Webinars for patients

Sickle Cell Disease

Topic on Focus

EuroBloodNet

Sickle cell disease and autoimmune diseases

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Network Hematological Diseases (ERN EuroBloodNet)

Conflicts of interest

I have no conflict of interest to declare.

Webinar rules

- 30 min presentation + 15 min Q&A session
- Microphones will be muted by host to avoid back noise
- Please, stop your video to improve internet conexion
- Send your questions during the presentation through the chat

Learning objectives

1. How could sickle cell disease (SCD) promote autoimmunity?
2. Are patients with SCD more prone to autoimmune diseases?
3. What are the therapeutic implications of autoimmunity in SCD?

Learning objectives

1. **How could sickle cell disease (SCD) promote autoimmunity?**
2. Are patients with SCD more prone to autoimmune diseases?
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Autoimmunity

"Autoimmunity is defined as an immune response leading to reaction with self antigen, i.e. any molecule that is a normal body constituent".

Delves, Encyclopedia of Immunology 1998

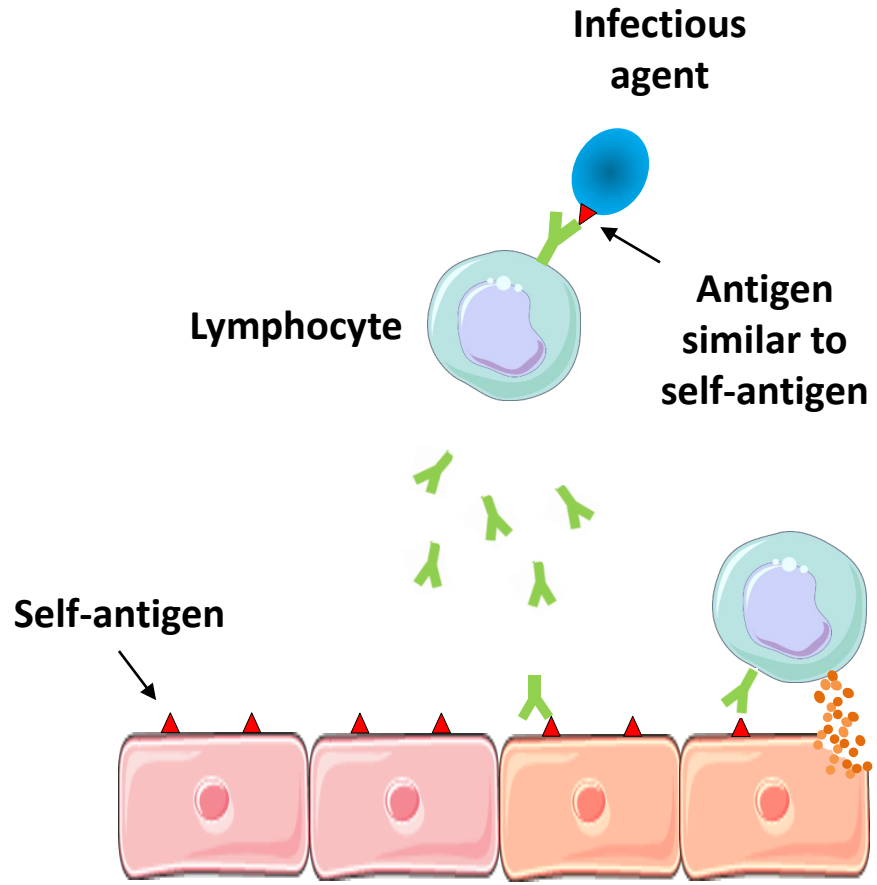
Autoimmune diseases

- Autoimmune diseases occur when immunity **fails to control autoreactive lymphocytes** that become responsible for **damages of tissues** containing the autoantigens.

- Breaking of peripheral tolerance may be caused by:
- **Molecular mimicry** (infectious agents…)
- **Inflammation**
- Abnormal **leukocytes**, **cytokines** or **complement**
- Sustained production of **type I interferon**

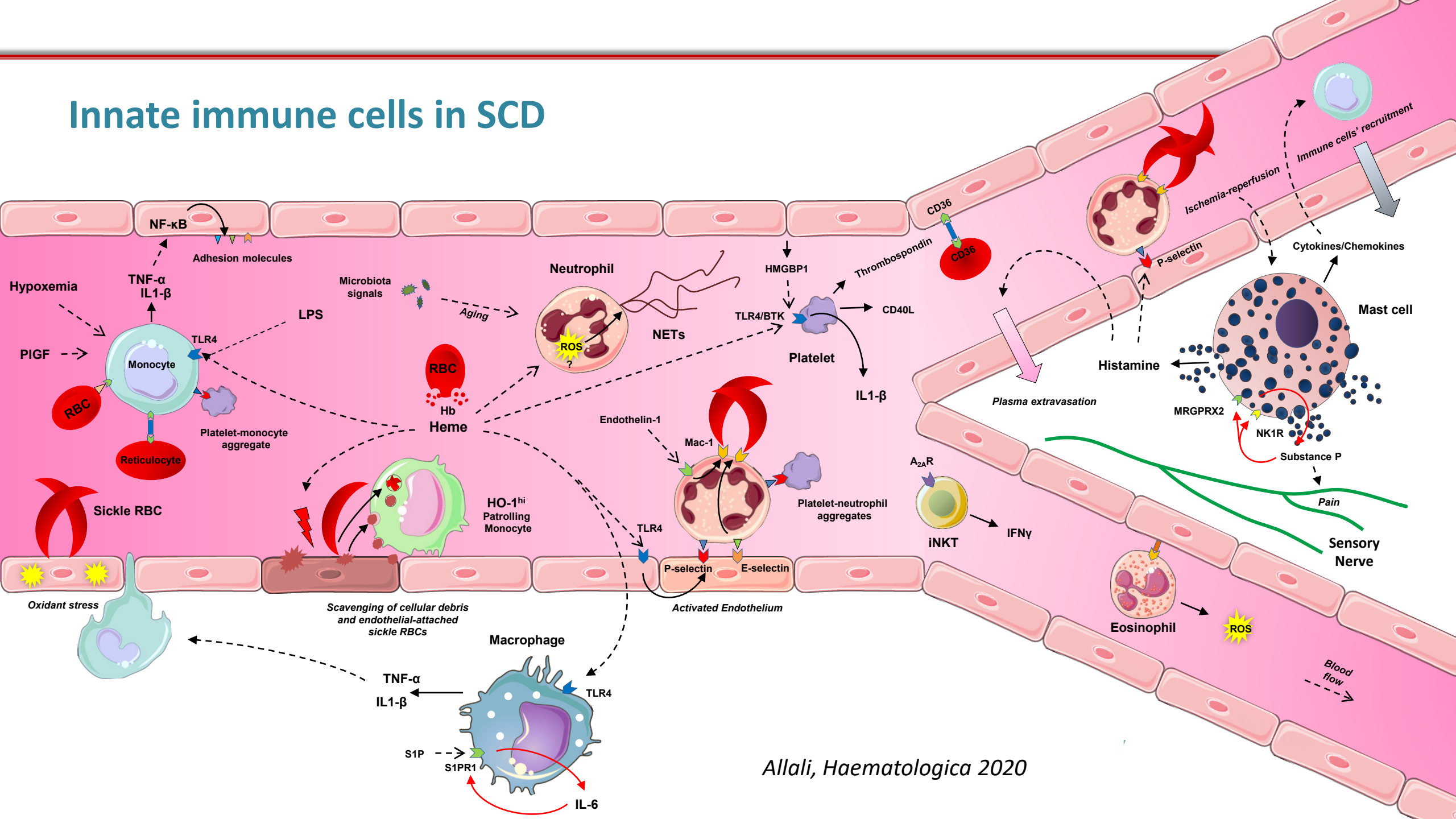
- Specific genotypes (HLA in particular) may predispose to autoimmune diseases.

