Mo/MΦ ontology, function and role in autoimmune diseases

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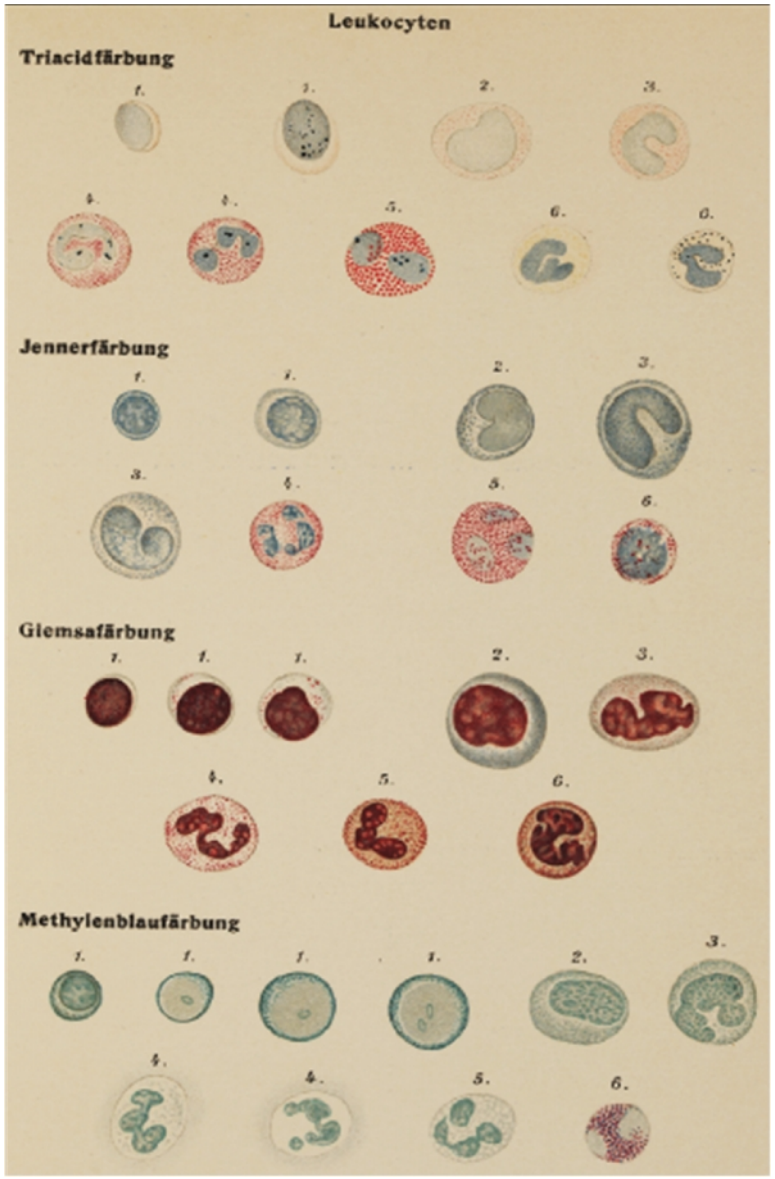
Heraklion 08/10/2021

Historical Monocyte identification



from Naegeli, 1908

1908: Ehrlich & Ilya Metchnikoff shared the Nobel Prize in Physiology or Medicine

1910: Artur Pappenheim introduces the term ‘‘monocyte’’

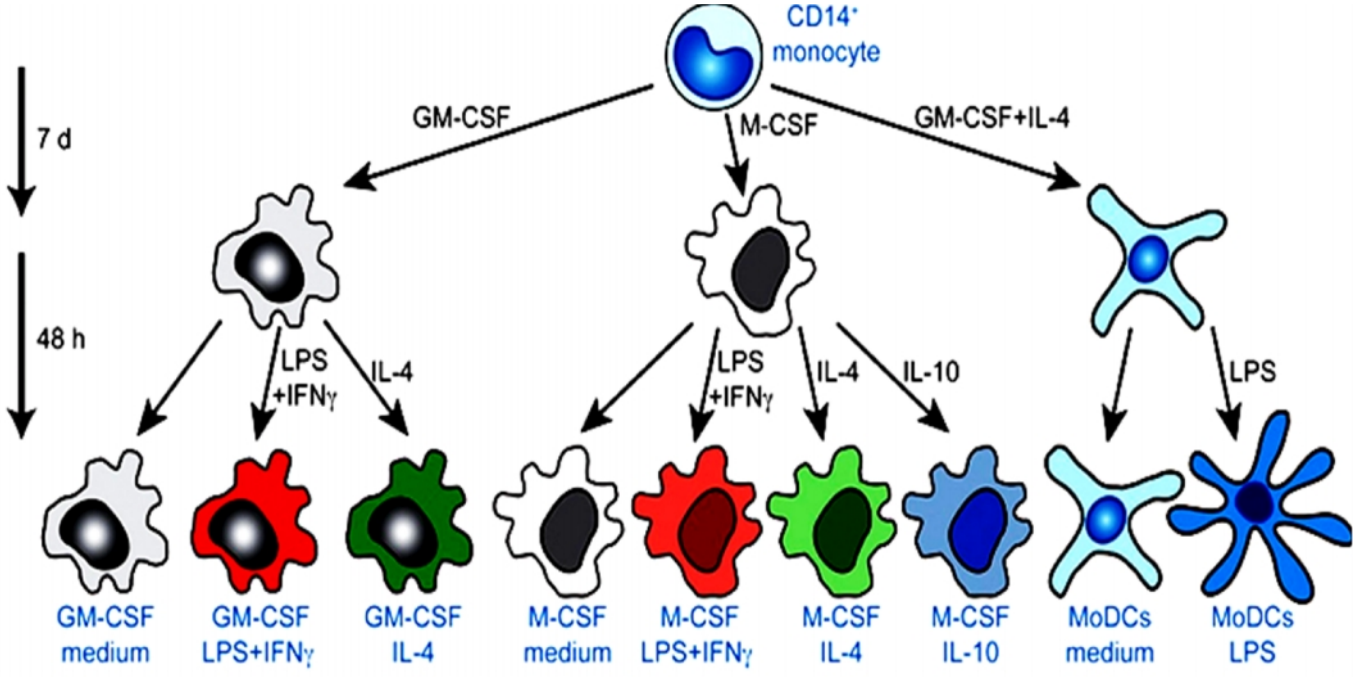
1914: Awrorow and Timofejewskij conduct the first *in vitro* cell culture of macrophages from human leukocytes

doi:10.1016/j.immuni.2018.10.005

Monocyte ontogeny and differentiation potential

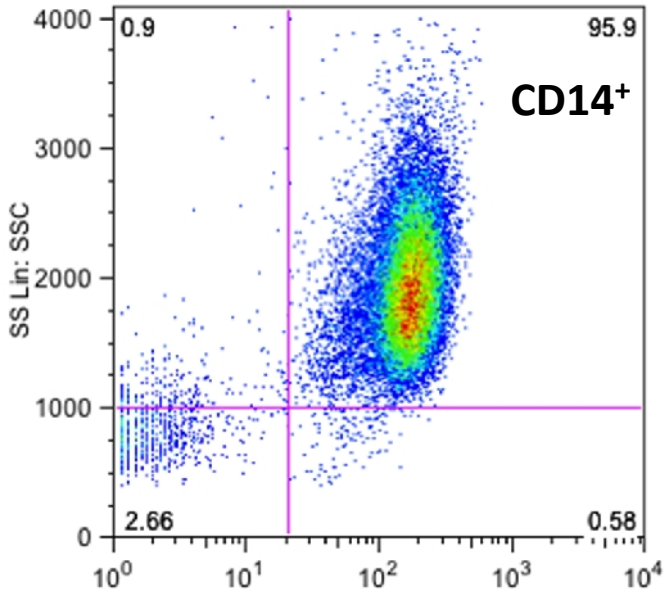
Circulating Monocytes:

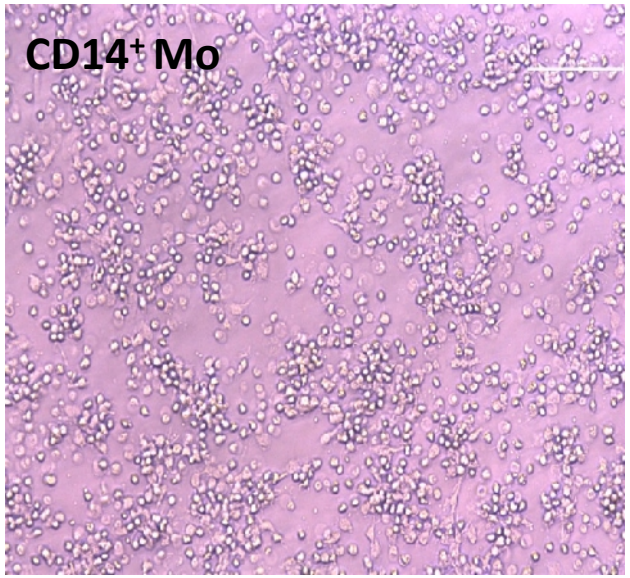
- white blood cells of myeloid origin that mediate innate immune responses
- Heterogeneous cell type with short life span in the blood 1-2 days
- Renewed from CMPs (common myeloid progenitors) in the bone marrow (BM)
- Differentiate to macrophages and dendritic cells in the periphery after



