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How Neutrophilic IL-23 production and Related Mechanisms Determine Spondyloarthropathy spectrum Immunity and Phenotypes

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Abstract

Neutrophilic inflammation is a pervasive characteristic present across the spondyloarthropathies (SpA) and the allied disorder spectrum. It manifests as ocular hypopyon, psoriatic skin Munroe's abscesses, intestinal crypt abscesses in intestinal inflammation, osteoarticular neutrophilic inflammation in psoriatic arthritis and neutrophilic macroscopic and microscopic Behcet's disease related inflammation. However, these diseases share strong MHC-I associations and represent "MHC-I-opathies" pointing towards CD8 T-cell immunopathology that is not well understood. Herein, we highlight emerging data on how the T-cell neutrophilic axis is not merely type 17 T-cell directed recruitment and activation of neutrophils but sequestration of the latter at disease sites may directly amplify type 17 T-cell responses via neutrophilic IL-23 protein production, neutrophil protease production and other feedback mechanisms that could be exquisitely regulated by local microbiota, pathogens or tissue damage. This innate-adaptive immunity cross-talk marries clinical phenotypes to immunology and offers a novel explanation for how bacterial and fungal microbes at barrier sites could innately control type 17 T-cell cross-talk towards optimal restoration of tissue homeostasis. This cross-talk has implications beyond clinical neutrophilic associated "sterile inflammation" disease phenotypes. It encompasses the surprisingly fast onset of action of IL-23 pathway blockade in some patients and could be crucial to understanding the non-efficacy of IL-23 blockers in the axial skeleton in ankylosing spondylitis; the axial skeleton being a site rich in neutrophils given that haematopoiesis with myelopoiesis retreats to the spine in adults.

Introduction

A group of inflammatory non-autoantibody associated diseases including psoriasis, psoriatic arthritis, ankylosing spondylitis (AS), acute anterior uveitis, Behcet's disease (BD), inflammatory bowel disease (IBD) and its associated arthropathy have been recognized to clinically overlap for nearly 50 years (1). This clinical overlap encompasses axial inflammation, oligoarthritis in particular, anterior uveitis, psoriasiform cutaneous inflammation, a link to gut inflammation and triggering infectious events (1). The associated "common thread" axial and peripheral arthropathies have since been termed the seronegative spondyloarthropathies (SpA) (1). Most of these entities have strong MHC-I associations, especially when axial SpA pattern arthropathy is considered, and share common genetic polymorphisms with the IL-23/IL-17 axis (2, 3). Most of these conditions have several genetic polymorphisms beyond MHC class I associations incriminating CD8 T-cells in the immunopathology including RUNX3 and TBX21 (encoding T-bet) (4) and many share ERAP-1 polymorphisms relevant to antigen presentation (5). Whilst MHC-I associations with IBD are weaker than other MHC-I-opathies they have nevertheless been well reported in both UC and Crohn's Disease (6). In recognition of these T-cell components we suggested that a substantial group of patients within these designated diseases had a common overlapping "MHC-I-opathy" flavor given the evidence pointing toward tissue specific MHC-I interactions with putative CD8 T-cell responses (7).

Despite these impressive MHC-I associations, the SpA group of diseases are also strongly linked to a predilection for neutrophilic driven inflammation that is evident both clinically and histologically. Clinically, this manifests as pus in the anterior chamber of the eye in iritis associated hypopyon and various neutrophilic rashes including pustules (8, 9). Histologically, neutrophilic cutaneous microabscesses are a key feature of psoriasis and neutrophils in the synovial fluid and synovial tissue have been reported as more common in psoriatic arthritis (PsA) compared to rheumatoid arthritis (RA) (10-12). Bone inflammation in early sacroiliitis and in HLA-B27 transgenic rats has a strong neutrophilic component and early biopsies from the sacroiliac joint in AS have also reported neutrophilic inflammation (13). Indeed, neutrophils are found elevated in AS patient blood and have been proposed for use as a predictor for active axial SpA disease (14). Furthermore, IBD gut related disease is characterized by neutrophilic inflammation including crypt abscesses (15). Beyond IBD itself, extra-intestinal features that accompany active IBD typically include neutrophilic related cutaneous lesions including pyoderma gangrenosum (PG) and Sweet's syndrome (16, 17), many of which were highlighted nearly 50 years ago in the original clinical descriptions by Moll and colleagues (1).

The precise inter-relationship between such putative early T-cell responses and neutrophils in disease is poorly defined. Our prior inflammatory model marrying the clinical, immunogenetic and translational therapeutic characteristics had the neutrophil as a mere terminal effector cell at the end of an immunological cascade (7). Indeed, the effects of the IL-23/IL-17 axis on recruitment and activation of neutrophils has been well described (18). IL-17-stimulated stroma releases chemokines such as IL-8 that are strongly chemotactic for neutrophils (19). Recruited neutrophils arrive to an already inflammatory tissue and subsequently become activated, resulting in the release of more inflammatory mediators and chemokines that exacerbate the existing inflammation and contribute to tissue damage (Figure 1A). In the current perspective, however, we highlight the implications of recently emergent knowledge on how neutrophils in these target tissues, by virtue of their ability to produce IL-23 and other mediators may feedback to closely regulate the T-cell responses, especially in the context of site specific threats from pathogens (Figure 1B). The clinical implications of this T-cell and neutrophilic axis in SpA spectrum disease

are discussed, including the sometimes rapid therapeutic onset of IL-23 blockers and the abundance of myelopoiesis in the axial skeleton where IL-23 blockade has thus far proved ineffective for AS (20, 21).