- Main triggers of autoimmune diseases are **infections**.



Classical pathophysiology

Innate immune cells in SCD



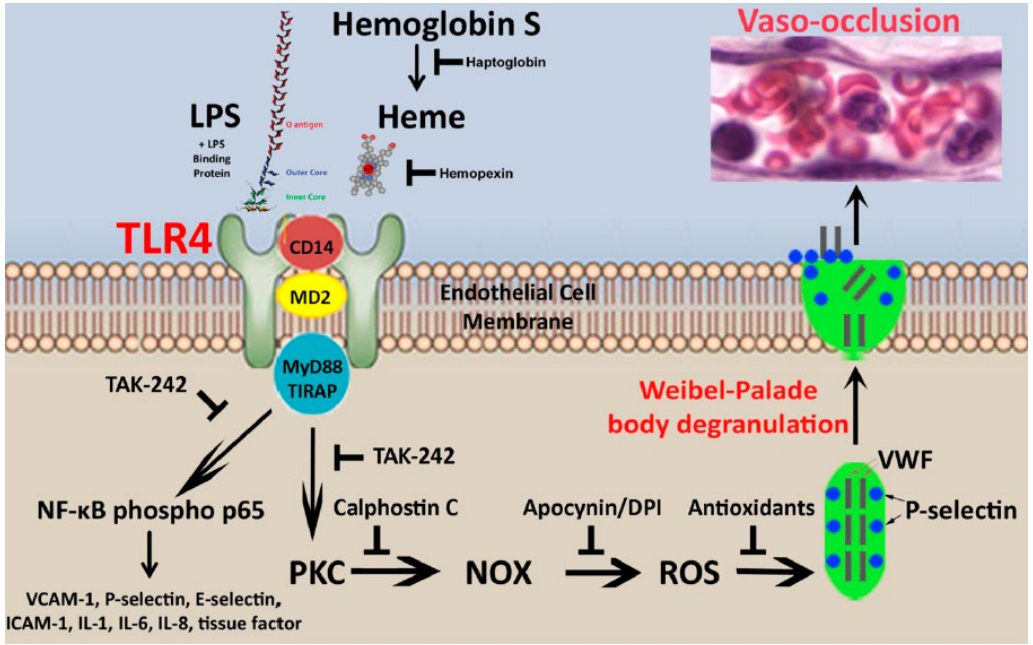
Allali, Haematologica 2020

How could SCD promote autoimmunity?

- **All innate immune cells** are **increased** (absolute count) **in SCD**.

Allali, Haematologica 2020

- **Chronic hemolysis activates innate immune cells in SCD**.



Belcher, Blood 2014

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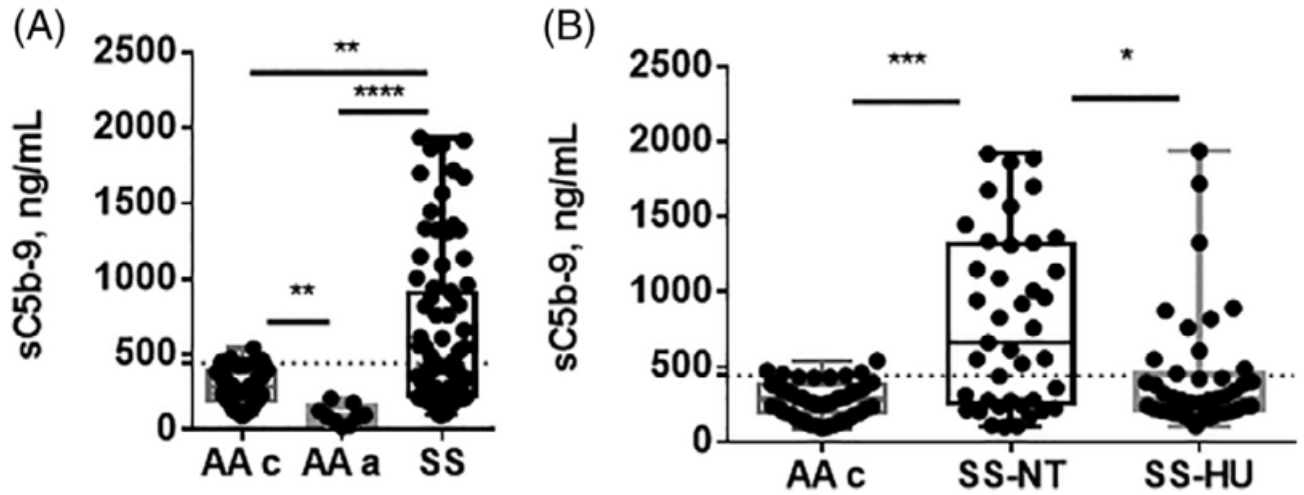
How could SCD promote autoimmunity?

- The **complement** pathway is **hyperactivated in SCD** patients, even in the **steady state**.

