REVIEW

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Novel neutrophil biology insights underlying atypical chemokine receptor-1/Duffy antigen receptor of chemokines-associated neutropenia

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Purpose of review
Atypical chemokine receptor-1 (ACKR1)/Duffy antigen receptor of chemokines (DARC)-associated neutropenia (ADAN; OMIM 611862), previously named benign ethnic neutropenia, and present in two-thirds of individuals identifying as Black in the USA, is associated with mild to moderate decreases in peripheral neutrophil counts that nevertheless do not lead to increased infections. Consequently, recent initiatives have sought to establish normal neutrophil count reference ranges for ADAN, considering it a normal variant rather than a clinical disorder requiring medical intervention.

Recent findings
A limited number of studies elucidating the mechanism of neutropenia in ADAN has suggested that neutrophils may redistribute from peripheral blood to the tissues including the spleen: this might explain why ADAN is not associated with increased risks of infection since the total number of neutrophils in the body remains normal. In this review, we critically examine the research underlying the molecular basis of ADAN.

Summary
Insights into the biology of neutrophils and their trafficking may inform the clinical interpretation of neutropenia in ADAN. The bulk of research suggests that ADAN does not lead to a diminished host defense as do other forms of neutropenia. However, ADAN may lead to increased proinflammatory signaling, with possible implications for senescence of the immune system and predisposition to autoimmunity and cancer.

Keywords
atypical chemokine receptor-1, atypical chemokine receptor-1 Duffy antigen receptor of chemokines-associated neutropenia, Duffy antigen receptor of chemokines, Duffy-null, neutropenia

INTRODUCTION

Duffy-null associated neutrophil count

Neutropenia has historically been defined as an absolute neutrophil count (ANC) of <1500 cells/μl in adults and associated with an increased risk of infection that correlates with its severity. The prevalence of neutropenia varies by the population studied, being rare in Europe and North America but more common in Africa and the Arabian Peninsula, suggesting a genetic influence. Over time, the neutropenia seen in individuals of African or Middle Eastern descent was recognized as not increasing the risk of infection or hematologic malignancy and was thus termed benign ethnic neutropenia (BEN). Subsequently, the molecular basis for BEN was linked to a variation in the atypical chemokine receptor-1 [ACKR1 or Duffy antigen receptor of chemokines (DARC)] gene, and BEN was renamed ACKR1/DARC-associated neutropenia (ADAN). A limited number of studies elucidating the mechanism of neutropenia in ADAN has suggested that neutrophils may redistribute from peripheral blood to the tissues including the spleen: this would explain why ADAN

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KEY POINTS

- Atypical chemokine receptor-1 (ACKR1)/Duffy antigen receptor of chemokines (DARC)-associated neutropenia (ADAN) was previously named benign ethnic neutropenia and is present in two-thirds of individuals identifying as Black in the USA.
- ADAN is caused by a mutation in the GATA1 erythroid transcription factor binding site in the promoter region of the *DARC/FY/ACKR1* gene, silencing expression only in red blood cells.
- The mechanism of neutropenia in ADAN is complex and involves redistribution of atypical neutrophils from peripheral blood to the tissues, as well as complex alterations in the numbers and transcriptomes of both neutrophils and hematopoietic stem and progenitor cells.
- The bulk of research suggests that ADAN does not lead to a diminished host defense as do other forms of neutropenia.
- However, ADAN may lead to increased proinflammatory signaling, with possible implications for senescence of the immune system and predisposition to autoimmunity and cancer.

is not associated with increased risks of infection since the total number of neutrophils in the body remains normal. In this review, we critically examine the research underlying the molecular basis of ADAN.

MOLECULAR BASIS OF ATYPICAL CHEMOKINE RECEPTOR-1/DUFFY ANTIGEN RECEPTOR OF CHEMOKINES-ASSOCIATED NEUTROPENIA

The Duffy blood group system, also known as the FY antigen system, is comprised of DARC glycoprotein antigens on red blood cells (RBCs) [1]. The DARC protein is produced by the *FY* gene located on chromosome 1. There are two primary Duffy antigens, Fya and Fyb, determined by the alleles FYA and FYB, respectively. These antigens differ by a single amino acid due to a point mutation in the *FY* gene. The Duffy blood group is clinically significant in transfusion medicine, as mismatched blood transfusions can lead to hemolytic reactions [2].

