Sickle cell and autoimmune disease: a double whammy

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In this issue of *Haematologica*, Tang and colleagues report in detail on the prevalence of autoimmune disease in 338 adults with sickle cell disorder (SCD) in the Netherlands.[1] They found a high proportion (10.7%) to have a concomitant autoimmune condition; this proportion is approximately double that in other reports. Mausoléo *et al.* recently reported a prevalence of autoimmune disorders of 5.6% in a 266-patient cohort of similar age.[2] Mausoléo *et al.* did not, however, include diabetes type 1, thyroid disorders, sudden deafness syndrome and alopecia areata in their analysis, which accounted for approximately half of the cases in the cohort described by Tang *et al.* When excluding these conditions, the prevalence of autoimmune disease in these two comparable cohorts is similar, confirming both authors' observation that autoimmune disorders are more prevalent among patients with SCD than in the general population.
What is remarkable about the Amsterdam cohort is the apparent absence of rheumatoid arthritis and autoimmune hepatitis, which were the most frequently noted conditions in other cohorts.[2]
Apart from the possibility of confirmation bias during clinical assessment in these retrospective cohorts, perhaps genetic and environmental factors could clarify the variability in autoimmune diagnoses.

Development of autoimmunity

People coming from the same geographical regions as patients with SCD are more likely to develop autoimmune conditions such as systemic lupus erythematosus in comparison with Caucasian people. However, the co-existence of SCD and autoimmune disease is very likely more than just due to geographical overlap. SCD has the ability to create a favorable micro-environment for autoimmunity to develop. Chronic inflammation and endothelial cell activation result in the release of cytokines such as tumor necrosis factor-α, interleukin (IL)-6 and IL-1, with subsequent activation of cells of the immune system. Increased susceptibility to infections in SCD probably has a similar effect, contributing to long-term exposure of the immune system to a variety of antigens (Figure 1).
In addition, SCD is characterized by high levels of circulating microparticles derived from red cells, platelets, monocytes and endothelial cells both in steady state and in acute crises. Microparticles are cellular components released from cells damaged through inflammation or apoptosis. One of their hallmark features is reduced cell membrane integrity, characterized by flipflopping of phosphatidylserines to the outer layer of the cell membrane, which attracts predominantly phagocytic cells. Red cell-derived microparticles have been shown to be prothrombotic with the ability to activate complement.[3] Microparticles of other cells also provide a source of pro-inflammatory substances, including auto-antigenic material due to the presence of cellular components such as DNA, RNA and histones. Microparticles may circulate before being cleared and may have affinity for binding specific tissues. A multitude of effects can take place, including recruitment of cells of the immune system with exposure of these cells to auto-antigenic material within the microparticles, and binding of antibodies and formation of immune complexes.[4]
The tendency towards developing autoimmunity in SCD is confirmed by the high prevalence of a variety of autoantibodies.[2,5] Prospective long-term follow-up of sickle cell patients without autoimmune symptoms but with a high autoantibody titer (in particular antinuclear antibody) suggests a high risk of developing autoimmune disease.[6]

Development of autoimmune disease

For autoimmunity to become pathological and lead to autoimmune disease, more than just increased exposure to (auto)antigens is required. To achieve T-cell hyperactivity and/or B-cell overstimulation, downregulation of immune tolerance is needed. There is an abundance of evidence on regulation and dysregulation of innate and adaptive im-