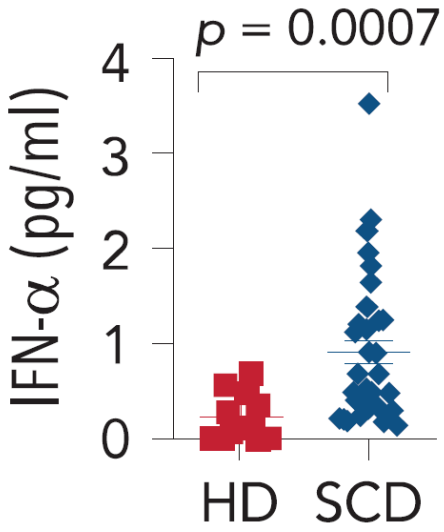
Roumenina, Am J Hematol 2020

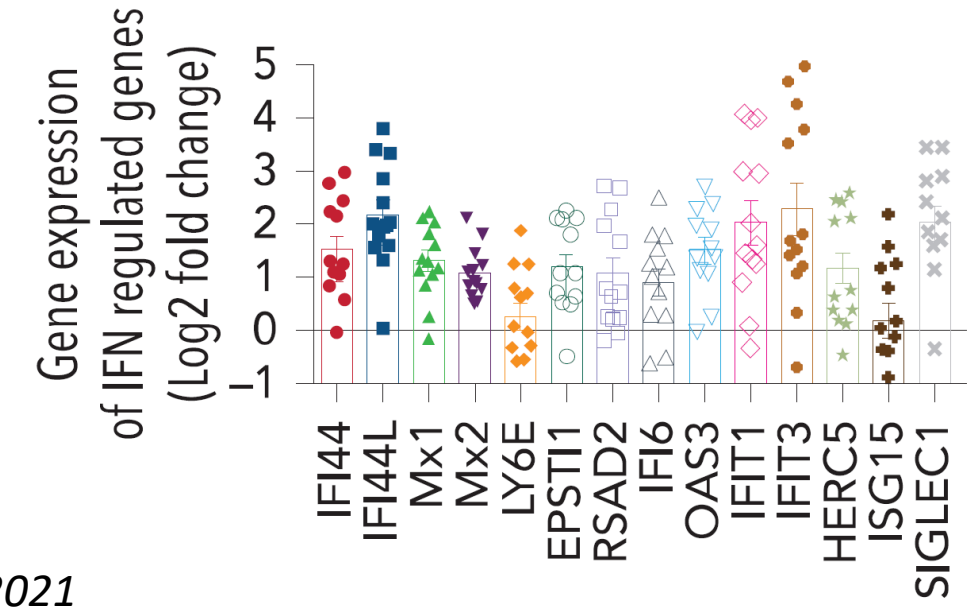


How could SCD promote autoimmunity?

- **Interferon alpha** plasma level is **increased in SCD patients** with **positive correlation with heme** level.

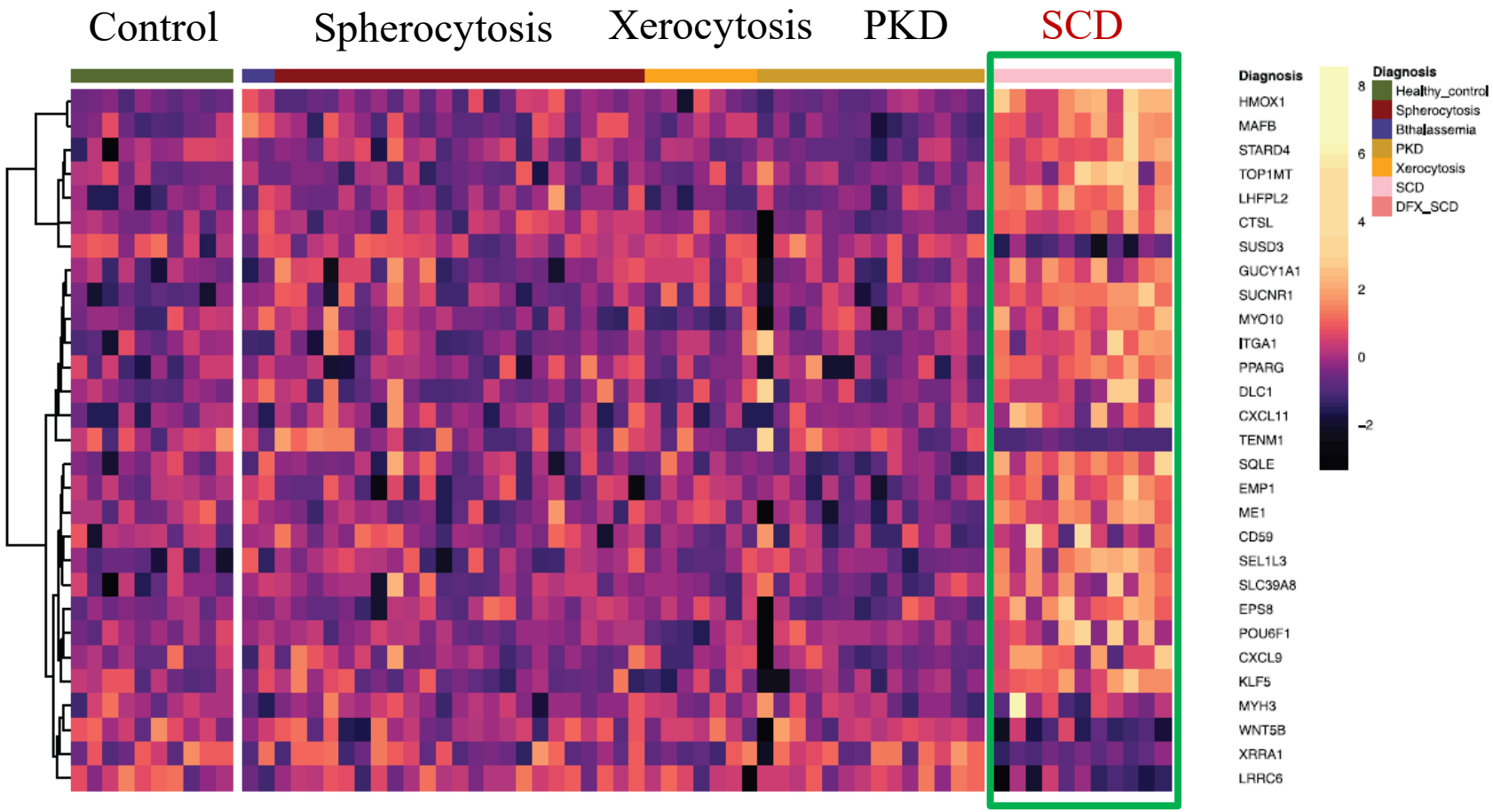
- **Type I IFN inducible genes** are **upregulated in monocytes** from **SCD patients**.





