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Neutrophils in pediatric autoimmune disease

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Abstract

Purpose of review: As first immune responders, neutrophils are essential mediators of host defense, but also contribute to chronic pathologic inflammation at the crossroads of innate and adaptive immunity. In this review we will highlight current understanding of the role of neutrophils in pediatric rheumatology with a focus on juvenile idiopathic arthritis (JIA) and lupus.

Recent Findings: In inflamed tissues, neutrophils extrude neutrophil extracellular traps (NETs) containing autoantigen that potentially drives lupus and rheumatoid factor positive JIA. However the contribution of NETs to pathogenesis remains an area of intense investigation. In JIA joints, neutrophils are activated to such an extent that associated circulating levels of S100A proteins may serve as biomarkers, correlating with disease activity, predicting response to treatment and heralding flares. Beyond the effects of “normal” activation, neutrophils in JIA and lupus display dysregulation in gene expression, subset activation and apoptosis.

Summary: The role of neutrophils in pediatric rheumatology is an understudied area, but garnering increasing attention. Although clearly implicated in JIA and lupus, the specific contributions of neutrophils to pathogenesis, and the use of neutrophil activity surrogates as biomarkers requires further study. Clarification of these outstanding issues will have implications for diagnosis and treatment of pediatric rheumatologic conditions.

Keywords

Juvenile Idiopathic Arthritis; NETosis; lupus; S100A proteins; biomarkers

Introduction

Neutrophils are key mediators of the innate immune response and are the first responders to sites of infection and tissue damage. Once at the site of infection, neutrophils play a critical role in host defense through phagocytosis, degranulation and secretion of antimicrobial factors, production of reactive oxygen species, and release of neutrophil extracellular traps

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(NETs) [1,2]. Although the primary function of neutrophils is to protect the host from pathogens, the influx of neutrophils to a tissue site can contribute directly to tissue damage and the progression to chronic inflammation. Neutrophils mediate a pro-inflammatory response to tissue damage or infection by releasing cytokines that recruit and activate other immune cells and lead to the activation of adaptive immunity. Classically considered an early responder that dies at the site of inflammation, new findings suggest that neutrophils are longer-lived cells with substantial plasticity. Indeed, there has been increased interest in the role of neutrophils in autoimmune disease.

As sentinels of the immune response in autoimmune arthritis, neutrophils contribute directly to joint damage and also pave the way for adaptive immunity by secreting cytokines and other factors that enhance antigen presentation. Neutrophils also secrete plasma B-lymphocyte stimulator (Blys) that promotes B cell activation [3]. In the tissue, neutrophils cause extensive injury via the release of proteases and reactive oxygen species, and thus could release potential autoantigens such as extracellular matrix proteins filaggrin and aggrecan [3,4]. Upon activation, neutrophils also can die in a process called NETosis in which chromatin is extruded to form a nuclear extracellular trap (NET). In addition to having an important role in the innate immune response against pathogens, NETs have also been implicated in the development of autoimmunity. Specifically, NETs display some of the citrullinated antigens that are known to be targets of anti-citrullinated protein antibodies (ACPAs) found in rheumatoid arthritis [5]. Chromatin NETs are an obvious source of nuclear material, which could also serve as an autoantigen.

Traditionally, neutrophils have been thought of as short-lived cells that die at sites of inflammation, however increasing evidence suggests that neutrophils can be long lived and can also “reverse” migrate away from sites of inflammation. Imaging studies in zebrafish and more recently in mice have demonstrated that neutrophils not only migrate to damaged tissue, but also can reverse migrate back into the vasculature [6,7]. In support of this idea, previous studies have suggested that there is an increased presence of CXCR1 low/CD54 high “reverse” transmigrated neutrophils in the blood of patients with systemic inflammation [8]. These “inflammation-experienced” neutrophils that re-enter the vasculature may have diverse functions including regulating other immune cells to mediate systemic inflammation and autoimmunity [8]. However, there remains a significant gap in understanding how neutrophils modulate the development and progression of autoimmune disease. Here we review what is currently known about the role of neutrophils in pediatric autoimmune disease with a focus on Juvenile Idiopathic Arthritis (JIA) and lupus.