The Duffy antigen DARC/FY, which later was redesignated ACKR1, is a nonsignaling chemokine receptor that is expressed on RBCs, endothelial cells, and Purkinje cells of the cerebellum. It has been found to act as a multispecific receptor, binding promiscuously to inflammatory chemokines of both the C–C and C–X–C families, including: CCL2/ MCP-1, CCL5/RANTES, CCL7, CCL11, CCL13, CCL14, CCL17, CXCL5/ ENA-78, CXCL6, IL8/CXCL8, CXCL11, CXCL1/ NAP-3/MSGA-α/KC/GRO-α, and CXCL7/NAP-2. ACKR1 structurally resembles a G-protein coupled receptor (GPCR) but does not couple to G proteins and therefore fails to induce the full spectrum of downstream intracellular signals that characterize GPCRs. It is often considered as an interceptor (internalizing receptor) or chemokine-scavenging receptor or chemokine decoy receptor. It can control chemokine levels and localization via high-affinity chemokine binding, resulting in chemokine sequestration, degradation, or transcytosis. ACKR1 may also affect the function of other receptors indirectly. For instance, ACKR1 has been shown to exist as a constitutive homo-oligomer but also hetero-oligomerizes with the CC chemokine receptor CCR5. The formation of this heterodimer impairs chemotaxis and calcium flux through CCR5, although CCR5 is not internalized in response [3,4]. ACKR1 also acts as the receptor for the human malarial parasites *Plasmodium vivax* (*P. vivax*) and *Plasmodium knowlesi* (*P. knowlesi*), and thus may modulate the process of RBC invasion in malaria: Duffy null individuals are resistant to infection by *P. vivax*.

The Duffy null phenotype or Fy(a-b-) leads to the absence of Duffy antigens on red blood cells. The genetic locus related to the Duffy null phenotype was mapped to a polymorphism (SNP rs2814778 at chromosome 1q23.2) [5]. This results in a mutation in the GATA1 erythroid transcription factor binding site in the promoter region of the *DARC/FY/ACKR1* gene, silencing expression only in red blood cells. The erythrocyte silent phenotype, FyB^{ES} is prevalent in Africa, parts of the Arabian Peninsula, and descendants from these regions. In the United States, approximately two in three individuals identifying as Black have the Duffy-null phenotype. The median ANC in Duffy-null individuals is significantly lower than in Duffy nonnull individuals, with approximately one-fourth of Duffy-null individuals having an ANC of <2000 cells/μl [6]. This results in a clinically lower ANC compared to the commonly used reference population established from individuals of Asian or European descent, of whom nearly 100% are Duffy nonnull [7]. Individuals with the Duffy null phenotype have no increased risk of infection but are often incorrectly labeled as having neutropenia. This can result in unnecessary, expensive, and invasive testing; delayed or discontinued chemotherapy or other critical medications; exclusion from clinical trials, and other negative consequences. Because of this, it is now being proposed by the American Society of Clinical Pathology: 'Don't perform an extensive work-up in otherwise healthy neutropenic patients of African or Middle Eastern ancestry prior to Duffy-null phenotype testing.' There are also ongoing efforts to establish normal ANC reference ranges for Duffy-null individuals. One recent single institution study of 120 Duffy-null adults

indicated a normal ANC reference range between 1210 and 5390 cells/μl [8▪]. Although this and other studies have reported similar ANC ranges, a smaller Swedish study of 66 adults found 9% with very low ANC values between 100 and 490 cells/μl [9▪]. Also, children may have lower ANC values (less than 500 cells/μl) according to anecdotal reports [10].

The mechanism leading to neutropenia in Duffy null individuals is a topic of investigation. ACKR1's primary function is regulation of chemokine bioavailability. When expressed in erythrocytes, it serves as a blood reservoir of cognate chemokines but also as a chemokine sink, buffering potential surges in plasma chemokine levels. Therefore, ACKR1 effectively sustains homeostatic levels of circulating chemokines and modulates chemokine gradients between tissues and the blood to mediate the influx of neutrophils and monocytes from blood vessels into tissues during immune responses. Due to the known role of ACKR1 in chemokine regulation, investigators have proposed that the Duffy null phenotype may lead to neutropenia by altering the concentrations and distribution of chemokines that regulate neutrophil production or migration.