Liu, Blood 2021

- A **monocyte transcriptome** involving **interferon signaling** discriminates **SCD** from other **hemolytic anemias**.



Van Duren, HemaSphere 2021

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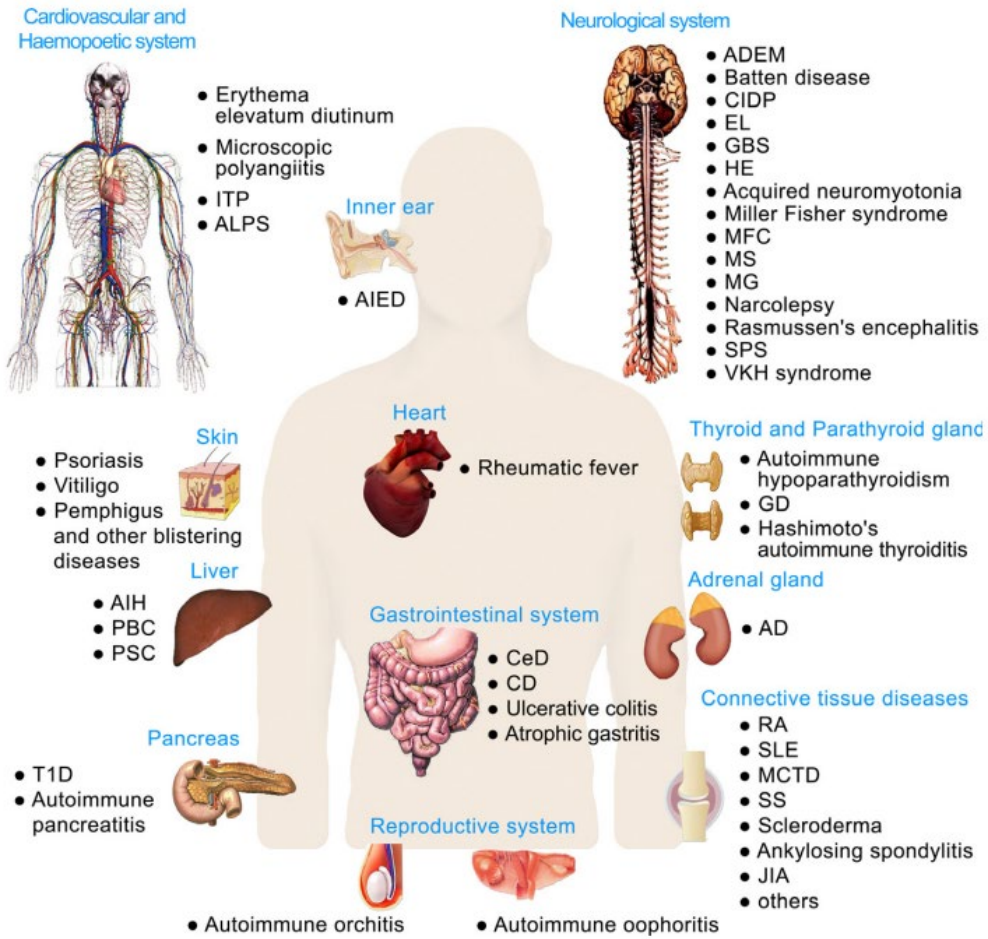
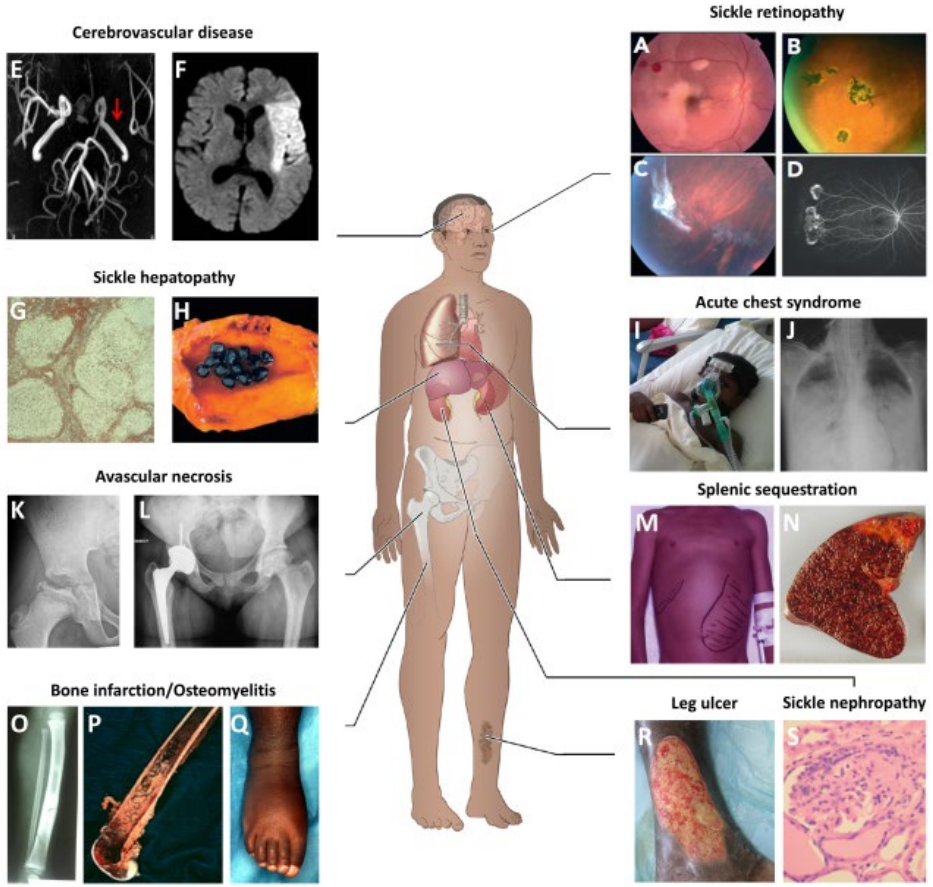
Autoimmune diseases