Autoinflammatory disease in childhood

Rheumatic diseases of children can typically be divided into autoimmune and autoinflammatory disorders. While neutrophil infiltration into tissues is often present in both classes of disease, autoinflammatory diseases typically are due to apparently unprovoked activation of the innate immune system while autoimmune disease are often driven by autoreactive T cells and autoantibodies. Herein we will not discuss the substantial progress that has been made in defining the molecular basis of monogenic autoinflammatory diseases and refer the reader to several excellent reviews [9,10]. However, it is important to note that

the discovery of these molecular mechanisms has provided new insight into how the innate immune system works and has helped provide a framework for further understanding of the innate immune response in autoimmune disease. Notably, the recent discovery of NLRC4 mutations in autoinflammation highlighted the concept that neutrophils, not T cells, can be the primary source of IL-17 downstream of IL1β signaling [11]. It is also important to consider that some "autoimmune" diseases like Behcet's disease or Systemic JIA may be better categorized as autoinflammatory diseases, highlighting the overlap between these disease categories. Indeed, pediatric patients who present with "autoimmune" disease at a young age often have inherited immune deficiencies. For instance, children may develop manifestations of inflammatory bowel disease with neutrophil inflammation due to primary defects in innate immunity including chronic granulomatous disease or mutations in IL-10 or the IL-10 receptor (reviewed in [12]).

Neutrophils in Juvenile Idiopathic Arthritis

JIA refers to a group of diseases with onset prior to 16 years of age unified by the presence of arthritis lasting at least 6 weeks. Taken together as a group, JIA constitutes the most common chronic autoimmune disease of childhood. The 2001 International League of Associations for Rheumatology (ILAR) classification criteria subdivides JIA into 7 categories based on the number of joints that are affected and systemic involvement: oligoarticular JIA, rheumatoid factor (RF) negative polyarticular JIA (more than 4 joints), RF positive JIA, Systemic JIA, Psoriatic JIA, Enthesitis-Related arthritis (ERA), and "undifferentiated" (not meeting category criteria or fulfilling >1 category). Although the different JIA categories share some pathogenic mechanisms and treatment approaches, both the heterogeneous clinical characteristics and underlying genetics suggest the subtypes are distinct entities and the role of neutrophils in pathogenesis likely differs by JIA subtype. Although neutrophils are the most abundant cell type found in JIA synovial fluid, the study of their role in JIA has been limited. Two major advances have been the study of neutrophil cell-intrinsic differences in JIA and the potential use of neutrophil-derived S100A proteins as biomarkers.

Oligoarticular and RF- polyarticular JIA are commonly considered "autoimmune diseases" related to numerous factors including the linkage with specific HLA haplotypes as well as the abundant $CD4^+CD45RO^+$ memory lymphocytes of the Th1 subtype in synovial fluid [13–15]. Genome wide association studies (GWAS) of regions outside the MHC have identified associations with PTPN22, PTPN2, STAT4, IL2RA and other loci that overlap with classic autoimmune diseases including adult rheumatoid arthritis (RA), type I diabetes and multiple sclerosis [14,16]. However, the purely "autoimmune" model does not take into account the complex interweaving of adaptive and innate immunity that occurs in JIA. Also, recent studies of JIA-associated non-coding genetic regions examining histone acetylation "enhancer" marks revealed shared active regions in CD4 T cells and neutrophils [17]. These results suggest that the genetic regions identified by GWAS could impact multiple immune cell types, including neutrophils.