doi:10.1038/cti.2015.39r

Human circulating Monocyte classification





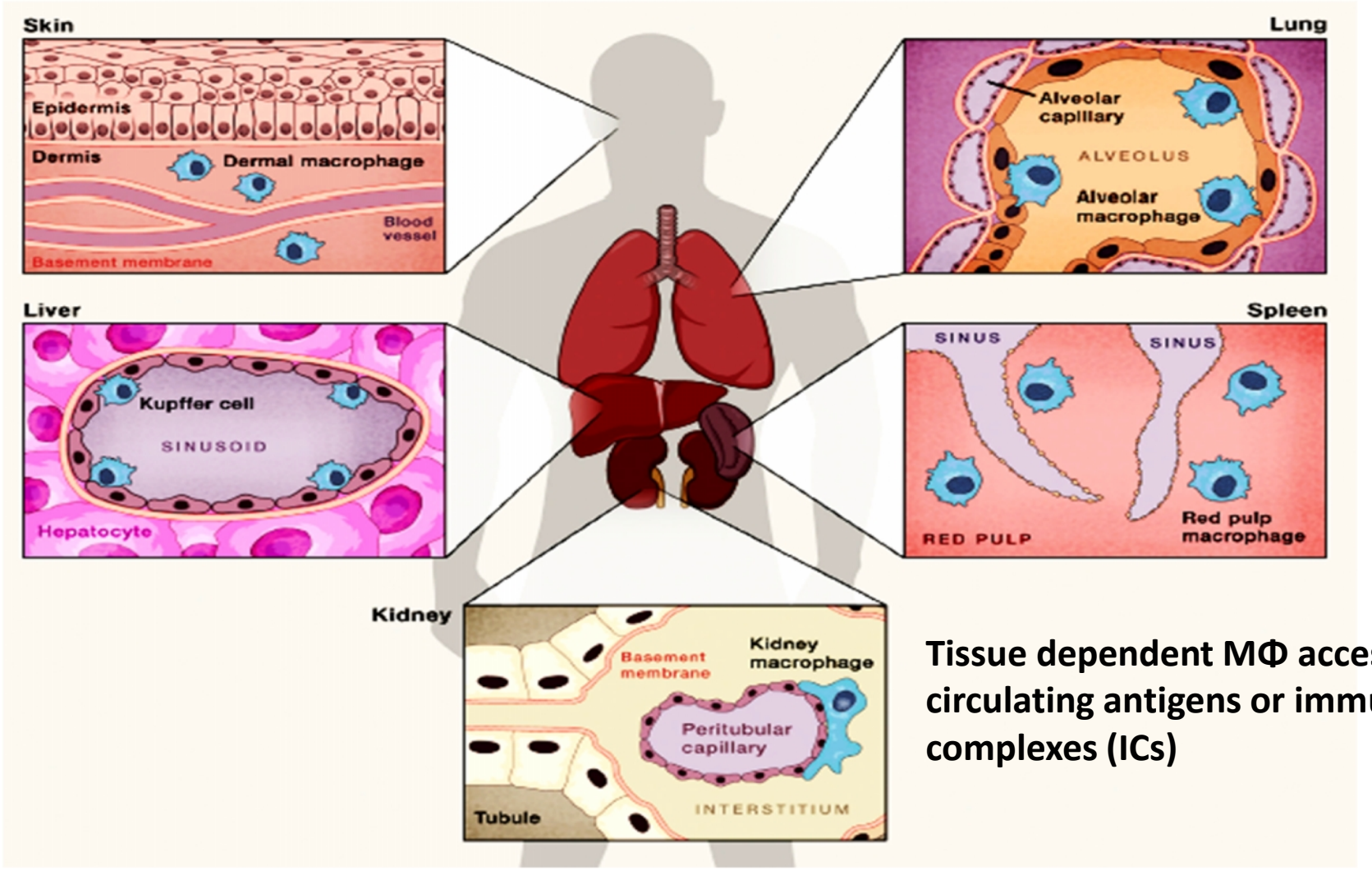
C. Stathopoulou

Monocytes comprise 3-10% of total human PBMCs

- Classical Mo: $CD14^{high}CD16^{-}$ (85% of total Mo)
- Intermediate Mo: $CD14^{+}CD16^{+}$ (5–10%)
- Non-classical Mo: $CD14^{-}CD16^{high}$ (5–10%)

doi:10.1016/j.immuni.2018.10.005

Tissue resident macrophage colonization and self-renewal in peripheral tissues



Tissue dependent MΦ access to circulating antigens or immune complexes (ICs)

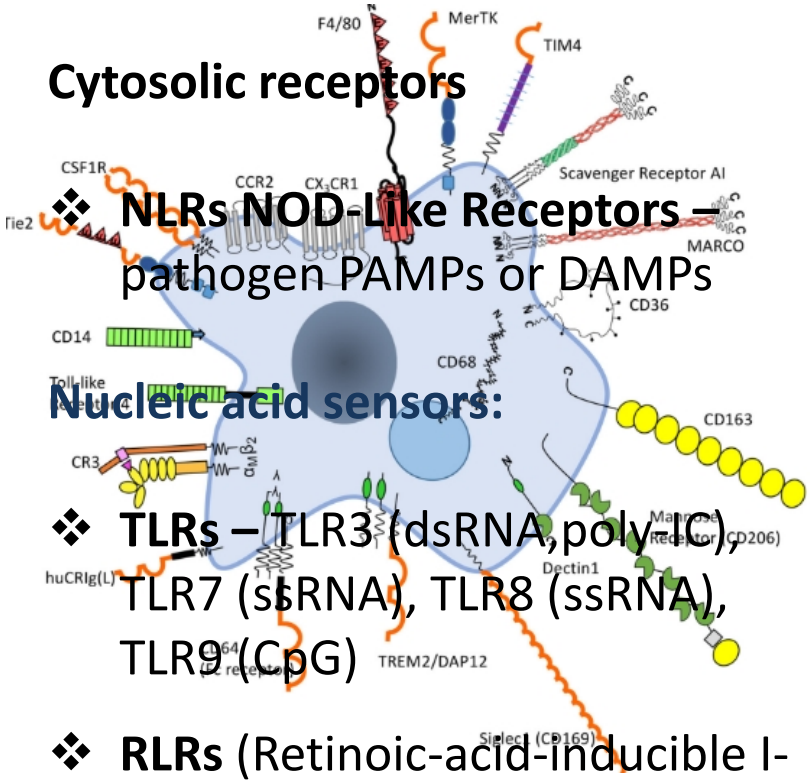
doi:10.1016/j.cell.2016.07.047

Homeostatic roles of Mo/MΦ in immune function

- Phagocytosis and antigen presentation of pathogen parts/apoptotic debris through MHC II molecules
- Immune modulatory cytokine, chemokine, metabolite, antimicrobial oxide secretion
- Chemoattraction of innate and adaptive immune cells
- Tissue repair and remodeling (angiogenesis, muscle-regeneration)
- Iron metabolism
- Glucose and lipid sensing, metabolism & storage
- Formation of epigenetic memory for future activation

doi:10.3389/fphys.2014.00146
doi:10.1016/j.immuni.2016.02.016
doi:10.3389/fimmu.2020.01066

MΦ receptors and signaling pathways



Cytosolic receptors

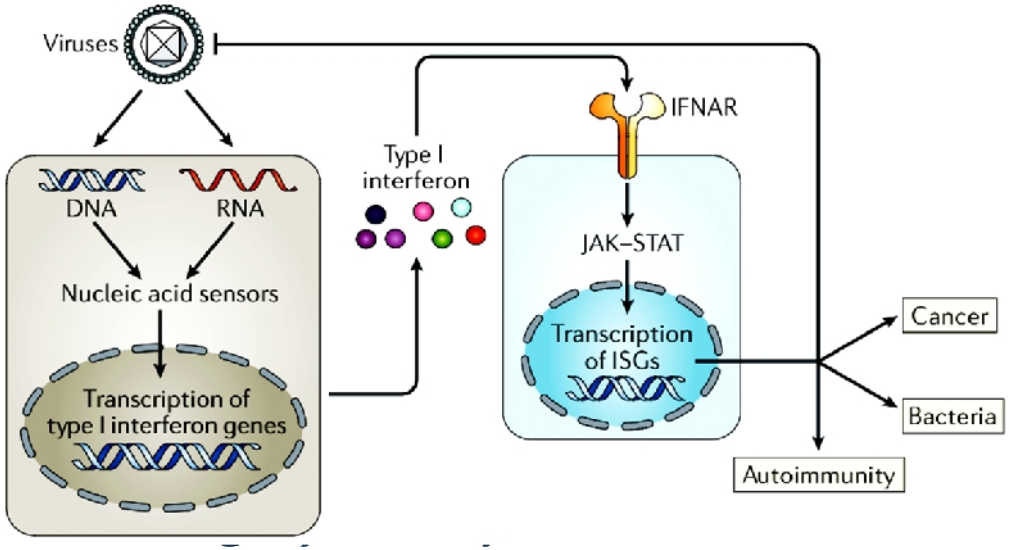
❖ **NLRs NOD-Like Receptors –** pathogen PAMPs or DAMPs

Nucleic acid sensors:

❖ **TLRs –** TLR3 (dsRNA,poly IC), TLR7 (ssRNA), TLR8 (ssRNA), TLR9 (CpG)