Wang, J Intern Med 2021

SCD



Adapted from Thein, Blood 2018

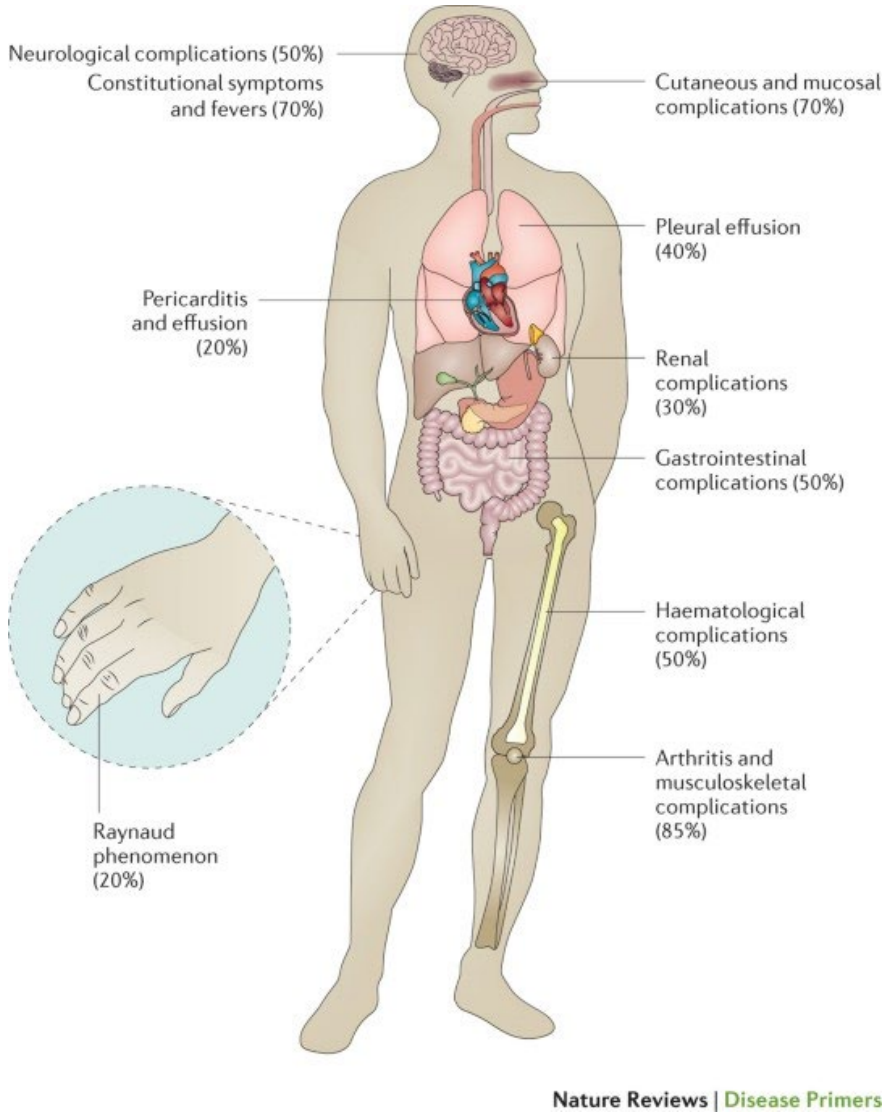
Autoimmune diseases

	Disease	Age at onset (years)	Gender (female/male)	Monozygotic twin concordance[a]	Incidence (per 100 000 person-years) Europe	North America	Asia and Middle East	References
Organ specific	Multiple sclerosis	20–40	2/1	9–31%	0.8–8.7	2.7–7.5	0.7–3.6	[12, 145]
	Type 1 diabetes	6–13	1/1	13–48%	>20	10–20	<1	[146, 147]
	Primary biliary cirrhosis	50–60	10/1	63%	1.4–3.1	2.7 (USA)	0.34–0.42	[148–151]
	Autoimmune hepatitis	<40 (T1) 2–14 (T2)	4/1 (T1) 10/1 (T2)	Only case reports	1.07–3.0	0.5 (USA)	0.08–0.15 (Japan)	[152–154]
	Graves' disease	50–60	5/1	17–60%	21–50	38	120	[155, 156]
	Crohn's disease	15–30, 60–80	1/1.2	4%	3.1–12.7	6.9–20.2	0.24–1.34	[157–159]
	Ulcerative colitis	15–30, 60–80	1/1	6.3–18.8%	4.1–16.5	8.3–19.2	0.36–6.02	[159, 160]
	Coeliac disease	Childhood	1/1	75–83%	1.5–8.7 (all ages)	0.9–9.1 (all ages)	Unclear	[161, 162]
	Addison's disease	15–45	0.8–2.4/1	Discordant pair	0.56–6.20	1 (USA)	Unclear	[163, 164]
Systemic disesases	Sjogren's syndrome	40–50	9/1	Only case reports	5.3 (north-west Greece)	3–5 (USA)	6.57	[165–167]
	Systemic lupus erythematosus	30–50	9/1	11–25%	1.0–5.0	1.2–8.7	0.9–3.1	[168–170]
	Rheumatoid arthritis	44–55	2/1	15–30%	9–36	31–45	8–42	[171–173]

Wang, J Intern Med 2021

Systemic lupus erythematosus (SLE)