Gene expression studies in neutrophils from RF- polyarticular JIA patients have revealed dysregulated clusters of IL-8 and IFNγ regulated genes [18]. Other altered genes in

neutrophils related to calcium flux and superoxide production have been reported. These gene expression abnormalities distinguished JIA and healthy controls, but not active and inactive disease, suggesting cell-intrinsic defects [18]. Further, like adult RA, there is evidence for chronic activation of peripheral neutrophils in pediatric patients with polyarticular disease. S100A proteins (also referred to as calgranulins) are zinc and calcium binding proteins that constitute up to 50% of the cytosolic protein in phagocytes. Neutrophils and early differentiating monocytes produce S100A8, S100A9 and the S100A8/S100A9 (MRP8/MRP14) heterodimer also known as calprotectin. S100A12 (EN-RAGE, calgranulin C) is predominantly produced by activated neutrophils. Upon binding the receptors for advanced glycation end products (RAGE), S100A proteins activate endothelial cells, inducing expression of adhesion molecules and chemoattractants, and thus increasing leukocyte recruitment. Calprotectin also triggers Toll-like receptor 4, promoting secretion of pro-inflammatory cytokines such as IL-6, IL-1β and TNFα [19]. Related to the intense neutrophil activation in inflamed joints, levels of calprotectin and S10012A rise to very high levels within joints, but also increased serum levels 5–10 fold higher than controls have been reported [12]. Elevated serum calprotectin is not specific to JIA, and can be found in Kawasaki's disease and sepsis [20,21]. However, the potential use of S100A serum levels as an activity biomarker has generated excitement in the field. Levels go up with active disease, down with systemic therapy (methotrexate or etanercept) and with intra-articular steroid injections [21]. Elevated serum calprotectin was more specific than clinical data, inflammatory cytokine levels, and standard laboratory parameters in predicting response to methotrexate [22]. Most intriguingly, increased calprotectin and S100A12 levels appear to herald a disease flare. In a prospective study, S100A12 was the best single predictor of disease flare after therapy withdrawal [23]. Reliability of an activity-related biomarker that could reveal sub-clinical disease or predict flares would represent significant progress for therapeutic decision-making.

RF+ JIA, accounting for <5% of patients, is generally thought to mark the early onset of adult RA, given patterns of joint involvement, ACPA and RF autoantibodies, and persistence into adulthood. Neutrophils have a unique niche in RF+ disease compared to other JIA subtypes: the capacity of neutrophils to extrude NETs containing citrullinated proteins may contribute to the generation of pathogenic anti-citrullinnated protein antibodies. The role of neutrophils in RA and NET formation have been extensively reviewed elsewhere and will not be further discussed [24].

Neutrophils in Systemic JIA

Calgranulin levels are of potentially even greater interest in systemic JIA, where neutrophils may be primary effectors. The prominent systemic features, including spiking fevers, rash, hepatosplenomegaly, and serositis distinguish systemic JIA from other subtypes. These clinical features and the underlying genetics (HLA-associations are conspicuously absent) place this disease firmly into the "autoinflammatory" category. IL-1 and IL-6 appear to play the dominant role in producing disease manifestations, as attested to by IL-1 gene signatures, elevated IL-6 levels and response to corresponding cytokine blockade [15]. During active disease, patients can develop neutrophilia, to levels observed in leukemia. Perhaps related to this intense neutrophil activation, levels of S100A12 soar to ~70X control

and 10X greater than other forms of JIA. Indeed this incredible elevation distinguishes systemic JIA from other forms of JIA as well as sepsis. Levels of S100A12 were 10 fold higher in joint fluid than in serum and like calprotectin, serum S100A12 levels were predictive of flares [21].

Neutrophils in spondyloarthritis

Calprotectin levels are also increased in ERA, and respond to treatment, but elevations are less than reported in other subtypes (2.5 fold vs. controls), consistent with a smaller role for neutrophils in spondyloarthritis [25]. Multiple studies in spondyloarthritis pathogenesis have highlighted the importance of the IL-23/IL-17 cytokine pathway and this topic has recently been reviewed [26]. Interestingly, evaluation of the cellular source of IL-17 production within biopsies supports an unexpected role for the innate immune system: in a study from Appel et al. of spinal facet joints, IL-17 was predominantly produced by MPO+ cells and CD15+ neutrophils (as opposed to T cells) [27]. This study and others suggest innate immune cells, including neutrophils, may be the predominant producers of pathogenic IL-17 in spondyloarthritis [26].