❖ **RLRs** (Retinoic-acid-inducible I-like gene) **–** viral ssRNA, dsRNA

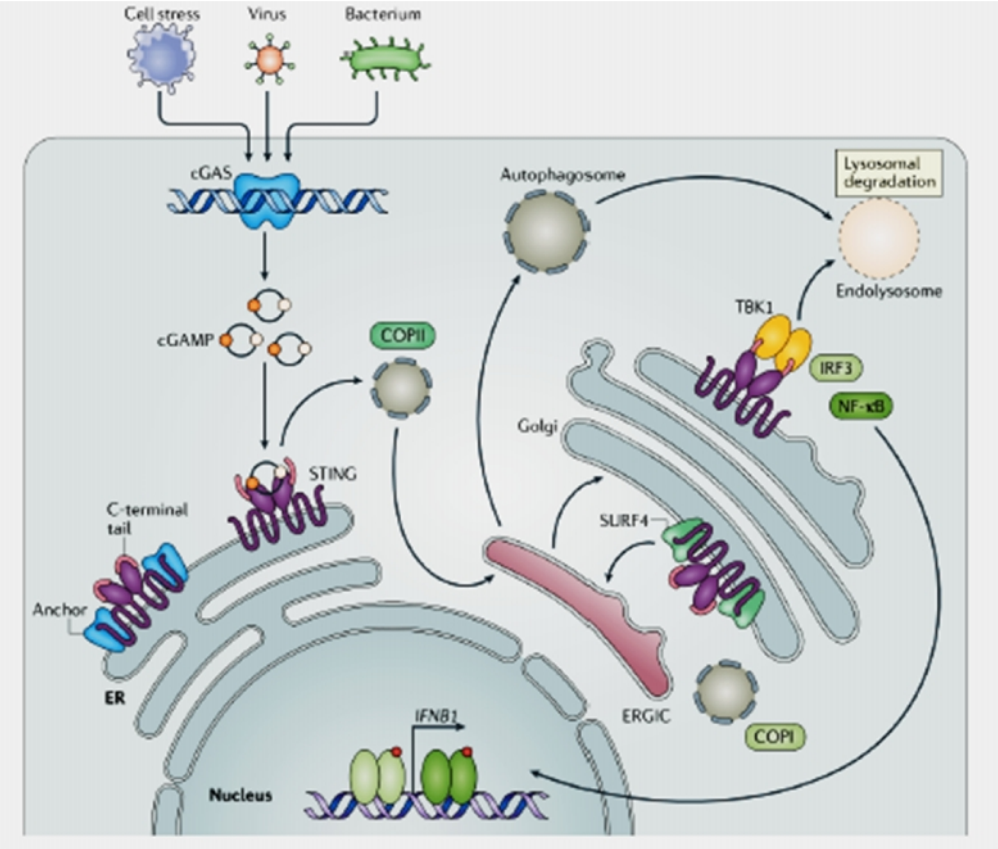
❖ **cGAS** (cyclic GMP- AMP synthase) – dsDNA



- **Non-opsonic –** i.e. Dectin-1, DC-SIGN, CD36,CD14
- **Opsonic –** receptors for IgG (FcRs), complement receptors (CRs)

doi:10.1002/path.5404l
doi:10.3389/fimmu.2020.01066
doi:10.1038/s41577-020-0288-3

MΦ signaling pathways with therapeutic potential in autoimmunity



Sources of alternate activation in autoimmunity :

- **mtDNA** - defective phagocytosis
- **cDNA** intermediates from

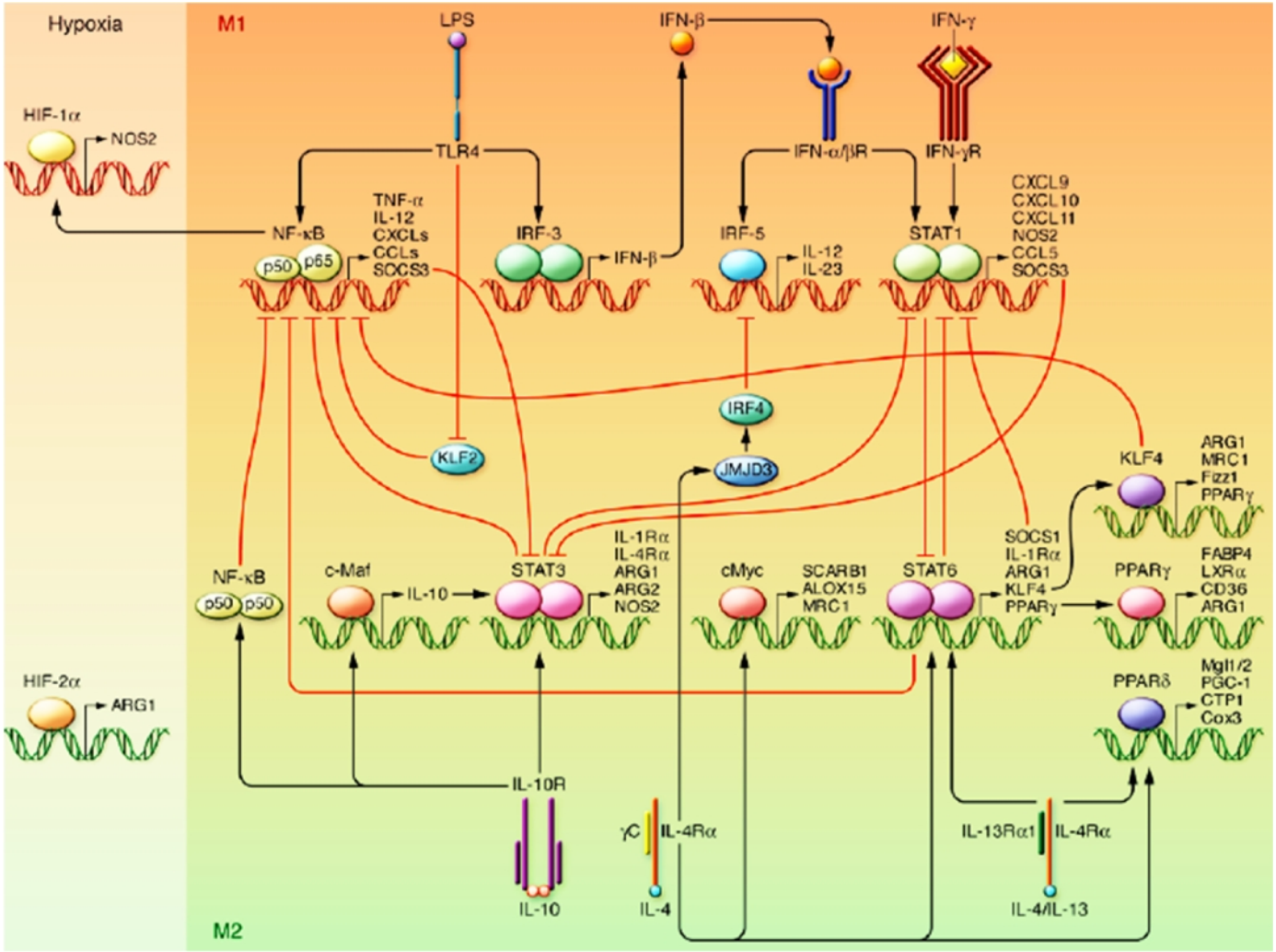
LINE-1 retrotransposition- imbalanced surveillance

Lupus-like symptom manifestation in families carrying gain of function STING mutations

Inhibitors reduce CXCL10, IFNβ *in vitro* and *in vivo* mouse models
(i.e. Antimalarian drugs, Tetrahydroisoquinolines, nitrofurans, indole ureas, acrylamides)

doi:10.1038/s41577-021-00524-z

MΦ plasticity, polarization and signaling pathways



doi:10.1172/JCI59643

MΦ secreted cytokines/receptors as drug targets in autoimmunity

TABLE 2 | Alternative biologic in autoimmune inflammatory diseases.

Drug	Target	Type of molecules	Indications
Abatacept (Orencia)	CD80 (B7-1) and CD86 (B7-2) and blocks activation of T-cell Ab4Ig	The extracellular domain of CTLA4 and Fc domain of IgG1	RA, JIA, SLE
Tocilizumab (Actemra)	IL-6	A humanized anti-human IL-6 receptor monoclonal antibody	RA after treatment failure with TNF inhibitors
Anakinra (Kineret)	IL-1	A recombinant human IL-1 receptor antagonist	RA
Ustekinumab	IL-12 and IL-23	Human IgG1k mAb	Psoriasis
Rituximab	CD20	A chimeric murine/human monoclonal IgG1k antibody	RA, SLE
Secukinumab	IL-17	A human IgG1κ monoclonal antibody	PP

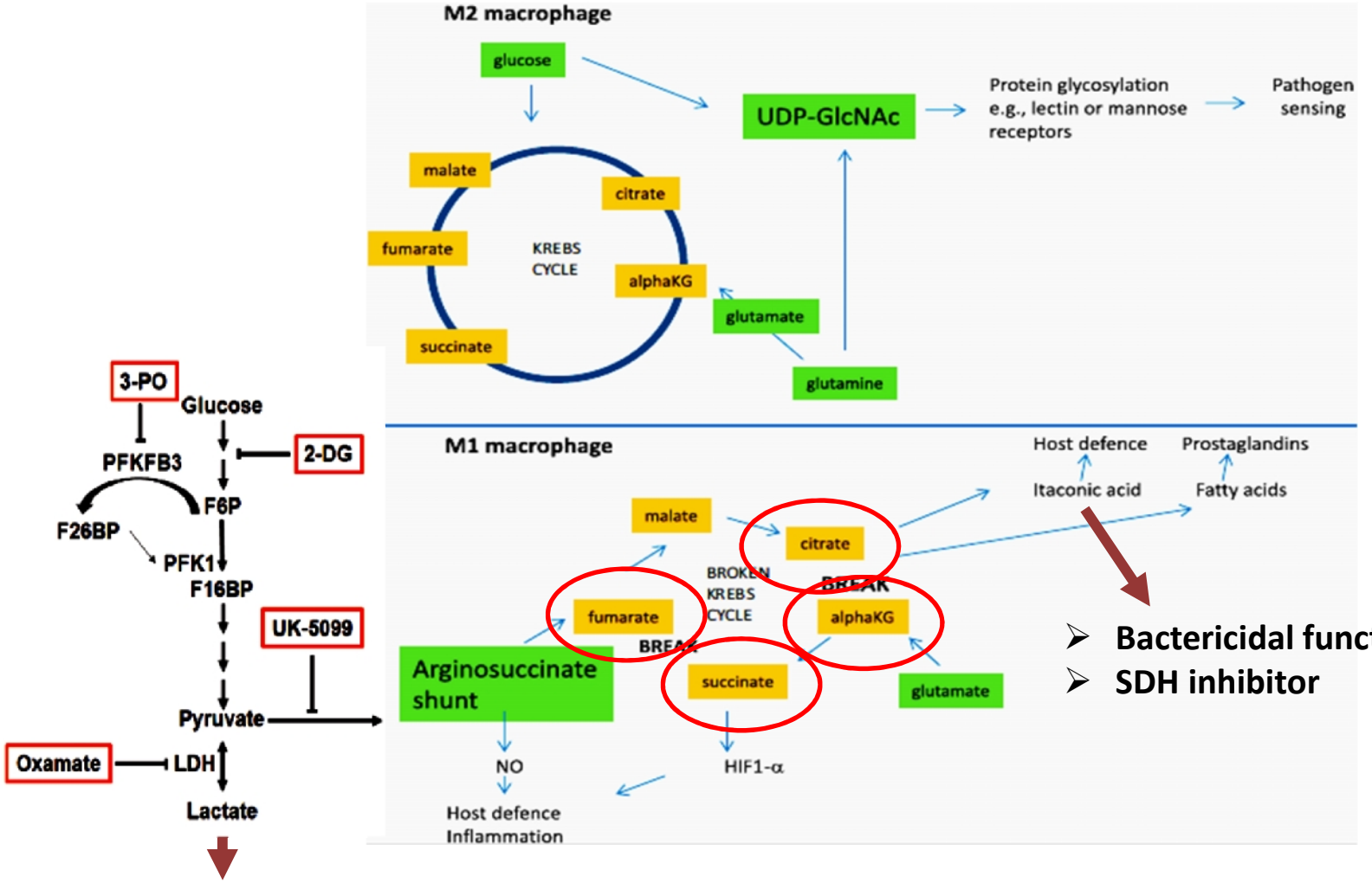
CTLA, cytotoxic T lymphocyte-associated; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus.