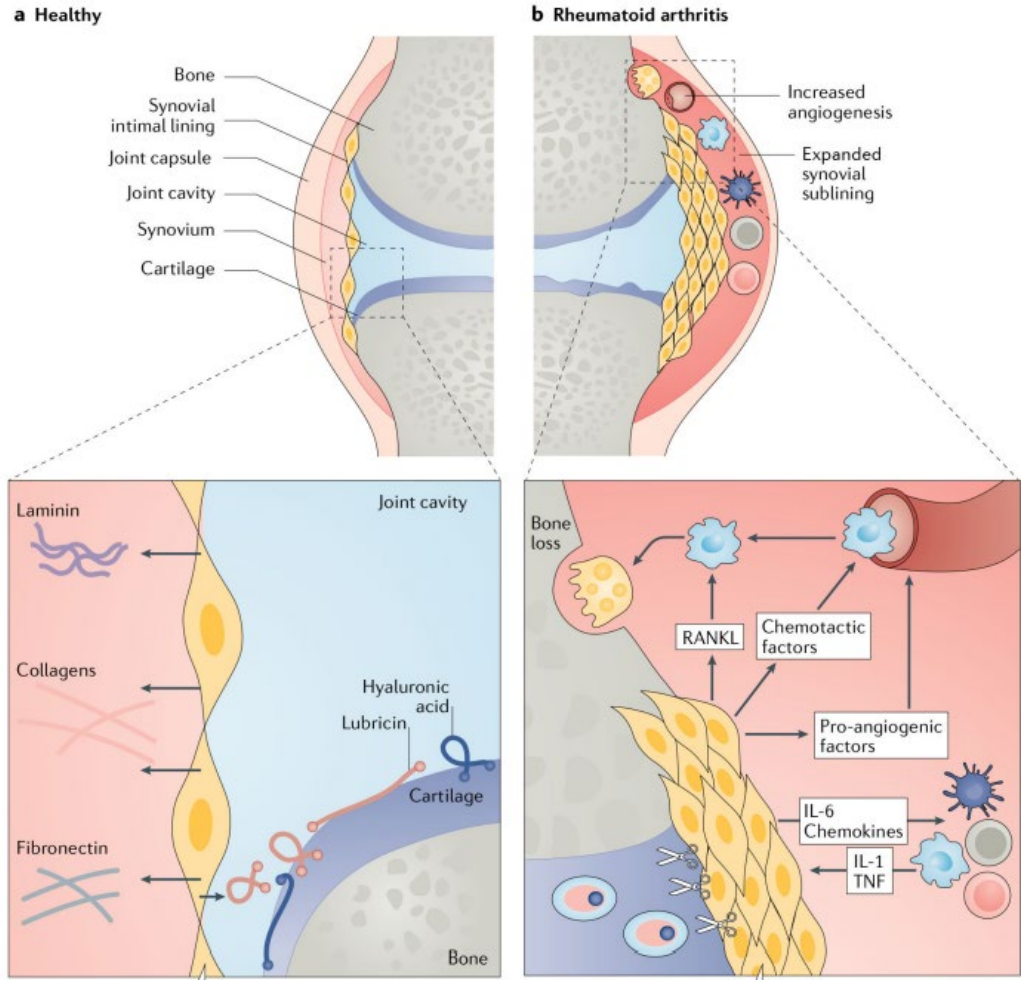
- SLE is a **frequent** autoimmune disease affecting **several organs**, including the joints, skin, brain, lungs, kidneys, blood vessels…
- SLE can affect people of **all age**, with a greater risk in **women** of childbearing age.
- The **symptoms are varied** and include: fatigue, fever, pain/swelling in the joints, skin rashes, photosensitivity, oral ulcers, pleural and heart effusions,…
- **Early diagnosis** and treatment initiation help reduce the damaging effects of SLE and improve quality of life.



Kaul, Nat Rev 2016

Rheumatoid arthritis (RA)

- RA is a **very frequent** autoimmune disease that primarily affects **the joints** but may also affect the skin, eyes, lungs, heart, nerves…
- RA affects people of **40-60 yrs**, with a greater risk in **women**.
- The most frequent **symptoms** include: **pain/swelling/stiffness/deformation of the joints**, rheumatoid nodules, (epi)scleritis, interstitial lung disease, fatigue,…
- **Anti-inflammatory treatments** (Methotrexate,…) improve symptoms and slow disease progression when started early.



Nygaard, Nat Rev Rheumatol 2020

Autoimmune diseases and SCD

- Main autoimmune diseases reported in SCD:
  - **Systemic lupus erythematosus (SLD)**
  - **Rheumatoid arthritis (RA)**

Piccin, Br J Haematol 2022

- **Overlapping symptoms** → diagnosis may be **difficult.**

  Pain (joints, musculature), fever, elevated inflammatory markers…

- **Specific symptoms of autoimmune diseases should be sought…**

  Malar rash, alopaecia, photosensitivity, oral ulcers, pericarditis, pleuritis…

Sibanda, BMJ Glob Health 2018

- … to avoid **diagnostic delays**

Li-Thiao-Te, Pediatr Rheumatol Online J 2018

Systemic lupus erythematosus (SLE) and SCD

- **1/1000** in the **general population** / unknown but possibly **increased prevalence in SCD (3-14/1000)**

Saxena, J Pediatr Hematol Oncol 2003

Li-Thiao-Te, Pediatr Rheumatol Online J 2018

- 2019 EULAR revised SLE diagnostic criteria **cannot be used for SCD patients**.

Fever, joint involvement, leuko/thrombocytopenia…: very frequent in SCD

Piccin, Br J Haematol 2022

- **Anti-ds-DNA** and **anti-Sm** antibodies have **greater specifity than ANA (↑ in 50% of SCD patients)**.

Toli-Ndour J Rheumatol 2011

Rheumatoid arthritis (RA) and SCD

- **Same incidence** (**1/100**) as in the general population **but occurs at a younger age**

Mc Farlane, Rheumatology 2017

- Suspected mechanism: **inflammation** and **complement activation** secondary to **synovial ischemia**

Piccin, Br J Haematol 2022

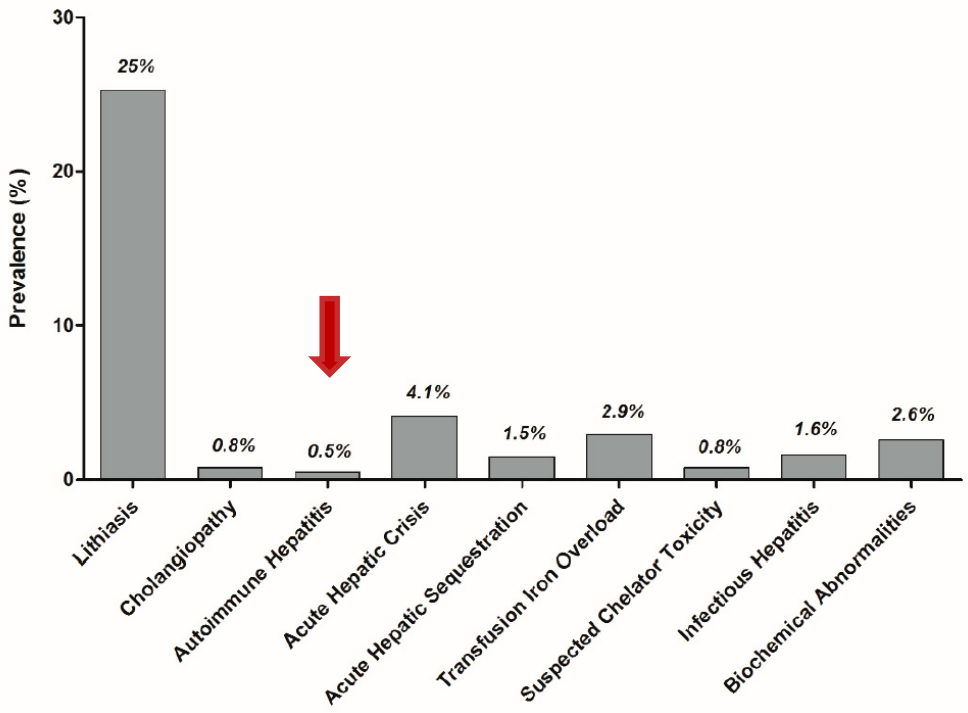
- **Difficult diagnosis** as persistant **joint pain** and biological **inflammation** are frequent in SCD