Neutrophils in lupus.

Lupus is a systemic autoimmune disease characterized by autoantibody formation with the deposition of immune complexes in tissues and multiorgan involvement. Although substantial focus has been on the role of the adaptive immune system in lupus pathogenesis recent studies have brought attention to the role of neutrophils in lupus (reviewed in [28, 29]). The role of neutrophils in lupus is likely different than in JIA where neutrophils are thought to traffic to the joint and create local inflammation and damage [28]. In contrast to JIA where neutrophils are generally “activated”, there is evidence that neutrophils from lupus patients have impaired activation with reduced chemokine-induced chemotaxis and oxidative burst [28, 29]. Moreover, lupus-associated variations in the ITGAM gene that encode the β chain of the leukocyte integrin MAC1 result in impaired leukocyte adhesion and phagocytosis (reviewed in [30]). However, lupus neutrophils can also have an activated phenotype, in particular in the vasculature where neutrophils contribute to vascular damage and the development of vasculitis [28,29,31,32]. One possible reason for the discrepancy about neutrophils in lupus is the presence of a subset of neutrophils in the peripheral blood called low density granulocytes, or LDGs, which have increased NET formation and enhanced ability to stimulate plasmacytoid dendritic cells [33].

Neutrophil NETs have been an area of significant focus in understanding the pathogenesis of lupus [33]. In pediatric lupus neutrophil NETs can activate plasmacytoid dendritic cells to secrete type I interferon, a major cytokine implicated in lupus [34]. Further, neutrophils that form NETs can cause endothelial cell damage in lupus [32]. NETs have also been thought to be a source of autoantigens in lupus, similar to rheumatoid arthritis [28], but there is conflicting data for this idea [29]. In mouse models, neutrophils do not make NETs in lupus-prone mice deficient in the NADPH oxidase complex component Nox2 despite having worsened disease [35]. Genetic variations in NADPH subunit NCF2 have been linked to increased risk for lupus in humans [36]. Interestingly, NCF2 variations associated with lupus risk result in reduced phagocyte ROS production, providing further evidence that ROS

production is not necessarily pro-inflammatory in lupus [37]. Further studies will be needed to dissect the immunomodulatory effects of phagocyte ROS signaling in the context of lupus [36]. Alternatively, neutrophils from pediatric patients with lupus have increased apoptosis that can also provide a source of autoantigen in lupus. In particular, serum from pediatric lupus patients induces neutrophil apoptosis and this may be abrogated by treatment with GMCSF, indicating potential therapeutic benefit of GMCSF in patients with lupus [38]. Thus, there is conflicting evidence regarding the function of neutrophils in lupus although to date much of the evidence supports a key role in disease pathogenesis. Taken together, more work is needed to clearly define the role of neutrophils in lupus, including dissecting the proinflammatory and immunomodulatory effects of neutrophils.

Conclusions

There are few studies that report on the role of neutrophils in pediatric autoimmunity, however there is recent growing interest in this area. For example, although neutrophils are the most common cell in JIA synovial fluid, their role in pathogenesis is greatly understudied. Studies of neutrophils in Oligo and Polyarticular JIA reveal intrinsic activity-independent abnormalities in gene expression. Circulating evidence of neutrophil activation, both calprotectin and S100A12, appear to be very promising biomarkers for overt and subclinical disease activity in JIA. More prospective studies regarding the practical application of these potential “neutrophil” biomarkers are needed both in the context of JIA and pediatric lupus. The role of NET formation, a current area of controversy in lupus pathogenesis, requires further elucidation. Distinct activated neutrophil subsets and altered apoptosis have been described in lupus. More information is needed regarding how the unique neutrophil characteristics described in JIA and lupus translate into altered function in pediatric autoimmune disease and ultimately disease pathogenesis and treatment.

