The role of neutrophils in antibody-driven autoimmune cytopenias

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Abstract

Autoimmune cytopenias are a consequence of autoantibodies that target blood cell lineages and mark them for their accelerated destruction, mostly through phagocytosis by monocytes and macrophages and complement activation. Neutrophils, although equipped with Fc and complement receptors and effector mechanisms that are critical in other autoimmune conditions, remained long time overlooked. Recent reports however propose a new and possibly critical role for neutrophils. In this review we gathered available evidences on the contribution of neutrophils to the development, onset and consequences of autoantibody-dependent cytopenias.

Keywords
neutrophils, autoimmune cytopenias, ITP, AIHA, AIN

Introduction

Autoimmune cytopenias are characterized by the immune-mediated destruction of hematopoietic cell lineages. At the origin of this cellular removal are autoantibodies that target platelets in autoimmune thrombocytopenia (ITP), erythrocytes in autoimmune hemolytic anemia (AIHA), and neutrophils in autoimmune neutropenia (AIN). The autoantibodies are produced by self-reactive B lymphocytes that receive support from T helper lymphocytes and escape tolerance. One can distinguish primary or idiopathic disorders and secondary manifestations that are associated with an underlying malignancy, systemic autoimmune disease, an infection or a specific drug. First line treatments of autoimmune cytopenias involve mild immunosuppressants (such as corticosteroids), except in AIN where the infectious risk is of major concern and patients receive granulocyte colony-stimulating factor and antibiotics. The mechanisms by which blood cells are removed are thought to involve mostly phagocytosis by monocytes and macrophages and complement activation[1,2]. However, recent reports propose a new and possibly critical role for neutrophils.

Neutrophils outnumber other immune cells in human blood and are notorious for their involvement in host defense to which they contribute through a broad arsenal of antimicrobial activities[3]. However, these same effector mechanisms also enable neutrophils to contribute to the initiation and propagation of immune dysregulation. Several lines of evidence imply that neutrophils could contribute to antibody-driven autoimmune disorder, including cytopenias. Indeed, neutrophils express receptors for antibody Fc fragments (FcRs) and complement (CRs)[4] that enable rapid responses to the presence of antibody-opsonized cells or particles that can trigger enhanced phagocytosis and an inflammatory response through production of reactive oxygen species (ROS), and release of potent proteases, cytokines, chemokines, and neutrophil extracellular traps (NETs)[3]. Moreover, specialized splenic neutrophils can produce cytokines such as interleukin-21 (IL-21), B cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL) that directly support B cell expansion and maturation into antibody-secreting plasma cells[5,6], which in turn sustain autoantibody production. Neutrophils therefore are not only potent effector cells of antibody-driven pathologies, but may also facilitate disease onset and tolerance rupture (Figure 1).

In this review we focus on our current understanding on the role of neutrophils in primary autoimmune cytopenias.

Immune thrombocytopenia

ITP is a rare autoimmune coagulation disorder characterized by isolated low platelet counts (< 100/mL) with an incidence of 2,9 per 100.000/year[7]. ITP results in variable clinical manifestations ranging from mild bleeding episodes to severe internal bleeding that can be life-threatening. Low platelet counts in ITP are mostly the consequence of accelerated platelet removal caused by autoantibodies that target glycoproteins on the platelet surface, mostly GPIIb/IIIa and GPIb/IX. These antibodies make platelets vulnerable to destruction through several mechanisms, including antibody-dependent and complement-dependent phagocytosis, cellular cytotoxicity, and desialylation of the platelet surface[8] . Platelet destruction occurs mostly in the spleen, where splenic macrophages appear to play a dual role, mediating antibody-driven platelet destruction and maintaining anti-platelet immunity through presentation of platelet-derived peptides.