The IL-23/IL-17 axis marries T-cell and neutrophil immunity

At the population level, the immunogenetic mechanisms in the SpA spectrum diseases are heterogeneous, but a remarkable feature is the shared genetic polymorphisms within the IL-23 signalling pathway including IL-23R and IL-12p40 single nucleotide polymorphisms (SNPs) (22, 23). The IL-23/IL-17 axis immunogenetics common thread is directly supported by highly effective disease control with IL-23- and IL-17-directed therapy, particularly in psoriasis but also associated PsA (24, 25). The IL-23/IL-17 axis is strongly associated with driving type 17 immunity, which under normal conditions is the body's response to fungal and extracellular resident bacterial pathogens (26). Clinically, the presence of psoriasis of the nails, scalp and genital regions is typically linked to subsequent PsA development, and this appears to represent a gain in immune function since vigorous suppression of the IL-23/IL-17 axis with single cytokine blockade is generally very efficient for psoriasis clearance (27). This is especially noteworthy since immunodeficiency states in the IL-23/IL-17 axis are associated with scalp, nail and genital infections – particularly fungal infections (28). Mechanistically, severe fungal infections are strongly linked to neutropenia and disorders of neutrophil biology including myelodysplastic syndromes and acute myeloid leukemia (29, 30). In the experimental setting, neutrophil biology including granulopoiesis, diapedesis, chemotaxis and activation is dependent on IL-17 family members (31). It is therefore not surprising that neutrophils are a feature of almost all cases of IL-23/IL-17-driven disease, yet their involvement in regulating T-cell responses has been under-appreciated, until very recently.

Despite the strong clinical neutrophilic inflammation flavor in some of the aforementioned conditions, the earliest cutaneous lesions in PG were not neutrophilic but perivascular and peripilosebaceous T-cell infiltration with increased gene transcripts for IL-17A, IL-8 and other genes known to be associated neutrophilic chemoattraction (32). Other studies have also corroborated the idea of clonal T-cell populations in the blood and PG lesions setting a precedent for T-cell and neutrophil co-involvement (33, 34). Likewise in psoriasis, it has recently emerged that tissue resident memory $CD8^+$ T-cells capable of IL-17 production may be the key cellular players determining cutaneous flares (35). According to this scheme the neutrophil is a terminal effector cell marching to the tune of type 17 tissue T-cells including innate and adaptive lymphocytes, but data from key skeletal sites of disease is still missing.

A case for for neutrophil involvement in SpA-associated inflammation

Whilst immune responses to intracellular infection are focused on targeted effects and containment, extracellular infections require the dissemination of warnings to surrounding tissue and signals for the recruitment of responding cells. Given the nature of immunity against extracellular organisms including fungi and extracellular resident bacterial species, the neutrophil has a pivotal role since CD8 T-cell cellular cytotoxicity mechanisms are of limited value and excessive T-helper cell cytokine production may trigger extensive collateral tissue damage (Figure 2). The traditional concept of the IL-23/IL-17 axis in SpA inflammation is that myeloid-derived IL-23 drives type 17 (IL-17 mediated) immune responses by engaging IL-23R expressed on innate and adaptive lymphocytes to cause downstream production of IL-17 and subsequent pathology, in which neutrophilic mediated inflammation plays a terminal effector role (36).

Neutrophilic proteases in IL-17-driven inflammation

Over recent years, increasing interest in the role of neutrophils in diseases associated with IL-17 has emerged. There has been much debate as to whether neutrophils can produce IL-17 themselves. Initial reports suggested both murine and human neutrophils produced IL-17A/F following stimulation with IL-6 and IL-23 (37, 38). However, subsequent research suggested that neutrophils are incapable of generating IL-17A/F message or protein after a broad range of stimuli and postulate that false positives have arisen through the use of cross-reactive commercial antibodies (39). Whilst neutrophils may not produce IL-17, it has been postulated that they may be able to sequester IL-17 from their local environment and later release it as bioactive cytokine. Indeed, this process has been demonstrated in mast cells, which are also granulocytes that share many functional characteristics with neutrophils including extracellular trap formation and specialized granule release following environmental stimulation (40). Given the clinical importance of neutrophils in SpA phenotypes we focus on this cell type.

Neutrophils express a host of proteolytic enzymes including neutrophil elastase (NE), proteinase 3 (PR3), and cathepsin G (CTSG) in specialized lysosomes termed granules and upon activation release these into the extracellular space during degranulation (41). These proteases are known to promote Th17 development through a variety of mechanisms including NE mediated truncation of IL-8 into an isoform that is recognized directly by T-cells and drives Th17 differentiation (Figure 3) (42). A study by Souwer et al demonstrated through co-incubation studies with ex vivo human neutrophils and T-cells that NE-truncated IL-8 is crucial for Th17 development (42). IL-8 is a strong chemokine for neutrophils and as a result the two are commonly found together in inflamed tissue. PR3 and NE are known to activate protease activated receptors (PARs) that are present on myeloid cells and can produce Th17-skewing cytokines such as IL-6 (43). Indeed, in vitro experiments have shown neutrophil elastase to directly promote human gamma delta (γδ) T-cell activation through stimulation of PAR1 (44). NE, PR3 and CTSG have all been shown to activate IL-1 and IL-36 cytokines, which once activated directly stimulate T-cells (IL-1α and IL-1β) or other myeloid cells (IL-36 cytokines) to produce Th17-driving cytokines; most notably IL-23 (Figure 3) (45-47).

Neutrophil-derived IL-23 in site specific inflammation

It is now clear that neutrophils offer an alternative source of IL-23 to monocyte-derived IL-23 which has important implications for the fine tuning of immune responses in microbe-rich barrier surfaces and for potentially regulating T-cells at disease sites. In 2016, immunohistological and transcript analysis from paediatric subjects with IBD reported that tissue infiltrating neutrophils, rather than macrophages, were the predominant cell expressing IL-23 (48). The same study identified IL-23 transcripts from neutrophils in addition to STAT3 activation of intestinal resident lymphocytes, suggesting the potential ability of neutrophils to regulate type 17 immunity, but the study in question provided no measurement of IL-23 protein (48). Subsequent in vitro studies demonstrated highly pure human neutrophils produced IL-23 following both TLR8 stimulation in a synergistic manner with TNFα, and LPS stimulation synergistic with IFNγ (49, 50). Tamassia et al further demonstrated that culture media from human neutrophils stimulated with the TLR8 agonist R848 could drive Th17 development and IL-17 production from T-cells in an IL-23-dependent fashion to a greater extent than R848-stimulated monocytes (49).