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References

1. Nathan C Neutrophils and immunity: challenges and opportunities. Nat Rev Immunol 2006; 6:173–182. [PubMed: 16498448]
2. Kruger P, Saffarzadeh M, Weber AN, Rieber N, Radsak M, von Bernuth H, Benarafa C, Roos D, Skokowa J, Hartl D: Neutrophils: Between host defence, immune modulation, and tissue injury. PLoS Pathog 2015, 11:e1004651. [PubMed: 25764063]
3. Jarvis JN, Jiang K, Petty HR, Centola M: Neutrophils: the forgotten cell in JIA disease pathogenesis. Pediatr Rheumatol Online J 2007, 5:13. [PubMed: 17567896]
4. Kamphuis S, Hrafnkelsdottir K, Klein MR, de Jager W, Haverkamp MH, van Bilsen JH, Albani S, Kuis W, Wauben MH, Prakken BJ: Novel self-epitopes derived from aggrecan, fibrillin, and matrix metalloproteinase-3 drive distinct autoreactive T-cell responses in juvenile idiopathic arthritis and in health. Arthritis Res Ther 2006, 8:R178. [PubMed: 17129378]
5. Khandpur R, et al. NETs Are a Source of Citrullinated Autoantigens and Stimulate Inflammatory Responses in Rheumatoid Arthritis. Science translational medicine.2013;5:178ra140.

6. Mathias JR, Perrin BJ, Liu TX, Kanki J, Look AT, Huttenlocher A. Resolution of inflammation by retrograde chemotaxis of neutrophils in transgenic zebrafish. J Leukoc Biol. 2006;80:1281–1288. [PubMed: 16963624]
7. Woodfin Voisin MB, Beyrau M, Colom B, Caille D, Diapouli FM, Nash GB, Chavakis T, Albelda SM, Rainger GE, Meda P, Imhof BA, Nourshargh S. The junctional adhesion molecule JAM-C regulates polarized transendothelial migration of neutrophils in vivo. Nature Immunology 2011; 12:761. [PubMed: 21706006]
8. Buckley CD, Ross EA, McGettrick HM, Osborne CE, Haworth O et al. Identification of a phenotypically and functionally distinct of long lived neutrophils in a model of reverse endothelial migration. J Leukoc Biol. 2006; 79: 303–11. [PubMed: 16330528]
9. Park H, Bourla AB, Kastner DL, Colbert RA, Siegel RM. Lighting the fires from within: the cell biology of autoinflammatory disease. Nat Rev Immunol. 2012 7 25;12(8):570–80. [PubMed: 22828911]
10. van Kempen TS, Wenink MH, Leijten EF, Radstake TR, Boes M. Perception of self: distinguishing autoimmunity from autoinflammation. Nat Rev Rheumatol. 2015 5 12. doi: 10.1038/nrrheum.2015.60.
11. Kitamura A, Sasaki Y, Abe T, Kano H, Yasutomo K. An inherited mutation in NLRC4 causes autoinflammation in human and mice. J Exp Med. 2014 11 17;211(12):2385–96. [PubMed: 25385754] * This study identified a novel link between NLRC4 and hereditary autoinflammatory disease. Inflammation was mediated by neutrophil production of IL-17.
12. Carneiro-Sampaio M, Coutinho A. Early onset autoimmune disease as a manifestation of primary immunodeficiency. Front Immunol. 2015 4 24;6:185. [PubMed: 25999944]
13. Wedderburn LR, Robinson N, Patel A, Varsani H, Woo P: Selective recruitment of polarized T cells expressing CCR5 and CXCR3 to the inflamed joints of children with juvenile idiopathic arthritis. Arthritis Rheum 2000, 43:765–774. [PubMed: 10765921]
14. Hinks A, Cobb J, Marion MC, Prahalad S, Sudman M, Bowes J, Martin P, Comeau ME, Sajuthi S, Andrews R, et al.: Dense genotyping of immune-related disease regions identifies 14 new susceptibility loci for juvenile idiopathic arthritis. Nat Genet 2013, 45:664–669. [PubMed: 23603761] * This study marks one of the most comprehensive GWAS studies in JIA. A methodologic limitation is the focus on autoimmunity associated SNPs.
15. Lin YT, Wang CT, Gershwin ME, Chiang BL: The pathogenesis of oligoarticular/polyarticular vs systemic juvenile idiopathic arthritis. Autoimmun Rev 2011, 10:482–489. [PubMed: 21320644]
16. Thompson SD, Sudman M, Ramos PS, Marion MC, Ryan M, Tsoras M, Weiler T, Wagner M, Keddache M, Haas JP, et al.: The susceptibility loci juvenile idiopathic arthritis shares with other autoimmune diseases extend to PTPN2, COG6, and ANGPT1. Arthritis Rheum 2010, 62:3265–3276. [PubMed: 20722033]
17. Jiang K, Zhu L, Buck MJ, Chen Y, Carrier B, Liu T, Jarvis JN: Disease-associated SNPs From non-coding regions in juvenile idiopathic arthritis are located within or adjacent to functional genomic elements of human neutrophils and CD4+ T Cells. Arthritis Rheumatol 2015.* In this study, evaluation of non-coding JIA associated SNP regions revealed shared active regions between CD4 T cells and neutrophils, implying that GWAS study findings could apply to cells in both adaptive and innate immune systems.
18. Jarvis JN, Petty HR, Tang Y, Frank MB, Tessier PA, Dozmorov I, Jiang K, Kindzelski A, Chen Y, Cadwell C, et al.: Evidence for chronic, peripheral activation of neutrophils in polyarticular juvenile rheumatoid arthritis. Arthritis Res Ther 2006, 8:R154. [PubMed: 17002793]
19. Vaos G, Kostakis ID, Zavras N, Chatzemichael A: The role of calprotectin in pediatric disease. Biomed Res Int 2013, 2013:542363. [PubMed: 24175291]
20. Frosch M, Strey A, Vogl T, Wulffraat NM, Kuis W, Sunderkotter C, Harms E, Sorg C, Roth J: Myeloid-related proteins 8 and 14 are specifically secreted during interaction of phagocytes and activated endothelium and are useful markers for monitoring disease activity in pauciarticular-onset juvenile rheumatoid arthritis. Arthritis Rheum 2000, 43:628–637. [PubMed: 10728757]
21. Foell D, Wittkowski H, Hammerschmidt I, Wulffraat N, Schmeling H, Frosch M, Horneff G, Kuis W, Sorg C, Roth J: Monitoring neutrophil activation in juvenile rheumatoid arthritis by S100A12 serum concentrations. Arthritis Rheum 2004, 50:1286–1295. [PubMed: 15077313]