Spontaneous ITP has been described in several animal species[9-12], but models to study its physiopathology have been predominantly developed in mice. These include passive models triggered by the transfer of monoclonal antibodies or autoimmune serum targeting platelet glycoproteins[13], that

allow to investigate acute effector mechanisms; and active models that depend on the immunization of knockout mice and subsequent transfer of splenocytes into severe combined immunodeficiency (SCID) mice[14,15] thus enabling investigation of the autoantibody induction and the contribution of other lymphocyte compartments. No existing model so far can adequately address the processes underlying the break of tolerance.

The role of neutrophils in ITP is very incompletely understood, in spite of documented evidence for their implication. It has been suggested that the neutrophil-to-lymphocyte ratio maybe inversely correlated with platelet numbers in patients[16] and elevated levels of NETs can be detected in the plasma ITP patients, suggestive of a chronic neutrophil activation[17]. However, it needs to be clarified, whether these NETs play an active role in the disease pathology or if they are a consequence of an ongoing immune reaction. Interestingly, it has been suggested that neutrophil activation and NETs may contribute to the paradoxically increased risk of thrombosis in patients with ITP[17] and other forms of thrombocytopenia[18-21], while this is a tempting hypothesis, it remains debated[17,22].

Neutrophils accumulate in the spleen of ITP patients[23,24], where they represent the vast majority of phagocytic cells. Given that the spleen is the major site of platelet destruction, it is surprising that the contribution of splenic neutrophils in platelet destruction has never been formally addressed. Blood neutrophils, are capable of platelet phagocytosis in thrombocytopenia patients[25] and this is also supported in animal models[11,26]. An early *in vitro* report even suggested neutrophil mediated ADCC as a possible effector mechanims[27]. Arguing against a dominant role for neutrophil in platelet removal, we found in human FcγRI transgenic mice that neutrophil depletion prior to ITP induction only yielded an insignificant increase in platelet counts[28].

Moreover, B-cell helper neutrophils were described that directly support B cell class switching and maturation into antibody-secreting plasma cells[5,6] and could thus contribute to maintain an abnormal B cell response in the spleen[5]. In mice it has been demonstrated that BAFF-producing splenic neutrophils localize in close proximity to long-lived plasma cells after B cell depletion, suggesting a particular role of neutrophils to promote the emergence of such long-lived plasma cells[29]. Whether this is also true in human ITP remains to be investigated, but support for this idea originates from the observation that augmented levels of the neutrophil attracting chemokine CCL-2 and of IL-6 were detectable in spleen cultures of ITP patients. Additionally, BAFF could be detected after B cell depletion[30].

Finally, and beyond this direct implication in disease pathology, neutrophils most certainly contribute to ITP-associated bleeding episodes. A body of elegant work shows that neutrophil diapedesis causes hemorrhage in the absence of vessel wall sealing platelets[31-33].

Autoimmune hemolytic anemia

AIHA is a heterogenous group of diseases characterized by the destruction of red blood cells (RBC) by the immune system [1,34,35]. It is considered a rare disease with an estimated incidence of 2 per 100.000/year[35]. The current classification is based on the thermal range at which autoantibodies agglutinate RBC, with “cold” AIHA being caused by immunoglobulin M (IgM) antibodies, and “warm” AIHA by IgGs. Warm AIHA accounts for about 65% of cases, and cold AIHA for about 25%. A minority of patients (5-10%) present a mixed form of the disease with features of both cold and warm AIHA.

In wAIHA, which touches mostly adults above 40, IgG autoantibodies are directed against the Rhesus system, and bind to RBC in the circulation. In humans, the main mechanism of RBC destruction is thought to be phagocytosis by splenic macrophages, even if recent data challenge this paradigm (see below).

Primary cAIHA is called Cold Agglutinin Disease (CAD) and is caused by an underlying lymphoproliferation in the bone marrow. It happens mostly in adults except for a rare entity called paroxysmal cold hemoglobinuria (PCH) which is linked to viral infections in young children[36]. In both cases, the IgM autoantibodies are directed against a single RBC antigen (I/i for CAD, P for PCH) and strongly activate complement. In CAD, hemolysis can be both intravascular by activation of the membrane attack complex of the complement system, or extravascular with phagocytosis of RBCs by Kupffer cells in the liver[37].