Experimentally, SpA disease can be modelled in SKG mice, which carry a ZAP-70 mutation that attenuates T-cell receptor signalling resulting in autoimmune disease susceptibility (51). Treatment of SKG mice with microbial pathogen-associated molecular patterns triggers experimental SpA that exhibits many disease

features including T-cell associated enthesitis, dactylitis, nail disease and associated IBD whereby disease is also driven by IL-23/IL-17 axis cytokines (52). The earliest phase of disease in this model was characterized by extensive entheseal infiltration by activated neutrophils with IL23A transcript expression (53). As a translational component to the same study, it was demonstrated that the normal human spinous process enthesis had abundant resident neutrophils in the bony anchorage region which contains normal bone marrow (53). With purification of both human entheseal and peripheral blood neutrophils and stimulation with LPS or fungal adjuvants we demonstrated using sandwich ELISA that robust neutrophilic IL-23 production was evident from human enthesis and blood (53).

Additional neutrophil mechanisms driving IL-17 inflammation

Neutrophils are capable of influencing T-cell differentiation through the secretion of various inflammatory factors. Neutrophils isolated from SpA patients have been shown to produce increased amounts of macrophage migration inhibitory factor (MIF) which can promote Treg cells to acquire a Th17 phenotype and induce production of IL-17A (Figure 1B) (54). Indeed, in the SKG murine model overexpression of MIF without supplemental adjuvant was adequate to drive the SpA phenotype. Conversely, blocking MIF when inducing SpA disease through treating SKG mice with curdlan abrogated disease (54). Furthermore, neutrophil-derived prostaglandin E2 (PGE_2), which is induced by IL-23 stimulation, is known to promote Th17 development and may additionally be able to block Th1 development by inhibiting IL-12 and IFNγ production further favouring Th17 development (Figure 1B) (55).

Neutrophils have also been shown to directly promote Th17 development as a result of NETosis. In addition to undergoing degranulation after activation, neutrophils release NETs (neutrophil extracellular traps) that are decorated with proteases, antimicrobial peptides, and histones (56), that can prime IL-17A by a number of mechanisms (Figure 3). A recent murine model confirmed human in vitro experiments that demonstrated histones were able to engage TLR2 expressed on naïve T-cells and drive Th17 development and IL-17 production when present in Th17-driving conditions by increasing expression of RORγt (57). Furthermore, conditioned media from IL-17-stimulated cells and specific IL-17-induced cytokines including IL-8 have been shown to induce NETosis and neutrophil degranulation, thereby reinforcing the type 17 environment (58).

LL37, an antimicrobial peptide secreted by neutrophils following activation and known to coat NETs, has long been associated with psoriatic inflammation and is recognized as a cutaneous T-cell autoantigen that may promote expansion of Tc17 cells (59). More recently, Minns et al demonstrated in an extensive study utilizing murine models and human T-cells that neutrophil-derived LL37 directly influences the development of Th17 cells through promoting expression of RORγt and IL-17 in activated T-cells and pushing Th1 cells to a Th17 phenotype (60). The authors go on to show that mice lacking LL37 are unable to increase IL-17A production in response to inflammation. NETs are commonly found in psoriatic skin and there is evidence of their presence in PsA synovial tissue (61, 62). Neutrophils isolated from patients with AS appear more prone to NETosis than from healthy volunteers (63). Therefore, aside from IL-23 production, there are several other mechanisms by which neutrophils at SpA afflicted sites could contribute to T-cell activation and their own further activation (Figure 3). It is also important to note that whilst there is plentiful data advocating the inflammatory potential of NETs, they have also been observed to temper inflammation by sequestering and degrading pro-inflammatory cytokines and activating anti-inflammatory cytokines (64, 65). Future experiments exploring the overall inflammatory or regulatory

role of NETs as catalysts for T-cell and cytokine activation or cytokine degradation in SpA should prove informative on the role of neutrophils in SpA.

Neutrophil regulation of both innate and adaptive T-cells

The production of IL-17 has largely been attributed to conventional type 17 adaptive immune cells, however other innate immune cell subsets have also been shown to produce IL-17 cytokines. γδ T-cells, type-3 innate lymphoid cells, mucosal-associated invariant T-cells and invariant natural killer T-cells have all been shown to generate both IL-17A and IL-17F. Intriguingly these cell types have all been shown to generate IL-17A and IL-17F independently of IL-23 (66-68). γδ T-cells, which have been shown to produce IL-17 independently of IL-23 at the normal human enthesis (69), express pattern recognition receptors including TLR2 and TLR4, are sensitive to cytokines such as IL-1β, and do not require antigen-recognition to respond to stimulation (70, 71). Given these factors it seems likely interaction of neutrophils with γδ T-cells may well promote such IL-17 production through stimulation with pro-inflammatory cytokines such as IL-1β, neutrophil proteases and TLR agonists (Figure 4). Indeed, as previously mentioned, neutrophil-derived NE is known to induce TNFα production from γδ T-cells through PAR1 stimulation (44). Interestingly, in a murine model of psoriatic arthritis, γδ T-cells have been shown to regulate neutrophil expansion and recruitment to sites of inflammation, which may allow a neutrophil-γδ T-cell feedback loop to establish at such sites (72).

The summation of these findings builds a picture of the neutrophil as a cell that is capable of significantly contributing to IL-17-dependent pathological inflammation in both the innate and adaptive T-cell compartments. Given the myriad of mechanisms that neutrophils regulate T-cells, it is probable that this can occur in both IL-23 dependent and IL-23 independent mechanisms in different scenarios (Figure 4). Evidence suggests these effects are also amplified through positive feedback loops promoting further activation of neutrophils and subsequent promotion of type 17 disease (Figure 3, 4) (58, 73). Further studies exploring the capacity of neutrophils to directly induce IL-17 production from innate T cell subsets in the context of SpA disease and the importance of IL-23 and IL-23 dependent mechanisms could prove to be very informative.