A 2017 study suggested that neutropenia in Duffy-null individuals was due to ACKR1 deficiency in nucleated erythroid cells (NECs) in the bone marrow. ACKR1 was found to be crucial for interaction between hematopoietic stem and progenitor cells (HSPCs) and NECs, which was essential for hematopoiesis and normal neutrophil maturation. Disruption of ACKR1 in NECs impaired this interaction, leading to the production of atypical neutrophils that redistributed to the spleen, thereby causing neutropenia [11]. This was associated with altered numbers and decreased proliferation of HSPCs, shifts in proportions of individual HSPC subpopulations, changes in HSPC transcriptomes and altered expression of their functional surface molecules. The exact mechanism of ACKR1-mediated interactions between NECs and HSPCs is yet to be fully understood [12], and several other studies have explored related mechanisms. A recent study revealed that dimeric CXCL12/SDF-1 bound to the extracellular N-terminus of ACKR1 with low nanomolar affinity and was internalized along with ACKR1 [13]. The binding of CXCL12 to ACKR1 was contingent on ACKR1's conformation, which underwent gradual alterations throughout erythroid development, leading to a lack of CXCL12 binding in mature erythrocytes. Notably, the binding of CXCL12 to erythrocytes could be triggered by pretreatment with interleukin (IL)-8 or antibodies that targeted specific epitopes on ACKR1 [14]. Given the key role of CXCL12 in hematopoiesis and granulopoiesis [15–18], the interaction between CXCL12 and ACKR1 adds another layer of regulation to neutrophil production.

Individuals with atypical chemokine receptor-1 disruption in all cell types

Most Duffy-null individuals carry the FyB^{ES} allele, and the gene is still transcribed in nonerythroid cells. However, individuals with ACKR1 disruption in all cell types have also been identified [1,19], although rare. The few documented cases of the Fy(a−b−) phenotype in Europeans and Asians arise from mutations in the coding region of the FY∗A or FY∗B allele, which often lead to a premature stop codon. These mutations, when present in the homozygous state, prevent Duffy antigen expression on any cell in the body and thus are true Duffy-null phenotypes. Consequently, these individuals are at risk of being allo-immunized when exposed to red blood cells expressing Fy antigens.

Significant neutropenia was not reported in individuals with ACKR1 disruption in all cell types. In fact, in the mouse model, neutropenia developed only when ACKR1 was absent in the BM but was expressed in the venular endothelial cells. Mechanistically, this was consistent with the known contribution of ACKR1 on endothelial cells to optimize chemokine-driven neutrophil egress into tissues. When ACKR1 is expressed in endothelial cells, like other silent receptors, it internalized chemokines but did not effectively scavenge them. Instead, ACKR1 mediated a process called chemokine transcytosis, which led to apical retention of intact chemokines and more extravasation across endothelial monolayers [20]. Recently, Girbl *et al.* [21] reported that CXCL2 produced by transmigrating neutrophils were retained at endothelial cell junctions by ACKR1, providing a paradigm of self-guided unidirectional luminal-to-abluminal migration. Thus, in individuals with ACKR1 disruption in all cell types, including endothelial cells, NECs and RBCs, ANC remained high since neutrophils failed to efficiently migrate to peripheral tissues when ACKR1 was disrupted in endothelial cells. This also explains why mice with a global ACKR1 deficiency, despite having altered neutrophils, were not neutropenic [11].

CLINICAL CONSEQUENCES OF ATYPICAL CHEMOKINE RECEPTOR-1/DUFFY ANTIGEN RECEPTOR OF CHEMOKINES-ASSOCIATED NEUTROPENIA

The complex (and sometimes contradictory) effects of ADAN on host defense

ACKR1 is the receptor for the human malarial parasites *P. vivax* and *P. knowlesi*. Individuals with the Duffy-null genotype are resistant to malaria infection. This has led to the belief that the Duffy-null phenotype is a genetic adaptation to an

environmental challenge (malaria). The low level of ACKR1 expression is associated with low susceptibility and resistance to infection. Red cells of heterozygotes for the silent allele bind substantially less *P. vivax* than those of individuals with two active FY alleles. Thus, even Duffy-negative heterozygosity offers significant protection, providing a selective advantage in regions where *P. vivax* is endemic. Of note, recent studies indicated that *P. vivax* infections can still occur in individuals with ADAN. It turns out that Fy protein is expressed in early erythropoietic stages in these individuals, enabling *P. vivax* invasion [22].