Severe complications of AIHA include infections (mostly due to splenectomy), thrombosis, and acute kidney failure.

AIHA mechanisms were mostly investigated in mouse models with a focus on tolerance rupture mechanisms (reviewed in[38]) . However, it has been shown that while splenic macrophages were the main effectors in senescent RBC clearance, neutrophils were involved in the clearance of antibody-opsonized RBC [39]. The degree of neutrophil erythrophagocytosis was linked to the degree of opsonization and regulated by CD47 expression by RBCs. This aligns with previous reports of neutrophils being able to phagocyte RBC [40,41],and a study that found signs of activated neutrophils to be more frequent in AIHA than in congenital hemolytic anemia[42].

Moreover, in the blood of dogs with spontaneous AIHA genes linked to neutrophil activation were overexpressed[43], and circulating NETs augmented[44]. Interestingly, data from New Zealand Black mice, which also spontaneously develop AIHA at 25 weeks, showed a link between exposure to reactive oxygen species and AIHA onset[45]. Altogether, this suggest that neutrophil activation could be linked to both RBC alteration leading to tolerance rupture, and autoantibody-coated RBC phagocytosis.

Finally, an interesting paper suggested that activation of neutrophils by heme released by the dying RBC could lead to the release of NETs. These NETs could in turn activate the coagulation pathway and promote thrombosis[46,47], one of the most frequent complications of the disease.

Autoimmune neutropenia

AIN is characterized by the presence of autoantibodies against membrane epitopes of mature neutrophils or their precursors in the bone marrow, mostly against polymorphic variants of FcγRIIIB (CD16B), causing the peripheral destruction of mature neutrophils and/or the inhibition of myelopoiesis in the bone marrow [49-51]. The decrease in the number of circulating neutrophils (<1,5 x 10^9/L), can result in a higher susceptibility to certain pathogens and unusual severe and/or frequent infections[48]. Mechanisms that drive the development of neutropenia are antibody- and complement-mediated opsonization and agglutination, which accelerate the phagocytic clearance of neutrophils mainly in the spleen. The more immature the stage targeted by the autoantibodies, the more severe is the resulting AIN[51]. This also means that some patients may be asymptomatic if autoantibodies only target fully mature neutrophils and an adequate number of young neutrophils can exit the bone marrow during infections. The risk for infections also depends on the duration of neutropenia and does not correlate with autoantibodies titers, which could point to an important contribution of the complement system to AIN[52].

Primary AIN arises mostly in early infancy and is extremely rare among adults. It presents with a mild to moderate phenotype and resolves almost always spontaneously over time, within 24 to 36 months after onset[53,54].

The role of neutrophils in the physiopathology of primary AIN has not been thoroughly investigated and the origin of autoantibodies remains unknown. Binding of autoantibodies to neutrophils

can lead to Fc receptor and complement activation and trigger aberrant neutrophil functions, including adherence of neutrophils to other leukocytes, decreased phagocytosis capacity, and decreased chemotaxis[52,55,56]. Cell surface-bound autoantibodies indeed resemble immune complexes that play a central role in the pathogenesis of autoimmune inflammatory diseases as they can induce neutrophil activation through Fc receptors, triggering ROS production, release of inflammatory mediators and NETs[57-59]. In the case of AIN the presence of NETs is of particular importance as these are decorated with cytoplasmic and granular proteins[60], which could represent an abundant source of antigenic material fueling the generation of new autoantibodies and further contribute to autoimmunity, as recently described in lupus patients[61]. However, this possibility remains to be investigated in primary AIN.

Interestingly, the lack of neutrophils allowed to discover new functions of neutrophils in immunity. Jaeger et al. found in a mouse model specifically lacking mature neutrophils that NK cells failed to undergo terminal maturation and could confirm this finding in AIN patients that showed affected NK cell maturation and responsiveness[62].