Clinical lessons highlight the importance of neutrophil IL-23

Tissue specific immune compartmentalization in the broadest sense is known to be key in the differential immunopathology seen across SpA spectrum disease (7, 74). The mounting evidence that neutrophils might be key players in perpetuating type 17 disease is intriguing when considered in the context of SpA and may go some way to explain clinical findings in response to anti-IL-17 and IL-23 treatments and non-drug based cellular depletion therapy across the SpA spectrum of disease. Whilst both IL-23 blockade and IL-17 blockade produce excellent improvements in psoriasis, one might expect a dramatically faster onset of action for IL-17 inhibition as this is viewed as an effector downstream cytokine. IL-17 cytokines directly contribute to the pathogenesis of SpA inflammation, whereas IL-23 is primarily thought to contribute through its role in driving and maintaining type 17 cell subsets (75). However, clinical trials in psoriasis with head-to-head comparisons between IL-23 and IL-17 blockers show no major differences in kinetics of responses. The IMMerge study comparing the anti-IL-23 biologic risankizumab to the anti-IL-17 biologic secukinumab for the treatment of psoriasis reported similar response rates between each drug group, with similar numbers achieving PASI75 and PASI100 after 4-8 weeks of treatment (76). Similarly, in the ECLIPSE study examining guselkumab verses secukinumab for psoriasis, rates of initial responders, although numerically higher for anti-IL-17A, were very similar between the two drug groups (77). Psoriatic

skin responds excellently to both anti-IL-23 therapy and to anti-IL-17A and dual IL-17A/F blockade (74). Given that IL-17A/F dual blockade with bimekizumab is superior to secukinumab for psoriasis (78) and that p19 blockers are very effective for psoriasis, it is likely that neutrophil IL-23 production also regulates type 17 T-cell IL-17 production.

Although there are no head-to-head studies between IL-23 and IL-17 blockers in PsA, a subgroup of PsA cases had a rapid onset of efficacy following anti-p19 IL-23 (24). Support for a pathological role of neutrophilic IL-23 production comes from the rapid responses of secondary neutrophilic dermatoses (ND) to IL-23 blockade with a recent report showing that ustekinumab treatment caused remission of ND in 83% of Crohn's disease patients despite the ND being refractory to numerous previous therapies (79). Intriguingly, there have also been recent case reports of secukinumab associated PG being successfully treated with the IL-23 blocker risankizumab and anti-p40 blocker ustekinumab (80, 81), that provides evidence towards potential neutrophilic IL-23 production at the fulcrum of the pathological process.

Patients with AS exhibit elevated neutrophil numbers that correlate with increased severity scores (82). Interestingly, depletion of neutrophils has been shown to have some benefit in treating SpA-associated conditions with therapeutic apheresis that selectively removes granulocytes and monocytes. Trials in UC with leucophoresis that removes monocytes and neutrophils could at least in part do so by blocking amplification of IL-23 production from these two cell types (83). Beyond IBD, neutrophilic depletion in murine imiquimod induced psoriasis was also associated with amelioration of disease that likely incriminates the paucity of IL-17A/F effector target cells as well as the removal of inflammatory cascade amplification feedback loops (84). Depletion of granulocytes in a mannan-induced mouse model of PsA also protected mice from developing disease (85). It seems likely that some of the benefit of anti-IL-17A inhibition in psoriasis may relate to blocking neutrophil accumulation in the skin and thus pre-emptively disabling the amplification loop (86). Several open studies have also directly supported the value of granulocyte macrophage apheresis in both refractory psoriatic arthritis and psoriasis (87). The removal of both neutrophils and monocytes as IL-23 producers might be an important mechanism of action for these therapies.

How might neutrophils impact immunotherapy in axial disease?Thus far, there is marginal difference between anti-IL-23 and IL-17 therapy in PsA, yet axial SpA, namely AS, does not respond well to anti-IL-23 therapy (20). This raises the possibility of hitherto unappreciated regulatory networks at play to different extents across the sites affected in the MHC-I-opathies. The interplay between innate and adaptive immune cells and their surrounding stroma may therefore vary at sites affected depending on the presence and abundance of various immune subsets. This is particularly evident when considering IBD. Anti-IL-17 directed therapy is known to have deleterious effects in the gut that may be a result of blocking crucial IL-17-dependent homeostatic functions (88). Yet anti-IL-23-targeted treatment is efficacious in the gut, which is believed to be due to IL-23-independent sources of IL-17 gut production, allowing maintenance of IL-17-dependent barrier function (89).

Whilst beneficial in the gut, IL-23-independent sources of IL-17 may present difficulties in other SpA-associated tissues and the axial skeleton, in particular. As discussed above, neutrophils through their interaction with unconventional T-cell subsets may drive production of IL-23-independent IL-17 (Figure 4A). This becomes important to consider in arthropathies and enthesitis due to the proximity to axial bone; a rich source of neutrophils due to normal haematopoiesis (Figure 5). Indeed, neutrophils are more abundant in red marrow, which is more common in the spine, than fatty non-haematopoietic marrow at

peripheral entheses, meaning neutrophils may be more available in spinal entheses (Figure 5) (90). Subsequently, there may be both more IL-23-dependent and IL-23-independent neutrophil-driven IL-17 inflammation in axial SpA than in the peripheral skeleton (Figure 4). This viewpoint has direct clinical relevance and would suggest that higher doses of anti-IL-23 therapy, akin to that used in IBD, or trialling dual IL-17/IL-23 therapy may also be effective in AS.

Implications for neutrophilic contribution to SpA pathogenesis

IL-17 production promotes both granulopoiesis and the influx of neutrophils via induction of chemokines from surrounding stroma and promotes neutrophil activation, inducing production of IL-23, degranulation and NETosis, ultimately amplifying inflammation. In this scenario, a neutrophil-centric environment exists to drive Th17 and Tc17 differentiation and the classical IL-23/IL-17 cytokine axis. The strategic placement of abundant neutrophils at the intestinal mucosa in IBD as described in humans thus offers pervasive neutrophil driven mechanisms, including IL-23 production, to limit or exacerbate anti-microbial responses (48).

Experimentally, intestinal neutrophils also play a key role in mucosal barrier protection and repair (91). Although traditionally thought of as short-lived cells whose aim is primarily to control and eliminate foreign bodies from sites of infection, novel tissue repair mechanisms including collecting and depositing of extracellular matrix at injury sites have emerged (92). Diseases of the SpA spectrum often feature reduced gut barrier function, with increased infiltration of gut microbes into the lamina propria (93). Subclinical intestinal inflammation is associated with the presence of MRI determined sacroiliitis in SpA patients (94). This loss of barrier integrity may allow entry of stimulatory environmental factors, either directly through impaired barriers or via circulation, that induce production of IL-23 from the local immune compartment and drive an IL-17-mediated immune response, the dysregulation of which may culminate in SpA phenotypes, including excessive pathological repair responses.