HIV-1 can also attach to RBCs via ACKR1, affecting trans-infection of target cells [23]. Moreover, ACKR1 expressed on RBCs influences plasma levels of HIV-1-suppressive and proinflammatory chemokines, such as CCL5/RANTES. ADAN has been implicated in higher rates of HIV-1 acquisition, but also associated with a survival advantage in leukopenic HIV-infected persons [24]. Low neutrophil counts in African mothers and newborns were associated with increased susceptibility to perinatal HIV infection [25]. However, neutrophil effector processes were not appreciably impaired in Duffy-null individuals regardless of HIV status [26].

In addition, neutrophils can sometimes also suppress the immune system (such as for myeloid-derived suppressor cells in cancer patients). Consequently, ADAN could theoretically impact other immune cell types, such as natural killer (NK) and $CD8^+$ T cells, leading to altered phenotype, functionality, or homeostatic activity. However, the Duffy-null phenotype was not associated with significant dysfunction of either NK cells or cytotoxic T cells [27].

Recent studies also established a role for ACKR1 in SARS-CoV-2 pathogenesis. Exceptionally low COVID-19 mortality rates were observed in sub-Saharan Africa, a unique geographic region where ADAN is prevalent [28]. ACKR1 was identified as the most highly upregulated chemokine receptor in infected lungs, localizing to endothelial cells of veins and arterioles. Mice with complete absence of Ackr1 were shown to resist lethal SARS-CoV-2 challenges, although this preliminary study did not determine if the protection against SARS-CoV-2 was due to absence of Ackr1 on RBCs or (perhaps more likely) on endothelial cells [29].

Neutropenia and host defense in atypical chemokine receptor-1/Duffy antigen receptor of chemokines-associated neutropenia

Despite severe neutropenia typically impairing host defense, it has been reported that individuals with Duffy- null neutropenia do not exhibit compromised defense [30]. This may be attributed to several potential mechanisms. First, neutrophils in ACKR1-deficient mice were reported to be produced aberrantly, potentially having enhanced pathogen-killing abilities. This increased functionality might compensate for the reduced neutrophil count. Also, both Duffy-null individuals and ACKR1-deficient mice have been described to express a distinct profile of neutrophil effector molecules [4]. Second, ACKR1's cytokine modulation ability during infection can regulate the inflammatory state. The absence of ACKR1 on RBCs may alter cytokine concentrations/responses in the infected host, potentially leading to improved host defense. Finally, the Duffy-null genotype is known to confer an evolutionary advantage through natural selection by offering protection against malaria. Selective pressure exerted by a broad range of other infectious agents may have also contributed to the selection and fixation of polymorphisms in genes beyond *ACKR1* within the Duffy-null population. In this scenario, selected pro-inflammatory mechanisms could emerge in any innate or adaptive immune component, so long as they enhanced host defense.

CONCLUSION

In conclusion, the infection response in Duffy-null individuals can be complex and context-dependent. The evidence supporting the notion that Duffy-null neutropenic individuals have normal responses to infection needs careful evaluation and confirmation across various infection and disease conditions. This remains a highly relevant question, as the decision to lower diagnostic standards for Duffy-null neutropenic individuals hinges on a significant assumption. This assumption, thus far backed by current clinical observations, is that neutropenia in these individuals does not increase their risk of infection.

Proinflammatory signaling and hematopoietic stem cell dynamics in atypical chemokine receptor-1/Duffy antigen receptor of chemokines-associated neutropenia

Despite the lack of association with increased infections, ADAN may not be benign in all contexts. In addition to having complex effects on HIV acquisition rate, as described above, ADAN individuals have been reported to have increased immunoglobulin IgE levels and susceptibility to asthma [31], higher rates of morbidity and mortality after acute lung injury [32], and a higher incidence of

triple-negative breast cancer (so-called because of low expression levels of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2) [33]. ACKR1 is a key regulator that binds chemokines involved in inflammatory responses, and its absence in erythrocytes and NECs was shown to provoke a proinflammatory profile that may favor autoimmune reactions or alterations in the tumor microenvironment [34]. Palmblad *et al.* found that 28 of 64 ADAN individuals tested had autoantibodies to neutrophils (as compared with less than 1% of control individuals) [9▪]. Excessive proinflammatory chemokine signaling in ADAN may also contribute to the senescence-associated secretory phenotype or SASP, believed to play a role in senescence of the immune system during aging [34]. Redistribution of peripheral blood neutrophils to tissues such as the spleen may also have complex effects on hematopoiesis or stem cell clonal dynamics, which are incompletely understood at present.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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