Chronic depletion of neutrophils in murine models is technically challenging (reviewed in[63]), but can be used to study AIN. In mice, injection of anti-Ly6G or anti-Gr1 antibodies may be used to simulate the effector phase of AIN. In mice humanized for CD16B[64-66], anti-CD16(B) antibodies could be used to model the disease with more relevant epitopes for the human disease, but to our knowledge this has not been done yet.

Conclusion

Collectively, these examples illustrate that while understudied the contribution of neutrophils to the development, onset and consequences of autoantibody-dependent cytopenias is likely to be important. The future will have to close this gap in order to obtain a more complete understanding of disease mechanisms, paving the way to new neutrophil-targeted treatment strategies.

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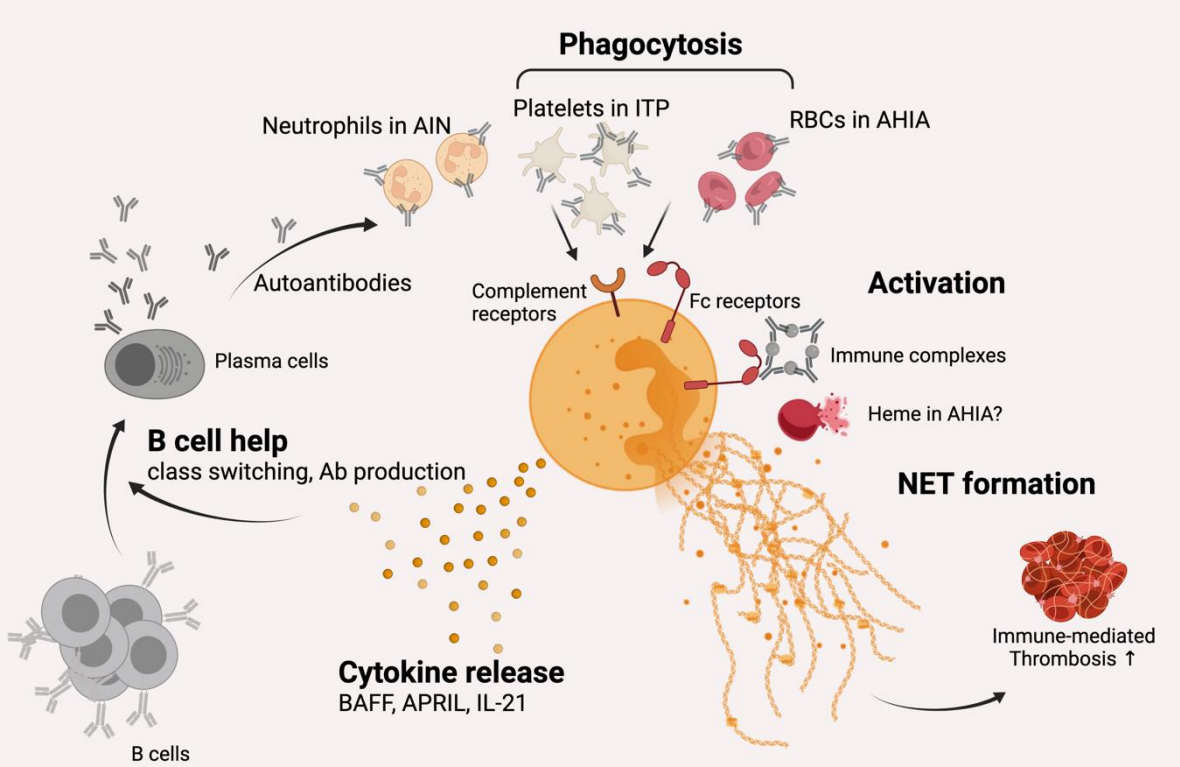

Figure 1: Model of neutrophil contributions to antibody-driven cytopenias.

Disclosure of Conflicts of Interest

The authors declare no conflict of interest.