Interestingly, it has long been established that phagocytosis of apoptotic neutrophils has a dampening effect on inflammation, and has specifically been shown to inhibit the production of IL-23 by monocytes and macrophages that clean up the apoptotic neutrophils after infection (95). Under healthy conditions this process dampens or may attenuate the IL-23/IL-17 axis loop allowing repair to progress. Integrating the recent findings that neutrophils produce IL-23, the notion that neutrophil stimulation persists when barrier function is impaired implies that neutrophils themselves may become the primary IL-23 producers. By providing a continual turnover of apoptotic neutrophils to dampen monocyte and macrophage IL-23 production yet responding themselves to persistent environmental stimulatory cues, neutrophils may maintain a pathological IL-23/IL-17 axis. This may be a particularly important consideration in tissues of patients that suffer constant barrier tissue disruption such as IBD and psoriasis.

It is worth mentioning that neutrophil inflammation manifests clinically in a number of T-cell independent inflammatory conditions. This is most notable in the IL-1 family receptor antagonist loss of function mutations such as deficiency of the interleukin-1 receptor antagonist (DIRA) and deficiency of the interleukin-36 receptor antagonist (DITRA) in which unopposed IL-1- or IL-36-mediated inflammation gives rise to generalized pustular psoriasis and sometimes arthropathy (96). In these conditions the neutrophilic regulation of the IL-23/IL-17 axis appears less important, perhaps suggestive of neutrophils acting in response to inflammation rather than driving inflammation. Clinically, this points to heterogeneous molecular mechanisms that regulate neutrophilic inflammation across the SpA spectrum and could inform future therapy stratification in subjects refractory to IL-23/IL-17 axis antagonism. Whilst

not defined in SpA per se, such a neutrophil IL-1 axis has recently been posited in the related IBD pathology (97).

Conclusions

We have drawn from the emerging evidence that neutrophils in barrier tissues and even within the stressed vascular compartments or peri-entheseal tissues are not merely terminal effector cells in pathology but likely exert complex positive feedback loops. It is now increasingly recognized that neutrophils may feedback on adaptive immune cells via IL-23 production and a host of other mechanisms to tune pivotal cytokines including IL-17 that further regulate immune responses in the SpA-associated inflammatory tissue environments. We believe that this likely accounts for the sterile inflammation most notably visible to clinical inspection in anterior uveitis, BD and psoriasis that are strongly MHC-I linked. The comparatively fast onset of action of IL-23 blockers that is not dissimilar to IL-17 pathway blockers could be a major factor in responses to therapy in psoriasis and the related seronegative SpA group of diseases.

Furthermore, the relative contribution of neutrophils in indirectly regulating IL-17 production in various tissue compartments may have a significant impact on the efficacy of anti-IL-23 therapy in neutrophil-rich tissues, especially in the axial skeleton marrow where abundant resident neutrophils may determine the inferior response to IL-23 inhibitors and their failure thus far for axial disease (Figure 5). The neutrophil-CD8 T-cell crosstalk appears key to understanding much of the pathology in the SpA spectrum disorders. Understanding that neutrophils, a dominant presence in SpA disease, vary in their topographic localization and numbers from tissue to tissue sets the scene for a better understanding of SpA immunopathogenesis. The ability of neutrophils to regulate T-cells via both IL-23 dependent and independent mechanisms that culminates in IL-17 pathway mediated inflammation is now an emergent concept in SpA. In particular, neutrophilic IL-23 production reveals a hitherto unappreciated cellular and cytokine axis that may be key to understanding and deciphering SpA disease.

Indeed, exploring these ideas in mouse models and clinical trials may prove illuminating. Modification of the SKG mouse model to remove neutrophils, or neutrophil-specific IL-23, may go some way to demonstrate the dependency of axial SpA on IL-23 or neutrophils. Subsequently examining the efficacy of high-dose p19 blockade in axial SpA where the axial bone represents a neutrophil-rich myelopoietic environment may also be informative, with efficacy supporting the importance of neutrophil-derived IL-23 dependent mechanisms and inefficacy favouring neutrophil activation of type 17 cells independently of IL-23.

This viewpoint brings together a large array of clinical, histological, immunogenetic, animal model, translational immunology and therapy data to help contextualize the theory that neutrophils have a key role in SpA disease. Nevertheless, further experiments such as those discussed above are required to properly delineate their importance and define the roles of neutrophil IL-23 and IL-23-independent IL-17 driving factors in SpA.

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Figures and Legends

Figure 1

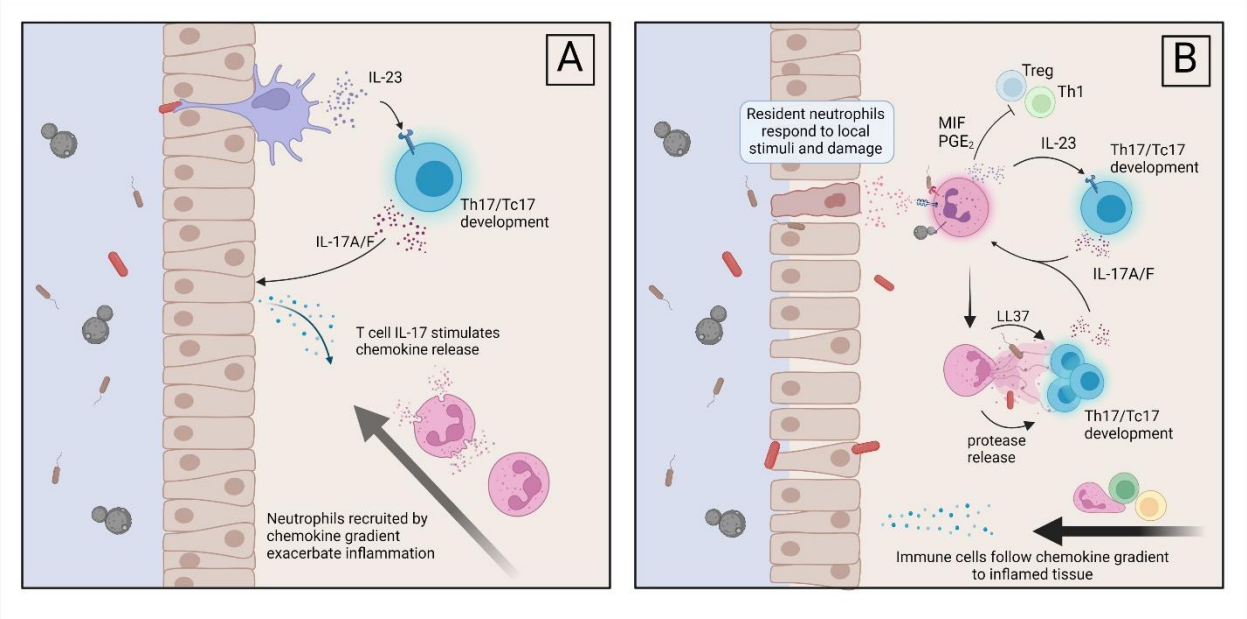

Figure 1: An updated model for the role of neutrophils in IL-23/IL-17 axis disease