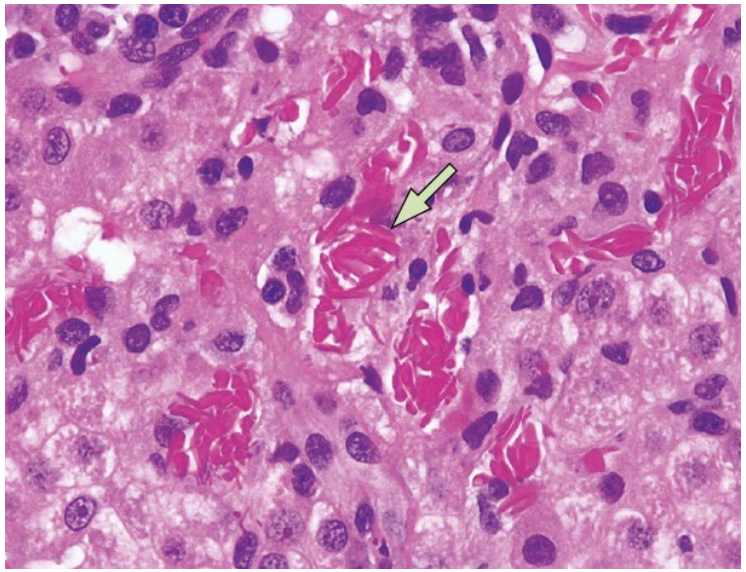
- **Positive serology** (**reumathoid factor** or **anticitrullinated protein antibodies**) and X-rays help **distinguish RA/SCD**.

Other autoimmune diseases and SCD

- Prevalence of **autoimmune liver disease** (**0,5%**) is **higher** than in the general population (**1/100 000**).

Allali, JCM 2019





Colli, Lancet 2018

Other autoimmune diseases and SCD

- **RBC autoantibodies** are **frequent** (≈ **8%**) in transfused patients: **risk factor for alloimmunization**.

Allali, Br J Haematol 2017

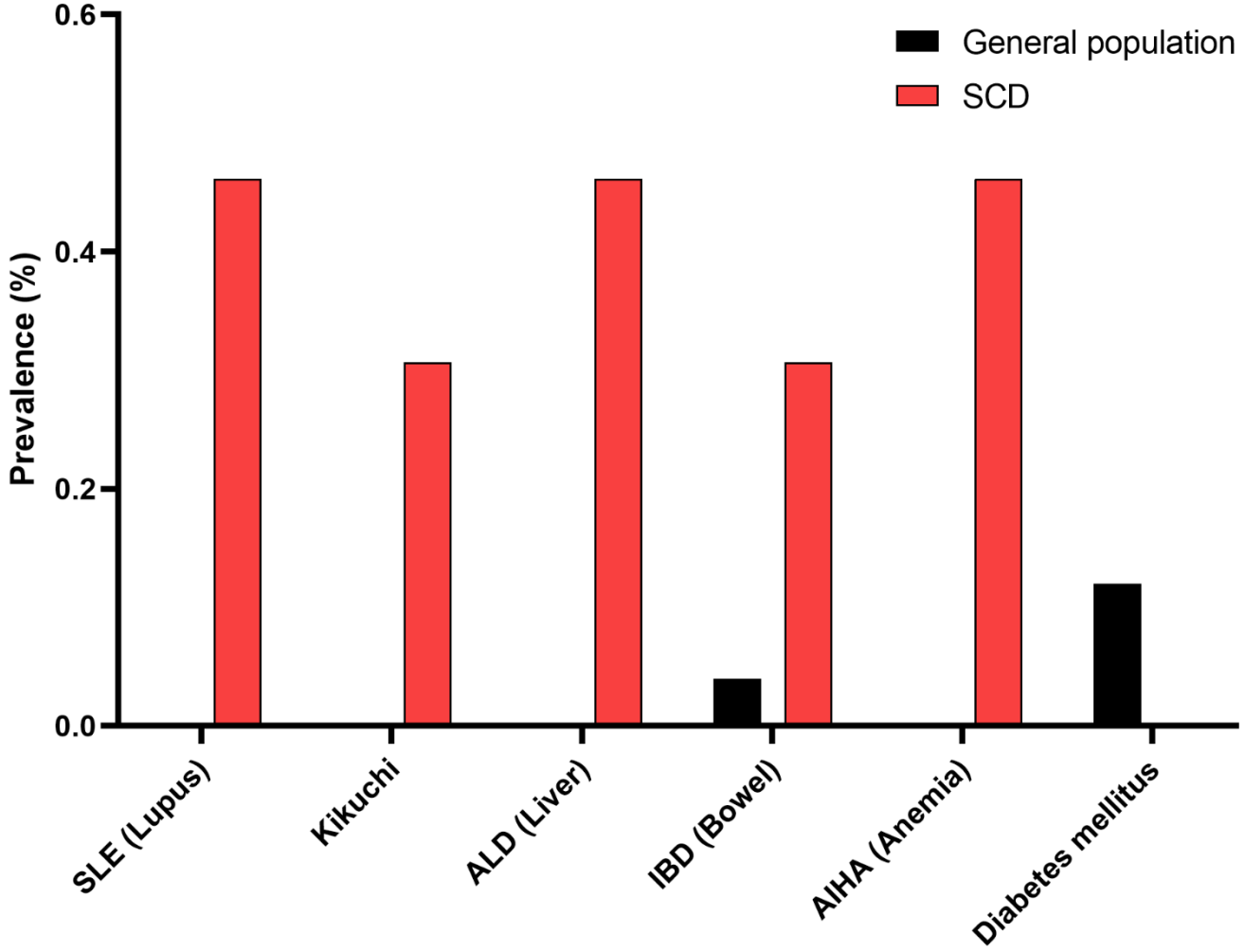
- Prevalence of type 1 an 2 **diabetes mellitus** is **lower** than in the general population.