Belimumab - soluble BAFF - **SLE**

Adalimumab, infliximab – membrane-bound/soluble TNF **- RA**, **PS**

doi:10.3389/fphar.2017.0046
doi:10.1007/s40259-019-00400-2

MΦ metabolism and polarization

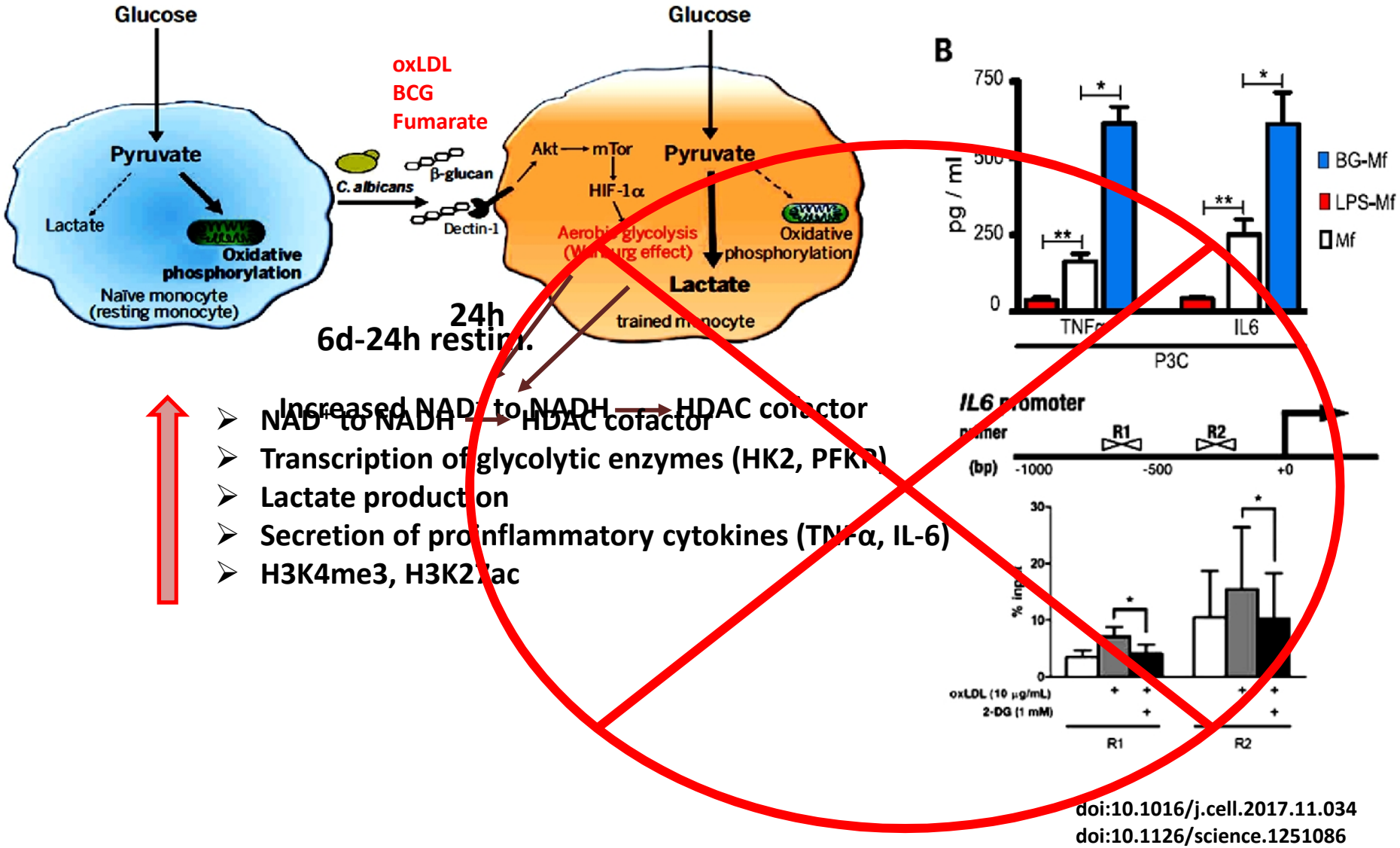


- Bactericidal function
- SDH inhibitor

- Suppressor of MAVS
- Inhibitor of T cell proliferation

doi:10.1016/j.immuni.2015.02.017
doi:10.1016/j.immuni.2017.04.016
doi:10.1016/j.immuni.2019.11.009
doi:0.1016/j.cell.2019.05.003

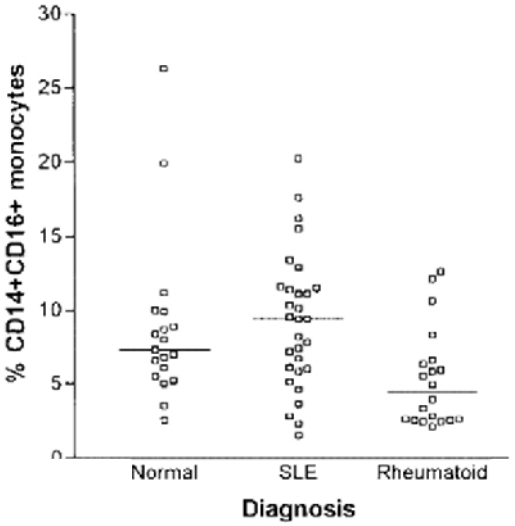
MΦ glycolytic metabolism in trained immunity

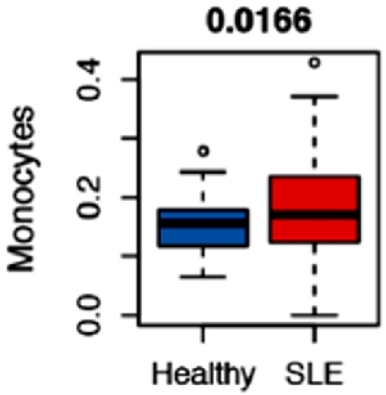


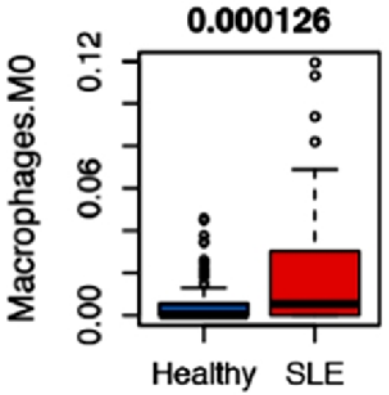
doi:10.1016/j.cell.2017.11.034
doi:10.1126/science.1251086
doi:10.1016/j.mam.2020.100897
doi:10.1007/s00109-020-01915-w

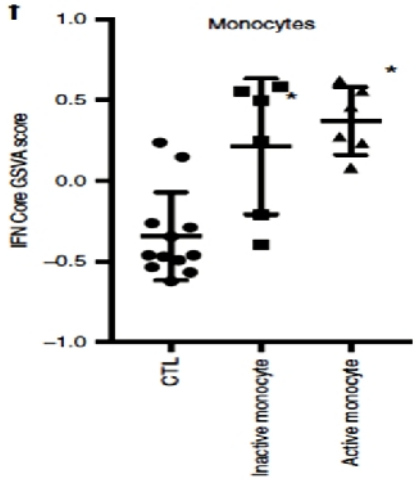
Features of Mo/MΦs in autoimmunity: Subpopulation count & polarization

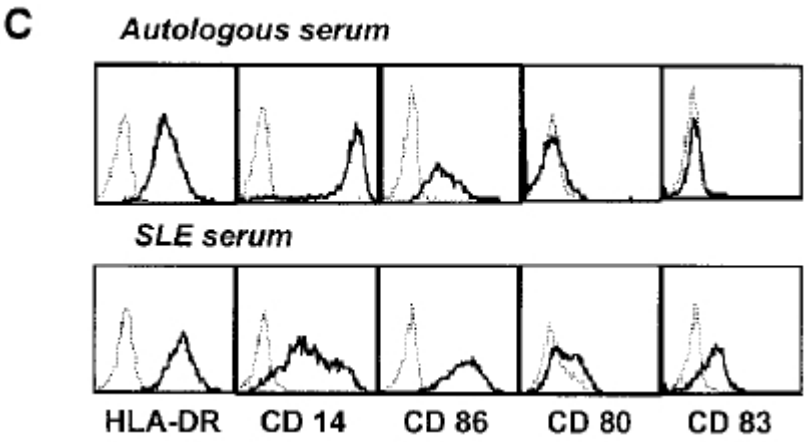
In SLE increased number of intermediate monocytes and DC-like skewing