22. Moncrieffe H, Ursu S, Holzinger D, Patrick F, Kassoumeri L, Wade A, Roth J, Wedderburn LR: A subgroup of juvenile idiopathic arthritis patients who respond well to methotrexate are identified by the serum biomarker MRP8/14 protein. Rheumatology (Oxford) 2013, 52:1467–1476. [PubMed: 23620557]

23. Gerss J, Roth J, Holzinger D, Ruperto N, Wittkowski H, Frosch M, Wulffraat N, Wedderburn L, Stanevicha V, Mihaylova D, et al. Phagocyte-specific S100 proteins and high-sensitivity C reactive protein as biomarkers for a risk-adapted treatment to maintain remission in juvenile idiopathic arthritis: a comparative study. Ann Rheum Dis 2012, 71:1991–1997. [PubMed: 22689317]

24. Wright HL, Moots RJ, Edwards SW. The multifactorial role of neutrophils in rheumatoid arthritis. Nat Rev Rheumatol 2014, 10:593–601. [PubMed: 24914698]

25. Rahman MT, Myles A, Gaur P, Misra R, Aggarwal A. TLR4 endogenous ligand MRP8/14 level in enthesitis-related arthritis and its association with disease activity and TLR4 expression. Rheumatology (Oxford) 2014, 53:270–274. [PubMed: 24231443]