Traditionally neutrophils have been thought of as terminal effector cells in inflammatory disease that exacerbate inflammation and tissue damage as a result of IL-17-driven disease. A) The established model describes Type 17 immunity development as a result of IL-23 production from activated myeloid cells. Subsequent IL-17 production drives pathological effects observed in disease and stimulates surrounding tissue to produce a chemokine gradient with neutrophilic tissue inflammation. B) Recent evidence, however, suggests a more involved role for neutrophils in regulating and fine-tuning T-cell responses with production of IL-23 by neutrophils gives room for an alternative and more active role for neutrophils. Resident neutrophils generate IL-23 as a result of tissue damage and pathogen recognition and undergo NETosis. Neutrophil IL-23 production, NETosis and release of proteases promote development of Th17 and Tc17 cells and subsequent IL-17 production, initiating IL-17-driven disease. Neutrophil factors such as MIF and PGE2 simultaneously promote Th17 by pushing Treg cells towards Th17 cells and inhibiting Th1 development, respectively. Production of IL-17 further promotes neutrophil recruitment and production of IL-23, resulting in a neutrophil-T-cell feedback loop.

Figure 2

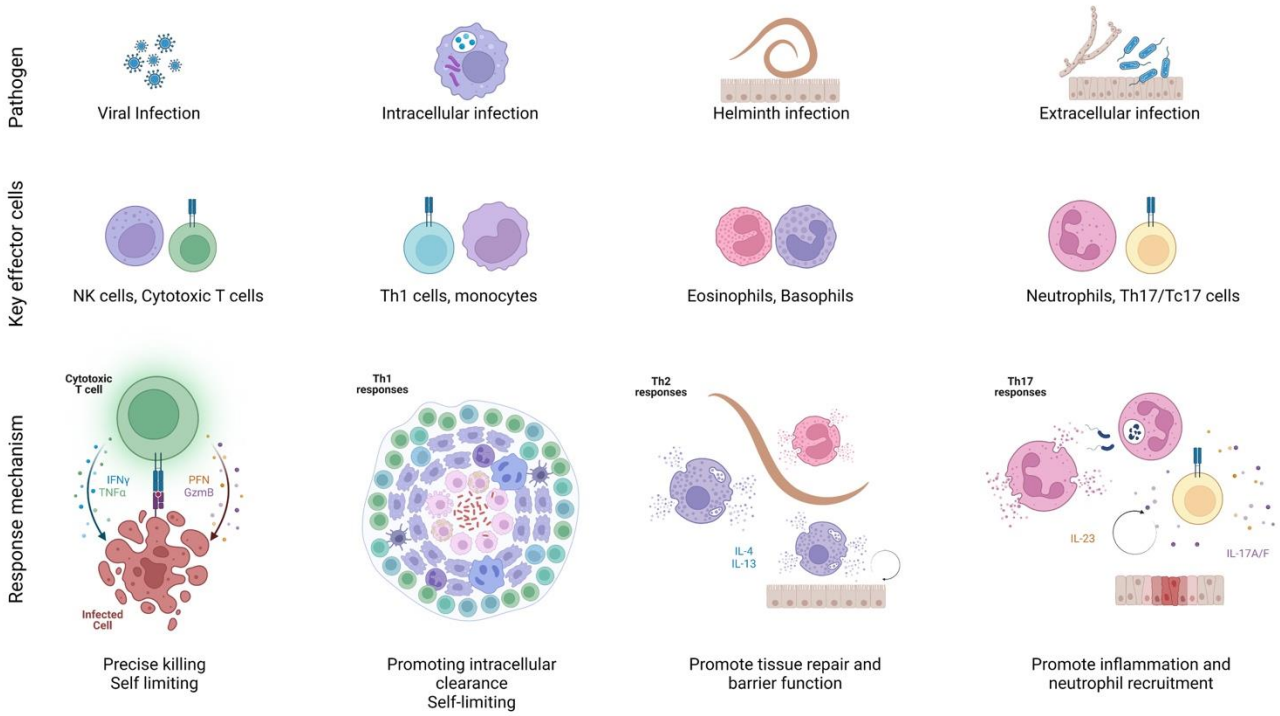

Figure 2: Four types of immunity including the place of IL-23/IL-17 pathway immunity.

Broadly speaking, an immune response can be divided into 4 types depending upon what type of infection the immune system is facing; viral infection, intracellular pathogens, parasites and helminths, and extracellular bacterial or fungal infection. Each type of infection has different characteristics and the immune system therefore employs different strategies to achieve clearance. Viral immunity including interferon responses and NK and cytotoxic T-cell responses to remove infected cells is well understood. Likewise, immunity against intracellular pathogens including TB that are difficult to degrade is also well recognized with Th1 responses with IFNγ and TNF driving granulomatous inflammation and pathogen clearance. Some pathogens including various helminths and also fungi live on the body surface of cavities with Th2 immunity encompassing prominent IL-4, IL-13 and IL-5 mediated degranulation reactions with prominent involvement of eosinophils and basophils. Fungal infection and hyphal networks and many bacteria are extracellular and, in this scenario, both $CD4^+$ and $CD8^+$ T-cell directed cytotoxicity of infected cells is irrelevant as the microbes reside outside cells. The immune system must therefore recruit neutrophils as 1st line innate immune cells specialized in the immobilization, phagocytosis and NETotic killing of extracellular pathogens. Accordingly, the adaptive immune response primes neutrophil innate immunity via ROS, NETosis and other mechanisms to effect capture and killing of invading extracellular pathogens.