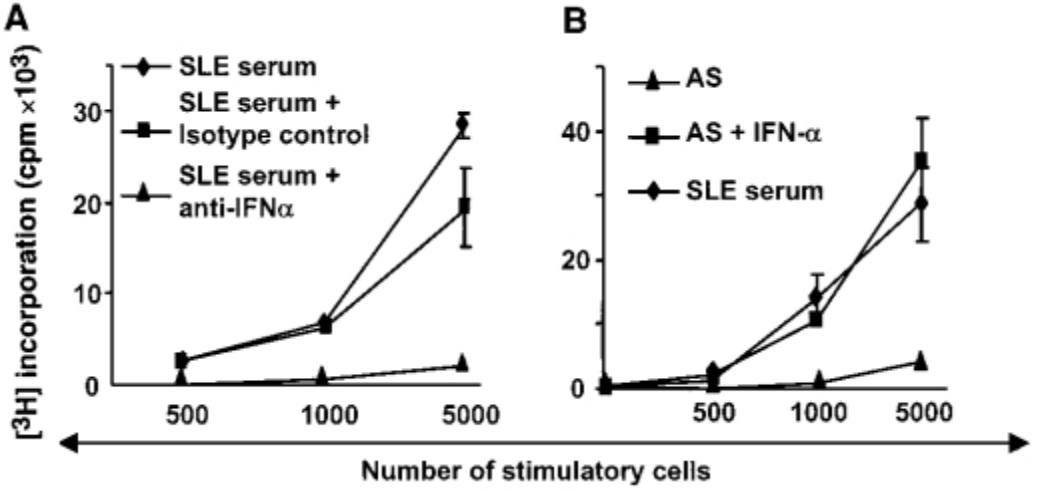








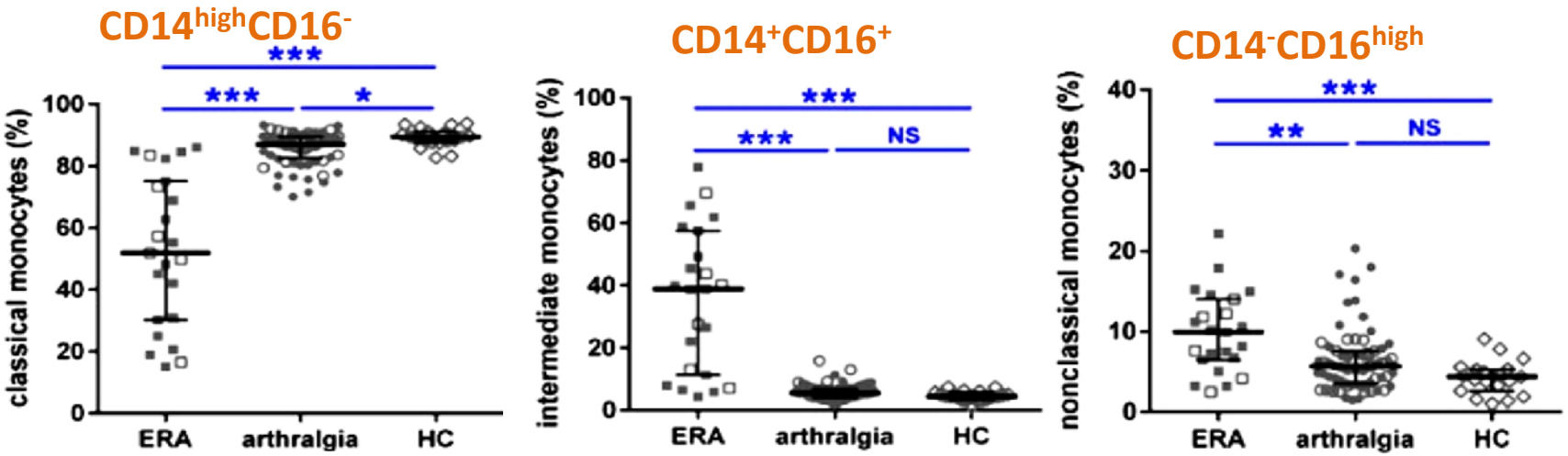


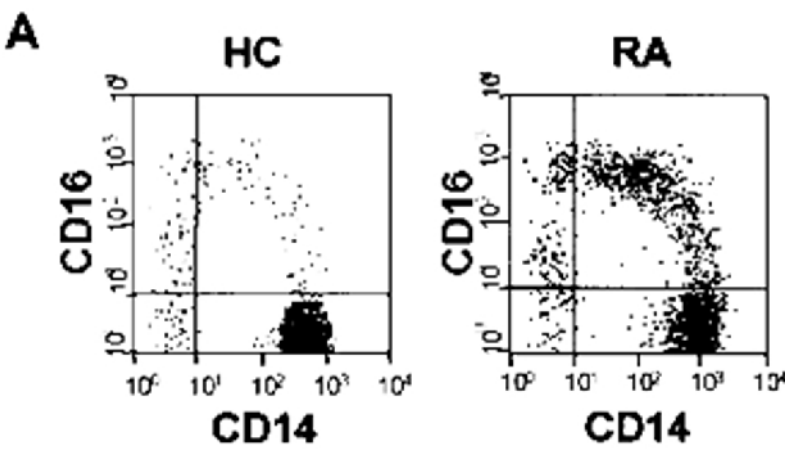


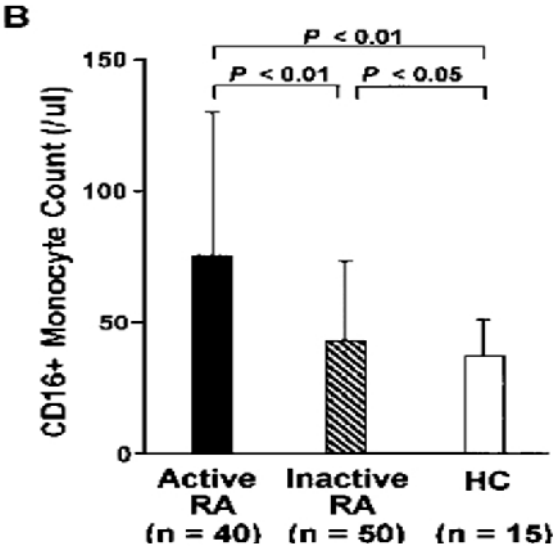
doi: 10.1126/science.1064890
doi: 10.1007/s00296-001-0165-8
doi:10.1136/annrheumdis-2018-214379

Features of Mo/MΦs in autoimmunity: Subpopulation count & polarization

In RA increased number of intermediate monocytes and M1 skewing



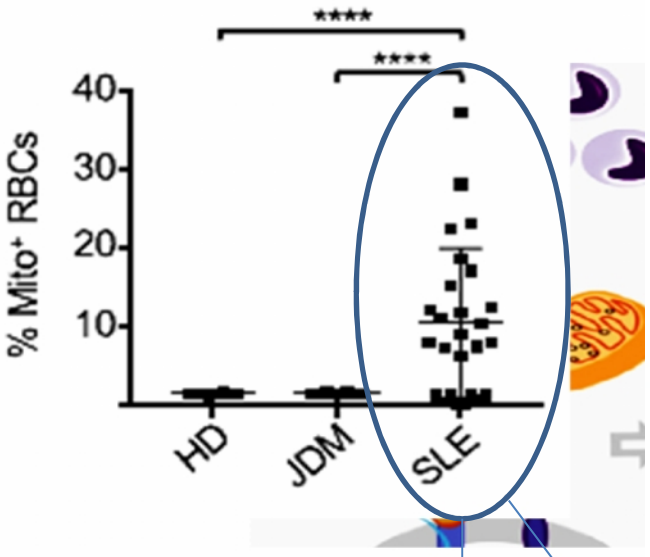


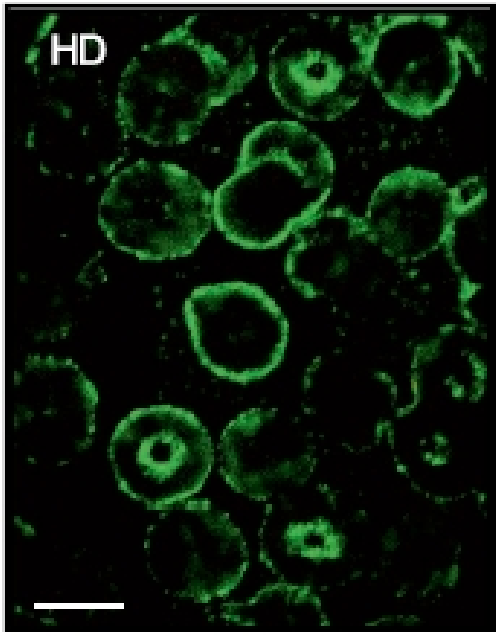


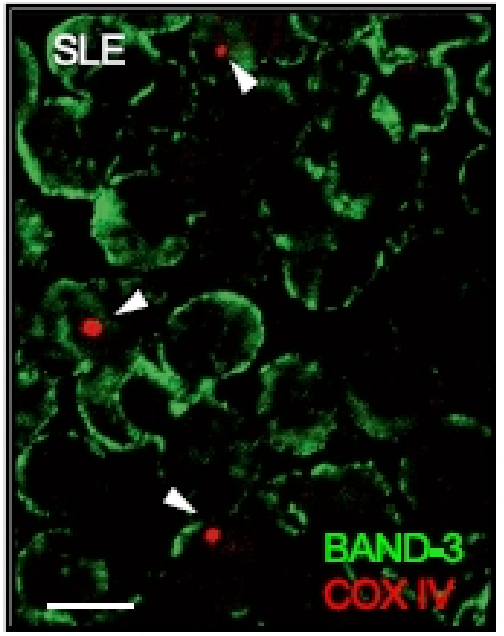
doi:10.1093/rheumatology/keaa518
doi:10.1002/art.10545

