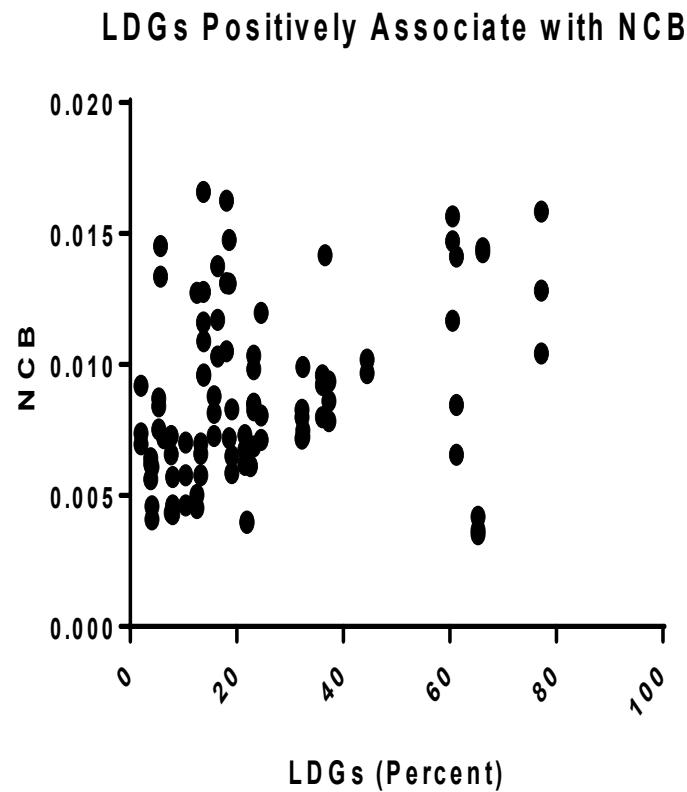
## Prepubescent children



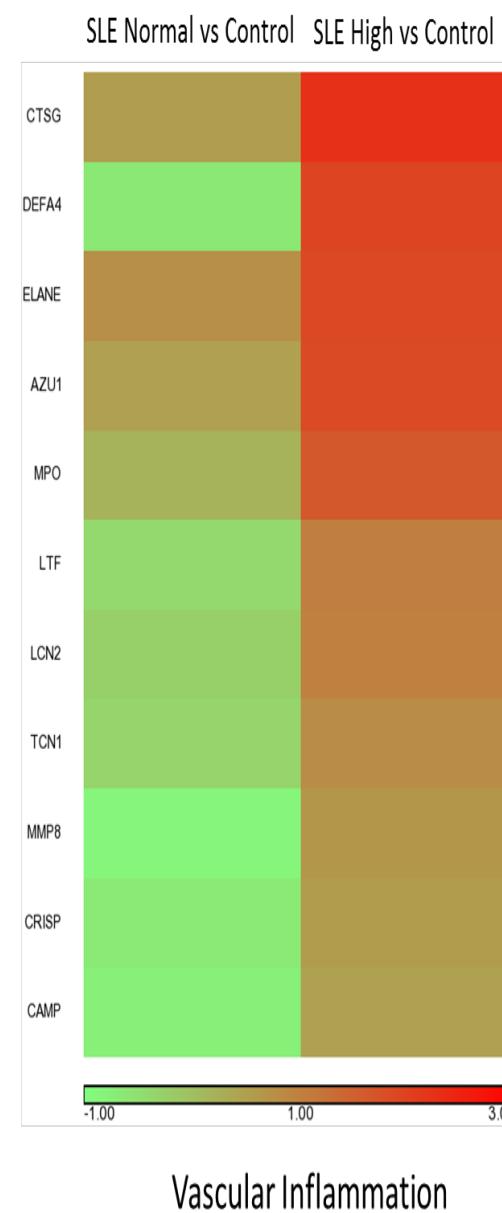
# Lupus is associated with enhanced vascular inflammation and coronary plaque burden



## SLE LDG numbers and gene signature associate with vascular inflammation and non-calcified coronary plaque burden (NCB)

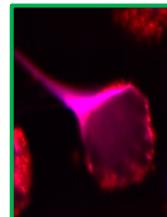
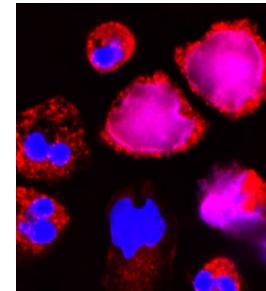


Carlucci et al. *JCI Insight* 2018



# Summary

- Sex differences in neutrophil biology may play a role in differential risk for autoimmunity.
- NETs are a source of modified autoantigens that may promote pathogenic autoimmunity in predisposed hosts.
- Targeting specific neutrophil subsets may contribute to the mitigation of vascular disease and end-organ damage in SLE and other autoimmune diseases.



- Luz Blanco Sarfaraz Hasni
- Carmelo Carmona-Rivera Sarthak Gupta
- Shuichiro Nakabo Yenealem Temesgen
- Pragnesh Mistry Elaine Poncio
- Gustaf Wigerblad Jun Chu
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