Figure 3

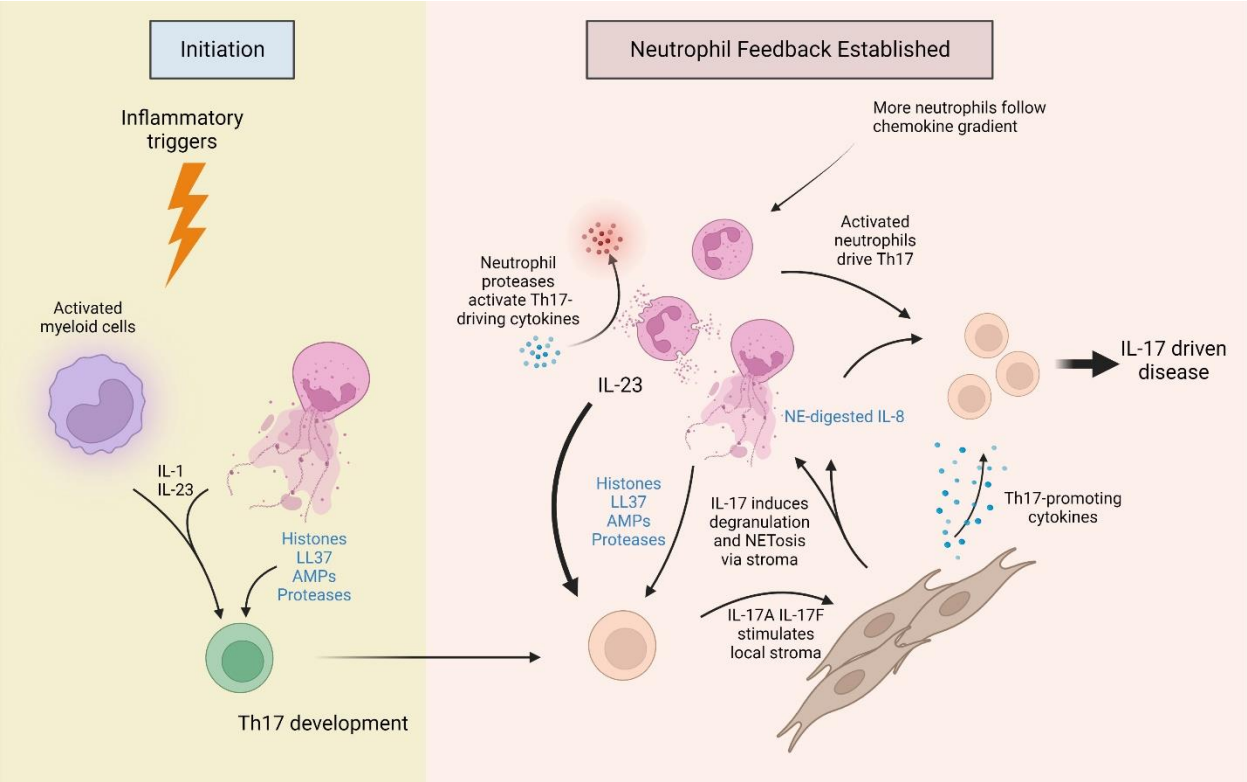

Figure 3: Neutrophil contribution to IL-17 production

Neutrophils contribute to both initiation and progression of type 17 driven disease. Once activated, neutrophils release proteolytic enzymes that amplify bioactivity of cytokines that drive Th17 development and production of IL-17A and IL-17F. NETosis releases LL37- and histone-coated NETs that promote development and expansion of Th/Tc17 cell subsets. Once inflammation is established, IL-17 stimulated stroma provide a chemokine gradient that allow an influx of more neutrophils to the inflamed area. IL-17-stimulated environment promotes further activation of infiltrating neutrophils, which induces IL-23 secretion alongside production of pro-inflammatory cytokines, release of neutrophil proteases that digest IL-8 to directly stimulate Th17 cells, and NETosis maintaining a Th17 drive. Established IL-17 inflammation generates an inflammatory environment that is reinforced through neutrophil feedback.

Figure 4

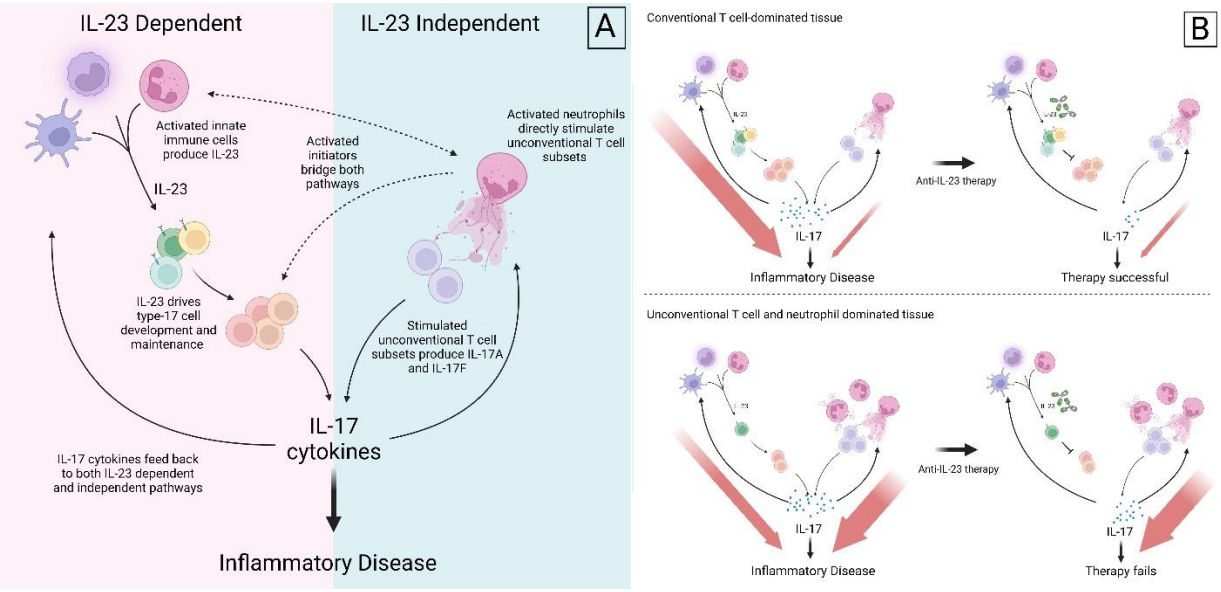

Figure 4: Neutrophil contribution to IL-23-independent IL-17 may impact anti-IL-23 therapy