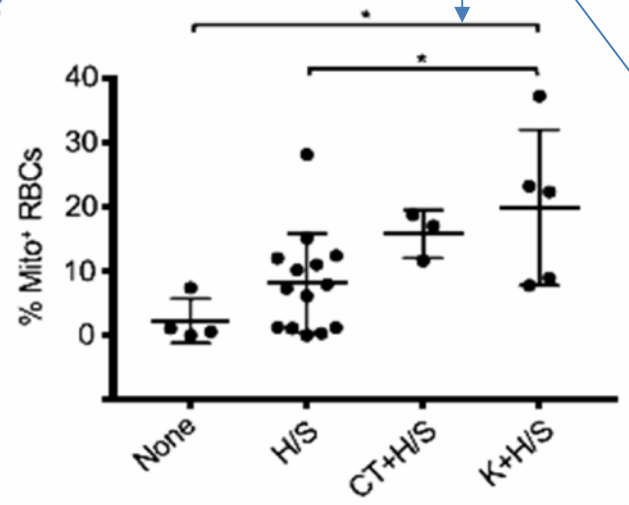
Features of Mo/MΦs in autoimmunity: Phagocytosis

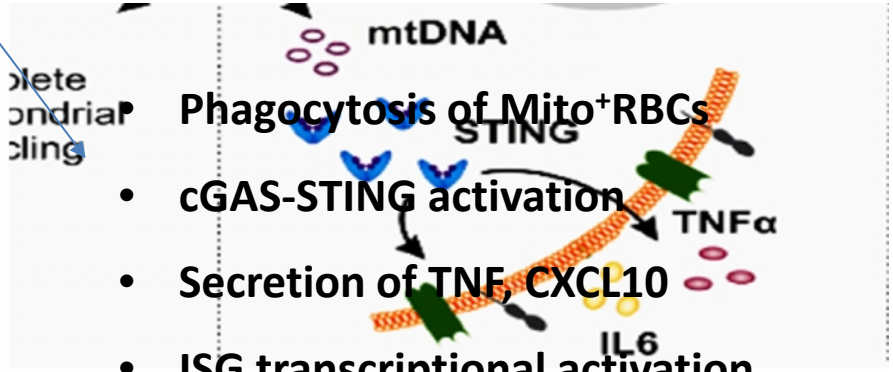
Defective clearance in SLE Mo perpetuating disease phenotype











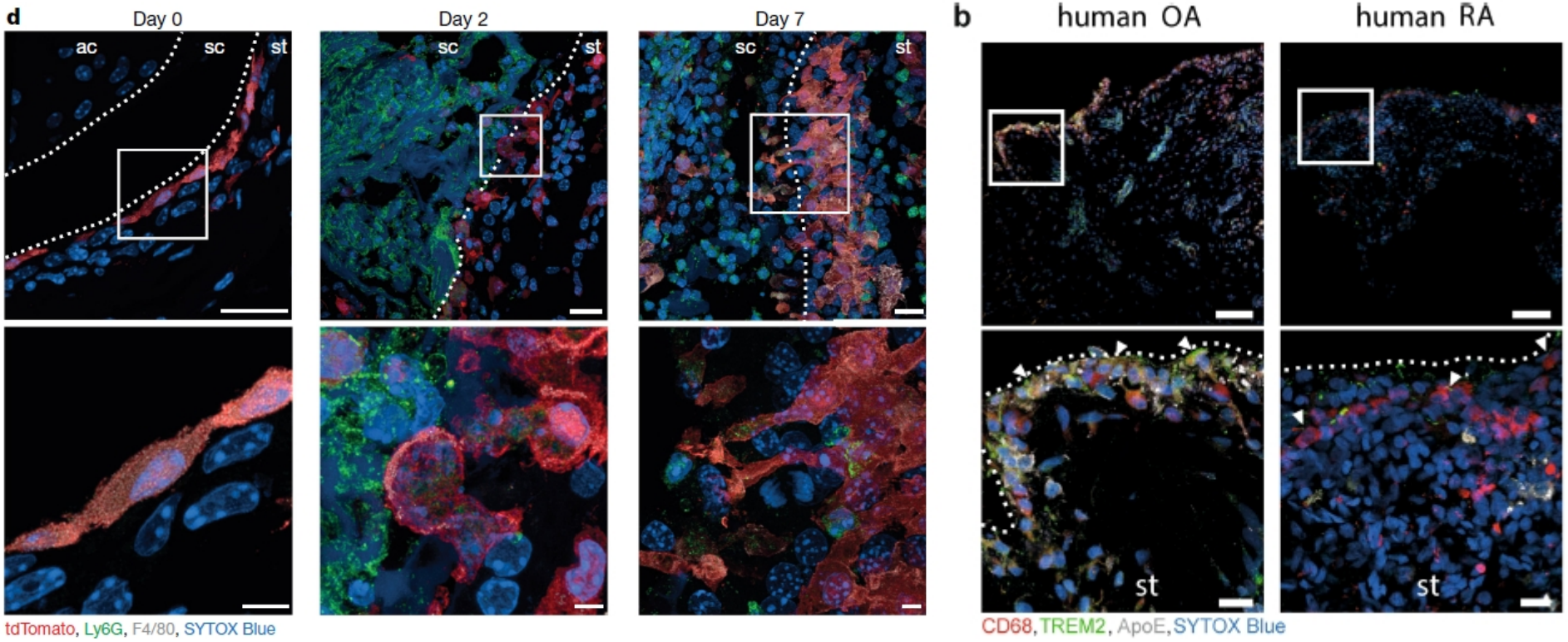
- Phagocytosis of Mito+RBCs
- cGAS-STING activation
- Secretion of TNF, CXCL10
- ISG transcriptional activation

doi:10.1016/j.cell.2021.07.021
doi:10.1016/j.celrep.2018.09.001

Features of Mo/MΦs in autoimmunity: Role in homeostasis and tissue integrity

The homeostatic role of resident synovial macrophages is altered in RA

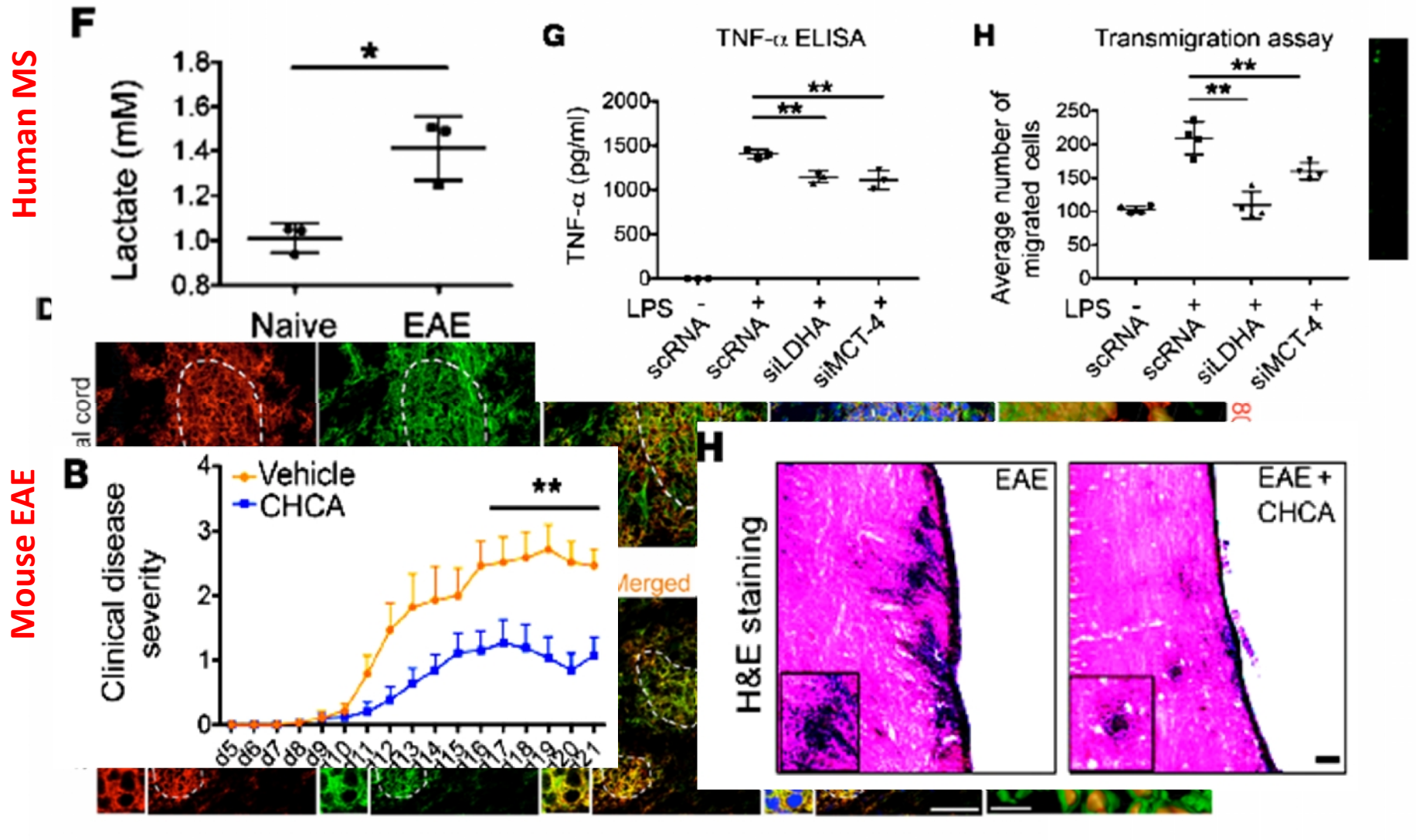
Macrophage lining of CD68^{+}F4/80^{+}**CX3CR1^{+} tissue-resident macrophages is lost in** RA synovium