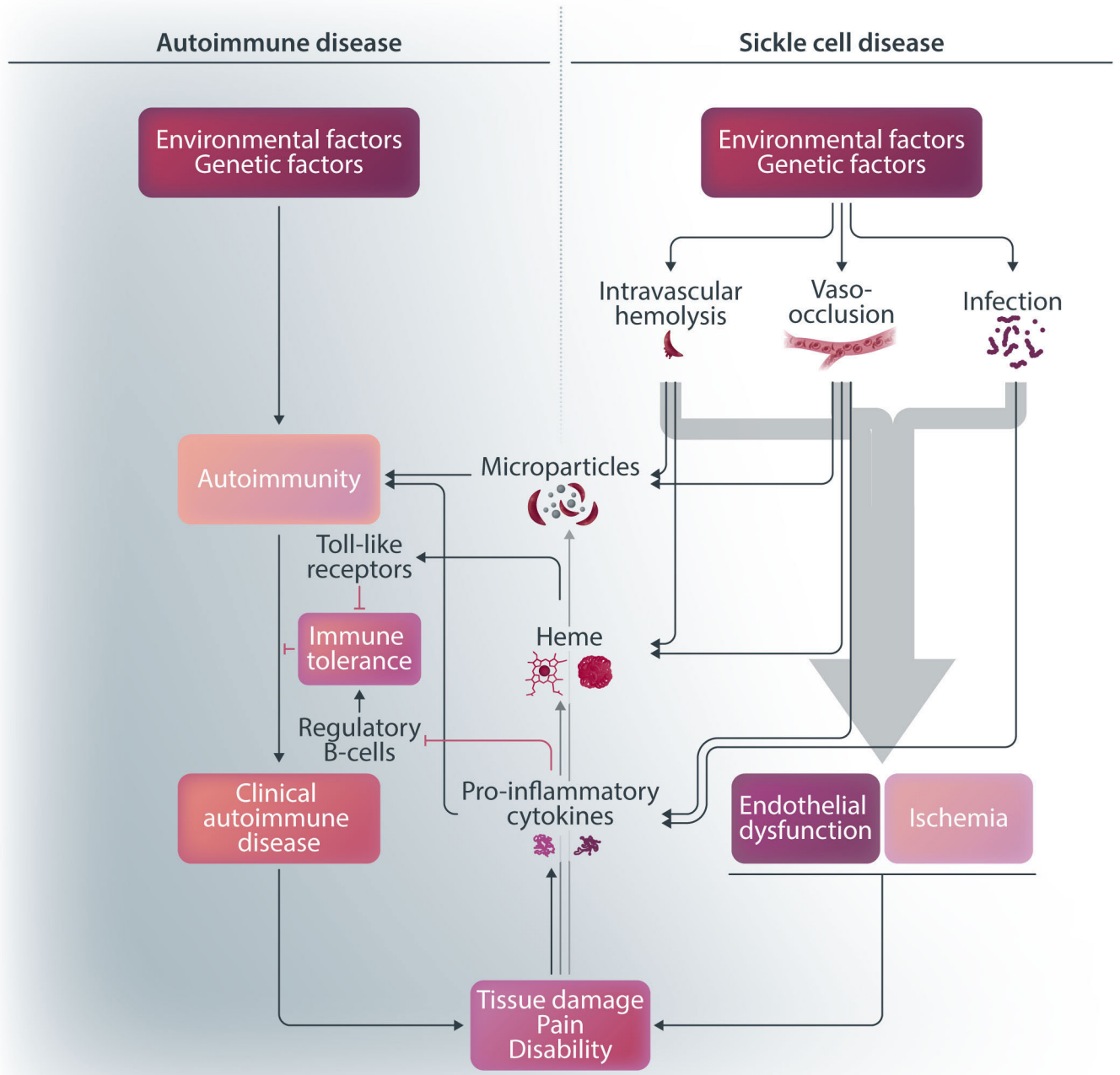

Figure 1. A simplified perspective of mechanisms contributing to autoimmune disease in sickle cell disorder. Key processes involved in sickle cell disorder (hemolysis, vaso-occlusion and infection) are responsible for endothelial dysfunction and ischemia, resulting in tissue damage and pain. Pro-inflammatory cytokines, free heme and microparticles generated during sickling can promote the development of autoimmunity as well as downregulate immune tolerance, ultimately advancing to clinical autoimmune disease. The gray zone of overlapping end-organ damage between sickle cell and autoimmune diseases results in further generation of pro-inflammatory cytokines and microparticles, promoting the environment for autoimmunity and autoimmune disease to develop.

munity, which goes well beyond the scope of this Editorial. However, it is worth noting that SCD appears to have a few downstream effects that may push autoimmunity towards the development of autoimmune disease. For example, free heme (resulting from intravascular hemolysis) was found to stimulate the innate immune system and downregulate tolerance via activation of, for example, toll-like receptor 4 (TLR4).[7] Activated toll-like receptors in turn play a pivotal role in the pathogenesis of autoimmune disease.[8]

Again, levels of elevated proinflammatory cytokines and growth factors are higher in SCD patients than in the healthy population due to chronic inflammation and endothelial cell activation. Of interest for the development of autoimmune disease is B-cell activating factor (BAFF), which promotes survival of autoantigen binding B cells. During inflammation, BAFF appears to downregulate anti-inflammatory (IL-10-positive) regulatory B cells. Indeed, sickle cell patients with clear autoimmune phenomena seem to have a reduced functionality of regulatory B cells, resulting in another mechanism of downregulation of tolerance.[9]

Relevance for clinical practice

The findings of Tang *et al.* have implications for daily practice. The high prevalence of autoimmune conditions raises the question of whether screening for these conditions should become part of the standard annual review in patients with SCD. Autoimmune disease requires a different therapeutic approach from SCD, and it is important that

clinicians looking after these patients try to unpick the intertwined symptoms of the two conditions. In particular in the cases of systemic lupus erythematosus and rheumatoid arthritis, an autoimmune genesis may very well be overlooked and symptoms dismissed as part of vaso-occlusive disease. Similarly, the often-elevated liver function tests in SCD may mask an underlying autoimmune hepatitis.
At the same time, one could hypothesize that uncontrolled SCD may drive towards further autoimmunity and autoimmune disease, although this theory is at present not supported by data showing a lower prevalence of autoimmune disease in patients on disease-modifying treatment either in the study by Tang *et al.* or in other papers. Nevertheless, it is a fact that certain treatments for autoimmune disorders, in particular corticosteroids, have the ability to worsen vaso-occlusion which in turn may require a different management strategy for the affected patient's SCD. Piccin *et al.* have published a useful algorithm for trying to discriminate between sickle cell and autoimmune conditions, and summarized possible implications for treatment.[10]
Future directions may include research into disease-modifiers that interact at the crossroads between vaso-occlusion, hemolysis and progression of autoimmune disease; from this perspective hemopexin would be an interesting target. From a clinical perspective, the data presented call for building up more joint expertise between hematologists and rheumatologists.

Disclosures

AMdK has received travel and educational fees from Global Blood Therapeutics and consultancy fees from Pfizer, in both cases for services unrelated to this work.

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