A) Diagram illustrating IL-23 dependent and independent pathways of IL-17 production at play in IL-17-driven disease. B) Illustration depicting how neutrophilic contribution to IL-23-independent IL-17 may impact on IL-23-targeted therapy. Where IL-17 production is largely IL-23-dependent, anti-IL-23 therapy is effective as the IL-23/IL-17 axis is successfully interrupted (top panel). However, disease compartments that are particularly rich in neutrophils and unconventional T-cells that do not require IL-23 to produce IL-17 may be less susceptible to anti-IL-23 biologics as a large proportion of IL-17 may be generated independently of IL-23 (lower panel). Anti-IL-23 therapy may therefore fail in these cases.

Figure 5

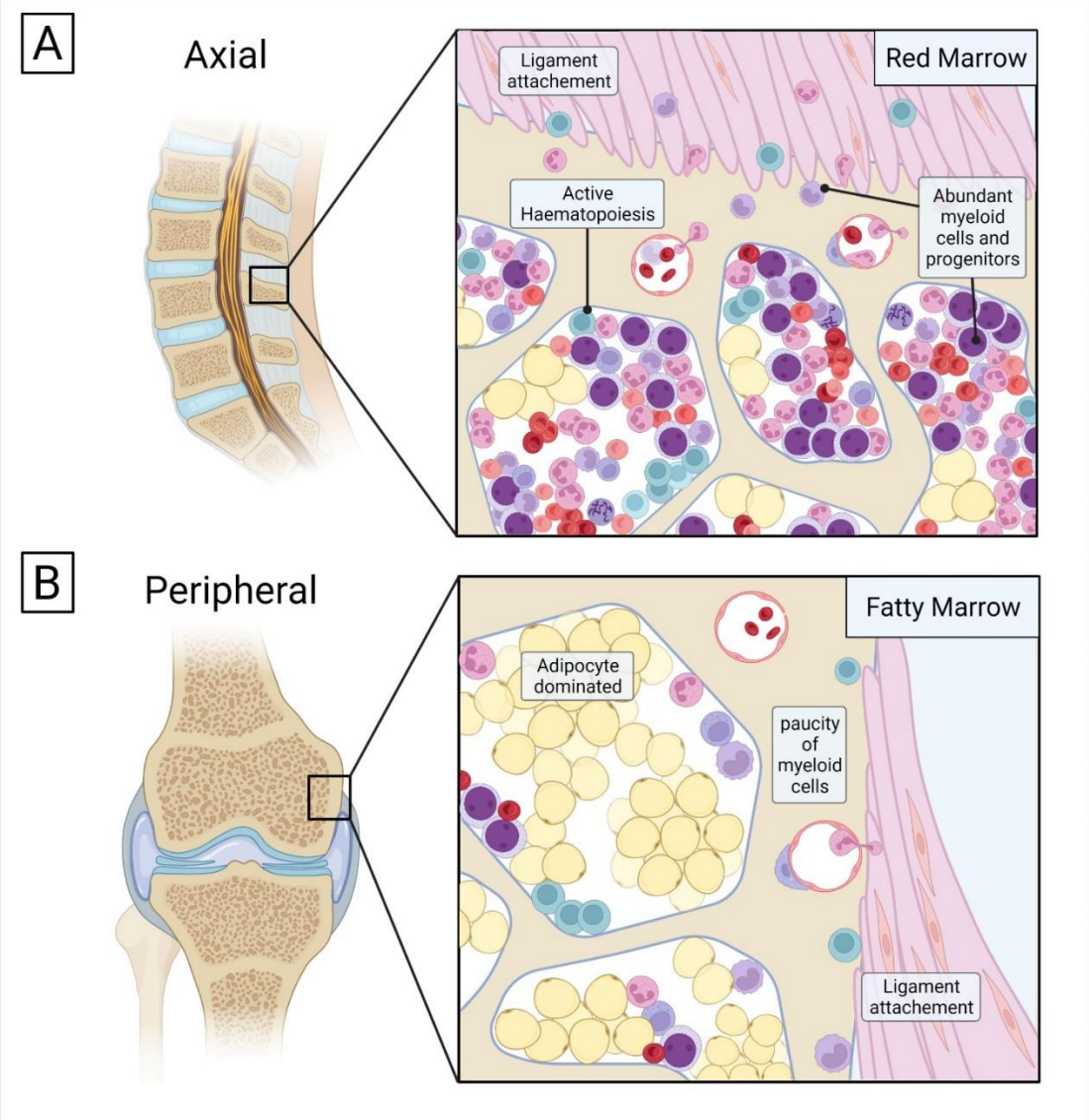

Figure 5: Cellular characteristics of axial vs peripheral bone marrow at enthesis attachments

A) Axial spinal disease in HLA-B27^{+} subjects is strongly linked to osteitis and this bone pathology coincides with red haematopoietic marrow. Unlike fatty marrow in the peripheral adult skeleton this site is rich in myeloid progenitors and mature myeloid cells including neutrophils and monocytes. The local inflammatory milieu related to the osteitis may further serve to active the myeloid cell compartment with comparatively high local IL-23 production. B) In adults the peripheral entheseal attachments are to sites of white or fatty marrow with enrichment of adipocytes but a relative paucity in myeloid cells. Therefore, the greater magnitude of neutrophil presence in health in the axial skeleton that is directly linked to this being the site of myelopoiesis could impact the magnitude IL-23 production from the spine, which could in turn require higher doses of anti-IL-23 to neutralize inflammation. Confirmation of this in clinical trials

would suggest that neutrophil and myeloid regulation of T-cells in the spine was in fact an IL-23 dependent process.

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Conflict of Interest

DM has received grant funding and honoraria from Janssen, Novartis, UCB, Lilly and Abbvie.

Author Contributions

TM, CB, DM conceived of manuscript concepts and manuscript structuring. TM and DM wrote the manuscript.