doi: 10.1038/s41586-019-1471-1

Features of Mo/MΦs in autoimmunity: Infiltration and metabolism

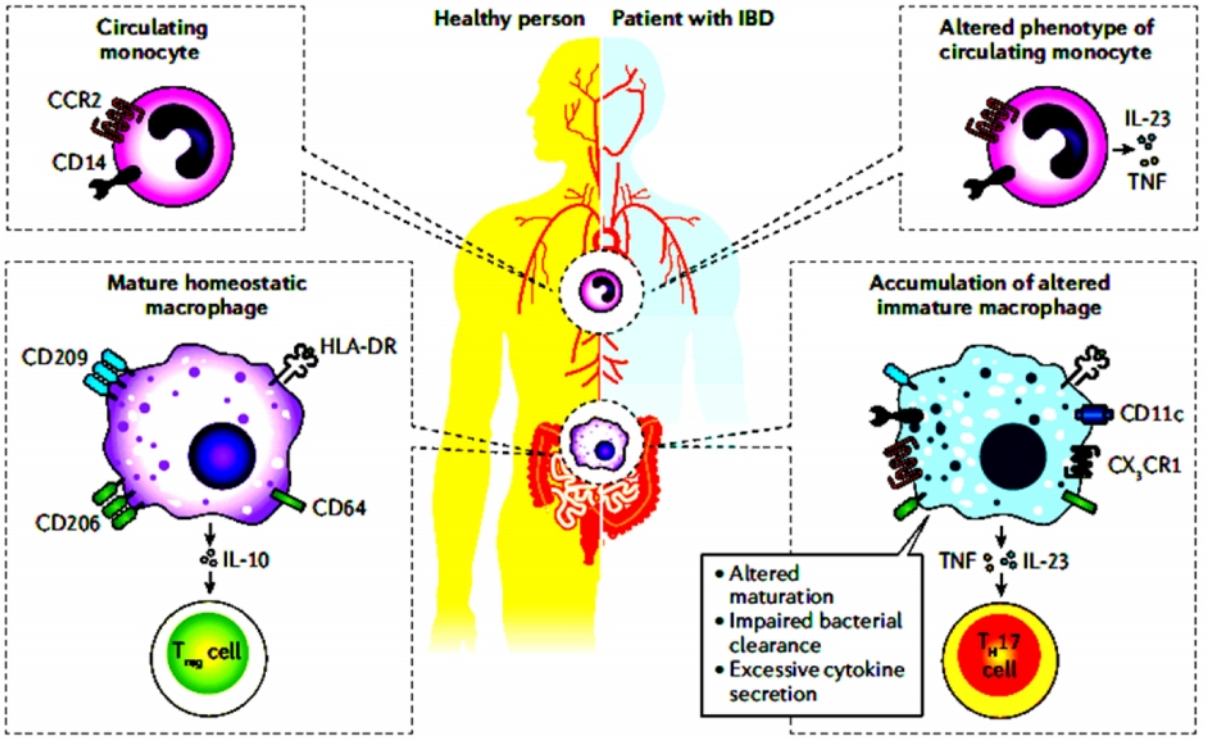
Increased infiltration of glycolytic Mo in MS parenchyma



doi:10.1172/JCI124012

Features of Mo/MΦs in autoimmunity: Infiltration and metabolism

Deregulation in metabolites as signaling molecules affects the inflammatory state of Mo/MΦ in IBD



Tolerogenic microbiota-derived metabolites

- **SCFAs** (i.e. butyrate)
- **AhR** ligands (i.e. indoles)

Inflammatory microbiota-derived metabolites

- **Succinate**
- **Arachidonic acid**

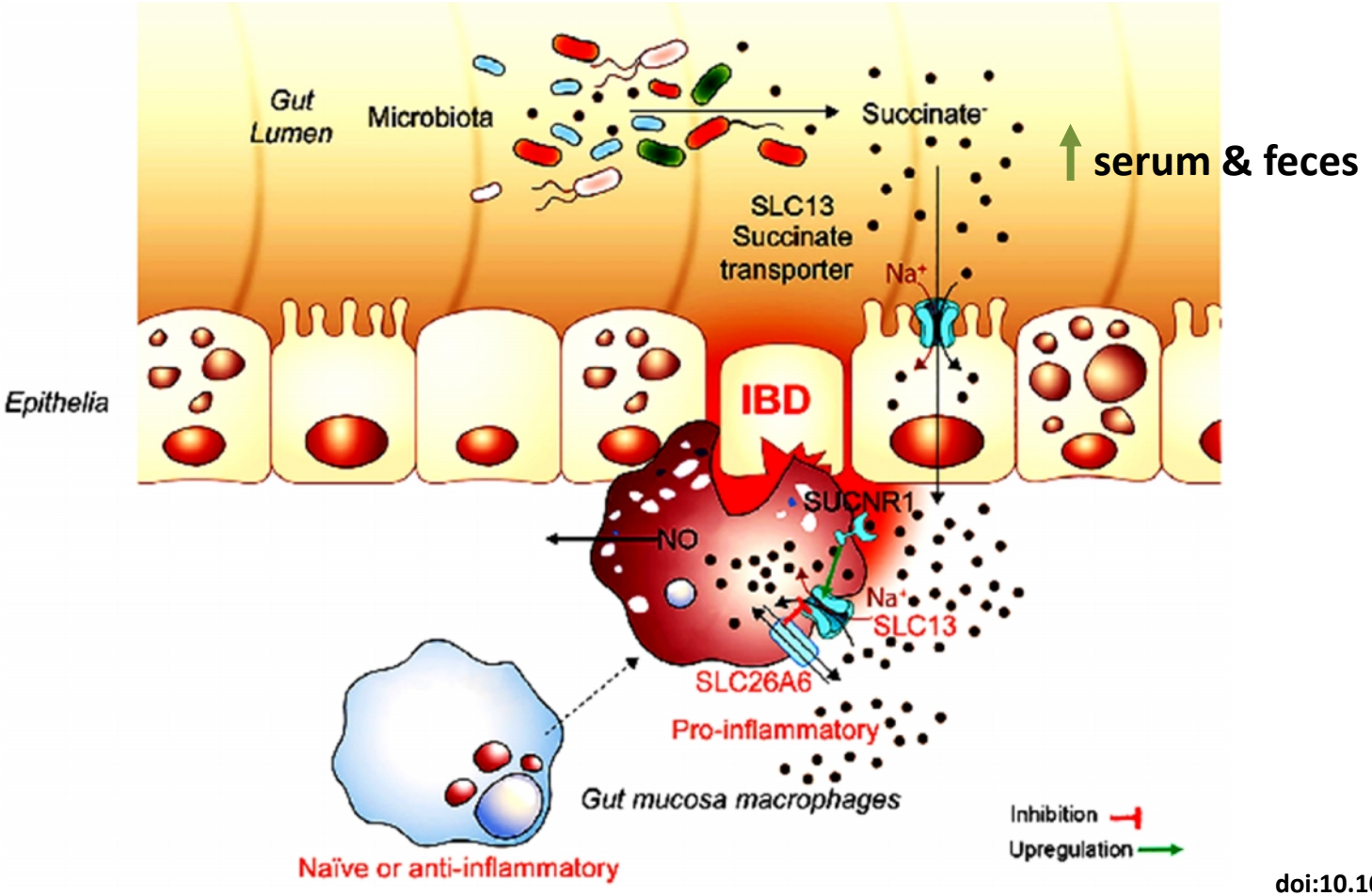
doi:10.1038/s41575-019-0172-4
doi:10.1038/ s41575-019-0258-z

Features of Mo/MΦs in autoimmunity: Infiltration and metabolism

SLC13A3-mediated succinate uptake and its regulation by SUCNR1 or SLC26A6 perpetuate the pro-inflammatory state of MΦs by elevating cytoplasmic succinate

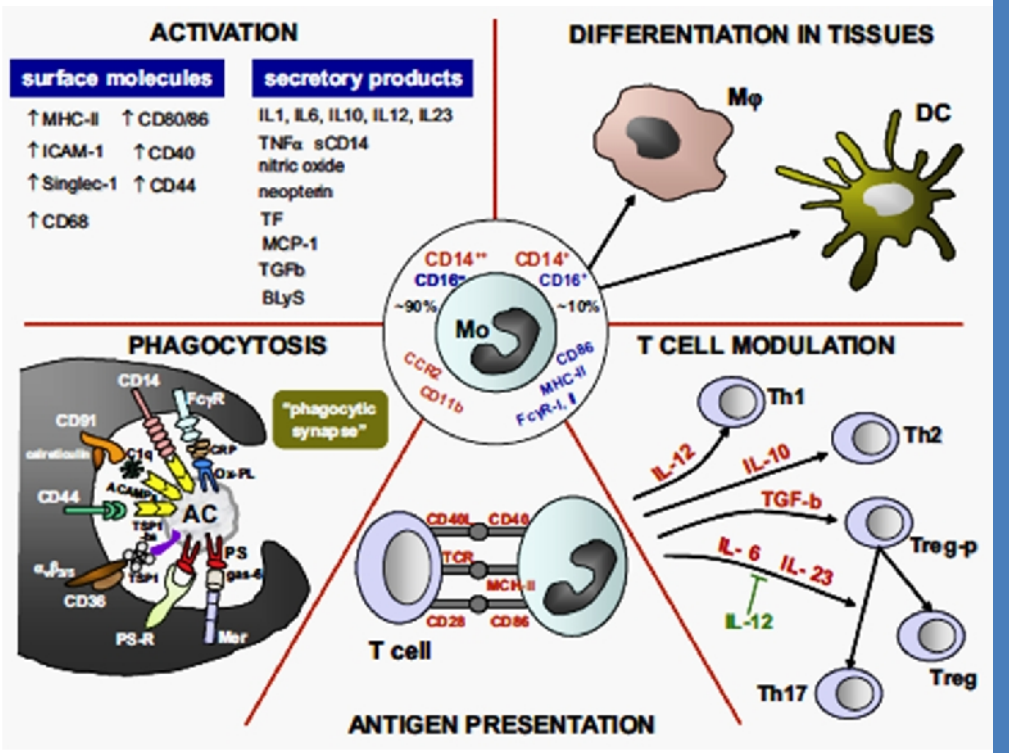
↑ Succinate producing bacteria (i.e. *B. fragilis*, *B. vulgatus*)

↓ Succinate consuming bacteria (i.e. *P. succinatutens*, *P. faecium*,)



doi:10.1016/j.celrep.2021.109521

Conclusions



doi:10.1016/j.semarthrit.2008.11.002

Mo/MΦ localize in blood and peripheral tissues, show increased plasticity and exert multiple functions via:

- ❖ Receptor signaling
- ❖ Cytokine secretion
- ❖ Modulation of adjacent cell function

Mo/MΦ are involved in both amplifying and suppressing inflammation

Mo/MΦ pro-inflammatory/fibrogenic properties are implicated in autoimmune diseases

THANK YOU!