26. Smith JA, Colbert RA. Review: The interleukin-23/interleukin-17 axis in spondyloarthritis pathogenesis: Th17 and beyond. Arthritis Rheumatol 2014, 66:231–241. [PubMed: 24504793]

27. Appel H, Maier R, Wu P, Scheer R, Hempfing A, Kayser R, Thiel A, Radbruch A, Loddenkemper C, Sieper J: Analysis of IL-17(+) cells in facet joints of patients with spondyloarthritis suggests that the innate immune pathway might be of greater relevance than the Th17-mediated adaptive immune response. Arthritis Res Ther 2011, 13:R95. [PubMed: 21689402]

28. Kaplan MJ. Neutrophils in the pathogenesis and manifestations of SLE. Nat Rev Rheumatol. 2011;7:691–699. [PubMed: 21947176]

29. Shelef MA, Tauzin S, Huttenlocher A. Neutrophil migration: moving from zebrafish models to human autoimmunity. Immunol Rev. 2013 11;256(1):269–81. [PubMed: 24117827]

30. Fagerholm SC, MacPherson M, James MJ, Sevier-Guy C, Lau CS. The CD11β integrin (ITGAM) and systemic lupus erythematosus. Lupus 2013 6;22(7):657–63. [PubMed: 23753600]

31. Hervier B, Hamidou M, Haroche J, Durant C, Mathian A, Amoura Z. Systemic lupus erythematosus associated with ANCA-associated vasculitis: an overlapping syndrome? Rheumatol Int. 2012 10;32(10):3285–90. [PubMed: 21805174]

32. Villanueva E, et al. Netting neutrophils induce endothelial damage, infiltrate tissues, and expose immunostimulatory molecules in systemic lupus erythematosus. J Immunol.2011;187:538–552. [PubMed: 21613614]

33. Knight JS, Kaplan MJ. Lupus neutrophils: ‘NET’ gain in understanding lupus pathogenesis. Curr Opin Rheumatol.2012;24:441–450. [PubMed: 22617827]

34. Lande R, et al. Neutrophils activate plasmacytoid dendritic cells by releasing self-DNA-peptide complexes in systemic lupus erythematosus. Sci Transl Med.2011;3:73ra19.

35. Campbell AM, Kashgarian M, Shlomchik MJ. NADPH oxidase inhibits the pathogenesis of systemic lupus erythematosus. Sci Transl Med.2012;4:157ra141.

36. Jacob CO, Eisenstein M, Dinauer MC, Ming W, Liu Q, et al. Neutrophil associated causal mutation in neutrophil cytosolic factor 2 (NCF2) brings unique insights to the structure and function of NADPH oxidases. Proc Natl Acad Sci U S A. 2012 1 10;109(2):E59–67. [PubMed: 22203994]

37. Armstrong DL, Eisenstein M, Zidovetzki R, Jacob CO. Systemic lupus erythematosis-associated neutrophil cytosolic factor 2 mutation affects the structure of NADPH oxidase complex. J Biol Chem. 2015 5 15;290(20):12595–602. [PubMed: 25795782] * This study reports that lupus-associated NCF2 mutations affect the structure and function of the NADPH oxidase complex resulting in impaired NADPH oxidase activity.

38. Chiewchengchol D, Midgley A, Sodsai P, Deekajorndech T, Hirankarn N, Beresford MW, Edwards SW. The protective effect of GM-CSF on serum-induced neutrophil apoptosis in juvenile systemic lupus erythematosus patients. Clin Rheumatol. 2015 1;34(1):85–91. [PubMed: 25344776]

Key Points

1. The role of neutrophils in pediatric rheumatologic disease is vastly understudied, but garnering increasing interest.
2. Neutrophils from JIA patients display abnormal gene expression patterns.
3. The S100A calgranulin proteins secreted by activated neutrophils have potential as biomarkers, particularly in identifying subclinical disease and predicting flares.
4. Neutrophil NETosis may provide autoantigen and trigger type I IFN in lupus, but the role of NET-associated ROS production remains controversial.
5. In lupus enhanced neutrophil apoptosis has been described, with unclear pathogenic implications.