Role of lower obesity rate in SCD patients (hypermetabolism, dysbiosis…)

Fung, Br J Haematol 2006

Zouh, Br J Haematol 2019

Autoimmune diseases in SCD children



Allali, unpublished

Learning objectives

1. How could SCD promote autoimmunity?

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3. **What are the therapeutic implications of autoimmunity in SCD?**

Main treatments of autoimmune diseases

- **Glucocorticoids** are the **most frequently used initial** anti-inflammatory drugs in autoimmune diseases.
- Many **adverse effects**: Cushing's syndrome, adrenal suppression, hyperglycemia, dyslipidemia, cardiovascular disease, osteoporosis, immunosuppression,…
- During **chronic** maintenance treatment, they **should be minimized** and, when possible, **withdrawn**.
- **Immunomodulatory agents** and **biological therapies** can help taper/discontinuate glucocorticoids.

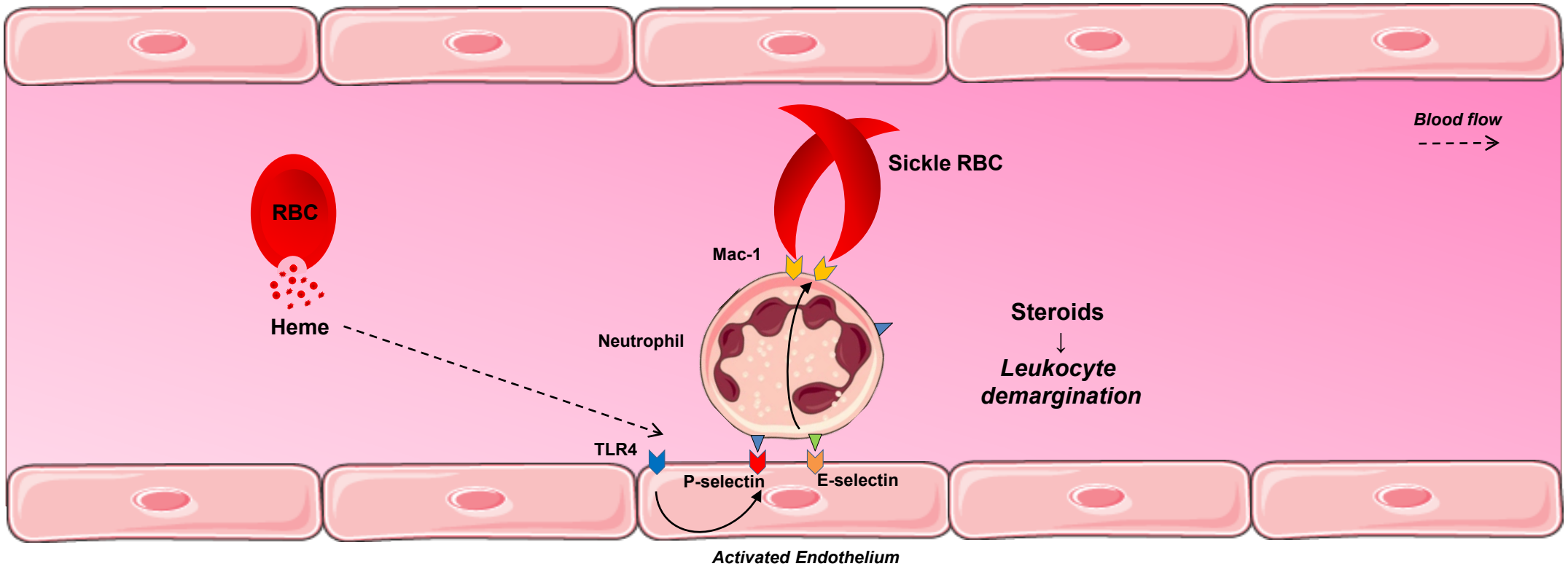
Fanouriakis, Ann Rheu Dis 2019

Glucocorticoids and SCD

- Increased risk of **VOC** and **ACS** with **glucocorticoids** in SCD, due to **leukocyte demargination**

Walter, Blood 2022

Allali, Haematologica 2020



Glucocorticoids and autoimmune diseases in SCD

- Increased incidence of **VOC** and **ACS** during **autoimmune diseases treated with glucocorticoids**.

Michel, Semin Arthritis Rheum 2008

Li-Thiao-Te, Pediatr Rheumatol Online J 2018

- **Transfusions/Exchange transfusions** are often **required with glucocorticoids**.

Li-Thiao-Te, Pediatr Rheumatol Online J 2018

Allali, JCM 2019

Other therapies for autoimmune diseases in SCD

- **Immunomodulators** and **biologics** (e.g. anti-TNF-α antibodies) are at **increased risk of infection**

  (azathioprine, methotrexate,…) *(infliximab, adalimumab,…)*

  ⟹ **Importance of vaccination** and immediate **consultation** in case **of signs of infection (fever,…)**

- **Methotrexate** and other disease-modifying antirheumatic drugs are at **increased risk of cytopenia**

- **Excellent tolerance** of these therapies **overall**

Li-Thiao-Te, Pediatr Rheumatol Online J 2018

Treatments of SCD and autoimmune diseases

- **Hydroxyurea reduces autoimmunity** by decreasing innate immune cell count and antibody production.

Piccin, Br J Haematol 2022

- **Hematopoietic stem cell transplantation can cure autoimmune diseases together with SCD.**

Li-Thiao-Te, Pediatr Rheumatol Online J 2018

- **Risk of recurrence** of autoimmune hepatitis after liver transplantation **if HCST is not done**.

Allali, JCM 2019

Take-home message

1. Increased risk of autoimmune diseases in SCD

2. Glucocorticoids should not be used without concomitant transfusions

3. Hydroxyurea reduces the risk and HSCT can cure autoimmune diseases

Discussion