Mo/MΦ metabolic targeting could have therapeutic potential in chronic inflammation

Metabolic targeting in autoimmunity

Table 3. Metabolic targeting implemented in treatment of autoimmune diseases.

Metabolic modulators	Target pathway	Effect	Autoimmune disease
Rapamycin	PI3K/Akt/mTOR pathway	mTORC1 inhibition	SLE, RA, Systemic sclerosis, Sjogren's syndrome
NAC	GSH metabolic pathway, PI3K/Akt/mTOR pathway	Lymphocyte GSH rescue, double-negative T cells mTORC1 blockade	SLE
MMF	PI3K/Akt/mTOR pathway	$CD4^+$ T cells, PI3K/Akt/mTOR blockade, glycolytic, oxidative metabolic reduction	SLE
2-DG	Glycolysis pathway (hexokinase)	Phospho-glucose isomerase inhibition, MΦ IL-1β blockade production	SLE
Metformin	AMPK pathway	Blockade of IFNα production, restoration of IL-2 production (in combination with 2-DG)	SLE
Methotrexate	Nucleotide metabolic pathway	Dihydrofolate reductase inhibition	RA, SLE, Crohn's disease, psoriasis, Wegener's vasculitis
DMF	Glycolysis pathway	GAPDH inhibition, glycolysis reduction, OXPHOS elevation	MS

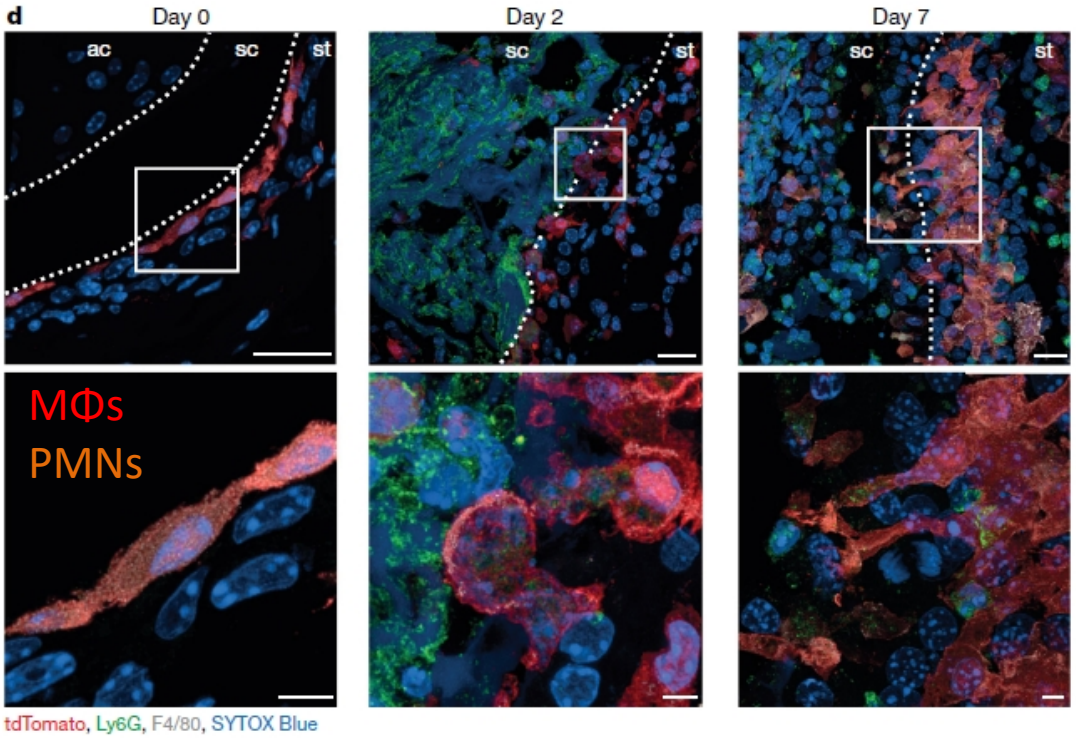
2-DG: 2-Deoxy-D-glucose; AMPK: AMP-activated protein kinase; DMF: Dimethyl fumarate; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase; GSH: Glutathione; IFN: Interferon; MΦ: Macrophage; MMF: Mycophenolate mofetil; MS: Multiple sclerosis; NAC: N-acetylcysteine; OXPHOS: Oxidative phosphorylation; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus.

doi:10.2217/imt-2019-0002

RA

- Macrophage lining of **CX3CR1⁺ tissue-resident macrophages is lost in** RA synovium

  (doi: 10.1038/s41586-019-1471-1)



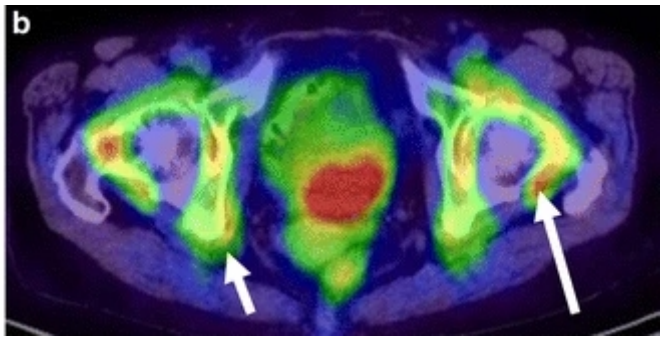
- Inflammatory **FLS** are mainly glycolytic

  (doi: 10.3389/fimmu.2019.01743)

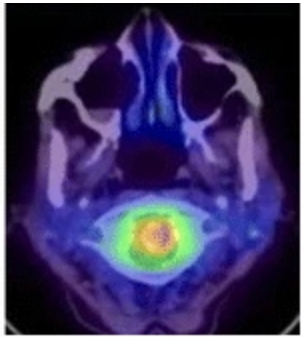
- Metabolomics in RA synovial tissues & FDG-PET/CT: increased glucose uptake

  (doi:10.1007/s12149-009-0305-x)

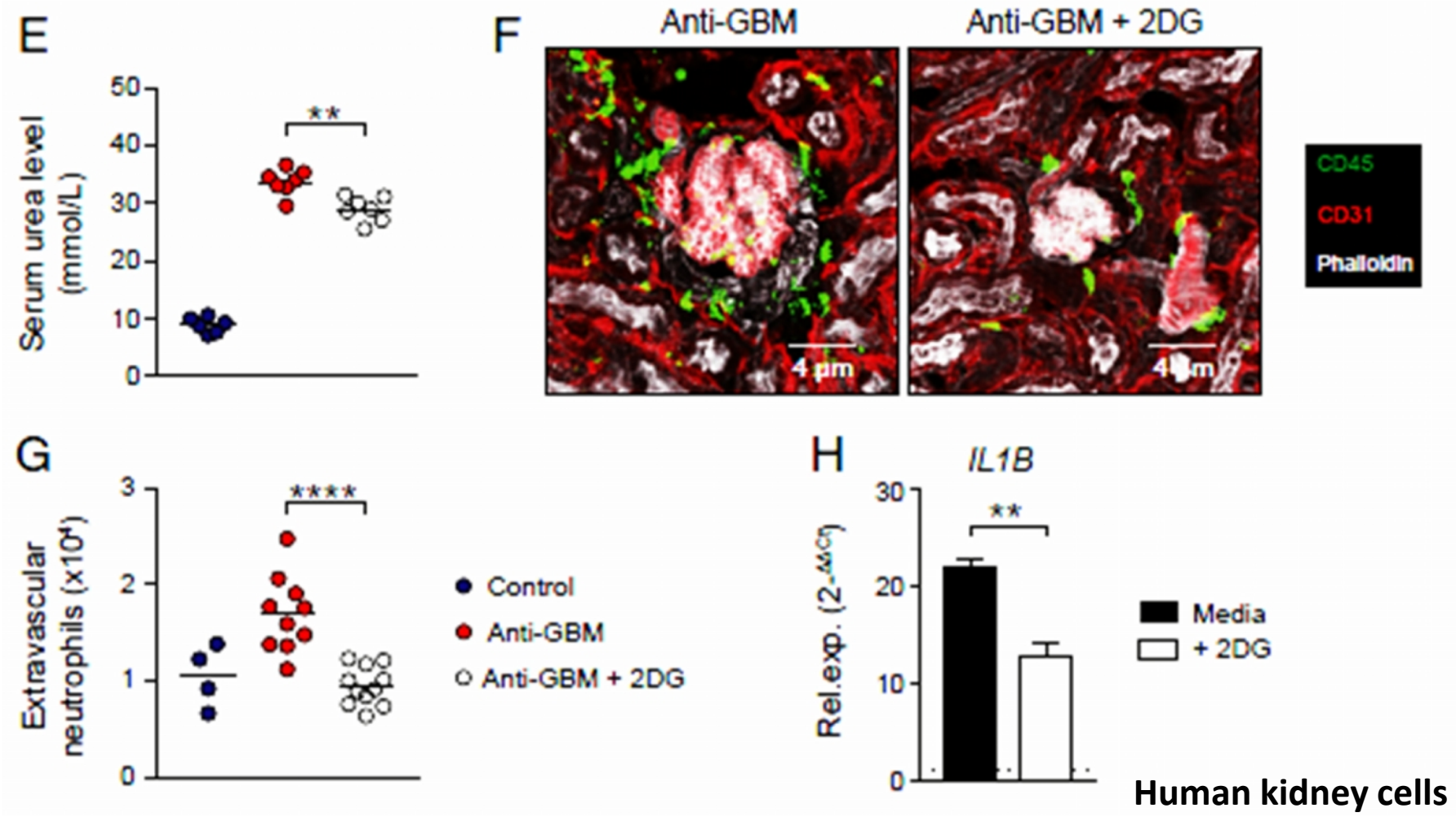
Human FDG-PET/CT : RA joints



knees



Inhibition of glycolytic switch reduces autoAb-mediated inflammation *in vivo*



Human kidney cells
OVA-IC±2DG 12h

doi.org/10.1073/pnas.2000943117